
A B7H3-targeting antibody–drug conjugate in advanced solid tumors: a phase 1/1b trial

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Supplementary Methods

The sB7H3 assay was based on the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for human B7-H3 (Abcam, ab227670, SP206) was precoated onto a microplate. Standards and samples were pipetted into the wells, and any B7-H3 present was captured by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for human B7-H3 (1:800 dilution) was introduced into the wells. Subsequently, a substrate solution was added to the wells, and color development occurred in proportion to the amount of B7-H3 bound in the initial step. The color development was then halted, and the intensity of the color was measured.

The exposure–response analyses were conducted using the dataset from Part 1 (dose escalation) of the YL201-INT-101-01 and YL201-CN-101-01 studies. The efficacy endpoint was the objective response rate (ORR). The most frequent grade 3 and above ($\text{Grade} \geq 3$) hematological treatment-related adverse events (TRAEs) were selected as safety endpoints for the exposure–response analysis, including neutropenia, anemia, and thrombocytopenia. A logistic regression model was performed for the exposure–response analysis using R (version 4.4.1) software.

Supplementary Results

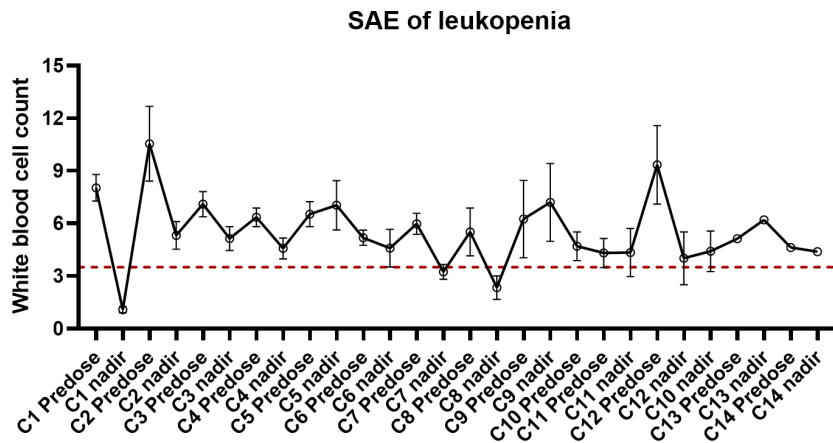
Pharmacokinetics (PK)

YL201 populational pharmacokinetic (PopPK) analysis was performed using a sequential modeling approach, where a PK model was first developed for YL201-ADC alone, and then an integrated model was developed for YL201-ADC and YL0010014 (payload). In the integrated model, the PK parameters for YL201 were fixed to their post-hoc estimates from the PK model of YL201-ADC alone, and the

PK parameters for YL0010014 were estimated. The base model structure is shown in **Supplementary Fig. 3**. In order to define the target saturation above 2 mg/kg, a nonlinear elimination with $V_{\max}$ and K_m parameters was incorporated into the ADC model.

The correlation analysis was used to preliminarily screen out baseline covariates that may affect the PK parameters of YL201-ADC and YL0010014. Subsequently, the stepwise covariate method (SCM) with $p < 0.05$ for forward inclusion and $p < 0.001$ for backward exclusion was employed to conduct a detailed covariate model analysis on the screened covariates and clinically relevant covariates of interest. After SCM analysis, the final model for YL201-ADC included the baseline body weight (BBWT), baseline estimated glomerular filtration rate (BEGFR), and baseline sum of target lesion diameters (BTMBD) as covariates affecting the central compartment clearance rate (CL) and BBWT affecting the central compartment distribution volume (VC). The final model for YL0010014 included baseline alkaline phosphatase (BALP) as a covariate affecting the rate constant of release (K_{rel}). The estimated effects of the PopPK parameters and covariates on PK parameters are shown in **Supplementary Fig. 4**. The estimated values of each parameter are reasonable, with the exception of the parameter RSE for the effect of BEGFR on CL being relatively high (52%), all other parameters have RSE less than 30%, indicating a relatively accurate estimation of the parameters. The model diagnostic plots for the final model are shown in **Supplementary Fig. 5**, which indicates that the observed values are evenly distributed around the line $y=x$ for the population predictions and individual predictions. The conditional weighted residuals (CWRES) are evenly distributed around the line $y=0$ for the population predictions and the time after the first dose, suggesting that the final model can describe the PK characteristics of YL201-ADC and YL0010014 well. A visual predictive check (pcVPC) evaluation of the final model after prediction correction is shown in **Supplementary Fig. 6**,

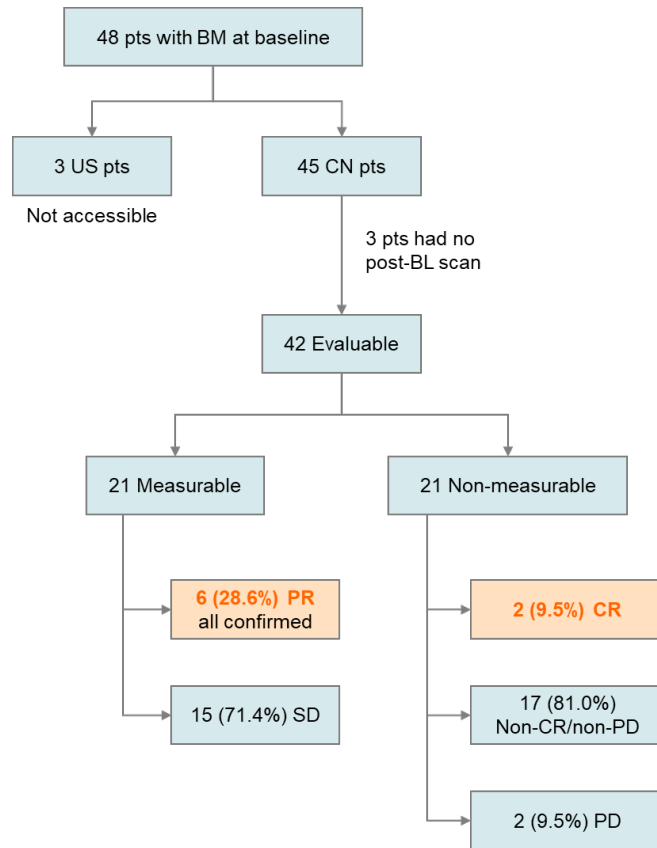
which shows that the 5%, 50%, and 95% quantile lines of the observed values after prediction correction mostly fall within the 95% confidence intervals of the corresponding quantiles predicted by the model, indicating a good predictive performance of the final model.



Supplementary Fig. 1. Lineage of the dynamic changes of white blood cell counts in patients with the serious adverse event (SAE) of leukopenia.

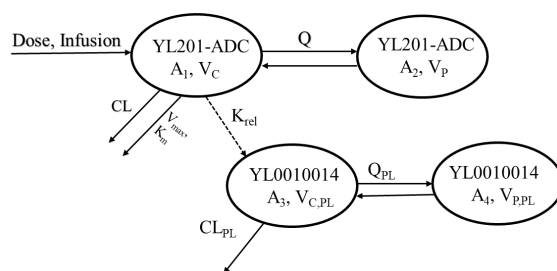
Nadir, lowest white blood cell counts after YL201 treatment. Lineage of the dynamic changes for 35 patients who experienced the SAE of leukopenia. The mean and standard error of the mean are shown.

The red line shows the lower limit of the normal white blood cell count ($3.5 \times 10^9/L$).



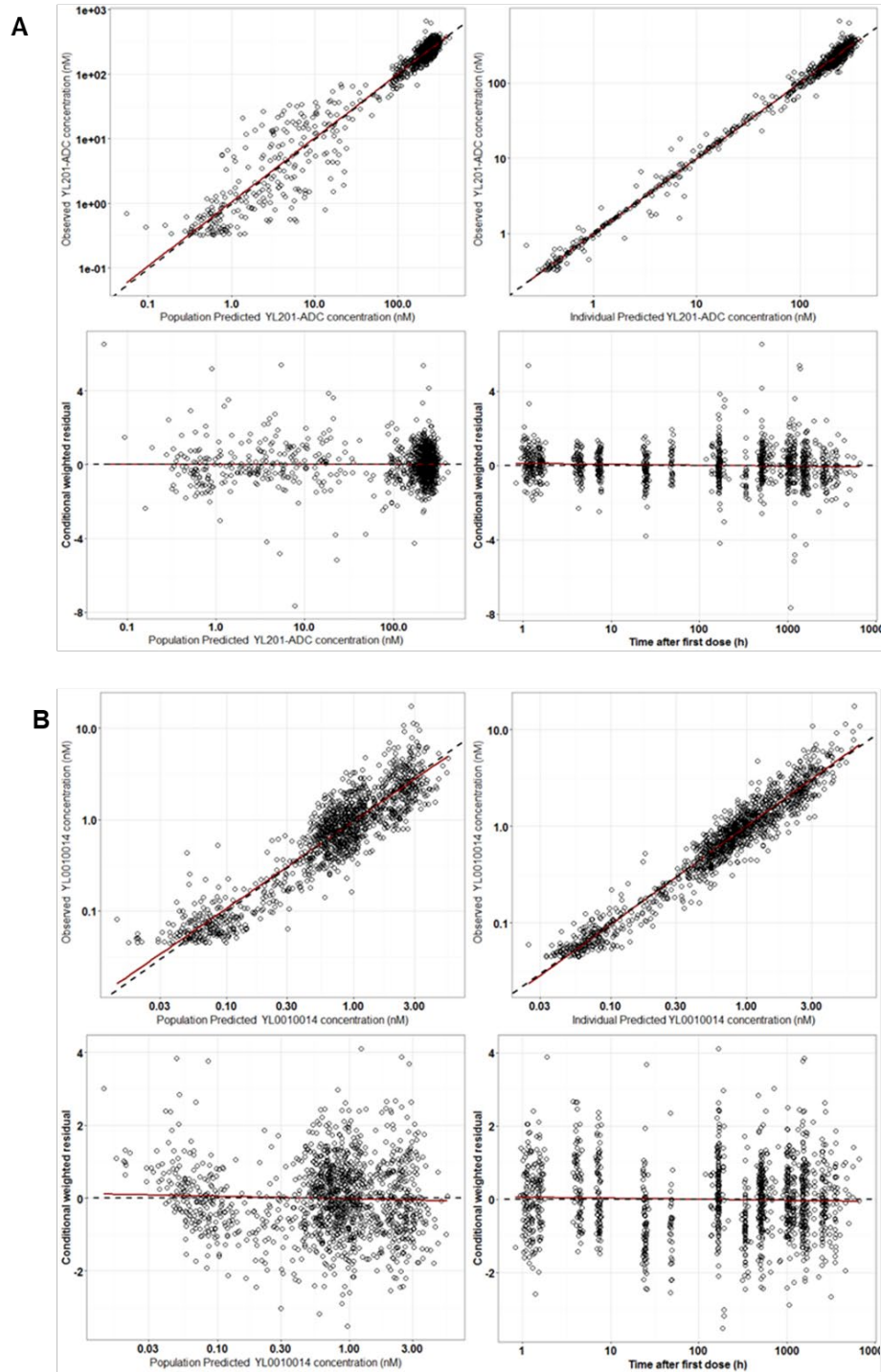
Supplementary Fig. 2. Flowchart for the assessment of patients with brain metastases at baseline.

Pts, patients; CN, China; US, United States; CR, complete response; PR, partial response; SD, stable disease.



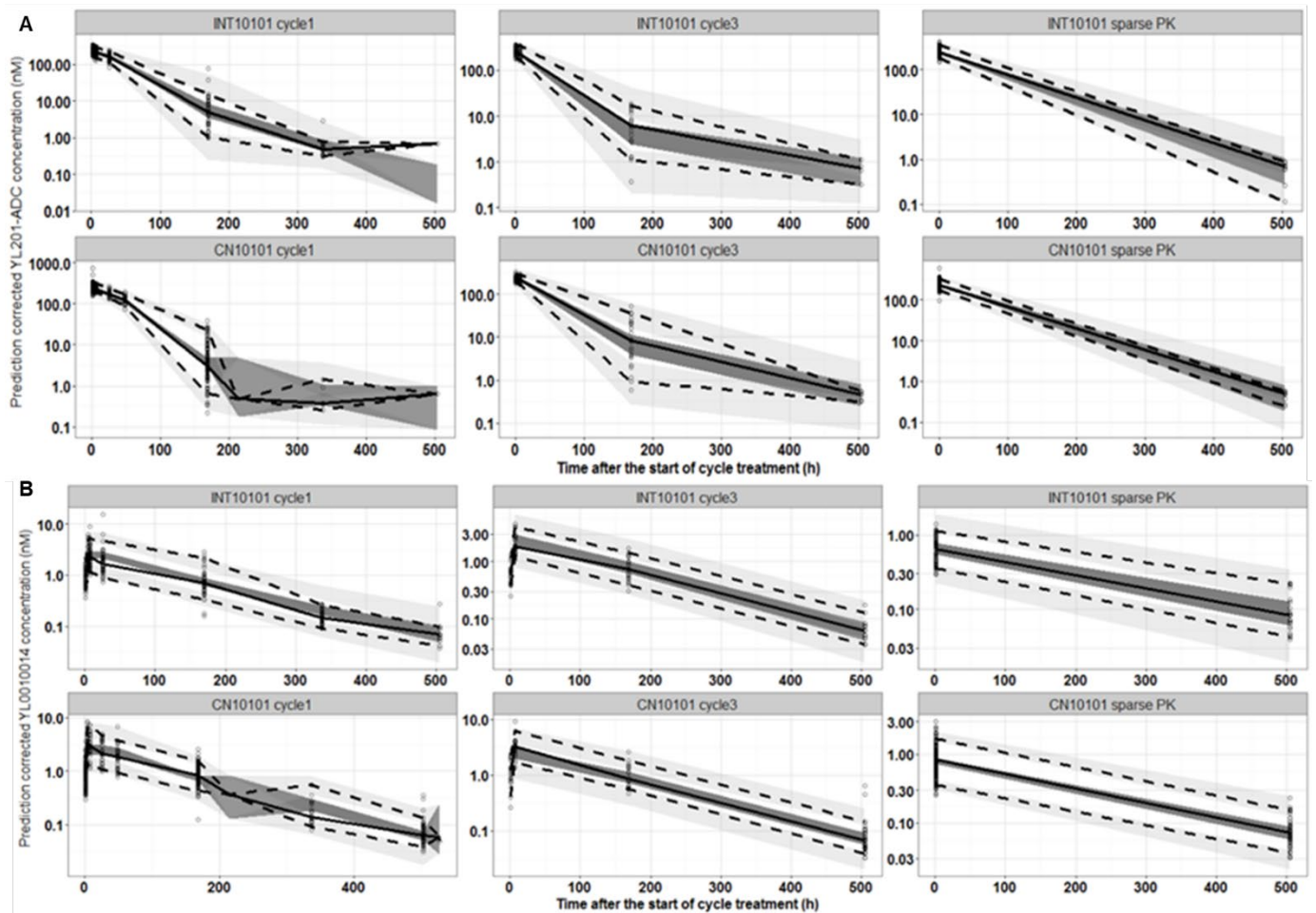
Supplementary Fig. 3. Integrated pharmacokinetic model structure for YL201-ADC and YL0010014.

CL: clearance of YL201-ADC in the central compartment; Vc: volume of distribution of YL201-ADC in the central compartment; Vp: volume of distribution of YL201-ADC in the peripheral compartment; Q: clearance of YL201-ADC between the central compartment and the peripheral compartment; V_{max}: maximum amount of drug cleared in a unit time by the nonlinear clearance portion of YL201-ADC; K_m: concentration of YL201-ADC at half of the V_{max}; K_{rel}: release rate constant; V_{C,PL}: volume of distribution of YL0010014 in the central compartment; CL_{PL}: clearance of YL0010014 in the central compartment; V_{P,PL}: volume of distribution of YL0010014 in the peripheral compartment; Q_{PL}: clearance of YL0010014 between the central compartment and the peripheral compartment.



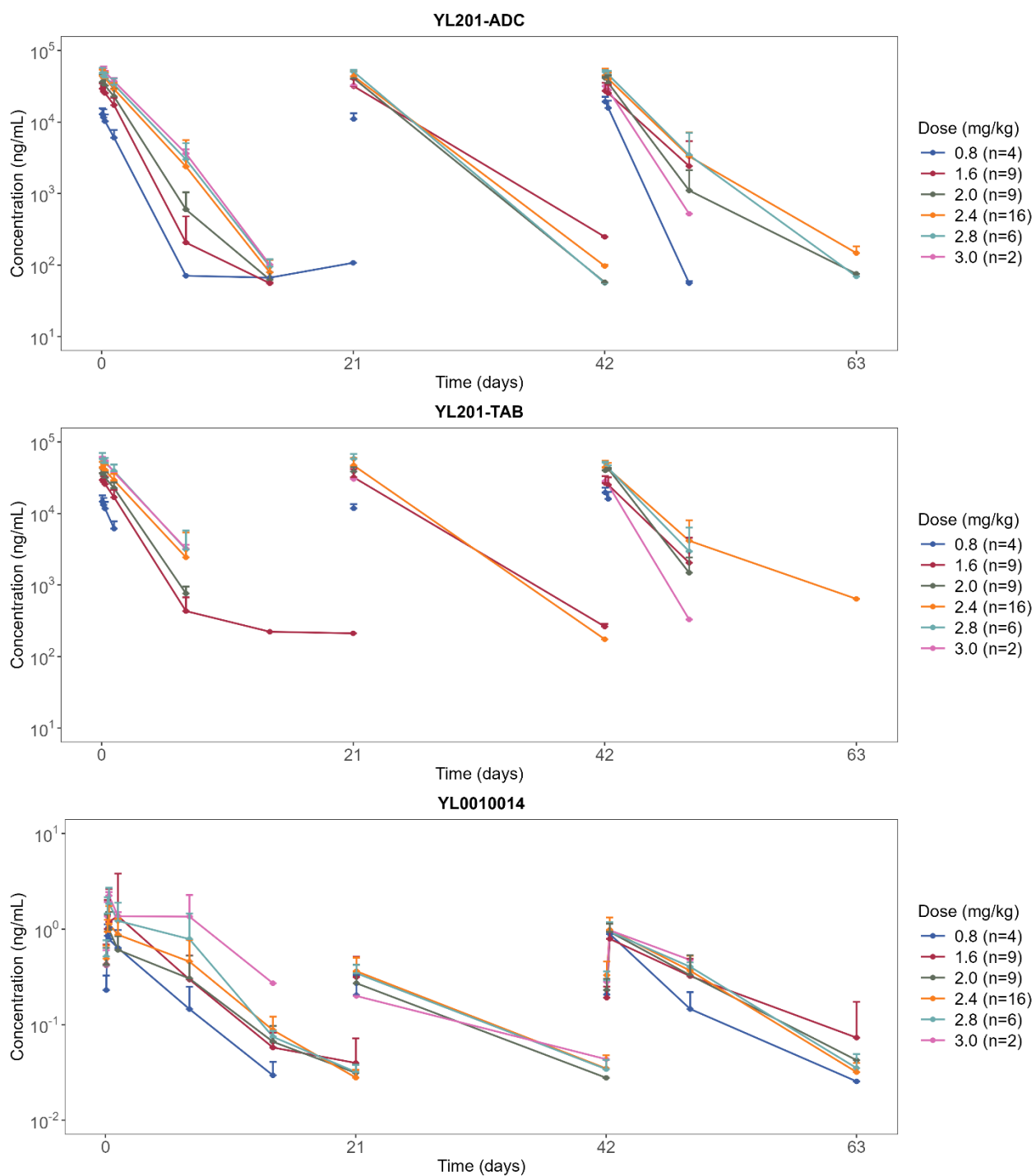
Supplementary Fig. 4. Diagnostic plots of the PopPK model.

A: YL201-ADC, B: YL0010014. The upper left panel presents observations versus population predictions; the upper right panel presents observations versus individual predictions; the lower left panel presents conditional weighted residual versus population predictions; the lower right panel presents conditional weighted residuals versus time after the first dose. The dashed line in the upper half of the figure is $y=x$; the dashed line in the lower half of the figure is $y=0$. The solid red line is a linear regression line.

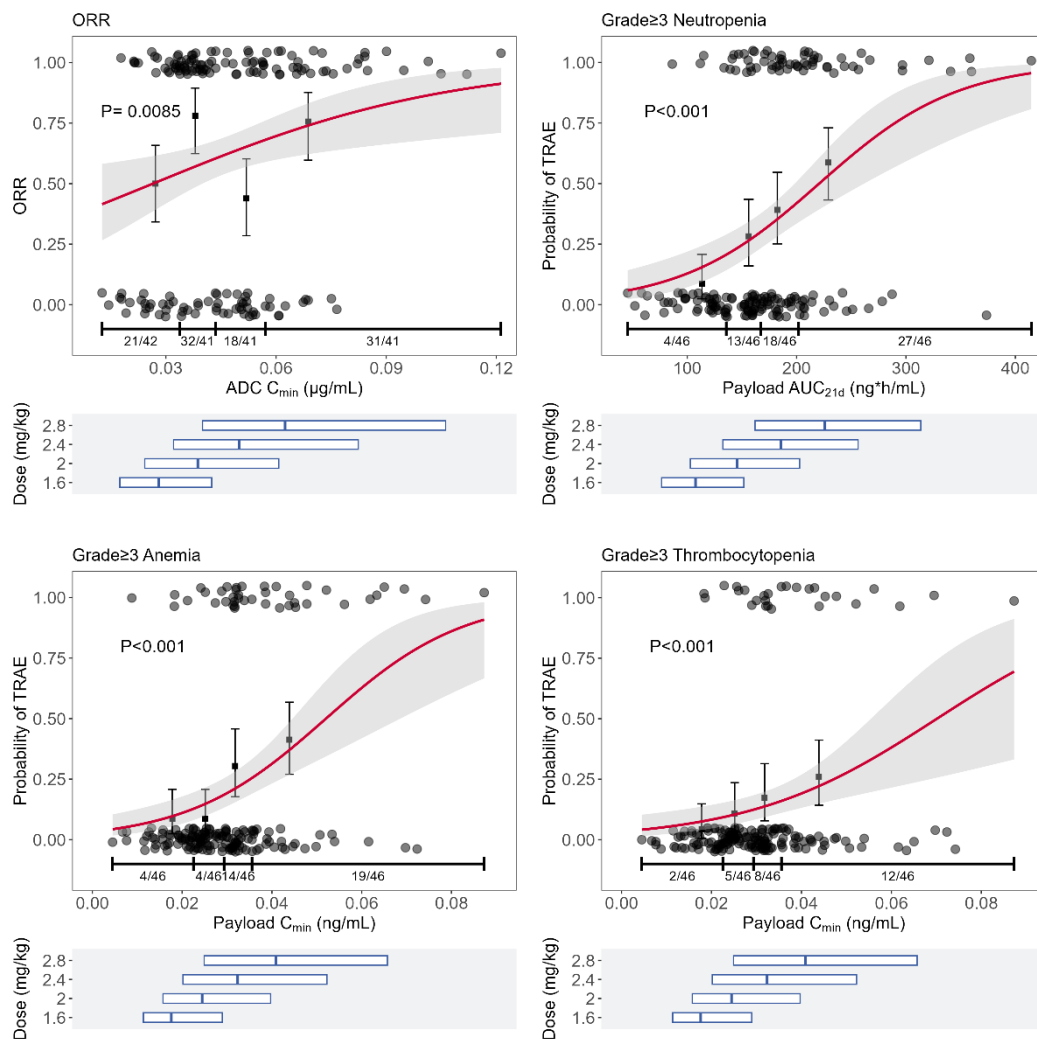


Supplementary Fig. 5. The pcVPC plots of the PopPK model.

A: YL201-ADC, B: YL0010014. pcVPC: prediction-corrected visual predictive check; INT10101: YL201-INT-101-01; CN10101: YL201-CN-101-01. Plots from left to right are intensive sampling in cycle 1, intensive sampling in cycle 3, and sparse sampling, respectively. The x-axis is the time after dosing in each cycle. The three lines from top to bottom are the prediction-corrected 5th, 50th, and 95th percentiles of observations, respectively; the shaded areas are the 95% confidence intervals of the corresponding percentiles predicted by the model.



Supplementary Fig. 6. PK profiles of YL201-ADC, YL201-TAB, and YL0010014 in the first three cycles in the phase 1 dose-escalation study. Data are presented as mean and standard derivation.



Supplementary Fig. 7. Logistic regression of exposure-response analyses for YL201.

ADC C_{min} = trough concentration of ADC in cycle 1. Payload AUC_{21d} = AUC of payload in cycle 1. Payload C_{min} = trough concentration of payload in cycle 1. Notes: The subjects were stratified into exposure quartiles. The black squares are the mean exposure and event rate per quartiles. The vertical black bars are the 95% confidential intervals of the event rate. The red line represents the linear logistic regression fit. The gray-shaded area represents the 95% confidence interval of the logistic regression prediction. The grey circles represent the actual subject exposure and response outcomes plotted at 0 for no event and 1 for an event. The horizontal bars below the plot illustrate the 10%, 50%, and 90% exposures at 1.6, 2, 2.4, and 2.8 mg/kg.

Supplementary Table 1. Baseline demographic and clinical characteristics of patients in the phase Ib dose-expansion study

	ES-SCLC (N=67)		NPC (N=68)		Wide-type NSCLC (N=51)		ESCC (N=35)		Others (N=42)		Total (N=263)	
	2.0 mg/kg (N=35)	2.4 mg/kg (N=32)	2.0 mg/kg (N=34)	2.4 mg/kg (N=34)	2.0 mg/kg (N=8)	2.4 mg/kg (N=43)	2.0 mg/kg (N=2)	2.4 mg/kg (N=33)	2.0 mg/kg (N=7)	2.4 mg/kg (N=35)	2.0 mg/kg (N=86)	2.4 mg/kg (N=177)
Age (years), median (range)	60.0 (48–73)	61.5 (54–72)	49.0 (32–71)	45.5 (32–71)	56.0 (45–71)	59.0 (24–72)	67.0 (62–72)	60.0 (48–73)	47.0 (19–70)	55.0 (33–74)	56.0 (19–73)	58.0 (24–74)
Race, <i>n</i> (%)												
Asian	35 (100.0%)	32 (100.0%)	34 (100.0%)	34 (100.0%)	8 (100.0%)	43 (100.0%)	2 (100.0%)	33 (100.0%)	7 (100.0%)	35 (100.0%)	86 (100.0%)	177 (100.0%)
White	0	0	0	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0	0	0	0
Sex, <i>n</i> (%)												
Male	31 (88.6%)	29 (90.6%)	27 (79.4%)	31 (91.2%)	5 (62.5%)	27 (62.8%)	2 (100.0%)	30 (90.9%)	5 (71.4%)	23 (65.7%)	70 (81.4%)	140 (79.1%)
Female	4 (11.4%)	3 (9.4%)	7 (20.6%)	3 (8.8%)	3 (37.5%)	16 (37.2%)	0	3 (9.1%)	2 (28.6%)	12 (34.3%)	16 (18.6%)	37 (20.9%)
Smoking history, <i>n</i> (%)												
Never	11 (31.4%)	4 (12.5%)	25 (73.5%)	21 (61.8%)	6 (75.0%)	20 (46.5%)	1 (50.0%)	19 (57.6%)	6 (85.7%)	20 (57.1%)	49 (57.0%)	84 (47.5%)
Yes	24 (68.9%)	28 (87.5%)	8 (23.5%)	13 (38.2%)	2 (25.0%)	23 (53.5%)	1 (50.0%)	13 (39.4%)	1 (14.3%)	13 (37.1%)	36 (41.9%)	90 (50.8%)
Unknown	0	0	0	0	0	0	0	1 (3.0%)	0	0	1 (1.2%)	3 (1.7%)
ECOG, <i>n</i> (%)												
0	2 (5.7%)	6 (18.8%)	10 (29.4%)	6 (17.6%)	3 (37.5%)	2 (4.7%)	0	3 (9.1%)	3 (42.9%)	6 (17.1%)	18 (20.9%)	23 (13.0%)
1	33 (94.3%)	26 (81.3%)	24 (70.6%)	28 (82.4%)	5 (62.5%)	41 (95.3%)	2 (100.0%)	30 (90.9%)	4 (57.1%)	29 (82.9%)	68 (79.1%)	154 (87.0%)
Brain metastasis at screening, <i>n</i> (%)	13 (37.1%)	10 (31.3%)	1 (2.9%)	0	0	8 (18.6%)	0	5 (15.2%)	0	5 (14.3%)	14 (16.3%)	28 (15.8%)
Number of organs with metastasis, median (range)	3.0 (1.0, 8.0)	3.0 (1.0, 8.0)	2.5 (0.0, 9.0)	3.0 (0.0, 8.0)	2.0 (0.0, 6.0)	3.0 (0.0, 6.0)	2.5 (2.0, 3.0)	1.0 (0.0, 8.0)	1.0 (0.0, 8.0)	3 (0.0, 7.0)	2.5 (0.0, 9.0)	3.0 (0.0, 8.0)
Number of prior treatment lines, median (range)	1.0 (1.0, 3.0)	1.0 (1.0, 4.0)	2.0 (1.0, 8.0)	3.0 (1.0, 7.0)	1.0 (1.0, 4.0)	2.0 (1.0, 6.0)	1.5 (1.0, 2.0)	2.0 (1.0, 5.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	1.5 (1.0, 8.0)	2 (1.0, 7.0)
1	28 (80.0%)	23 (71.9%)	6 (17.6%)	5 (14.7%)	5 (62.5%)	10 (23.3%)	1 (50.0%)	10 (30.3%)	3 (42.9%)	14 (40.0%)	43 (50.0%)	62 (35.0%)
2	4 (11.4%)	6 (18.8%)	14 (41.2%)	9 (26.5%)	1 (12.5%)	17 (39.5%)	1 (50.0%)	12 (36.4%)	2 (28.6%)	10 (28.6%)	22 (25.6%)	54 (30.5%)
3+	3 (8.6%)	3 (9.4%)	14 (41.2%)	20 (58.8%)	2 (25.0%)	16 (37.2%)	0	11 (33.3%)	2 (28.6%)	11 (31.4%)	21 (24.4%)	61 (34.5%)
Prior regimens, <i>n</i> (%)												
Prior PBC	35 (100.0%)	32 (100.0%)	34 (100.0%)	34 (100.0%)	8 (100.0%)	43 (100.0%)	2 (100.0%)	30 (90.9%)	2 (28.6%)	27 (77.1%)	81 (94.2%)	166 (93.8%)
Prior anti-PD-1/PD-L1	35(100.0%)	32(100.0%)	34(100.0%)	34(100.0%)	8 (100.0%)	42 (97.7%)	2 (100.0%)	33 100.0%)	3 (42.9%)	18 (51.4%)	82 (95.3%)	159 (89.8%)
Prior other chemo	4 (11.4%)	2 (6.3%)	22 (64.7%)	27 (79.4%)	2 (25.0%)	26 (60.5%)	1 (50.0%)	18 (54.5%)	4 (57.1%)	19 (54.3%)	33 (38.4%)	92 (52.0%)
Prior ADC	0	1 (3.1%)	1 (2.9%)	2 (5.9%)	0	0	0	1 (3.0%)	1 (14.3%)	0	2 (2.3%)	4 (2.3%)
Prior radiotherapy	18 (51.4%)	12 (37.5%)	32 (94.1%)	30 (88.2%)	1 (12.5%)	16 (37.2%)	2 (100.0%)	23 (69.7%)	3 (42.9%)	19 (54.3%)	56 (65.1%)	100 (56.5%)

ES-SCLC, extensive-stage small cell lung cancer; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; LELC, lymphoepithelioma-like carcinoma; Adeno, adenocarcinoma; Squamous, squamous cell carcinoma; LELC, lymphoepithelioma-

like carcinoma; ESCC, esophageal squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; PBC, platinum-based chemotherapy; ICI, immune checkpoint inhibitors; anti-PD-1/PD-L1, programmed cell death protein 1/programmed death ligand 1 antibody, including monoclonal and bispecific antibody; TOP1, topoisomerase I; ADC, antibody-drug conjugate.

Supplementary Table 2 Patient characteristics at baseline by different tumor type in Efficacy analysis set

	ES-SCLC (N=72)	NPC (N=70)	Wild-type NSCLC (N=64)			ESCC (N=36)	Others (N=45)	Total (N=287)
			Adeno (N=28)	Squamous (N=12)	LELC (N=24)			
Age (years), median (range)	61.0 (45, 76)	46.5 (28, 71)	60.5 (33, 72)	65.5 (55, 79)	53.5 (24, 69)	60.0 (48, 73)	55.0 (33, 87)	57.0 (19, 87)
Race, n (%)								
Asian	68 (94.4%)	70 (100.0%)	28 (100.0%)	8 (66.7%)	24 (100.0%)	36 (100.0%)	41 (91.1%)	275 (95.8%)
White	4 (5.6%)	0	0	4 (33.3%)	0	0	3 (6.7%)	11 (3.8%)
Other	0	0	0	0	0	0	1 (2.2%)	1 (0.3%)
Sex, n (%)								
Male	61 (84.7%)	60 (85.7%)	17 (60.7%)	11 (91.7%)	8 (34.8%)	33 (91.7%)	31 (68.9%)	221 (77.0%)
Female	11 (15.3%)	10 (14.3%)	11 (39.3%)	1 (8.3%)	16 (66.7%)	3 (8.3%)	14 (31.1%)	66 (23.0%)
Smoking History, n (%)								
Never	18 (25.0%)	48(68.6%)	16 (57.1%)	0	18 (75.0%)	20 (55.6%)	25 (55.6%)	145 (50.5%)
Yes	54 (75.0%)	21 (30.0%)	12 (42.9%)	12 (100.0%)	6 (25.0%)	15 (41.7%)	18 (40.0%)	138 (48.1%)
Unknown	0	1 (1.4%)	0	0	0	1 (2.8%)	2 (4.4%)	4 (1.4%)
ECOG, n (%)								
0	8 (11.1%)	18 (25.7%)	3 (10.7%)	1 (8.3%)	1 (4.3%)	3 (8.3%)	8 (17.8%)	42 (14.6%)
1	64 (88.9%)	52 (74.3%)	25 (89.3%)	11 (91.7%)	23 (95.8%)	33 (91.7%)	37 (82.2%)	245 (85.4%)
Brain metastasis at screening, n (%)	23 (31.9%)	1 (1.4%)	8 (28.6%)	0	0	6 (16.7%)	7 (15.6%)	45 (15.7%)
Number of organs with metastasis, median (range)	3 (0,8)	2.5 (0,9)	3 (0,6)	1 (0,4)	3 (0,5)	2 (0,8)	3 (0,8)	2 (0,9)
Number of prior treatment line, median (range)	1 (1,5)	2.5 (1,10)	2 (1,6)	2 (1,5)	3 (1,6)	2 (1,5)	2 (1,7)	2 (1,10)
1	49 (68.1%)	11 (15.7%)	10 (35.7%)	4 (33.3%)	5 (20.8%)	11 (30.6%)	18 (40.0%)	108 (37.6%)
2	13 (18.1%)	24 (34.3%)	9 (32.1%)	3 (25.0%)	6 (25.0%)	13 (36.1%)	10 (22.2%)	78 (27.2%)
3+	10 (13.9%)	35 (50.0%)	9 (32.1%)	5 (41.7%)	13 (54.2%)	12 (33.3%)	17 (37.8%)	101 (35.2%)
Prior regimens, n (%)								
Prior PBC	72 (100.0%)	70 (100.0%)	28 (100.0%)	11 (91.7%)	23 (95.8%)	33 (91.7%)	31 (68.9%)	268 (93.4%)
Prior anti-PD-1/PD-L1	68 (94.4%)	70 (100.0%)	25 (89.3%)	12 (100.0%)	24 (100.0%)	35 (97.2%)	22 (48.9%)	256 (89.2%)
Prior TOP1 inhibitor	5 (6.9%)	0	0	1 (8.3%)	0	0	1 (2.2%)	7 (2.4%)
Prior other chemo	7 (9.7%)	51 (72.9%)	14 (50.0%)	6 (50.0%)	14 (58.3%)	20 (55.6%)	27 (60.0%)	139 (48.4%)
Prior ADC	1 (1.4%)	4 (5.7%)	0	0	0	1 (2.8%)	1 (2.2%)	7 (2.4%)
Prior radiotherapy	36 (50.0%)	64 (91.4%)	7 (25.0%)	5 (41.7%)	11 (45.8%)	26 (72.2%)	25 (55.6%)	174 (60.6%)

ES-SCLC, extensive-stage small cell lung cancer; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; LELC, lymphoepithelioma-like carcinoma; Adeno, adenocarcinoma;

Squamous, squamous cell carcinoma; ESCC, esophageal squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; PBC, platinum-based chemotherapy; anti-PD-1/PD-L1, including anti-PD-1/PD-L1 monoclonal and bispecific antibody; ADC, antibody-drug conjugate; TOP1, topoisomerase I. adeno, adenocarcinoma;

Supplementary Table 3 Summary of treatment-emergent adverse events

	All (N=312)		2.0 mg/kg (N=96)		2.4 mg/kg (N=195)		<i>P</i> (2.0 mg/kg vs. 2.4 mg/kg)	
TEAE	312 (100.0%)		96 (100.0%)		195 (100.0%)			
Associated with treatment discontinuation	34 (10.9%)		10 (10.4%)		21 (10.8%)		0.9270	
Associated with dose reduction	57 (18.3%)		13 (13.5%)		42 (21.5%)		0.1014	
Associated with treatment interruption	135 (43.3%)		43 (44.8%)		85 (43.6%)		0.8460	
Associated with death	31 (9.9%)		12 (12.5%)		16 (8.2%)		0.2428	
Grade ≥3 TEAE	193 (61.9%)		51 (53.1%)		128 (65.6%)		0.0391	
SAE	129 (41.3%)		31(32.3%)		91 (46.7%)		0.0195	
TEAE in ≥10% of all patients	Any grade	Grade≥3	Any grade	Grade≥3	Any grade	Grade≥3	Any grade	Grade ≥3
Hematological								
Anemia	218 (69.9%)	78 (25.0%)	65 (67.7%)	15 (15.6%)	142 (72.8%)	55 (28.2%)	0.3655	0.0182
Leukopenia	208 (66.7%)	92 (29.5%)	59 (61.5%)	17 (17.7%)	138 (70.8%)	70 (35.9%)	0.1103	0.0014
Neutropenia	192 (61.5%)	99 (31.7%)	49 (51.0%)	21 (21.9%)	134 (68.7%)	72 (36.9%)	0.0033	0.0096
Lymphopenia	114 (36.5%)	65 (20.8%)	26 (27.1%)	15 (15.6%)	79 (40.5%)	42 (21.5%)	0.0249	0.2321
Thrombocytopenia	107 (34.3%)	45 (14.4%)	33 (34.4%)	10 (10.4%)	67 (34.4%)	32 (16.4%)	0.9978	0.1713
Non-hematological								
Anorexia	125 (40.1%)	5 (1.6%)	25 (26.0%)	2 (2.1%)	90 (46.2%)	3 (1.5%)	0.0010	0.7366
Nausea	86 (27.6%)	4 (1.3%)	26 (27.1%)	2 (2.1%)	50 (25.6%)	2 (1.0%)	0.7923	0.4662
Hypoalbuminemia	86 (27.6%)	3 (1.0%)	26 (27.1%)	1 (1.0%)	56 (28.7%)	0	0.7707	0.1534
Constipation	86 (27.6%)	0	20 (20.8%)	0	62 (31.8%)	0	0.0507	NA
Hyponatremia	79 (25.3%)	6 (1.9%)	16 (16.7%)	1 (1.0%)	57 (29.2%)	3 (1.5%)	0.0201	0.7322
Weight decreased	79 (25.3%)	1 (0.3%)	19 (19.8%)	0	50 (25.6%)	1 (0.5%)	0.2700	0.4821
Fatigue	67 (21.5%)	6 (1.9%)	18 (18.8%)	4 (4.2%)	41 (21.0%)	2 (1.0%)	0.6498	0.0763
Hypokalemia	66 (21.2%)	17 (5.4%)	15 (15.6%)	4 (4.2%)	46 (23.6%)	11 (5.6%)	0.1165	0.5928
Alanine aminotransferase increased	66 (21.2%)	2 (0.6%)	16 (16.7%)	2 (2.1%)	47 (24.1%)	0	0.1476	0.0431
Diarrhea	64 (20.5%)	3 (1.0%)	17 (17.7%)	1 (1.0%)	44 (22.6%)	2 (1.0%)	0.3387	0.9898
Alopecia	63 (20.2%)	0	21 (21.9%)	0	39 (20.0%)	0	0.7101	NA
Vomiting	62 (19.9%)	5 (1.6%)	15 (15.6%)	2 (2.1%)	38 (19.5%)	3 (1.5%)	0.4222	0.7366

Aspartate aminotransferase increased	61 (19.6%)	2 (0.6%)	15 (15.6%)	1 (1.0%)	43 (22.1%)	1 (0.5%)	0.1970	0.6077
Hypertriglyceridemia	58 (18.6%)	3 (1.0%)	17 (17.7%)	2 (2.1%)	39 (20.0%)	1 (0.5%)	0.6410	0.2124
Pyrexia	55 (17.6%)	1 (0.3%)	17 (17.7%)	1 (1.0%)	33 (16.9%)	0	0.8674	0.1534
Cough	55 (17.6%)	0	15 (15.6%)	0	34 (17.4%)	0	0.6979	NA
Hyperuricemia	53 (17.0%)	0	17 (17.7%)	0	35 (17.9%)	0	0.9599	NA
Pneumonia	51 (16.3%)	25 (8.0%)	17 (17.7%)	9 (9.4%)	32 (16.4%)	15 (7.7%)	0.7808	0.6237
Hypercholesterolemia	44 (14.1%)	0	17 (17.7%)	0	26 (13.3%)	0	0.3228	NA
Abdominal pain	39 (12.5%)	2 (0.6%)	11 (11.5%)	1 (1.0%)	26 (13.3%)	1 (0.5%)	0.6517	0.6077
Hyperglycemia	35 (11.2%)	1 (0.3%)	11 (11.5%)	0	23 (11.8%)	1 (0.5%)	0.9330	0.4821
Gamma-glutamyltransferase increased	33 (10.6%)	5 (1.6%)	5 (5.2%)	2 (2.1%)	27 (13.8%)	3 (1.5%)	0.0268	0.7366
Stomatitis	32 (10.3%)	3 (1.0%)	8 (8.3%)	1 (1.0%)	22 (11.3%)	2 (1.0%)	0.4367	0.9898
Rash	32 (10.3%)	2 (0.6%)	6 (6.3%)	0	21 (10.8%)	2 (1.0%)	0.2115	0.3194
Dizziness	32 (10.3%)	1 (0.3%)	6 (6.3%)	0	23 (11.8%)	1 (0.5%)	0.1376	0.4821
Blood alkaline phosphatase increased	32 (10.3%)	1 (0.3%)	8 (8.3%)	0	21 (10.8%)	1 (0.5%)	0.5142	0.4821
Hypocalcemia	32 (10.3%)	1 (0.3%)	5 (5.2%)	0	26 (13.3%)	1 (0.5%)	0.0347	0.4821
AESI	Any grade	G≥3	Any grade	G≥3	Any grade	G≥3	Any grade	Grade ≥3
Interstitial lung disease	4 (1.3%)	4 (1.3%)	2 (2.1%)	2 (2.1%)	2 (1.0%)	2 (1.0%)	0.4662	0.4662
Infusion related reaction	2 (0.6%)	0	1 (1.0%)	0	0	0	0.1534	NA

AESI, adverse event of special interest; TEAE, treatment-emergent adverse event; SAE, severe adverse event.

Supplementary Table 4. Parameter estimates for the YL201 PopPK model.

	Parameter	Unit	Typical Value	RSE (%)	IIV (%)	IIV RSE (%); Shrinkage (%)
YL201-ADC	CL	L/day	0.731	6	41.7	11; 24
	V _C	L	3.65	1	11.8	9; 24
	Q	L/day	0.324	7	--	--; --
	V _p	L	4.21	6	--	--; --
	V _{max}	nmol/h	2.31	4	--	--; --
	K _m	nM	5.1	11	54	12; 39
	Proportional error	%	19.5	1	--	--; 13
	BBWT on CL	--	1.48	18	--	--
	BBWT on V _C	--	0.621	11	--	--
	BTMBD on CL	--	0.337	14	--	--
	BEGFR on CL	--	0.218	52	--	--
YL0010014	CL _{PL}	L/h	1.27	3	14.8	17; 36
	V _{C,PL}	L	5.76	6	27	14; 42
	Q _{PL}	L/h	1.89	4	--	--; --
	V _{p,PL}	L	95.9 fixed	--	--	--; --
	K _{rel}	1/h	0.00946	5	29.9	7; 18
	Proportional error	%	34	3	--	--; 10
	BALP on K _{rel}	--	0.269	28	--	--

RSE: relative standard error; IIV: inter-individual variability; Shrinkage: shrinkage value; CL: clearance of YL201-ADC in the central compartment; V_C: volume of distribution of YL201-ADC in the central compartment; V_P: volume of distribution of YL201-ADC in the peripheral compartment; Q: clearance of YL201-ADC between the central compartment and the peripheral compartment; V_{max}: maximum amount of drug cleared in a unit time by the nonlinear clearance portion of YL201-ADC; K_m: concentration of YL201-ADC at half of V_{max}; K_{rel}: release rate constant; V_{C,PL}: volume of distribution of YL0010014 in the central compartment; CL_{PL}: clearance of YL0010014 in the central compartment; V_{P,PL}: clearance of YL0010014 in the peripheral compartment; Q_{PL}: clearance of YL0010014 between the central compartment and the peripheral compartment; BBWT: baseline body weight; BTMBD: baseline sum of target lesion diameters; BEGFR: baseline estimated glomerular filtration rate; BALP: baseline alkaline phosphatase.

Supplementary Table 5. PK parameters of YL201-ADC, YL201-TAB and YL0010014 in the first cycle of the dose-escalation phase.

	Dose (mg/kg)	C _{max} (µg/mL)	AUC _{0-21d} (µg·h/mL)	t _{1/2} (h)	CL (mL/h)	V _z (L)
YL201-ADC	0.8 (n=4)	12.7 (24.5%)	292	NA	NA	NA
	1.6 (n=9)	29.0 (19.9%)	1047 (26.2%)	21.7 (23.0%)	96.9 (33.4%)	3.03 (20.2%)
	2.0 (n=9)	35.3 (24.9%)	1516 (33.9%)	27.1 (24.5%)	83.8 (25.2%)	3.27 (22.0%)
	2.4 (n=16)	43.8 (23.9%)	2314 (30.0%)	32.4 (20.6%)	67.6 (35.1%)	3.16 (37.7%)
	2.8 (n=6)	48.2 (17.7%)	2787 (27.6%)	37.6 (21.4%)	57.6 (34.5%)	3.13 (22.7%)
	3.0 (n=2)	57.8 (56.7, 58.9)	3538 (3371, 3705)	40.9 (37.3, 44.5)	72.2 (56.0, 88.4)	4.18 (3.60, 4.76)
	0.8 (n=4)	14.7 (24.7%)	NA	NA	NA	NA
	1.6 (n=9)	29.1 (22.4%)	1665 (1514, 1815)	27.8	66.6	2.67
	2.0 (n=9)	36.5 (18.4%)	1670 (22.7%)	29.3 (5.1%)	79.2 (20.6%)	3.34 (21.7%)
	2.4 (n=16)	44.3 (20.1%)	2320 (30.5%)	32.1 (35.8%)	68.2 (37.0%)	3.16 (24.9%)
YL201-TAB	2.8 (n=6)	57.7 (18.6%)	3154 (33.6%)	36.8 (30.3%)	50.9 (40.5%)	2.71 (27.4%)
	3.0 (n=2)	60.1 (58.9, 61.3)	3531 (3467, 3595)	43.0 (41.4, 44.6)	72.8 (54.5, 91.1)	4.56 (3.25, 5.86)
	Dose (mg/kg)	C _{max} (ng/mL)	AUC _{0-21d} (ng·h/mL)	t _{1/2} (h)		
YL0010014	0.8 (n=4)	0.891 (39.1%)	62.4 (60.3, 64.5)	66.1 (64.1, 68.1)		
	1.6 (n=9)	0.915 (109.0%)	117 (110.9%)	91.1 (13.9%)		
	2.0 (n=9)	0.917 (53.1%)	96.8 (34.9%)	97.3 (18.8%)		
	2.4 (n=16)	1.061 (48.2%)	124 (51.9%)	84.6 (25.9%)		
	2.8 (n=6)	1.698 (58.9%)	205 (52.9%)	76.4 (28.9%)		
	3.0 (n=2)	2.239 (2.096, 2.381)	306	128		

AUC, area under the curve; CL, clearance rate; C_{max}, maximum concentration; t_{1/2}, half-life time; V_d, volume of distribution.

Rac_Cmax: accumulation ratio based on Cmax; Rac_AUC: accumulation ratio calculated based on AUC0-21d

Pharmacokinetic parameters are presented as geometric mean (geometric CV%) (n≥3), mean (min, max) (n=2) or individual value (n=1), or not available (NA) (n=0).

Rules applied to determine if the λ_z could be calculated accurately: 1. At least three data points in the terminal phase were required for the calculation of λ_z (excluding the C_{max}); 2. Percentage of AUC extrapolation for the calculation of AUC0-inf should not exceed 20% (AUC_%Extrap ≤20%); 3. Adjusted coefficient of determination for the regression of λ_z should not be less than 0.9 (Adj_Rsq ≥0.9). When λ_z could not be accurately calculated, the parameters AUC0-21d, t_{1/2}, CL, V_z and Rac_AUC calculated based on λ_z were inaccurate and were not included in the statistical analysis.

Supplementary Table 6. PK parameters of YL201-ADC, YL201-TAB and YL0010014 in the third cycle of the dose-escalation phase

	Dose (mg/kg)	C _{max} (µg/mL)	AUC _{0-21d} (µg·h/mL)	t _{1/2} (h)	CL (mL/h)	V _z (L)	Rac_C _{max}	Rac_AUC
YL201- ADC	0.8 (n=2)	12.7 (24.5%)	292	NA	NA	NA	1.37 (1.07, 1.67)	NA
	1.6 (n=5)	29.0 (19.9%)	1047 (26.2%)	21.7 (23.0%)	96.9 (33.4%)	3.03 (20.2%)	0.984	NA
	2.0 (n=3)	35.3 (24.9%)	1516 (33.9%)	27.1 (24.5%)	83.8 (25.2%)	3.27 (22.0%)	1.17 (1.07, 1.27)	NA
	2.4 (n=10)	43.8 (23.9%)	2314 (30.0%)	32.4 (20.6%)	67.6 (35.1%)	3.16 (37.7%)	0.987 (10.9%)	1.25
	2.8 (n=3)	48.2 (17.7%)	2787 (27.6%)	37.6 (21.4%)	57.6 (34.5%)	3.13 (22.7%)	0.933 (8.4%)	1.11
	0.8 (n=2)	14.7 (24.7%)	NA	NA	NA	NA	1.29 (1.03, 1.55)	NA
	1.6 (n=5)	29.1 (22.4%)	1665 (1514, 1815)	27.8	66.6	2.67	0.920 (0.861, 0.979)	NA
	2.0 (n=3)	36.5 (18.4%)	1670 (22.7%)	29.3 (5.1%)	79.2 (20.6%)	3.34 (21.7%)	1.11 (1.01, 1.20)	NA
YL201- TAB	2.4 (n=10)	44.3 (20.1%)	2320 (30.5%)	32.1 (35.8%)	68.2 (37.0%)	3.16 (24.9%)	1.00 (6.9%)	NA
	2.8 (n=3)	57.7 (18.6%)	3154 (33.6%)	36.8 (30.3%)	50.9 (40.5%)	2.71 (27.4%)	0.847 (20.0%)	NA
	Dose (mg/kg)	C _{max} (ng/mL)	AUC _{0-21d} (ng·h/mL)	t _{1/2} (h)			Rac_C _{max}	Rac_AUC
	0.8 (n=2)	0.891 (39.1%)	62.4 (60.3, 64.5)	66.1 (64.1, 68.1)			0.848 (0.821, 0.874)	1.66
	1.6 (n=5)	0.915 (109.0%)	117 (110.9%)	91.1 (13.9%)			1.47 (1.22, 1.73)	NA
	2.0 (n=3)	0.917 (53.1%)	96.8 (34.9%)	97.3 (18.8%)			0.696 (0.618, 0.775)	NA
YL00100 14	2.4 (n=10)	1.061 (48.2%)	124 (51.9%)	84.6 (25.9%)			1.08 (30.4%)	1.22 (36.0%)
	2.8 (n=3)	1.698 (58.9%)	205 (52.9%)	76.4 (28.9%)			0.643 (47.8%)	1.21

AUC, area under the curve; CL, clearance rate; C_{max}, maximum concentration; t_{1/2}, half-life time; V_d, volume of distribution.

Rac_C_{max}: accumulation ratio based on C_{max}; Rac_AUC: accumulation ratio calculated based on AUC_{0-21d}. PK parameters are presented as the geometric mean (geometric CV%) (n≥3) or mean (min, max) (n=2), individual value (n=1) or not available (NA) (n=0).

Rules applied to determine if the λ_z could be calculated accurately: 1. At least three data points in the terminal phase were required for the calculation of λ_z (excluding the C_{max}); 2. Percentage of AUC extrapolation for the calculation of AUC_{0-inf} should not exceed 20% (AUC_%Extrap ≤20%); 3. Adjusted coefficient of determination for the regression of λ_z should not be less than 0.9 (Adj_Rsq ≥0.9). When λ_z could not be accurately calculated, the parameters AUC_{0-21d}, t_{1/2}, CL, V_z and Rac_AUC calculated based on λ_z were inaccurate and were not included in the statistical analysis.

Supplementary Table 7. Overall summary of the safety and efficacy in the 2.0 mg/kg and 2.4 mg/kg groups of SCLC, NPC, and all patients

	All patients		SCLC		NPC	
	Safety					
	2.0 mg/kg (N=96) ^a	2.4 mg/kg (N=195) ^b	2.0 mg/kg (N=36) ^c	2.4 mg/kg (N=38) ^d	2.0 mg/kg (N=37) ^e	2.4 mg/kg (N=37) ^f
TRAEs	94 (97.9%)	190 (97.4%)	36 (100.0%)	37 (97.4%)	36 (97.3%)	36 (97.3%)
Associated with treatment discontinuation	5 (5.2%)	11 (5.6%)	1 (2.8%)	3 (7.9%)	2 (5.4%)	3 (8.1%)
Associated with dose reduction	13 (13.5%)	38 (19.5%)	9 (25.0%)	13 (34.2%)	4 (10.8%)	5 (13.5%)
Associated with treatment interruption	38 (39.6%)	70 (35.9%)	20 (55.6%)	16 (42.1%)	14 (37.8%)	14 (37.8%)
Associated with death	1 (1.0%)	6 (3.1%)	0	1 (2.6%)	1 (2.7%)	2 (5.4%)
Grade ≥3 TRAE	44 (45.8%)	114 (58.5%)	18 (50.0%)	27 (71.1%)	18 (48.6%)	21 (56.8%)
TR-SAE	23 (24.0%)	64 (32.8%)	12 (33.3%)	14 (36.8%)	8 (21.6%)	10 (27.0%)
	Efficacy					
	2.0 mg/kg (N=87)	2.4 mg/kg (N=184)	2.0 mg/kg (N=31)	2.4 mg/kg (N=36)	2.0 mg/kg (N=35)	2.4 mg/kg (N=34)
Median follow-up (95% CI), mo	6.5 (6.2–7.6)	7.4 (6.4–8.6)	6.9 (6.2–7.7)	8.1 (7.4–9.6)	7.9 (6.2–8.5)	9.2 (7.0–9.9)
BOR, <i>n</i> (%)						
CR (confirmed)	1 (1.1%)	1 (0.5%)	0	0	1 (2.9%)	1 (2.9%)
PR (confirmed and pending confirmation)	43 (49.4%)	72 (39.1%)	22 (71.0%)	23 (63.9%)	16 (45.7%)	16 (47.1%)
PR (confirmed)	41 (47.1%)	68 (37.0%)	21 (67.7%)	23 (63.9%)	16 (45.7%)	15 (44.1%)
SD	32 (36.8%)	84 (45.7%)	7 (22.6%)	11 (30.6%)	16 (45.7%)	15 (44.1%)
PD	6 (6.9%)	26 (14.1%)	2 (6.5%)	0	2 (5.7%)	2 (5.9%)
NE	7 (8.0%)	5 (2.7%)	1 (3.2%)	2 (5.6%)	0	1 (2.9%)
ORR (confirmed and pending confirmation), % (95% CI)	50.6 (39.6–61.5)	39.7 (32.6–47.1)	71.0 (52.0–85.8)	63.9 (46.2–79.2)	48.6 (31.4–66.0)	50.0 (32.4–67.6)
ORR (confirmed), % (95% CI)	48.3(37.4–59.2)	37.5 (30.5–44.9)	67.7 (48.6–83.3)	63.9 (46.2–79.2)	48.6 (31.4–66.0)	47.1 (29.8–64.9)
DCR, % (95% CI)	85.1 (75.8–91.8)	83.2 (76.9–88.3)	90.3 (74.2–98.0)	94.4 (81.3–99.3)	94.3 (80.8–99.3)	91.2 (76.3–98.1)
mDOR (95% CI), mo	6.3 (4.6–6.7)	6.4 (4.3–8.4)	6.1 (3.5–6.4)	4.3 (3.4–6.4)	8.7 (4.6–11.1)	8.4 (4.7–NE)
mPFS (95% CI), mo	7.6 (6.0–7.8)	5.6 (4.9–7.2)	7.6 (6.0–NE)	5.7 (4.9–7.9)	7.8 (5.6–12.5)	9.6 (5.7–NE)

a. Including 10 patients enrolled in the dose-escalation study and 86 patients enrolled in the dose-expansion study; b. Including 18 patients enrolled in the dose-escalation study and 177 patients enrolled in the dose-expansion study; c. Including 1 patient enrolled in the dose-escalation study and 35 patients enrolled in the dose-expansion study; d. Including 6 patients enrolled in the dose-escalation study and 32 patients enrolled in the dose-expansion study; e. Including 3 patients enrolled in the dose-escalation study and 34 patients enrolled in the dose-expansion study; f. Including 3 patients enrolled in the dose-escalation study and 34 patients enrolled in the dose-expansion study. SCLC, small cell lung cancer; NPC, nasopharyngeal carcinoma; TRAE, treatment-related adverse event; TR-SAE, treatment-related severe adverse event; CI, confidence interval; mo, months; BOR, the best of response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; ORR, objective response rate; DCR, disease control rate; mDOR, median duration of response; mPFS, median progression-free survival; NE, not evaluated.

Supplementary Table 8. The institutional review boards at all participating sites.

Site Number	Site Name	Principal Investigator	Institutional Review Board/ Ethics Committee
For YL201 INT 101 01			
201	Sun yat-sen University Cancer Center	LI Zhang	Ethics Committee of Sun Yat-Sen University Cancer Center
202	Henan Cancer Hospital	Suxia Luo	Medical Ethics Committee of Henan Provincial Cancer Hospital
101	Hematology Oncology Assoc of the Treasure Coast	Seth Rosen	Advarra Institutional Review Board
102	The University of Texas - MD Anderson Cancer Center	Siqing Fu	Advarra Institutional Review Board
103	NEXT Oncology	David Sommerhalder	Salus Institutional Review Board
For YL201 CN 101 01			
01	Sun Yat-Sen University Cancer Center	Li Zhang	Ethics Committee of Sun Yat-Sen University Cancer Center
02	The First Affiliated Hospital of Zhengzhou University	Mingjun Li	The Ethics Committee for Scientific Research and Clinical Trials of the First Affiliated Hospital of Zhengzhou University
03	The First Affiliated Hospital of Zhengzhou University	Feng Wang	The Ethics Committee for Scientific Research and Clinical Trials of the First Affiliated Hospital of Zhengzhou University
04	Shandong Cancer Hospital and Institute	Xiangjiao Meng	Ethics Committee of the Affiliated Cancer Hospital of Shandong First Medical University
05	The First Affiliated Hospital of USTC	Yueyin Pan	The Medical Research Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China
06	The First Affiliated Hospital of USTC	Dong Qian	The Medical Research Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China
08	The Second Hospital of Anhui Medical University	Mingjun Zhang	Ethics Committee for Clinical Drug Trials of the Second Affiliated Hospital of Anhui Medical University

09	The First Affiliated Hospital of Anhui Medical University	Yingying Du	The Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University
10	Binzhou Medical University Hospital	Fangling Ning	Clinical Trial Ethics Committee of the Affiliated Hospital of Binzhou Medical University
11	Dongguan People's Hospital	Yifen Wu/Ruinian Zheng	Medical Ethics Committee of Dongguan People's Hospital
12	The Frist People's Hospital of Foshan	Weineng Feng	Medical Ethics Committee of Foshan First People's Hospital
13	Fujian Cancer Hospital	Wu Zhuang	Ethics Committee for Drug Clinical Trials of Fujian Cancer Hospital
14	Fujian Cancer Hospital	Shaojun Lin	Ethics Committee for Drug Clinical Trials of Fujian Cancer Hospital
15	Gansu Provincial Cancer Hospital	Lei Yang/Yuhua Liu	Medical Ethics Committee of Gansu Cancer Hospital
16	The People's Hospital of Guangxi Zhuang Autonomous Region	Heming Lu	Ethics Committee of People's Hospital of Guangxi Zhuang Autonomous Region
17	Affiliated Cancer Hospital of Guangxi Medical University	Qitao Yu/Wei Jiang	Ethics Committee of Guangxi Medical University Affiliated Cancer Hospital
18	Affiliated Cancer Hospital of Guangxi Medical University	Song Qu	Ethics Committee of Guangxi Medical University Affiliated Cancer Hospital
19	The Second Affiliated Hospital of Guilin Medical University	Bihui Li	Drug Clinical Trial Ethics Committee, the Second Affiliated Hospital of Guilin Medical College
20	Harbin Medical University Cancer Hospital	Yanqiao Zhang	Ethics Committee of the Affiliated Tumor Hospital of Harbin Medical University
21	The First Affiliated Hospital of Hainan Medical University	Jinsheng Wu	The Medical Ethics Committee of the First Affiliated Hospital of Hainan Medical University
23	Henan Cancer Hospital	Yanqiu Zhao/Shujun Yang	Medical Ethics Committee of Henan Cancer Hospital
25	Hunan Cancer Hospital	Lin Wu	Medical Ethics Committee of Hunan Cancer Hospital
26	Hunan Cancer Hospital - Department of Medical Oncology	Xianli Yin	Medical Ethics Committee of Hunan Cancer Hospital

27	Union Hospital,Tongji Medical College,Huazhong University of Science and Technology。	Kunyu Yang	Tongji Medical College of Huazhong University of Science and Technology,Union Hospital-Medical Ethics Committee
28	Jiangmen Central Hospital	Fangming Li	Clinical Trial Ethics Committee of Jiangmen Central Hospital
29	Affiliated Hospital of Jiangnan University	Yong Mao	Ethics Committee of Jiangnan University Hospital
30	Jiangxi Cancer Hospital (Jiangxi Second People's Hospital)	Zhijia Liu	Medical Ethics Committee of Jiangxi Provincial Cancer Hospital
31	Jiangxi Cancer Hospital (Jiangxi Second People's Hospital)	Jingao Li	Medical Ethics Committee of Jiangxi Provincial Cancer Hospital
32	Jiangyin People's Hospital	Qiong Wang	Ethics Committee of Jiangyin People's Hospital
34	Linyi Cancer Hospital	Jianhua Shi	Ethics Committee of Linyi Cancer Hospital
35	Liuzhou Worker's Hospital	Ying Lu	Ethics Committee of Liuzhou Workers' Hospital
36	The First Affiliated Hospital of Nanchang University	Longhua Sun	Medical Ethics Committee of the First Affiliated Hospital of Nanchang University
38	West China Hospital of Sichuan University	Xingchen Peng	West China Hospital, Sichuan University Clinical Trial Ethics Review Committee
39	The First Affiliated Hospital of Xinxiang Medical University	Yinghua Ji	Ethics Committee of the First Affiliated Hospital of Xinxiang Medical College
40	Yuebei People's Hospital	Suming Pan	IRB,Yue Bei People's Hospital
41	The First Affiliated Hospital, Zhejiang University School of Medicine	Yulong Zheng/Jian Liu	Clinical Trail Ethics Committee of the First Affiliated Hospital, College of Medicine,Zhejiang University
42	Taizhou Hospital of Zhejiang Province	Dongqing Lv	Medical Ethics Committee of Taizhou Hospital
43	Zhejiang Cancer Hospital	Yun Fan	Medical Ethics Committee of Zhejiang Cancer Hospital
44	The Frist Hospital of China Medical University	Mingfang Zhao	Medical Ethics Committee ofthe First Hospital of China Medical University

46	Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University	Xiaoming Huang	Medical Ethics Committee of Sun Yat sen Memorial Hospital,Sun Yat-Sen University
47	Chongqing University Cancer Hospital	Jianlin Long	Ethics Committee of Cancer Hospital Affiliated to Chongqing University
48	First Affiliated Hospital of Gannan Medical University	Haiyu Yang/Jie Li	Clinical Trial Ethics Committee of the First Affiliated Hospital of Gannan Medical University
50	The First People's Hospital of Changzhou	Chong Li	Ethics Committee of The First People's Hospital of Changzhou
51	Shandong Provincial Hospital	Caixia Wang	Ethics Committee for Clinical Drug Trials of Shandong Provincial Hospital
53	Liuzhou Worker's Hospital	Li Qin	Ethics Committee of Liuzhou Workers' Hospital
57	Affiliated Cancer Hospital and Institute of Guangzhou Medical University	Weidong Li	Medical Ethics Committee of Guangzhou Medical University Affiliated Cancer Hospital
59	The Fifth Affiliated Hospital Sun Yat-Sen University	Siyang Wang	Medical Ethics Committee of The Fifth Affiliated Hospital Sun Yat-Sen University
60	The Affiliated Hospital of Nanjing University Medical School	Yongsheng Wang	Medical Ethics Committee of Drum Tower Hospital, Nanjing University School of Medicine
62	Sichuan Cancer Hospital	Peng Zhang	Sichuan Cancer Hospital Clinical Trial Ethics Committee
63	Renji Hospital, Shanghai Jiao Tong University School of Medicine	Liwei Wang	Shanghai Jiao Tong University School of Medicine, Renji Hospital Ethics Committee
64	Peking University People's Hospital	Xiaodong Tang	Ethics Review Committee of Peking University People's Hospital

Supplementary File. Study Protocols and SAP

CLINICAL STUDY PROTOCOL

A Phase 1, Multicenter, Nonrandomized, Open-Label, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of YL201 in Patients with Advanced Solid Tumors

Protocol Number:	YL201-INT-101-01
Protocol Version:	4.0
Protocol Date:	13 April 2023
Investigational Product:	YL201
Development Phase:	Phase 1
Indication Studied:	Advanced solid tumors
Sponsor Name and Address:	MediLink Therapeutics (Suzhou) Co., Ltd. Unit 101, B3, BioBAY, No. 218, Xinghu Street, Suzhou Industrial Park, Suzhou, China Telephone Number: +86 512 6285 8368

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of MediLink Therapeutics, and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable institutional review board or independent ethics committee. This information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You must not disclose any of the information to others without written authorization from MediLink Therapeutics, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

PROTOCOL SIGNATURE PAGE

The signature below constitutes the approval of this protocol and its appendices and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality and according to the local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Title: A Phase 1, Multicenter, Nonrandomized, Open-Label, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of YL201 in Patients with Advanced Solid Tumors

Protocol Number: YL201-INT-101-01

Protocol Version: 4.0

Protocol Date: 13 April 2023

Sponsor's Authorized Representative:

Signed:		Date	
Name Title			

PRINCIPAL INVESTIGATOR'S SIGNATURE PAGE

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the sponsor's representative.

I understand that all information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from MediLink Therapeutics. It is, however, permissible to provide information to a patient to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the ethical principles originating from the Declaration of Helsinki, International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 guidelines on good clinical practice, and applicable regional regulatory requirements.

I agree to make available to sponsor personnel, their representatives, and relevant regulatory authorities, my patient's study records to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a principal investigator as provided by the sponsor.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; and such decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the sponsor.

Principal Investigator:

Signed:		Date	
Name Title			

1. SYNOPSIS

Protocol Number	YL201-INT-101-01
Investigational Product	YL201
Sponsor	MediLink Therapeutics
Study Title	A Phase 1, Multicenter, Nonrandomized, Open-Label, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of YL201 in Patients with Advanced Solid Tumors
Study Phase	Phase 1
Indication Under Investigation	Advanced solid tumors
Planned Number of Sites	3 to 6 investigative sites in China and the United States
Study Objectives	<u>Primary Objectives:</u> - To assess the safety and tolerability of YL201 in patients with advanced solid tumors - To determine the maximum tolerated dose (MTD) and select the recommended expansion dose(s) (RED(s)) of YL201 in patients with advanced solid tumors <u>Secondary Objectives:</u> - To characterize the pharmacokinetics (PK) of YL201 antibody-drug conjugate (YL201-ADC), YL201 total antibody (YL201-TAb), and unconjugated payload YL0010014 - To evaluate immunogenicity as measured by the presence of anti-drug antibodies (ADAs) in patients treated with YL201 - To document any preliminary evidence of YL201 efficacy in patients with advanced solid tumors <u>Exploratory Objectives:</u> - To evaluate the level of soluble B7 homolog 3 (B7H3) in peripheral blood before and after treatment and its relationship with efficacy
Study Design	This is a phase 1, multicenter, nonrandomized, open-label, first-in-human study of YL201 conducted in China and the United States. The study will estimate the MTD/RED(s) in dose-escalation cohorts of patients with advanced solid tumors unresponsive to currently available therapies or for whom no standard therapy is available. Patients will be treated with YL201 intravenous (IV) infusion once every 3 weeks (Q3W) as a cycle. The number of treatment cycles is not fixed in this study. Patients who continue to derive clinical benefit from this study treatment in the absence of unacceptable toxicity, progressive disease (PD), or withdrawal of consent may continue the study treatment. Dose escalation will begin in patients with advanced solid tumors (SCLC, mCRPC, ESCC, and NSCLC are preferred). The proposed human starting dose of YL201 is 0.8 mg/kg, based on one-sixth of the human equivalent dose (HED) of the highest non-severely toxic dose (HNSTD) in monkeys (15 mg/kg). Six dose levels are initially planned and include 0.8, 1.6, 3, 4.5, 6, and 8 mg/kg. After observing two

	DLTs at 3.0 mg/kg, which were deemed intolerable, three intermediate dose levels including 2.4, 2.8, and 2.0 mg/kg are added after discussion with the safety review committee (SRC) according to the toxicity data accrued in preceding dose levels. <table><tr><th colspan="7">Proposed Dose-Escalation Scheme</th></tr><tr><th>Dose level</th><th>Level 1</th><th>Level 2</th><th>Level 3</th><th>Level 4</th><th>Level 5</th><th>Level 6</th></tr><tr><td>Dose (mg/kg, Q3W)</td><td>0.8</td><td>1.6</td><td>3</td><td>4.5</td><td>6</td><td>8</td></tr><tr><td>Dosage increment</td><td>—</td><td>100%</td><td>88%</td><td>50%</td><td>33%</td><td>33%</td></tr></table> Starting from 0.8 mg/kg, the standard 3+3 design will be used for the escalation/de-escalation decision. A cohort of 3 patients will receive YL201 IV infusion on Day 1 of Cycle 1. A 21-day observation period (Cycle 1) will then occur, at the end of which all relevant safety data will be reviewed. If no DLTs occur in this cohort of 3 patients during Cycle 1, a new cohort of 3 patients will be treated at the next higher dose level. If 1 of 3 patients experience a DLT, that cohort will be expanded to 6 patients. If only 1 of the 6 patients has a DLT, the next cohort of 3 patients will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, that dose level will be considered above the MTD (the highest dose where no more than 1 of 6 patients has experienced a DLT), and new patients will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 patients. This lower dose level will be considered the MTD if ≤ 1 in 6 patients has a DLT. An intermediate dose may be explored if the increment is $\geq 50\%$ or considered appropriate by the SRC. For each dose level, the first enrolled patient will be observed as the sentinel patient for a minimum of 72 hours for occurrence of AEs prior to treating the other patients at the same dose level. Upon completion of Cycle 1, patients may continue to receive YL201 Q3W at the discretion of the investigator, until unacceptable toxicity, PD, or withdrawal of consent. To better estimate the MTD/RED(s) and characterize the safety, PK parameters, and efficacy of YL201, additional patients with preferred tumor types (SCLC, mCRPC, ESCC, and NSCLC) or other tumor types agreed upon after discussion with the sponsor may be enrolled in 1 or more dose levels that have been deemed to be safe and tolerable, defined as backfill enrollment. This backfill enrollment may be concurrent with dose escalation to estimate the MTD/RED(s). No intra-patient dose escalation will be allowed under any circumstances.	Proposed Dose-Escalation Scheme							Dose level	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	Dose (mg/kg, Q3W)	0.8	1.6	3	4.5	6	8	Dosage increment	—	100%	88%	50%	33%	33%
Proposed Dose-Escalation Scheme																													
Dose level	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6																							
Dose (mg/kg, Q3W)	0.8	1.6	3	4.5	6	8																							
Dosage increment	—	100%	88%	50%	33%	33%																							
Dose-Limiting Toxicity Definition	A DLT is defined as any of the following treatment-emergent adverse events (TEAEs) that occur during the first cycle (Day 1 to Day 21 in Cycle 1), except those unequivocally due to the underlying malignancy or an extraneous cause. Severity of TEAEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. • Hematological toxicity – Grade 4 neutropenia lasting for >7 days – Grade ≥ 3 febrile neutropenia (defined as Grade ≥ 3 neutropenia and a single body temperature >38.3°C or a sustained temperature of $\geq 38^{\circ}\text{C}$ for more than 1 hour)																												

	– Grade 4 lymphocyte count decreased lasting for ≥ 14 days – Grade 4 anemia – Grade ≥ 3 thrombocytopenia lasting for > 7 days or of any duration if accompanied by Grade ≥ 2 hemorrhage • Hepatic organ toxicity – Grade ≥ 3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increased – ALT or AST $> 3 \times$ upper limit of normal (ULN) concurrent with elevation in bilirubin $> 2 \times$ ULN • Nonhematological, nonhepatic major organ toxicity – Any grade ≥ 3 toxicities that are considered nonhematological, nonhepatic major organ toxicity The following TEAEs are NOT considered DLTs: – Alopecia of any grade – Grade 3 fatigue lasting for < 7 days – Grade 3 nausea, vomiting, diarrhea, or anorexia that has resolved to Grade ≤ 2 within 3 days – Isolated laboratory findings lasting for < 3 days without signs or symptoms, including Grade 3/4 ALP increased, hyperlipemia, serum amylase increased, and lipase increased
Patient Eligibility Criteria	Inclusion Criteria Patients must satisfy all of the following criteria to be included in the study: 1) Informed of the trial before the start of the trial and voluntarily sign their name and date on the ICF 2) Aged ≥ 18 years 3) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 4) Adequate organ and bone marrow function, defined as: • Hemoglobin ≥ 90 g/L (have not received blood transfusion or erythropoietin treatment within 14 days before the first dose) • Absolute neutrophil count $\geq 1.5 \times 10^9/L$ (have not received granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor treatment within 14 days before the first dose) • Platelet count $\geq 100 \times 10^9/L$ if no demonstrable liver lesion(s) (primary or metastases) or $\geq 75 \times 10^9/L$ in the presence of liver lesion(s) (have not received platelet transfusion, thrombopoietin, or interleukin-11 treatment within 14 days before the first dose) • Total bilirubin $\leq 1.5 \times$ ULN if no demonstrable liver lesion(s) (primary or metastases) or $\leq 3 \times$ ULN in the presence of liver lesion(s) • ALT and AST $\leq 3 \times$ ULN if no demonstrable liver lesion(s) (primary or metastases) or $\leq 5 \times$ ULN in the presence of liver lesion(s) • Creatinine clearance ≥ 60 mL/min (calculated according to Cockcroft-Gault formula) • Activated partial thromboplastin time and international normalized ratio $\leq 1.5 \times$ ULN for patients not receiving therapeutic anticoagulation, or have stable anticoagulant regimen for patients receiving therapeutic anticoagulation

- 5) Female patients of childbearing potential must agree to use a highly effective form of contraception and not donate, or retrieve for their own use, ova from the time of screening and throughout the study period, and for at least 6 months after the last dose of study drug. Male patients must agree to use a highly effective form of contraception and not freeze or donate sperm from the time of screening and throughout the study period, and for at least 6 months after the last dose of study drug
- 6) Life expectancy of ≥ 3 months
- 7) Able and willing to comply with protocol visits and procedures
- 8) Pathologically confirmed diagnosis of an advanced solid tumor (SCLC, mCRPC, ESCC and NSCLC are preferred) for which prior standard treatment had proven to be ineffective or intolerable, or no standard treatment is available
- 9) Have at least 1 evaluable tumor lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Participants with prostate cancer who have bone only disease may be eligible on a case-by-case basis after discussion with the sponsor

Exclusion Criteria

Patients who meet any of the following criteria will be disqualified from entering the study:

- 1) Prior treatment with an agent targeting B7H3 (including antibody, ADC, chimeric antigen receptor T cell [CAR-T], and other drugs)
- 2) Intolerant to prior treatment with a topoisomerase I inhibitor or an ADC that consists of a topoisomerase I inhibitor, including but not limited to topotecan, irinotecan, and Dxd (eg, severe diarrhea)
- 3) Concurrent enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study
- 4) Prior systemic anticancer treatment including chemotherapy, molecular-targeted therapy, hormonal therapy, immunotherapy, or biological therapy within 3 weeks before the first dose of study drug (use of oral fluorouracil [eg, tegafur and capecitabine] or small molecular-targeted therapy within 2 weeks or 5 half-life periods [whichever is shorter] before the first dose; use of mitomycin or nitrosoureas within 6 weeks before the first dose; use of herbal medicine with antitumor indications or nonspecific immunomodulators [eg, thymosin, interferon, and interleukin] within 2 weeks before the first dose)
Note: For patients with PC, androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) analog (GnRH agonist or GnRH antagonist) is allowed.
- 5) Prior radiation therapy, including palliative stereotactic radiation with abdominal, within 4 weeks before the first dose of study drug (if palliative stereotactic radiation therapy without abdominal, within 2 weeks)
- 6) Undergone major surgery (not including diagnostic surgery) within 4 weeks before the first dose of study drug or expect major surgery during the study
- 7) Undergone allogeneic hematopoietic stem cell transplantation (HSCT) before the first dose of study drug, or autologous HSCT within 3 months before the first

	dose of study drug 8) Received systemic steroids (>10 mg/day of prednisone or its equivalent) or other immunosuppressive therapy within 2 weeks before the first dose of study drug. The following are exceptions to this criterion: • Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection) • Systemic steroids at physiological doses as replacement therapy (eg, physiological corticosteroid replacement therapy for adrenal or pituitary insufficiency) • Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication) 9) Received any live vaccine within 4 weeks before the first dose of study drug or intend to receive a live vaccine during the study 10) A history of leptomeningeal carcinomatosis 11) Brain metastases or spinal cord compression unless asymptomatic or treated and stable off steroids and anti-convulsants for at least 2 weeks before the first dose of study drug 12) Uncontrolled or clinically significant cardiovascular disease, including but not limited to: • Medical history of symptomatic congestive heart failure (New York Heart Association class II to IV) or any arterial thromboembolic event (eg, myocardial infarction, unstable angina, cerebrovascular accident, and transient ischemic attack) within 6 months before the first dose • Uncontrolled hypertension, defined as systolic blood pressure (SBP) >160 mm Hg and/or diastolic blood pressure (DBP) >100 mm Hg after antihypertensive therapy • Serious cardiac arrhythmia that requires treatment • Corrected QT interval by Fridericia's formula (QTcF) prolongation to >470 ms 13) A history of (noninfectious) interstitial lung disease (ILD)/pneumonitis that requires steroids, current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening 14) Clinically significant concomitant pulmonary disease, including but not limited to: • Pulmonary emboli within 3 months of the start of study treatment • Any autoimmune, connective tissue, or inflammatory disorder (eg, rheumatoid arthritis, Sjögren's syndrome, sarcoidosis) where there is documented or suspicion of pulmonary involvement at the time of screening • Prior complete pneumonectomy 15) Have a diagnosis of Gilbert's syndrome 16) Uncontrolled third-space fluid (eg, pleural effusions, ascites, pericardial effusions) that requires repeated drainage 17) Active gastric and duodenal ulcers, ulcerative colitis, or other gastrointestinal conditions that may cause bleeding or perforation by the investigator's discretion 18) Uncontrolled infection that requires systemic therapy within 1 week before the first dose
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	19) Known human immunodeficiency virus (HIV) infection 20) Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Active HBV is defined as hepatitis B core antibody (HBcAb) or hepatitis B surface antigen (HBsAg) positive, and HBV DNA level above ULN at the study site; active HCV is defined as positive hepatitis C antibody and HCV RNA level above ULN at the study site 21) Unresolved toxicities from previous anticancer therapy, defined as toxicities not yet resolved to NCI CTCAE Grade ≤ 1, baseline, or the level specified in the inclusion/exclusion criteria with the exception of alopecia (any grade), pigmentation (any grade), and peripheral neuropathy (Grade ≤ 2). Patients with irreversible toxicity (eg, hearing loss) that is reasonably not expected to be aggravated by the study drug can be enrolled after discussion with the sponsor 22) A history of severe hypersensitivity reactions to the drug substances, inactive ingredients in the drug product, or other mAbs 23) Women who are breastfeeding or pregnant as confirmed by pregnancy tests performed within 3 days before the first dose 24) Any illness, medical condition, organ system dysfunction, or social situation, including but not limited to mental illness or substance/alcohol abuse, deemed by the investigator to be likely to interfere with a patient's ability to sign informed consent, adversely affect the patient's ability to cooperate and participate in the study, or compromise the interpretation of study results
Investigational Product and Route of Administration	The YL201 drug product is provided as a lyophilized powder containing 200 mg of YL201 in a glass vial. Each glass vial should be reconstituted to a concentration of 25 mg/mL. The drug for IV infusion is prepared by dilution of the required volume of the drug product calculated on the basis of the patient's body weight. Prepared medicinal solutions should be used immediately. The study drug will be administered Q3W. The initial dose of YL201 will be infused IV into each patient for 90$\pm$10 minutes. If there is no infusion-related reaction after the initial dose, the second and subsequent doses of YL201 will be infused IV into each patient for 60$\pm$10 minutes. The patient's weight at screening (baseline) will be used to calculate the initial dose. If, during the course of the treatment, the patient's weight changes by more than 10% of the baseline weight, the patient's dose will be recalculated based on the patient's updated weight.
Planned Sample Size	Up to 36 DLT-evaluable patients will be enrolled in this part. The actual number of patients enrolled will depend upon tolerability and efficacy of YL201.
Study Endpoints	<u>Primary Endpoints:</u> • Occurrence of DLTs during the first cycle <u>Secondary Endpoints:</u> • AEs as characterized by type, frequency, severity, timing, seriousness and relationship to study treatment • Laboratory abnormalities as characterized by type, frequency, severity and timing • Physical examination findings, ECOG PS, vital signs and peripheral oxygen saturation (SpO₂) measurements, and electrocardiogram (ECG) parameters • Single- and multiple-dose PK parameters of YL201-ADC, YL201-TAb, and

	unconjugated payload YL0010014, including but not limited to area under the curve (AUC), maximum concentration (C_{max}), trough concentration (C_{trough}), clearance rate (CL), volume of distribution (V_d), and half-life time ($t_{1/2}$) - Incidence of anti-YL201 antibodies <u>For patients with prostate cancer (PC):</u> Prostate-specific antigen (PSA) response rate, best PSA response, PSA progression-free survival (PFS), radiological PFS (rPFS), failure-free survival (FFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), duration of response (DoR), time to response (TTR), and best tumor response, assessed using RECIST version 1.1 modified based on Prostate Cancer Working Group 3 (PCWG3) criteria <u>For patients with non-PC:</u> ORR, DCR, DoR, TTR, PFS, OS, and best tumor response, assessed using RECIST version 1.1 <u>Exploratory Endpoints:</u> - The level of sB7H3 in peripheral blood before and after treatment
Statistical Analysis	Descriptive statistics will be provided for selected demographic, safety, PK, efficacy and biomarker data by dose level/cohort within each part and time as appropriate. Descriptive statistics on continuous data will include the number of patients (N), mean, standard deviation, median, minimum and maximum (as well as geometric mean and geometric coefficient of variation for C_{max} and AUC PK parameters), while categorical data will be summarized using frequency count and percentage. All data will be listed, and summary tables will be provided. Graphical summaries of the data may be presented. <u>Safety Analysis:</u> The safety profile will be based on AEs, clinical laboratory measurements, vital signs and SpO₂ measurements, ECG recordings, physical examination findings, and ECOG PS assessments. AEs will be graded according to the NCI CTCAE version 5.0. In the dose-escalation part, the incidence of DLTs will also be evaluated. Safety analysis in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. The number of DLTs identified among the DLT-evaluable patients will be listed and summarized for each cohort of YL201. <u>PK Analysis:</u> The concentration-time data for YL201-ADC, YL201-TAb, and YL0010014 will be listed, plotted, and summarized using descriptive statistics by dose level/cohort within each part at each point. Single- and multiple-dose PK parameters of YL201-ADC, YL201-TAb, and YL0010014 will be listed and summarized using descriptive statistics by dose level/cohort within each part. <u>Immunogenicity Analysis:</u> The immunogenicity analysis will be performed for the immunogenicity analysis set. The percentage of patients with a positive ADA status will be summarized by dose level/cohort within each part and time as appropriate. For patients with a positive ADA status, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. <u>Efficacy Analysis:</u> The efficacy variables will be listed and summarized. For ORR, DCR and PSA response rate, the point estimates and 2-sided corresponding 95% exact binomial

	confidence interval (CI) will be provided. Time-to-event variables, including DoR, TTR, PFS, OS, PSA-PFS, rPFS, and FFS, will be summarized descriptively using the Kaplan-Meier method to provide the median event time and 2-sided 95% CI. PFS rate at 3 and 6 months and OS rate at 6 and 12 months will be estimated by Kaplan-Meier method. Descriptive statistics for best tumor response and best PSA response will be provided. A waterfall plot will be presented for each patient. <u>Biomarker Analysis:</u> Explorative analysis for biomarkers will be listed and summarized using descriptive statistics.
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3. LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
B7H3	B7 homolog 3
BI	before infusion
CAR-T	chimeric antigen receptor T cell
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance rate
C _{max}	maximum concentration
CRC	colorectal carcinoma
CRO	contract research organization
CRPC	castration-resistant prostate cancer
CT	computed tomography
C _{trough}	trough concentration
DBP	diastolic blood pressure
DCR	disease control rate
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
ECOG PS	Eastern Cooperative Oncology Group performance status
EDC	electronic data capture
EOI	end of infusion
EOT	end of treatment
ESCC	esophageal squamous cell carcinoma
FFS	failure-free survival
GCP	good clinical practice
GnRH	gonadotropin-releasing hormone
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

ABBREVIATION	DEFINITION
HNSTD	highest non-severely toxic dose
HED	human equivalent dose
hERG	human Ether-à-go-go-related gene
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
Ig	immunoglobulin
ILD	interstitial lung disease
IRB	institutional review board
IRF	independent review facility
IV	intravenous(ly)
LD	longest diameter
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
mCRPC	metastatic castration-resistant prostate cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PC	prostate cancer
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic(s)
PSA	prostate-specific antigen
PT	preferred term
Q3W	once every 3 weeks
QTcF	corrected QT interval by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RED	recommended expansion dose
rPFS	radiological progression-free survival
SAE	serious adverse event
SAP	statistical analysis plan
sB7H3	soluble B7H3

ABBREVIATION	DEFINITION
SBP	systolic blood pressure
SCLC	small cell lung cancer
SLD	sum of longest dimensions
SOC	system organ class
SOP	standard operating procedure
SpO ₂	peripheral oxygen saturation
SRC	safety review committee
STD ₁₀	severely toxic dose in 10% of the rats
SUSAR	suspected unexpected serious adverse reaction
t _{1/2}	half-life time
TAb	total antibody
TcR	T-cell antigen receptor
TEAE	treatment-emergent adverse event
TTR	time to response
ULN	upper limit of normal
V _d	volume of distribution
WOCBP	women of childbearing potential

4. INTRODUCTION

4.1. Background on B7H3

The B7 family of cell surface molecules consists of structurally related protein ligands that bind to receptors on lymphocytes and regulate immune responses. Activation of T and B lymphocytes is initiated by engagement of antigen-specific receptors, T-cell antigen receptor (TcR), and membrane-bound immunoglobulin (Ig), respectively, but additional signals delivered simultaneously to members of the CD28 family of receptors by B7 ligands determine the ultimate immune response (Collins et al 2005). B7 homolog 3 (B7H3) is a novel member of the B7 family. B7H3 has been implicated in the delivery of both co-stimulatory and co-inhibitory signals (Hofmeyer et al 2008). The apparent contrasting activities of B7H3 may be attributed to multiple factors. While the murine B7H3 molecule exists as a 2-Ig form, the human counterpart has undergone gene duplication and exists primarily as a 4-Ig molecule (Steinberger et al 2004). Further, as with other members of the B7 family, B7H3 may bind, on different cells, to multiple receptors that remain to be identified.

B7H3 is an attractive target for anticancer therapy with regard to its role in promoting tumorigenesis. Tissue expression studies have demonstrated that the B7H3 protein is not expressed in most normal tissues; rather, its expression is inducible on certain antigen-presenting cells (Suh et al 2003, Chapoval et al 2001) and vasculature, exists on certain endocrine tissues (most notably in the cytoplasm of epithelial cells of the adrenal cortex), and is overexpressed in a wide range of cancers (including cultured cancer stem-like cells). B7H3 is broadly overexpressed on many malignant neoplasms with limited heterogeneity, including small cell lung cancer (SCLC) (Carvajal-Hausdorf et al 2019, Qiu et al 2021), non-small cell lung cancer (NSCLC) (Sun et al 2006, Wu et al 2016, Altan et al 2017, Yonesaka et al 2018), prostate cancer (PC) (Zang et al 2007, Roth et al 2007, Thompson et al 2009, Chavin et al 2009), esophageal squamous cell carcinoma (ESCC) (Song et al 2016), gastric cancer (Wu et al 2006), colorectal carcinoma (CRC) (Sun et al 2010), renal cell carcinoma (Crispen et al 2008), bladder cancer (Boorjian et al 2008, Xu et al 2018), ovarian cancer (Zang et al 2010), endometrial cancer (Brunner et al 2012), head and neck squamous cell carcinoma (unpublished data), and melanoma (Loo et al 2012). Most notably, in various solid tumors, expression of B7H3 is highly associated with metastatic behavior and poor prognosis.

4.2. Background on YL201

Antibody-drug conjugates (ADCs) are being developed to improve the therapeutic index of cytotoxic anticancer agents. The strategy makes use of an immunoconjugate in which a cytotoxic agent is chemically linked to an antibody that selectively binds to an internalizing tumor-associated antigen. This strategy allows the delivery of the cytotoxic agent to the tumor site while minimizing the exposure to normal tissues.

YL201 is an ADC that targets B7H3. YL201 consists of an anti-B7H3 antibody component and a drug component, bound via a novel tripeptide linker. The anti-B7H3 antibody component is a recombinant human IgG1 anti-B7H3 monoclonal antibody (mAb), comprised of 2 heavy chains (γ 1 chains) and 2 light chains (κ chains) linked by interchain disulphide bonds. The drug component (“YL0010014” hereafter) is a topoisomerase I inhibitor, which is derived from the

antitumor agent camptothecin with an innovative structure. One molecule of recombinant human IgG1 anti-B7H3 mAb is conjugated to 8 molecules of YL0010014 via the coupling sites on the reduced interchain disulphide bonds.

4.2.1. Nonclinical Studies

YL201 was characterized in a series of binding, blocking, and functional cell-based assays, as well as in the in vivo preclinical studies in mice and monkeys.

4.2.1.1. Pharmacology

Various in vitro pharmacology studies were conducted to study the mechanism of action, effectivity, and specificity of YL201, including binding affinity, specificity, species binding selectivity, Fc receptor and C1q binding affinity, effects on binding of endogenous B7H3 receptors, internalization by tumor cells and ability in inducing apoptosis, effects on tumor cell proliferation, signal transduction pathways, and bystander killing.

In vitro, YL201 and YL201-mAb bind to the human recombinant B7H3 protein but not to other B7 family proteins. High affinity and specificity binding of YL201 to B7H3 on the cell surface led to B7H3-YL201 complex internalization, arrested cell cycle at the G2/M stage, and induced apoptosis in various tumor cells. YL201 imparted cytotoxic activity to both targets via ADC internalization of the tumor cells. YL0010014 alone mediated cancer cell arrest in the G2/M or S stage and induced apoptosis in various tumor cells, subsequently suppressing cancer cell proliferation. The specificity of YL201 was mediated through the B7H3 specific antibody, YL201-mAb, whereas toxicity was mainly mediated through YL0010014.

In vivo antitumor efficacy was determined in various human cancer xenograft models in immune-deficient mice. The results indicated that YL201 was well tolerated, and suppressed preexisting tumor growth in a dose-dependent manner in various cancer cells or patient-derived (solid tumor) xenograft models, including castration-resistant prostate cancer (CRPC), ESCC, NSCLC, and CRC. After administration of YL201 into tumor-bearing mice, YL201 was stable in the body's circulation, and the cytotoxic payload YL0010014 was mainly detected in tumor tissues in a YL201 dose-dependent manner.

4.2.1.2. Safety Pharmacology

For safety pharmacology evaluation on YL0010014, the following studies were conducted:

1) hERG (human Ether-à-go-go-related gene) potassium channels in the Chinese hamster ovary (CHO) cell line; 2) central nervous system effects or respiratory functions in Sprague Dawley rats; and 3) cardiovascular parameters and respiratory functions in cynomolgus monkeys.

In vitro, YL0010014 did not show any potential effects on the hERG channel current up to 30 $\mu\text{mol/L}$ ($\text{IC}_{50} > 30 \mu\text{M}$). In a safety pharmacology study, YL0010014 did not show any effects on the central nervous system or respiratory system in rats at a single dose of 1.5 mg/kg prodrug. YL201 did not have any significant effects on blood pressure, heart rate, electrocardiogram (ECG) parameters, or body temperature in conscious and unrestrained telemetered male cynomolgus monkeys after a single 15-mg/kg dose.

4.2.1.3. Pharmacokinetics and Drug Metabolism

Pharmacokinetics (PK), tissue distribution, metabolism, and excretion of YL201 and YL0010014 have been studied extensively in a panel of in vitro and in vivo tests by using native or radiolabeled materials. YL201 is moderately stable in the plasma of rats, monkeys, and humans and indicates no significant species difference in the plasma stability of YL201. PK of YL0010014 were evaluated in Sprague Dawley rats via a single or repeat intravenous (IV) injection of YL0010014. PK of YL201 were evaluated in cynomolgus monkeys via a single or repeat IV injection of YL201. Exposures of YL201-ADC (ADC mixture with a drug-to-antibody ratio of ≥ 1), YL201 total antibody (YL201-TAb, ADC mixture with a drug-to-antibody ratio of ≥ 0), and unconjugated YL0010014 were analyzed with validated quantification methods. The immunogenicity of YL201 was also investigated with validated quantification methods. Tissue distribution, metabolism, and excretion of YL201 and YL0010014 were investigated in combined studies using radiolabeled agents in human tumor xenograft-bearing mice or in normal Sprague Dawley rats. Each component was traced separately with ^3H -labels on toxin or on YL201-mAb as part of YL201, and compared with ^3H -labeled YL0010014 and ^3H -labeled YL201-mAb without conjugation.

The PK of YL201 was primarily driven by YL201-mAb in tumor-bearing mice, rats, and cynomolgus monkeys. In cynomolgus monkeys, the maximum concentration (C_{max}) increased dose dependently and the area under the curve (AUC) increased disproportionately with a dose increase from 0.5 to 6 mg/kg after a single IV administration of YL201. There were no accumulation or sex-related differences in PK parameters after IV administration of YL201 at 2, 10, or 15 mg/kg once every 3 weeks (Q3W) for a total of 3 doses. The main catabolite was the deconjugated YL0010014. Formation of YL0010014 accounts for $<0.001\%$ of systemic exposure of ADC after a single administration. YL201 mainly distributes in the body's circulation with B7H3-mediated uptake and retention in tumor and reproductive organs after a single administration of [^3H -YL0010014]YL201 to tumor-bearing mice. The main catabolite, deconjugated YL0010014, is primarily metabolized in liver and excretes via bile/feces, and YL201-mAb, after degraded into peptides or amino acid, excretes via kidney/urine.

The catabolism and metabolism of YL201 and YL0010014 were investigated in a panel of in vitro studies. The stability and metabolic profile of YL0010014 was examined separately, including liver microsomal/hepatic stability, metabolites identification both in hepatocytes of 4 species and in vivo after injection of YL201 or YL0010014 into tumor-bearing mice and Sprague Dawley rats. YL0010014 showed a low release rate from YL201 after incubation with mouse, rat, monkey, and human plasma at 37°C for 96 hours. The metabolite profile of YL0010014 in humans was comparable to that in toxicity species, and no human-specific metabolites were observed in vitro.

Potential drug-drug interactions caused by YL0010014 were studied with a panel of in vitro studies including cytochrome P450 enzyme induction, inhibition, and time-dependent interaction. No drug interference potential was noted by examining interactions of YL0010014 and cytochrome P450 enzymes.

4.2.1.4. Toxicology

Selection of the cynomolgus monkey for toxicology evaluation was based on the results of B7H3 binding potency and tissue cross-reactivity. Similar binding affinity of YL201 to human

and monkey B7H3 was observed, while no binding affinity of YL201 to mouse or rat B7H3 was observed. The tissue cross-reactivity patterns of YL201 in humans and monkeys were generally similar. With the similar binding affinity and potency of YL201 against human and monkey B7H3, the monkey was selected as the appropriate model for the assessment of YL201 toxicity. Rats were selected to evaluate the toxicity profile of the payload (YL0010014).

The safety profile of YL201 was established in a series of in vitro cross-reactivity and hemolysis assays, as well as in repeated-dose (up to 6 weeks) IV toxicity studies. The single-dose toxicities of YL201 and YL0010014 were addressed in the dose-range finding studies and the first dose of repeated-dose toxicity. The payload (YL0010014) was also evaluated in genotoxicity studies and repeated-dose (up to 4 weeks) IV toxicity studies. Because of the poor solubility of YL0010014, YL0010033 was synthesized as the prodrug to evaluate toxicity of YL0010014 by IV administration route. The prodrug YL0010033 is rapidly hydrolyzed in vivo and converted to YL0010014. Therefore, in the following rat toxicity studies, the discussion is based on YL0010014.

The YL201-induced toxicity and target organ toxicities of potential clinical concern were identified by repeated-dose toxicity studies in monkeys. In the 6-week cynomolgus monkey study, YL201 at the highest dose of 15 mg/kg was administered with a Q3W dose regimen for a total of 3 doses. The major observed target organs of toxicity at 15 mg/kg included skin (slight to moderate hyperpigmentation), ovary (severe reduction of ovarian follicles), thymus (mild to moderate reduction of lymphocyte), spleen (mild to moderate reduction of white pulp lymphocyte), and lymph nodes (slight to moderate reduction of secondary follicles). All histological findings were reversible by the end of the recovery period. The highest non-severely toxic dose (HNSTD) was considered to be 15 mg/kg (mean AUC_{0-504h} of 24.78 mg·h/mL for YL201, and AUC_{0-504h} of 0.125 µg·h/mL for YL0010014). IV administration of up to 5 mg/kg YL0010033 (4.25 mg/kg of YL0010014 equivalent) once weekly to rats resulted in similar target organs of toxicity to those observed in toxicology studies with YL201, with additional findings of femur bone marrow, stomach, colon, cecum, jejunum, testis, epididymis, and sciatic nerve. The severely toxic dose in 10% of the rats (STD_{10}) was considered to be 4.25 mg/kg of YL0010014 equivalent, with the once-weekly dose regimen for a total of 5 doses.

The YL201-related toxicities in repeated-dose toxicity studies indicated that the organs with high expression of B7H3 are the primary target organs of YL201, including the skin and ovary, while the YL0010014-related toxicities were noted in both monkeys and rats with different severity, including immunosuppression, myelotoxicity, and diarrhea. Additionally, all histological findings were reversible by the end of the recovery period, and no off-target toxicities were identified in the YL201-treated groups.

YL0010014 was clastogenic in an in vitro Chinese hamster lung chromosome aberration assay but not mutagenic in an in vitro bacterial reverse mutation assay or clastogenic in an in vivo rat bone marrow micronucleus assay. No standalone carcinogenicity or reproductive toxicity studies were conducted per the recommendations by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S9 guidance.

4.2.2. Clinical Studies

This is the first-in-human study of YL201. Limited clinical experience of YL201 is available. As of 2 December 2022, a total of 14 patients were enrolled in this study. The preliminary data showed that YL201 had a manageable safety profile. Among 9 patients who completed at least one cycle of safety observation, the most common ($\geq 15\%$) treatment-related AEs of any grade occurring during the first cycle included neutrophil count decreased, lymphocyte count decreased, anemia, platelet count decreased, fatigue, and infusion related reactions. In addition, alopecia, diarrhea, lower gastrointestinal hemorrhage, and aspartate aminotransferase increased were observed in one (11%) patient for each and considered as treatment related.

DS-7300, an anti-B7H3 ADC with an exatecan derivative payload, is now being studied in a phase 1/2 study. The dose escalation results indicated that DS-7300 was tolerated across all dose levels (0.8 mg/kg to 16.0 mg/kg) with no dose-limiting toxicities (DLTs) observed in 70 patients enrolled. All grade of interstitial lung disease (ILD)/pneumonitis occurred in 2/70 (2.9%) patients and were adjudicated as treatment related, including one case of grade 5 ILD at 16 mg/kg and another case of grade 1 ILD at 12 mg/kg. No hepatotoxicity occurred. The most common treatment-emergent adverse events (TEAEs) of any grade included nausea (39/70, 55.7%), infusion-related reactions (28/70, 40.0%), decreased appetite (20/70, 28.6%), and vomiting (19/70, 27.1%). Grade 3 or higher TEAEs regardless of causality occurred in 31.4% of patients (n=22) with the most common being anemia (11/70, 15.7%) and lymphocyte count decreased (2/70, 2.8%). The only Grade ≥ 3 treatment-related AEs were anemia (n=6), lymphocyte count decreased (n=2), neutropenia, asthenia, neutrophil count decreased, and ILD (n=1 each) ([Johnson et al 2021](#)).

4.3. Risks and Benefits of YL201

Nonclinical studies have demonstrated the potent antitumor activity of YL201 in various tumor-bearing mouse models including CRPC, ESCC, NSCLC, and CRC. Thus, YL201 is expected to demonstrate efficacy in patients with advanced solid tumors.

In nonclinical toxicology studies, the toxicity in ovary and skin were considered to be related to YL201. In addition to these toxicities, the possibility of pulmonary toxicity or embryo-fetal toxicity occurring in patients receiving YL201 cannot be excluded as these toxicities were noted in other products of the same class. As with any therapeutic antibodies, there is a possibility of infusion-related reactions and immune responses causing allergic or anaphylactic reactions to YL201. The likelihood of an adverse reaction after administration of YL201 in the proposed clinical trial is considered to be low, and the absence of significant toxicity in nonclinical studies provides confidence that the safety profile is appropriate for the proposed human starting dose.

Based on the efficacy and safety data observed in the nonclinical studies and the information from other products of the same class, the benefit-risk balance supports clinical development of YL201.

4.4. Study Rationale

4.4.1. Rationale for Tumor Type Selection

Malignant tumors have become an important serious health threat and also the most life-threatening disease for humans. Despite the progress made after 40 years of clinical research that has used combinations of chemotherapy, immunotherapy, radiotherapy, and surgery, there remains a significant unmet medical need for additional treatment options for patients with advanced solid tumors that are recurrent or refractory.

This study will be conducted in adult patients with advanced solid tumors including but not limited to SCLC, metastatic CRPC (mCRPC), ESCC, and NSCLC. The following rationales support the proposed investigation of YL201 monotherapy in these patients:

- B7H3 is overexpressed in a wide range of solid tumors with limited normal tissue expression and correlates with the disease severity and poor outcome, thus making it suitable for ADC-targeted therapies ([Section 4.1](#)).
- Several anti-B7H3 ADCs, including DS-7300 and MGC018, have demonstrated potential therapeutic effects in patients with advanced solid tumors in the early clinical development stage. In a phase 1 escalation study of DS-7300, 15 of 70 (21%) patients with advanced solid tumors who progressed after prior standard treatment had a partial response after administration of DS-7300, including 6 of 8 (75%) patients with SCLC ([Johnson et al 2021](#)). In a phase 1 dose-expansion study of MGC018, the best response rate was 25% (4 of 16) in both the mCRPC and the NSCLC cohorts ([Shenderov et al 2021](#)).
- Nonclinical studies have demonstrated the potent antitumor activity of YL201 in various tumor-bearing mouse models including CRPC, ESCC, NSCLC, and CRC ([Section 4.2.1.1](#)).

4.4.2. Rationale for Starting Dose

The initial human starting dose is determined by using the HNSTD in cynomolgus monkeys, which exhibits a level of cross-reactivity similar to that of humans. For the HNSTD in cynomolgus monkeys, the human equivalent dose (HED) was used. It was converted so that the dose per body surface area (mg/m^2) was the same in the experimental animals and in humans, in accordance with the extrapolation method that is widely used for drug products that exhibit cytotoxicity.

The HED of HNSTD was calculated to be 4.8 mg/kg by dividing the HNSTD in cynomolgus monkeys, 15 mg/kg, by the correction factor for cynomolgus monkeys of 3.1. In accordance with the Nonclinical Evaluation for Anticancer Pharmaceuticals (the ICH S9 guidelines), the estimated maximum starting dose for a phase 1 clinical study will be 0.8 mg/kg as one-sixth of the HED of HNSTD.

The efficacious clinical doses were estimated via YL201-treated HT29 xenografted mouse using PK/PD modeling. Stasis concentration of YL201 in mouse was used for the human efficacious dose prediction. Human PK parameters were predicted by interspecies scaling from cynomolgus monkey PK data. A clinical dose of 2.5 to 9.7 mg/kg of YL201 administered once every 3 weeks is expected to achieve concentrations of YL201 sufficient to drive efficacy.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Study Objectives

Primary Objectives

- To assess the safety and tolerability of YL201 in patients with advanced solid tumors
- To determine the maximum tolerated dose (MTD) and select the recommended expansion dose(s) (RED(s)) of YL201 in patients with advanced solid tumors

Secondary Objectives

- To characterize the PK of YL201-ADC, YL201-TAb, and unconjugated payload YL0010014
- To evaluate immunogenicity as measured by the presence of anti-drug antibodies (ADAs) in patients treated with YL201
- To document any preliminary evidence of YL201 efficacy in patients with advanced solid tumors

Exploratory Objectives

- To evaluate the level of soluble B7H3 (sB7H3) in peripheral blood before and after treatment and its relationship with efficacy

5.2. Study Endpoints

Primary Endpoints

- Occurrence of DLTs during the first cycle

Secondary Endpoints

- Adverse events (AEs) as characterized by type, frequency, severity, timing, seriousness, and relationship to study treatment
- Laboratory abnormalities as characterized by type, frequency, severity, and timing
- Physical examination findings, Eastern Cooperative Oncology Group performance status (ECOG PS), vital signs and peripheral oxygen saturation measurements (SpO₂), and ECG parameters
- Single- and multiple-dose PK parameters of YL201-ADC, YL201-TAb, and unconjugated payload YL0010014, including but not limited to AUC, C_{max}, trough concentration (C_{trough}), clearance rate (CL), volume of distribution (V_d), and half-life time (t_{1/2})
- Incidence of anti-YL201 antibodies
- *For patients with PC:* Prostate-specific antigen (PSA) response rate, best PSA response, PSA progression-free survival (PFS), radiological PFS (rPFS), failure-free survival (FFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR),

duration of response (DoR), time to response (TTR), and best tumor response, assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 modified based on Prostate Cancer Working Group 3 (PCWG3) criteria

- For patients with non-PC: ORR, DCR, DoR, TTR, PFS, OS, and best tumor response, assessed using RECIST version 1.1

Exploratory Endpoints

- The level of sB7H3 in peripheral blood before and after treatment

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan

This is a phase 1, multicenter, nonrandomized, open-label, first-in-human study of YL201 conducted in China and the United States. The study will estimate the MTD/RED(s) in dose-escalation cohorts of patients with advanced solid tumors unresponsive to currently available therapies or for whom no standard therapy is available.

Patients will be treated with YL201 IV infusion Q3W as a cycle. The number of treatment cycles is not fixed in this study. Patients who continue to derive clinical benefit from this study treatment in the absence of unacceptable toxicity, PD, or withdrawal of consent may continue the study treatment.

The study is expected to be completed in approximately 3 years from the time the first patient is enrolled to the time the last patient is off the study.

The sponsor will stop the study for unacceptable toxicity (eg, any death attributable to YL201 treatment), regulatory, legal, or other reasons aligned with good clinical practice (GCP) after discussion with the safety review committee (SRC). This study may be terminated at the discretion of the sponsor or any regulatory agency. An investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

6.2. Dose Escalation

Dose escalation will begin in patients with advanced solid tumors (SCLC, mCRPC, ESCC, and NSCLC are preferred). The proposed human starting dose of YL201 is 0.8 mg/kg, based on one-sixth of the HED of the HNSTD in monkeys (15 mg/kg). Six dose levels are initially planned and include 0.8, 1.6, 3, 4.5, 6, and 8 mg/kg ([Table 1](#)). After observing two DLTs at 3.0 mg/kg, which were deemed intolerable, three intermediate dose levels including 2.4, 2.8, and 2.0 mg/kg are added after discussion with the SRC according to the toxicity data accrued in preceding dose levels. The study schema is shown in [Figure 1](#).

Table 1. Proposed Dose-Escalation Scheme

Dose level	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6
Dose (mg/kg, Q3W)	0.8	1.6	3	4.5	6	8
Dosage increment	—	100%	88%	50%	33%	33%

Abbreviation: Q3W, once every 3 weeks.

Starting from 0.8 mg/kg, the standard 3+3 design will be used for the escalation/de-escalation decision. A cohort of 3 patients will receive YL201 IV infusion on Day 1 of Cycle 1. A 21-day observation period (Cycle 1) will then occur, at the end of which all relevant safety data will be reviewed. If no DLTs occur in this cohort of 3 patients during Cycle 1, a new cohort of 3 patients will be treated at the next higher dose level. If 1 of 3 patients experience a DLT, that cohort will be expanded to 6 patients. If only 1 of the 6 patients has a DLT, the next cohort of 3 patients will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, that dose level will be considered above the MTD (the highest dose where no more than 1 of 6 patients has experienced a DLT), and new patients will be enrolled at the previous lower

(tolerated) dose level until that cohort has 6 patients. This lower dose level will be considered the MTD if ≤ 1 in 6 patients has a DLT. An intermediate dose may be explored if the increment is $\geq 50\%$ or considered appropriate by the SRC.

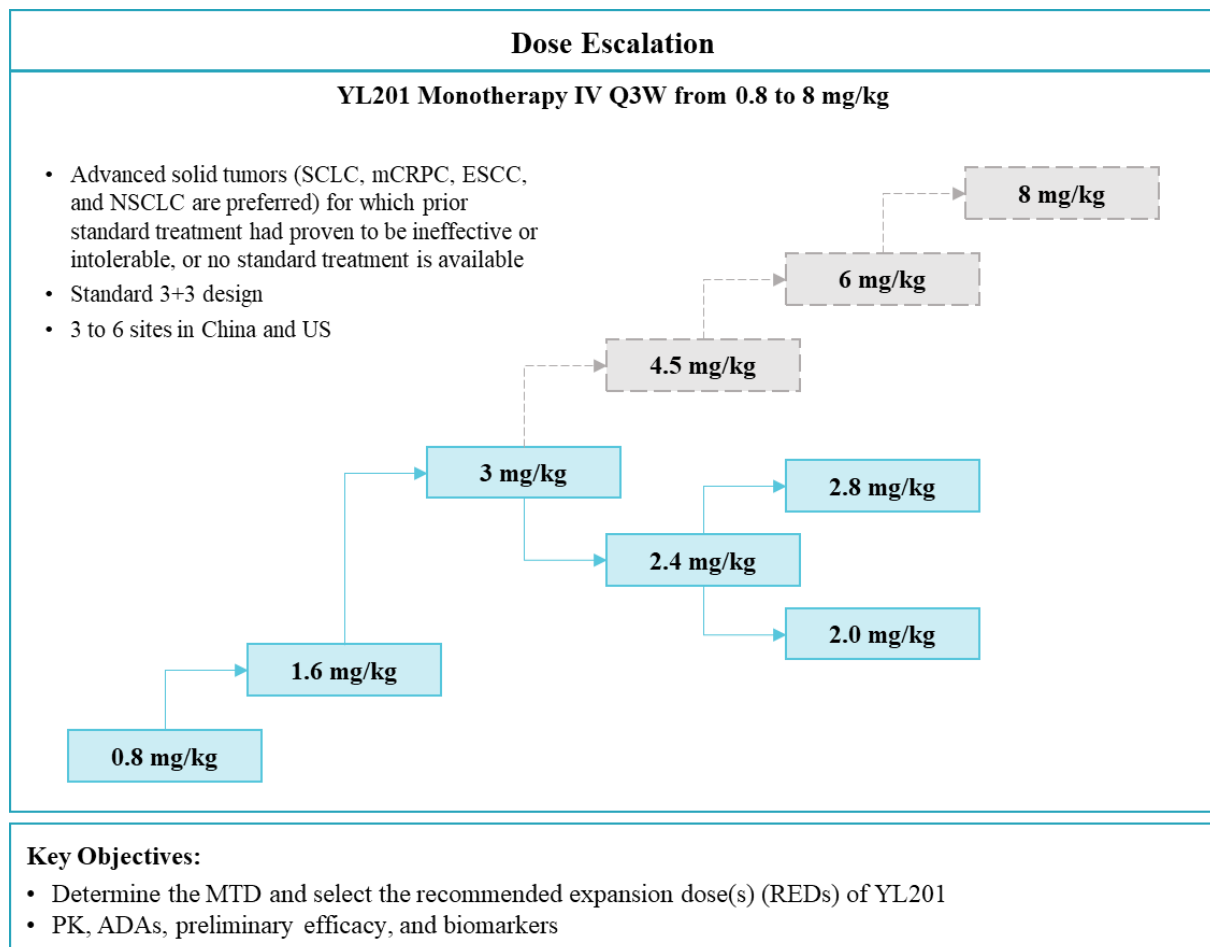
For each dose level, the first enrolled patient will be observed as the sentinel patient for a minimum of 72 hours for occurrence of AEs prior to treating the other patients at the same dose level.

Upon completion of Cycle 1, patients may continue to receive YL201 Q3W at the discretion of the investigator, until unacceptable toxicity, PD, or withdrawal of consent.

To better estimate the MTD/RED(s) and characterize the safety, PK parameters, and efficacy of YL201, additional patients with preferred tumor types (SCLC, mCRPC, ESCC, and NSCLC) or other tumor types agreed upon after discussion with the sponsor may be enrolled in 1 or more dose levels that have been deemed to be safe and tolerable, defined as backfill enrollment. This backfill enrollment may be concurrent with dose escalation to estimate the MTD/RED(s).

No intra-patient dose escalation will be allowed under any circumstances.

Figure 1. Study Schema



6.3. Dose-Limiting Toxicity Definition

A DLT is defined as any of the following TEAEs that occur during the first cycle (Day 1 to Day 21 in Cycle 1), except those unequivocally due to the underlying malignancy or an extraneous cause. Severity of TEAEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

- Hematological toxicity
 - Grade 4 neutropenia lasting for >7 days
 - Grade ≥ 3 febrile neutropenia (defined as Grade ≥ 3 neutropenia and a single body temperature $>38.3^{\circ}\text{C}$ or a sustained temperature of $\geq 38^{\circ}\text{C}$ for more than 1 hour)
 - Grade 4 lymphocyte count decreased lasting for ≥ 14 days
 - Grade 4 anemia
 - Grade ≥ 3 thrombocytopenia lasting for >7 days or of any duration if accompanied by Grade ≥ 2 hemorrhage
- Hepatic organ toxicity
 - Grade ≥ 3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increased
 - ALT or AST $>3 \times$ upper limit of normal (ULN) concurrent with elevation in bilirubin $>2 \times$ ULN
- Nonhematological, nonhepatic major organ toxicity
 - Any grade ≥ 3 toxicities that are considered nonhematological, nonhepatic major organ toxicity

The following TEAEs are NOT considered DLTs:

- Alopecia of any grade
- Grade 3 fatigue lasting for <7 days
- Grade 3 nausea, vomiting, diarrhea, or anorexia that has resolved to Grade ≤ 2 within 3 days
- Isolated laboratory findings lasting for <3 days without signs or symptoms, including Grade 3/4 ALP increased, hyperlipemia, serum amylase increased, and lipase increased

If any of the above toxicities are observed during the DLT evaluation period, whether the toxicity is regarded as a DLT will be determined based on consultation between the investigator and the sponsor.

In principle, a patient needs to be on study for at least 21 days to be evaluable for DLT observation and may be replaced if they terminate study participation earlier than 21 days. However, in circumstances of an event not related to the study drug (eg, traffic accident, clear disease progression) that leads to study termination close to or before 21 days, the patient

might be deemed evaluable if the investigator and sponsor agree.

Premedication, which is treatment before study drug administration to avoid AEs, is prohibited during the DLT evaluation period. However, supportive therapy for AE treatment (eg, hematopoietic growth factors for hematological toxicities) is permitted after study drug administration.

7. STUDY POPULATION

Each patient will sign (and date) an informed consent form (ICF) provided by the site. A patient is considered enrolled in the study upon the investigator or designee obtaining written informed consent from the patient at the time of screening and upon initiation of the first dose of study drug.

The investigator will maintain a confidential screening log of all potential study candidates that includes limited patient information (initials, age, sex) and the outcome of the screening process (ie, enrollment in the study, reason for ineligibility, refused to participate).

The investigator will be expected to maintain an enrollment log of all patients enrolled in the study indicating their assigned patient number. The unique patient number for all patients who provide written informed consent will be assigned by the sponsor.

The date of enrollment is defined as the date that the patient receives the first dose of study drug. The date of screen failure is defined as the date that the patient is considered ineligible. The investigator will maintain a confidential patient identification code list. This confidential list of all patient names and allocated patient numbers on enrolling in the study, allows the investigator to reveal the identity of any patient when necessary.

7.1. Inclusion Criteria

Patients must satisfy all of the following criteria to be included in the study:

- 1) Informed of the trial before the start of the trial and voluntarily sign their name and date on the ICF
- 2) Aged ≥ 18 years
- 3) ECOG PS of 0 or 1
- 4) Adequate organ and bone marrow function, defined as:
 - Hemoglobin ≥ 90 g/L (have not received blood transfusion or erythropoietin treatment within 14 days before the first dose)
 - Absolute neutrophil count $\geq 1.5 \times 10^9$ /L (have not received granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor treatment within 14 days before the first dose)
 - Platelet count $\geq 100 \times 10^9$ /L if no demonstrable liver lesion(s) (primary or metastases) or $\geq 75 \times 10^9$ /L in the presence of liver lesion(s) (have not received platelet transfusion, thrombopoietin, or interleukin-11 treatment within 14 days before the first dose)
 - Total bilirubin $\leq 1.5 \times$ ULN if no demonstrable liver lesion(s) (primary or metastases) or $\leq 3 \times$ ULN in the presence of liver lesion(s)
 - ALT and AST $\leq 3 \times$ ULN if no demonstrable liver lesion(s) (primary or metastases) or $\leq 5 \times$ ULN in the presence of liver lesion(s)
 - Creatinine clearance ≥ 60 mL/min (calculated according to Cockcroft-Gault formula)

- Activated partial thromboplastin time and international normalized ratio $\leq 1.5 \times \text{ULN}$ for patients not receiving therapeutic anticoagulation, or have stable anticoagulant regimen for patients receiving therapeutic anticoagulation
- 5) Female patients of childbearing potential must agree to use a highly effective form of contraception and not donate, or retrieve for their own use, ova from the time of screening and throughout the study period, and for at least 6 months after the last dose of study drug. Male patients must agree to use a highly effective form of contraception and not freeze or donate sperm from the time of screening and throughout the study period, and for at least 6 months after the last dose of study drug
 - 6) Life expectancy of ≥ 3 months
 - 7) Able and willing to comply with protocol visits and procedures
 - 8) Pathologically confirmed diagnosis of an advanced solid tumor (SCLC, mCRPC, ESCC and NSCLC are preferred) for which prior standard treatment had proven to be ineffective or intolerable, or no standard treatment is available
 - 9) Have at least 1 evaluable tumor lesion according to RECIST version 1.1. Participants with prostate cancer who have bone only disease may be eligible on a case-by-case basis after discussion with the sponsor

7.2. Exclusion Criteria

Patients who meet any of the following criteria will be disqualified from entering the study:

- 1) Prior treatment with an agent targeting B7H3 (including antibody, ADC, chimeric antigen receptor T cell [CAR-T], and other drugs)
- 2) Intolerant to prior treatment with a topoisomerase I inhibitor or an ADC that consists of a topoisomerase I inhibitor, including but not limited to topotecan, irinotecan, and Dxd (eg, severe diarrhea)
- 3) Concurrent enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study
- 4) Prior systemic anticancer treatment including chemotherapy, molecular-targeted therapy, hormonal therapy, immunotherapy, or biological therapy within 3 weeks before the first dose of study drug (use of oral fluorouracil [eg, tegafur and capecitabine] or small molecular-targeted therapy within 2 weeks or 5 half-life periods [whichever is shorter] before the first dose; use of mitomycin or nitrosoureas within 6 weeks before the first dose; use of herbal medicine with antitumor indications or nonspecific immunomodulators [eg, thymosin, interferon, and interleukin] within 2 weeks before the first dose).

Note: For patients with PC, androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) analog (GnRH agonist or GnRH antagonist) is allowed.

- 5) Prior radiation therapy, including palliative stereotactic radiation with abdominal, within 4 weeks before the first dose of study drug (if palliative stereotactic radiation therapy

without abdominal, within 2 weeks)

- 6) Undergone major surgery (not including diagnostic surgery) within 4 weeks before the first dose of study drug or expect major surgery during the study
- 7) Undergone allogeneic hematopoietic stem cell transplantation (HSCT) before the first dose of study drug, or autologous HSCT within 3 months before the first dose of study drug
- 8) Received systemic steroids (>10 mg/day of prednisone or its equivalent) or other immunosuppressive therapy within 2 weeks before the first dose of study drug. The following are exceptions to this criterion:
 - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
 - Systemic steroids at physiological doses as replacement therapy (eg, physiological corticosteroid replacement therapy for adrenal or pituitary insufficiency)
 - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)
- 9) Received any live vaccine within 4 weeks before the first dose of study drug or intend to receive a live vaccine during the study
- 10) A history of leptomeningeal carcinomatosis
- 11) Brain metastases or spinal cord compression unless asymptomatic or treated and stable off steroids and anti-convulsants for at least 2 weeks before the first dose of study drug
- 12) Uncontrolled or clinically significant cardiovascular disease, including but not limited to:
 - Medical history of symptomatic congestive heart failure (New York Heart Association class II to IV) or any arterial thromboembolic event (eg, myocardial infarction, unstable angina, cerebrovascular accident, and transient ischemic attack) within 6 months before the first dose
 - Uncontrolled hypertension, defined as systolic blood pressure (SBP) >160 mm Hg and/or diastolic blood pressure (DBP) >100 mm Hg after antihypertensive therapy
 - Serious cardiac arrhythmia that requires treatment
 - Corrected QT interval by Fridericia's formula (QTcF) prolongation to >470 ms
- 13) A history of (noninfectious) ILD/pneumonitis that requires steroids, current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening
- 14) Clinically significant concomitant pulmonary disease, including but not limited to:
 - Pulmonary emboli within 3 months of the start of study treatment
 - Any autoimmune, connective tissue, or inflammatory disorder (eg, rheumatoid arthritis, Sjögren's syndrome, sarcoidosis) where there is documented or suspicion of pulmonary involvement at the time of screening

- Prior complete pneumonectomy
- 15) Have a diagnosis of Gilbert's syndrome
 - 16) Uncontrolled third-space fluid (eg, pleural effusions, ascites, pericardial effusions) that requires repeated drainage
 - 17) Active gastric and duodenal ulcers, ulcerative colitis, or other gastrointestinal conditions that may cause bleeding or perforation by the investigator's discretion
 - 18) Uncontrolled infection that requires systemic therapy within 1 week before the first dose
 - 19) Known human immunodeficiency virus (HIV) infection
 - 20) Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Active HBV is defined as hepatitis B core antibody (HBcAb) or hepatitis B surface antigen (HBsAg) positive, and HBV DNA level above ULN at the study site; active HCV is defined as positive hepatitis C antibody and HCV RNA level above ULN at the study site
 - 21) Unresolved toxicities from previous anticancer therapy, defined as toxicities not yet resolved to NCI CTCAE Grade ≤ 1 , baseline, or the level specified in the inclusion/exclusion criteria with the exception of alopecia (any grade), pigmentation (any grade), and peripheral neuropathy (Grade ≤ 2). Patients with irreversible toxicity (eg, hearing loss) that is reasonably not expected to be aggravated by the study drug can be enrolled after discussion with the sponsor
 - 22) A history of severe hypersensitivity reactions to the drug substances, inactive ingredients in the drug product, or other mAbs
 - 23) Women who are breastfeeding or pregnant as confirmed by pregnancy tests performed within 3 days before the first dose
 - 24) Any illness, medical condition, organ system dysfunction, or social situation, including but not limited to mental illness or substance/alcohol abuse, deemed by the investigator to be likely to interfere with a patient's ability to sign informed consent, adversely affect the patient's ability to cooperate and participate in the study, or compromise the interpretation of study results

7.3. Rescreening

Individuals who sign the ICF to participate in the study but do not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria and therefore do not enroll (screen failures) may be rescreened. Such individuals may be allowed to rescreen only once. The initial screening information and the reason why the patient is ineligible for the initial evaluation will be recorded on the screening log. The data from the initial evaluation will be entered into the clinical database for a patient who is rescreened.

7.4. Study Withdrawal, Removal, and Replacement of Patients

If a patient discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the sponsor. The date and the reason for study

discontinuation must be recorded on the electronic case report form (eCRF). Patients who discontinue from the study treatment will be asked to return to the study site to complete end-of-treatment (EOT), safety follow-up, and survival follow-up assessments as indicated in the Schedule of Activities ([Table 5](#)).

In the event that a patient discontinues prematurely from the study because of a TEAE or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or baseline values), stabilizes, or is judged by the investigator to no longer be clinically significant.

Once a patient is withdrawn from the study, the patient may not reenter the study.

A patient may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- PD
- Unacceptable toxicity or AE
- Patient withdrawal of consent
- Intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that becomes apparent during treatment and necessitates the patient's termination from the study
- General or specific changes in the patient's condition that renders him/her ineligible for further treatment on the basis of the investigator's judgment
- Non-adherence to the protocol requirements (eg, drug noncompliance, failure to return for visits)
- Lost to follow up: the patient stops coming for visits, and study personnel are unable to contact the patient
- Pregnancy, as indicated in [Section 10.7.6](#)
- Death

Additionally, the sponsor will stop the study for unacceptable toxicity (eg, any death attributable to YL201 treatment), regulatory, legal, or other reasons aligned with GCP after discussion with the SRC. This study may be terminated at the discretion of the sponsor or any regulatory agency. An investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

8. STUDY TREATMENT(S)

8.1. Study Drug(s)

8.1.1. Description

The YL201 drug product is provided as a lyophilized powder containing 200 mg of YL201 in a glass vial. Each glass vial should be reconstituted to a concentration of 25 mg/mL. Each vial is designed for single use only and is not to be used to treat more than 1 patient.

8.1.2. Labeling and Packaging

YL201 will be supplied by the sponsor, which will be labeled in compliance with regulatory requirements and packaged. The labeling or packaging will clearly display the name of the investigational product, the investigational product manufacturing code, storage conditions, and other required information in accordance with local regulations.

8.1.3. Preparation

The drug for IV infusion is prepared by dilution of the required volume of the drug product calculated on the basis of the patient's body weight. Prepared medicinal solutions should be used immediately. The preparation will be conducted in accordance with the pharmacy manual provided by the sponsor. Procedures for proper handling and disposal of anticancer drugs should be followed in compliance with the standard operating procedures (SOPs) of the study site. Refer to the pharmacy manual for detailed information about preparation and administration of YL201.

8.1.4. Administration

The study drug will be administered Q3W. The initial dose of YL201 will be infused IV into each patient for 90±10 minutes. If there is no infusion-related reaction after the initial dose, the second and subsequent doses of YL201 will be infused IV into each patient for 60±10 minutes. The patient's weight at screening (baseline) will be used to calculate the initial dose. If, during the course of the treatment, the patient's weight changes by more than 10% of the baseline weight, the patient's dose will be recalculated based on the patient's updated weight.

8.1.5. Storage

Drug supplies must be stored in a secure, limited-access storage area under the storage conditions listed below:

- Stored at 2°C to 8°C

If storage conditions are not maintained per specified requirements, the sponsor or contract research organization (CRO) should be contacted.

8.1.6. Drug Accountability

When a study drug shipment is received, the investigator or designee will check the amount and condition of the drug, the appropriateness of the label, and drug expiration date and sign the Receipt of Shipment Form provided by the sponsor. The original Receipt of Shipment Form

will be retained at the site. In addition, the investigator or designee shall contact the sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the study drug. The record must be kept current and should contain the dates and quantities of the study drug received, the patient's information (the site patient identifier and the patient number) for whom the study drug was dispensed, the drug number, the date and quantity of the study drug dispensed and remaining, and the initials or seal of the dispenser.

At the end of the study, all unused YL201 will be returned or destroyed per local laws or institutional/site policy and only after the study monitor has completed a final inventory. As applicable, the study site must file a copy of the appropriate institutional/site policy within their investigator site file and provide a copy to the sponsor. Please see the pharmacy manual for details.

All investigational product inventory forms must be made available for inspection by a sponsor-authorized representative or designee and regulatory agency inspectors.

8.2. Control Treatment

Not applicable.

8.3. Dose Modifications

8.3.1. Dose Interruptions

The investigator will evaluate which toxicities are attributable to YL201 and adjust the dose of YL201 as recommended below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed (graded according to NCI CTCAE version 5.0).

Specific criteria for dose interruption of YL201 are listed in [Table 4](#). However, the criteria in [Table 4](#) should provide guidance for, but not act as a replacement for, sound clinical judgment. The investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

If a treatment interruption continues beyond Day 21 of the current cycle, the day when treatment is restarted will be counted as Day 1 of the next cycle.

Initiation of the next cycle can only be delayed by a maximum of 28 days. Therefore, if a persisting toxicity does not allow for YL201 treatment resumption within 49 days from Day 1 of the previous cycle, this will result in discontinuation of the patient from treatment unless discussed and agreed with the sponsor.

8.3.2. Dose Reductions

If the dose is interrupted because of toxicities, dose reduction may need to be conducted on the next administration when treatment is resumed.

A maximum of 2 dose reductions are permitted, and the dose level will not be below 0.8 mg/kg. After 2 dose reductions, further dose reduction should not be conducted and the study treatment should be discontinued unless discussed and agreed with the sponsor.

The reference scheme of dose reduction is shown in [Table 3](#). This scheme can be adjusted based on the dose levels actually investigated in the study (e.g., when an intermediate dose level is added to the dose escalation scheme, it is allowed to reduce the dose from a higher level to that intermediate level).

Table 3. Reference Scheme of Dose Reduction

Dose Level before Dose Interruption		Dose Level after First Dose Reduction		Dose Level after Second Dose Reduction
0.8 mg/kg	→	Discontinuation	→	—
1.6 mg/kg	→	0.8 mg/kg	→	Discontinuation
2.4 mg/kg	→	1.6 mg/kg	→	0.8 mg/kg
3 mg/kg	→	2.4 mg/kg	→	1.6 mg/kg
4.5 mg/kg	→	3 mg/kg	→	2.4 mg/kg
6 mg/kg	→	4.5 mg/kg	→	3 mg/kg
8 mg/kg	→	6 mg/kg	→	4.5 mg/kg

Once the dose of YL201 has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level, unless further dose reduction is required. Dose re-escalation is not allowed.

Specific criteria for dose reduction and/or discontinuation of YL201 are listed in [Table 4](#). However, the criteria in [Table 4](#) should provide guidance for, but not act as a replacement for, sound clinical judgment. The investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

Patients who experience a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved.

Table 4. Dose or Schedule Modification for YL201

Worst Toxicity (NCI CTCAE version 5.0)	Management Guideline for YL201
Grade 1 or Grade 2 toxicity, unless otherwise specified	Maintain dose and schedule
Infusion-Related Reaction	
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	- If infusion-related reaction is observed during administration, the infusion speed should be reduced by 50% and patient should be closely monitored. - If no other reactions appear, the subsequent infusion speed could be resumed at the initial planned speed.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	- Administration of YL201 should be interrupted briefly. - If the event resolves or improves to Grade ≤ 1, infusion can be restarted at a 50% reduced infusion speed. - Subsequent administrations should be conducted at the reduced speed.

Worst Toxicity (NCI CTCAE version 5.0)	Management Guideline for YL201
Grade 3 Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Administration of YL201 should be discontinued immediately and permanently.
Grade 4 Life-threatening consequences; urgent intervention indicated	Administration of YL201 should be discontinued immediately and permanently.
Hematologic Toxicity	
Neutrophil Count Decreased	
Grade 3 ($<1.0 \times 10^9/L$ to $0.5 \times 10^9/L$)	Delay dose until resolved to Grade ≤ 2 , then maintain dose
Grade 4 ($<0.5 \times 10^9/L$)	Delay dose until resolved to Grade ≤ 2 , then reduce dose by 1 level
Febrile neutropenia (ANC $<1.0 \times 10^9/L$, fever $>38.3^\circ C$ or a sustained temperature of $\geq 38^\circ C$ for more than 1 hour)	Delay dose until resolved, then reduce dose by 1 level
Lymphocyte Count Decreased	
Grade 1 to Grade 3 lymphopenia	No dose modification
Grade 4 ($<0.2 \times 10^9/L$)	Delay dose until resolved to Grade ≤ 2 , then: - If resolved in ≤ 14 days from day of onset, maintain dose - If resolved in >14 days from day of onset, reduce dose by 1 level
Anemia	
Grade 3 (hemoglobin <8.0 g/dL) Transfusion indicated	Delay dose until resolved to Grade ≤ 2 , then maintain dose
Grade 4 Life-threatening consequences; urgent intervention indicated	Delay dose until resolved to Grade ≤ 2 , then reduce dose by 1 level
Platelet Count Decreased	
Grade 3 (platelet count $<50 \times 10^9/L$ to $25 \times 10^9/L$)	Delay dose until resolved to Grade ≤ 1 , then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in >7 days from day of onset, reduce dose by 1 level
Grade 4 (platelet count $<25 \times 10^9/L$)	Delay dose until resolved to Grade ≤ 1 , then reduce dose by 1 level
Pulmonary Toxicity	
ILD/Pneumonitis	
Grade 3	Delay dose until resolved to Grade ≤ 1 , then: - If resolved in ≤ 28 days from day of onset, maintain dose - If resolved in >28 days from day of onset, reduce dose by 1 level
Grade 4	Permanently discontinue patient from study treatment

Worst Toxicity (NCI CTCAE version 5.0)	Management Guideline for YL201
Hepatic Toxicity	
ALT or AST Concurrent with TBIL Increased	
ALT or AST $>3.0 \times \text{ULN}$, concurrent with TBIL $>2.0 \times \text{ULN}$	Delay study medication until drug-induced liver injury can be ruled out. If drug-induced liver injury is ruled out, the patient should be treated accordingly, and resumption of study drug may occur after discussion between the investigator and the sponsor. If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment.
ALT or AST Increased	
Grade 3 (>5.0 to $20.0 \times \text{ULN}$ in patients without liver metastases and patients with liver metastases and baseline level $\leq 3 \times \text{ULN}$)	Repeat testing within 3 days. Delay dose until resolved to Grade ≤ 1 if baseline $\leq 3 \times \text{ULN}$; otherwise, delay dose until resolved to $\leq$ baseline level, then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level
Grade 3 (>8.0 to $20.0 \times \text{ULN}$ in patients with liver metastases, if the baseline level was $>3 \times \text{ULN}$)	Repeat testing within 3 days. Delay dose until resolved to $\leq$ baseline level, then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level
Grade 4 ($>20.0 \times \text{ULN}$)	Permanently discontinue patient from study treatment
TBIL Increased	
Grade 2 (>1.5 to $3.0 \times \text{ULN}$)	If no liver lesions at baseline, delay dose until resolved to Grade ≤ 1, then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level If documented liver lesions at baseline, continue study treatment.
Grade 3 (>3.0 to $10.0 \times \text{ULN}$)	If no liver lesions at baseline, repeat testing within 3 days. Delay dose until resolved to Grade ≤ 1, then: - If resolved in ≤ 7 days from day of onset, reduce dose by 1 level - If resolved in > 7 days from day of onset, discontinue YL201 If liver lesions at baseline, repeat testing within 3 days. Delay dose until resolved to Grade ≤ 2, then: - If resolved in ≤ 7 days from day of onset, reduce dose by 1 level - If resolved in > 7 days from day of onset, discontinue YL201
Grade 4 ($>10.0 \times \text{ULN}$)	Permanently discontinue patient from study treatment
Gastrointestinal	
Nausea	
Grade 3	Delay dose until resolved to Grade ≤ 1, then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level
Diarrhea/Colitis	
Grade 3	Delay dose until resolved to Grade ≤ 1, then: - If resolved in ≤ 3 days from day of onset, maintain dose - If resolved in > 3 days from day of onset, reduce dose by 1 level
Grade 4	Permanently discontinue patient from study treatment

Worst Toxicity (NCI CTCAE version 5.0)	Management Guideline for YL201
Other Laboratory Adverse Events with Signs or Symptoms	
Grade 3	Delay dose until resolved to Grade ≤ 1 or baseline level, then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level
Grade 4	Permanently discontinue patient from study treatment
Other Non-Laboratory Adverse Events, except Alopecia	
Grade 3	Delay dose until resolved to Grade ≤ 1 or baseline level, then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level
Grade 4	Permanently discontinue patient from study treatment

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ILD, interstitial lung disease; IV, intravenous; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TBIL, total bilirubin; ULN, upper limit of normal.

8.4. Method of Assessing Treatment Compliance

All doses of the study drug will be administered by the investigator or other designated study personnel. Therefore, treatment compliance will be guaranteed as long as the patient attends each visit for the administration of study drug. Start and stop date/time of injection, amount of drug administered, and reason for change or interruption (if applicable) must be recorded in the medical record by clinical study personnel. These data will be recorded in the eCRF.

8.5. Concomitant Medications

Medications used from the time the patient signs the ICF to the safety follow-up visit will be recorded. All concomitant medications will be recorded in the eCRF including the name of the drug and daily dose, the reason for using the medication, as well as the start and stop date of the medication.

8.5.1. Prohibited Concomitant Medications/Activities

The following medications and products are prohibited during this study. The sponsor must be notified if a patient receives any of these during the study.

- Other anticancer therapy, including but not limited to surgery, radiotherapy, chemotherapy, molecular-targeted therapy, hormonal therapy, immunotherapy, biological therapy, or herbal medicine with anticancer indications
 - Palliative radiation to known metastatic sites is permitted as long as it does not affect assessment of response or interrupt treatment for more than the maximum time specified in dose modification section ([Section 8.3](#))
 - Patients with PC could be maintained on a GnRH analog (GnRH agonists or GnRH antagonists) throughout the study
 - Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable

- Other investigational agents
- Live vaccines
- Concomitant use of chronic systemic (IV or oral) steroids or other immunosuppressive medications except if it is standard practice for managing specific AEs. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of steroids are permitted in this study
 - Patients with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study
- Premedication (treatment before study drug administration to avoid AEs) is prohibited during the DLT-evaluation period (Day 1 to 21 of Cycle 1). However, supportive therapy for AE treatment (eg, hematopoietic growth factors for hematological toxicities) is permitted after study drug administration

8.5.2. Restricted Therapies/Products

- Use of e-cigarettes; vaping is strongly discouraged but not prohibited
- Concomitant use of dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments is discouraged but not prohibited

9. STUDY PROCEDURES

[Table 5](#) (Schedule of Activities) summarizes the study procedures to be performed for all patients. All assessments will be performed at time points specified in the Schedule of Activities.

Table 5. Schedule of Activities

	Screening ¹	Treatment												Posttreatment		
		Cycle 1				Cycle 2		Cycle 3			Cycle 4 and Every Cycle Thereafter		EOT ²	Safety F/U ³	Survival F/U ⁴	
		D1		D2	D8	D15	D1		D8	D1						
		BI	EOI				BI	EOI		BI	EOI	BI				EOI
Visit window	≤28 days	-		-	±1 day	±1 day	+2 day		±2 days		±2 days	±2 or ±4 days ⁵		+7 days	±7 days	±7 days
GENERAL & SAFETY																
Informed consent ⁶	X															
Demographic information ⁷	X															
Oncology/medical history ⁸	X															
Physical examination ⁹	X	X					X		X			X		X	X	
ECOG PS ¹⁰	X						X		X			X		X	X	
Height ¹¹	X															
Weight ¹²	X	X					X		X			X		X	X	
Vital signs ¹³	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
SpO ₂ ¹⁴	X	X					X		X			X		X	X	
12-lead ECG ¹⁵	X	X	X		X		X	X	X	X		X		X	X	
AE monitoring ¹⁶	←=====→															
Concomitant medications ¹⁷	←=====→															
New anticancer therapy														X	X	X
Survival status																X
LABORATORY																
Hematology ¹⁸	X				X	X	X		X		X	X		X	X	
Biochemistry ¹⁹	X				X	X	X		X		X	X		X	X	
Coagulation ²⁰	X						X		X			X		X	X	
Urinalysis ²¹	X				X	X	X		X		X	X		X	X	
Pregnancy test ²²	X								X			X		X	X	
Serology ²³	X															

	Screening ¹	Treatment											Posttreatment			
		Cycle 1				Cycle 2		Cycle 3			Cycle 4 and Every Cycle Thereafter		EOT ²	Safety F/U ³	Survival F/U ⁴	
		D1		D2	D8	D15	D1		D8	D1						
		BI	EOI				BI	EOI		BI	EOI					
Visit window	≤28 days	-		-	±1 day	±1 day	+2 day		±2 days		±2 days	±2 or ±4 days ⁵		+7 days	±7 days	±7 days
EFFICACY ASSESSMENT																
Tumor assessment ²⁴	X								X			X		X		
PSA (prostate cancer only) ²⁵	X						X		X			X		X		
DOSING																
YL201 IV infusion ²⁶		X					X		X			X				
PK, ADA, AND BIOMARKER ASSESSMENT																
PK ²⁷		X	X	X	X	X	X	X	X	X	X	X	X			
ADA ²⁸		X			X		X					X		X	X	
Soluble B7H3 ²⁹		X					X		X			X		X		

Abbreviations: ADA, anti-drug antibody; AE, adverse event; B7H3, B7 homolog 3; BI, before infusion; CT, computed tomography; DBP, diastolic blood pressure; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; EOI, end of infusion; EOT, end of treatment; F/U, follow up; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; hCG, human chorionic gonadotropin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous; MRI, magnetic resonance imaging; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PC, prostate cancer; PD, progressive disease; PK, pharmacokinetic; PSA, prostate-specific antigen; Q3W, once every 3 weeks; QTcF, corrected QT interval by Fridericia's formula; SBP, systolic blood pressure; SpO₂, peripheral oxygen saturation.

- ¹ **Screening:** To be conducted within 28 days before treatment start.
- ² **EOT:** To be conducted within 7 days after the date that the patient is discontinued from the study treatment. If assessments at EOT are performed within the last 7 days, these assessments can be considered the EOT assessments and do not need to be repeated.
- ³ **Safety F/U:** To be conducted 42 days (±7 days) after the last dose of study drug or before starting a new anticancer treatment, whichever occurs first. Patients will return for clinical and laboratory assessments, review of concomitant medications, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this time point will continue to undergo follow up at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. If assessments at EOT are performed within this period, these assessments can be considered as the safety follow-up assessments and do not need to be repeated.
- ⁴ **Survival F/U:** To be conducted every 3 months (±7 days) after the EOT visit until death or lost to follow up.
- ⁵ **Visit window for Cycle 4+:** Will be ±2 days for Cycle 4 to Cycle 8, and ±4 days for Cycle 9 and every cycle thereafter.

- ⁶ **Informed consent:** Should be obtained before undergoing any study specific procedures.
- ⁷ **Demographic information:** Includes age, sex, race, and ethnicity.
- ⁸ **Oncology/medical history:** Includes primary oncology history, prior oncology treatment history, and significant medical history. Additional preexisting conditions present at the time when informed consent is given and up to the time of first dosing are to be regarded as concomitant. Medical history will include alcohol consumption and smoking history, if applicable.
- ⁹ **Physical examination:** Includes an assessment of all the major body systems (head, eyes, ears, nose, and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and neurological and musculoskeletal systems). The assessment will be performed by a qualified person at screening (within 7 days before treatment start), Day 1 of every cycle (within 24 hours BI), the EOT visit, the safety F/U visit, and when clinically indicated.
- ¹⁰ **ECOG PS:** Will be performed at screening (within 7 days before treatment start), Day 1 of every cycle from Cycle 2 (within 3 days BI), the EOT visit, the safety F/U visit, and when clinically indicated. See [Appendix 16.1](#) for ECOG PS score.
- ¹¹ **Height:** Will be performed at screening (within 7 days before treatment start) only.
- ¹² **Weight:** Will be performed at screening (within 7 days before treatment start), Day 1 of every cycle (within 24 hours BI), the EOT visit, the safety F/U visit, and when clinically indicated. The patient's weight at screening (baseline) will be used to calculate the initial dose. If the patient's weight changes by more than 10% of the baseline weight, the patient's dose will be recalculated based on the patient's updated weight.
- ¹³ **Vital signs:** Includes SBP and DBP, pulse rate, respiratory rate, and body temperature. The assessment will be performed at screening (within 7 days before treatment start), each visit during study treatment, the EOT visit, the safety F/U visit, and when clinically indicated. On C1D1, C2D1, and C3D1, vital signs should be collected before infusion start (predose) and within 30 minutes after the EOI (postdose). Beginning at Cycle 4, only predose assessments are required. The assessment will be taken after the patient has been at rest in a sitting position for at least 5 minutes. When matched with PK sampling, the vital sign assessment should preferably be carried out before each PK sample drawing such that the PK sample is collected at the nominal time.
- ¹⁴ **SpO₂:** Will be performed at screening (within 7 days before treatment start), Day 1 of every cycle (within 24 hours BI), the EOT visit, the safety F/U visit, and when clinically indicated. The assessment will be performed using pulse oximetry and on the location with the best pulsatile vascular bed (finger, earlobe) after the patient has been at rest in a sitting position for at least 5 minutes. When matched with PK sampling, the SpO₂ assessment should preferably be carried out before each PK sample drawing such that the PK sample is collected at the nominal time.
- ¹⁵ **12-lead ECG:** Will be performed at screening (within 7 days before treatment start), C1D1 (within 24 hours BI), C1D8, C2D1 and Day 1 of every cycle thereafter (within 24 hours BI), the EOT visit, the safety F/U visit, and when clinically indicated. On C1D1 and C3D1, ECGs should be collected before infusion start (predose), within 15 minutes after the EOI, and at 6 hours (± 15 minutes) after the EOI (postdose). On C2D1, ECGs should be collected before infusion start (predose) and within 15 minutes after the EOI (postdose). Beginning at Cycle 4, only predose assessments are required. The assessment will be taken after the patient has been in a supine/semirecumbent position for at least 5 minutes. When matched with PK sampling, the ECG assessment should preferably be carried out before or after each PK sample drawing such that the PK sample is collected at the nominal time. If the QTcF is prolonged (value of >500 ms), the ECGs should be re-evaluated by a qualified person at the institution for confirmation.
- ¹⁶ **AE monitoring:** AEs should be documented and recorded at each visit using NCI CTCAE version 5.0. The period of observation for collection of AEs extends from the time the patient gives informed consent until the safety F/U visit. Follow up of the AE, even after the date of safety F/U visit, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.
- ¹⁷ **Concomitant medications:** All concomitant medications from the time the patient gives informed consent until the safety F/U visit should be recorded including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or diseases, and non-drug supportive interventions (eg, transfusions).
- ¹⁸ **Hematology:** Will be performed at screening (within 7 days before treatment start), C1D8, C1D15, C2D1 and Day 1 of every cycle thereafter (within 3 days BI), C3D8, the EOT visit, the safety F/U visit, and when clinically indicated. See [Table 6](#) for hematology assessments list.
- ¹⁹ **Biochemistry:** Will be performed at screening (within 7 days before treatment start), C1D8, C1D15, C2D1 and Day 1 of every cycle thereafter (within 3 days BI), C3D8, the EOT visit, the safety

- F/U visit, and when clinically indicated. See [Table 6](#) for biochemistry assessments list.
- ²⁰ **Coagulation:** Will be performed at screening (within 7 days before treatment start), C2D1 and Day 1 of every cycle thereafter (within 3 days BI), the EOT visit, the safety F/U visit, and when clinically indicated. See [Table 6](#) for coagulation assessments list.
- ²¹ **Urinalysis:** Will be performed at screening (within 7 days before treatment start), C1D8, C1D15, C2D1 and Day 1 of every cycle thereafter (within 3 days BI), C3D8, the EOT visit, the safety F/U visit, and when clinically indicated. The test will be analyzed by dipstick, and a microscopic analysis will be performed if dipstick abnormal. See [Table 6](#) for urinalysis assessments list.
- ²² **Pregnancy test:** For pregnancy testing in women of childbearing potential, serum hCG should be tested at screening (within 3 days before treatment start). After study drug administration, a serum or urine hCG pregnancy test should be performed at Day 1 of every 2 cycles from Cycle 3 (within 3 days BI), the EOT visit, the safety F/U visit, and when deemed necessary. A positive urine pregnancy will be confirmed using serum test.
- ²³ **Serology:** Includes tests for HBV (HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb), HCV (HCV antibody), and HIV (HIV antibody). HBV DNA should be further tested for patients positive for HBsAg and/or HBcAb; HCV RNA should be further tested for patients positive for HCV antibody. The tests will be performed at screening, and afterwards retest will be conducted only if deemed necessary by the investigator.
- ²⁴ **Tumor assessment:** Will include all known or suspected disease sites, and may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scans for patients with known or suspected brain metastases; bone scans for patients with PC and other patients with known or suspected bone metastases. The screening scans must be performed within 28 days before enrollment and will be used as baseline. After study drug administration, scans will be performed at Day 1 of every 2 cycles for the first 4 assessments (Cycle 3, 5, 7, and 9) and every 3 cycles (eg, Cycle 12, 15, and 18, and so on) thereafter (within 3 days BI), with additional scans when clinically indicated. Assessments will continue until PD is suggested in the image. For patients who discontinue the treatment for reasons other than imaging PD (eg, unacceptable toxicity), a tumor assessment should be carried out at the EOT visit and every 3 cycles (± 7 days) after treatment discontinuation until PD, starting a new anticancer treatment, withdrawal of consent by patients, or death, whichever occurs first. For each patient, the same imaging technique used to characterize each identified and reported lesion at screening will be employed to follow the same lesion throughout the clinical study.
- ²⁵ **PSA:** For patients with prostate cancer, PSA samples should be collected at screening (within 7 days before treatment start), Day 1 of every cycle from Cycle 2 (within 3 days BI), the EOT visit, and when clinically indicated.
- ²⁶ **YL201 IV infusion:** YL201 will be administered Q3W as an IV infusion. The initial dose of YL201 will be infused IV into each patient for 90 ± 10 minutes. If there is no infusion-related reaction after the initial dose, the second and subsequent doses of YL201 will be infused IV into each patient for 60 ± 10 minutes.
- ²⁷ **PK sampling:** Specific timing for collection of blood pharmacokinetic samples can be found in [Table 9](#) below.
- ²⁸ **ADA sampling:** Specific timing for collection of ADA samples can be found in [Table 10](#) below.
- ²⁹ **Soluble B7H3 sampling:** Specific timing for collection of soluble B7H3 samples can be found in [Table 11](#) below.

9.1. Screening

All patients being considered for the study and eligible for screening must provide evidence of informed consent for the study before any study-specific procedures are conducted. Once a signed and dated ICF is obtained, the following activities and/or assessments will be performed during the screening period.

Within 28 days before the first dose of YL201

- Record the patient's demographics (ie, age, sex, race, ethnicity)
- Record the patient's primary oncology history, prior oncology treatment history, and significant medical history
- Perform a serology test for HBV, HCV, and HIV. HBV DNA should be further tested for patients positive for HBsAg and/or HBcAb, and HCV RNA should be further tested for patients positive for HCV antibody.
- Perform a tumor assessment by the following imaging techniques:
 - *For patients with non-PC:* Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis are mandatory. Brain CT or MRI scans should only be done when symptoms associated with brain metastasis occur. Bone scans should only be done when symptoms associated with bone metastasis occur. If no clinical symptoms are observed, brain and bone scans are not mandatory.
 - *For patients with PC:* CT or MRI scans of the chest, abdomen, and pelvis and bone scans are mandatory. Brain CT or MRI scans should only be done when symptoms associated with brain metastasis occur. If no clinical symptoms are observed, brain CT or MRI scans are not mandatory.

Note: Imaging assessments performed as part of standard of care prior to signing informed consent may be used if performed within 28 days before the first dose. Bone scans may be performed within 42 days before the first dose.

- Assess the patient for AEs
- Record the patient's prior and concomitant medications

Within 7 days before the first dose of YL201

- Record the patient's height and weight
- Perform a complete physical examination
- Assess the patient's functional status using the ECOG PS scale
- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) and SpO₂ measurements
- Perform a 12-lead ECG

- Obtain blood samples for hematology, biochemistry, and coagulation testing
- Obtain urine samples for urinalysis
- *For patients with PC only:* Obtain blood samples for PSA testing

Within 3 days before the first dose of YL201

- Obtain serum samples for pregnancy testing in women of childbearing potential (WOCBP). For postmenopausal patients (no childbearing potential, as indicated by a lapse of at least 12 months after the last menstruation) or female patients who have no possibility of pregnancy due to sterilization surgery, etc., no pregnancy test will be required. Female patients who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as WOCBP and required to undergo the pregnancy test.

9.2. Treatment Period**9.2.1. Cycle 1, Day 1****9.2.1.1. Before Infusion**

The following procedures will be completed at predose on Cycle 1, Day 1.

Within 24 hours before infusion

- Record the patient's weight
- Perform a complete physical examination
- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) and SpO₂ measurements
- Perform a 12-lead ECG
- Assess the patient for AEs
- Record the patient's concomitant medications

Within 8 hours before infusion

- Obtain PK blood samples
- Obtain blood samples for ADA assessment
- Obtain blood samples for sB7H3 assessment

9.2.1.2. Administration and After Infusion

The following procedures will be completed on Cycle 1, Day 1:

- Administer YL201

The following procedures will be completed at postdose on Cycle 1, Day 1:

- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature)

measurements within 30 minutes after the end of infusion (EOI)

- Perform a 12-lead ECG within 15 minutes after the EOI, and at 6 hours (± 15 minutes) after the EOI
- Obtain PK blood samples within 15 minutes after the EOI, and at 3 hours (± 15 minutes) and 6 hours (± 15 minutes) after the EOI
- Assess the patient for AEs
- Record the patient's concomitant medications

9.2.2. Cycle 1, Day 2

The following procedures will be performed on Cycle 1, Day 2:

- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) measurements
- Obtain PK blood samples at 24 hours (± 2 hours) after the EOI
- Assess the patient for AEs
- Record the patient's concomitant medications

9.2.3. Cycle 1, Day 8

The following procedures will be performed on Cycle 1, Day 8 (± 1 day):

- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) measurements
- Perform a 12-lead ECG
- Obtain blood samples for hematology and biochemistry testing
- Obtain urine samples for urinalysis
- Obtain PK blood samples at 168 hours (± 24 hours) after the EOI
- Obtain blood samples for ADA assessment
- Assess the patient for AEs
- Record the patient's concomitant medications

9.2.4. Cycle 1, Day 15

The following procedures will be performed on Cycle 1, Day 15 (± 1 day):

- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) measurements
- Obtain blood samples for hematology and biochemistry testing
- Obtain urine samples for urinalysis

- Obtain PK blood samples at 336 hours (± 24 hours) after the EOI
- Assess the patient for AEs
- Record the patient's concomitant medications

9.2.5. Cycle 2, Day 1

9.2.5.1. Before Infusion

The following procedures will be completed at predose on Cycle 2, Day 1:

Within 3 days before infusion

- Assess the patient's functional status using the ECOG PS scale
- Obtain blood samples for hematology, biochemistry, and coagulation testing
- Obtain urine samples for urinalysis
- *For patients with PC only:* Obtain blood samples for PSA testing

Within 24 hours before infusion

- Record the patient's weight
- Perform a complete physical examination
- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) and SpO₂ measurements
- Perform a 12-lead ECG
- Assess the patient for AEs
- Record the patient's concomitant medications

Within 8 hours before infusion

- Obtain PK blood samples
- Obtain blood samples for ADA assessment
- Obtain blood samples for sB7H3 assessment

9.2.5.2. Administration and After Infusion

The following procedures will be completed on Cycle 2, Day 1 (+2 days):

- Administer YL201

The following procedures will be completed at postdose on Cycle 2, Day 1:

- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) measurements within 30 minutes after the EOI
- Perform a 12-lead ECG within 15 minutes after the EOI

- Obtain PK blood samples within 15 minutes after the EOI
- Assess the patient for AEs
- Record the patient's concomitant medications

9.2.6. Cycle 3, Day 1

9.2.6.1. Before Infusion

The following procedures will be completed at predose on Cycle 3, Day 1:

Within 3 days before infusion

- Assess the patient's functional status using the ECOG PS scale
- Obtain blood samples for hematology, biochemistry, and coagulation testing
- Obtain urine samples for urinalysis
- Obtain serum or urine samples for pregnancy testing in WOCBP. For postmenopausal patients (no childbearing potential, as indicated by a lapse of at least 12 months after the last menstruation) or female patients who have no possibility of pregnancy due to sterilization surgery, etc., no pregnancy test will be required. Female patients who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as WOCBP and required to undergo the pregnancy test. A positive urine pregnancy will be confirmed using serum test.
- Perform a tumor assessment by the same imaging techniques as at the time of screening:
 - *For patients with non-PC*: CT or MRI scans of the chest, abdomen, and pelvis are mandatory. Brain CT or MRI scans are not required unless there is brain metastasis at the time of screening or if symptoms associated with brain metastasis occur. Bone scans are also not required unless clinically indicated or positive at the time of screening.
 - *For patients with PC*: CT or MRI scans of the chest, abdomen, and pelvis and bone scans are mandatory. Brain CT or MRI scans are not required unless there is brain metastasis at the time of screening or if symptoms associated with brain metastasis occur.
- *For patients with PC only*: Obtain blood samples for PSA testing

Within 24 hours before infusion

- Record the patient's weight
- Perform a complete physical examination
- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) and SpO₂ measurements
- Perform a 12-lead ECG

- Assess the patient for AEs
- Record the patient's concomitant medications

Within 8 hours before infusion

- Obtain PK blood samples
- Obtain blood samples for sB7H3 assessment

9.2.6.2. Administration and After Infusion

The following procedures will be completed on Cycle 3, Day 1 (± 2 days):

- Administer YL201

The following procedures will be completed at postdose on Cycle 3, Day 1:

- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) measurements within 30 minutes after the EOI
- Perform a 12-lead ECG within 15 minutes after the EOI, and at 6 hours (± 15 minutes) after the EOI
- Obtain PK blood samples within 15 minutes after the EOI, and at 6 hours (± 15 minutes) after the EOI
- Assess the patient for AEs
- Record the patient's concomitant medications

9.2.7. Cycle 3, Day 8

The following procedures will be performed on Cycle 3, Day 8 (± 2 days):

- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) measurements
- Obtain blood samples for hematology and biochemistry testing
- Obtain urine samples for urinalysis
- Obtain PK blood samples at 168 hours (± 48 hours) after the EOI
- Assess the patient for AEs
- Record the patient's concomitant medications

9.2.8. Cycle 4 and Subsequent Cycles, Day 1**9.2.8.1. Before Infusion**

The following procedures will be completed at predose on Day 1 of Cycle 4 and subsequent cycles:

Within 3 days before infusion

- Assess the patient's functional status using the ECOG PS scale
- Obtain blood samples for hematology, biochemistry, and coagulation testing
- Obtain urine samples for urinalysis
- *For patients with PC*: Obtain blood samples for PSA testing

On Day 1 of every 2 cycles from Cycle 5 to the end of treatment (EOT) (eg, Day 1 of Cycle 5, 7, 9, and so on)

- Obtain serum or urine samples for pregnancy testing in WOCBP. For postmenopausal patients (no childbearing potential, as indicated by a lapse of at least 12 months after the last menstruation) or female patients who have no possibility of pregnancy due to sterilization surgery, etc., no pregnancy test will be required. Female patients who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as WOCBP and required to undergo the pregnancy test. A positive urine pregnancy will be confirmed using serum test.

On Day 1 of every 2 cycles from Cycle 5 to Cycle 9 (Day 1 of Cycle 5, 7, and 9) and thereafter every 3 cycles from Cycle 9 to the EOT (eg, Day 1 of Cycle 12, 15, and so on)

- Perform a tumor assessment by the same imaging techniques as at the time of screening:
 - *For patients with non-PC*: CT or MRI scans of the chest, abdomen, and pelvis are mandatory. Brain CT or MRI scans are not required unless there is brain metastasis at the time of screening or if symptoms associated with brain metastasis occur. Bone scans are also not required unless clinically indicated or positive at the time of screening.
 - *For patients with PC*: CT or MRI scans of the chest, abdomen, and pelvis and bone scans are mandatory. Brain CT or MRI scans are not required unless there is brain metastasis at the time of screening or if symptoms associated with brain metastasis occur.

Within 24 hours before infusion

- Record the patient's weight
- Perform a complete physical examination
- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) and SpO₂ measurements
- Perform a 12-lead ECG
- Assess the patient for AEs
- Record the patient's concomitant medications

Within 8 hours before infusion

On Day 1 of every 2 cycles from Cycle 4 to the EOT (eg, Day 1 of Cycles 4, 6, 8, and so on)

- Obtain PK blood samples
- Obtain blood samples for ADA assessment

On Day 1 of every cycle from Cycle 4 to the EOT (eg, Day 1 of Cycles 4, 5, 6, and so on)

- Obtain blood samples for sB7H3 assessment

9.2.8.2. Administration and After Infusion

The following procedures will be completed on Day 1 of Cycle 4 and subsequent cycles (a visit window of ± 2 days for Cycle 4 to Cycle 8, and ± 4 days for Cycle 9 and every cycle thereafter):

- Administer YL201

The following procedures will be completed at postdose on Day 1 of Cycle 4 and subsequent cycles:

- Assess the patient for AEs
- Record the patient's concomitant medications

On Day 1 of every 2 cycles from Cycle 4 to the EOT (eg, Day 1 of Cycles 4, 6, 8, and so on)

- Obtain PK blood samples within 15 minutes after the EOI

9.3. End of Treatment

The EOT date is defined as the date the investigator decides to discontinue study treatment. The following assessments will be performed at the EOT visit (within 7 days after the date of discontinuation). **If assessments at EOT are performed within the last 7 days, these assessments can be considered the EOT assessments and do not need to be repeated.**

- Record the patient's weight
- Perform a complete physical examination
- Assess the patient's functional status using the ECOG PS scale
- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) and SpO₂ measurements
- Perform a 12-lead ECG
- Obtain blood samples for hematology, biochemistry, and coagulation testing
- Obtain urine samples for urinalysis
- Obtain serum or urine samples for pregnancy testing in WOCBP. For postmenopausal patients (no childbearing potential, as indicated by a lapse of at least 12 months after the last menstruation) or female patients who have no possibility of pregnancy due to sterilization surgery, etc., no pregnancy test will be required. Female patients who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as WOCBP and required to undergo the pregnancy test. A positive urine pregnancy will be confirmed using serum test.

- Obtain blood samples for ADA assessment
- Obtain blood samples for sB7H3 assessment
- For patients who discontinue the treatment for reasons other than imaging PD (eg, unacceptable toxicity): Perform a tumor assessment at the EOT visit and every 3 cycles (± 7 days) after treatment discontinuation by the same imaging techniques as at the time of screening, until PD, starting a new anticancer treatment, withdrawal of consent by patients, or death, whichever occurs first:
 - For patients with non-PC: CT or MRI scans of the chest, abdomen, and pelvis are mandatory. Brain CT or MRI scans are not required unless there is brain metastasis at the time of screening or if symptoms associated with brain metastasis occur. Bone scans are also not required unless clinically indicated or positive at the time of screening.
 - For patients with PC: CT or MRI scans of the chest, abdomen, and pelvis and bone scans are mandatory. Brain CT or MRI scans are not required unless there is brain metastasis at the time of screening or if symptoms associated with brain metastasis occur.
- For patients with PC: Obtain blood samples for PSA testing
- Assess the patient for AEs
- Record the patient's concomitant medications including any new anticancer treatment
- Record the reason for treatment discontinuation

9.4. Safety Follow-up

The safety follow-up visit should occur 42 days (± 7 days) after the last dose of YL201. If the patient begins another anticancer therapy before the end of the 42 days (± 7 days), every effort will be made to complete all safety follow-up assessments before commencing the new therapy. In case of any unresolved AEs, the investigator will follow the AE at least every 4 weeks until the event has resolved or the condition has stabilized as possible. **If assessments at EOT are performed within this period, these assessments can be considered as the safety follow-up assessments and do not need to be repeated.**

The following information will be collected at this safety follow-up visit:

- Record the patient's weight
- Perform a complete physical examination
- Assess the patient's functional status using the ECOG PS scale
- Obtain vital sign (SBP and DBP, pulse rate, respiratory rate, and body temperature) and SpO₂ measurements
- Perform a 12-lead ECG
- Obtain blood samples for hematology, biochemistry, and coagulation testing

- Obtain urine samples for urinalysis
- Obtain serum or urine samples for pregnancy testing in WOCBP. For postmenopausal patients (non-childbearing potential, as indicated by a lapse of at least 12 months after the last menstruation) or female patients who have no possibility of pregnancy due to sterilization surgery, etc., no pregnancy test will be required. Female patients who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as WOCBP and required to undergo the pregnancy test. A positive urine pregnancy will be confirmed using serum test.
- Obtain blood samples for ADA assessment. For patients with a positive ADA status at the safety follow-up visit, additional ADA blood samples may be collected every 3 months (± 1 month) for up to 1 year from the last dose of the study drug, or if the patient's ADA status becomes negative, the ADA titer becomes less than baseline (applicable when preexisting ADAs are observed), the patient starts another anticancer therapy, or the patient withdraws consent from the study, whichever occurs first.
- Assess the patient for AEs
- Record the patient's concomitant medications including any new anticancer treatment

9.5. Survival Follow-up

After completing the EOT visit, patients will be followed up via a telephone call or site visit to confirm survival status and new cancer treatments every 3 months (± 7 days) until death or lost to follow up. Even if the patient moves to another hospital, the investigator will confirm new anticancer therapy and survival status, if possible.

10. SAFETY ASSESSMENTS

Safety assessments will include physical examinations (including weight and height), ECOG PS, vital signs and SpO₂ measurements, 12-lead ECGs, clinical laboratory assessments (including pregnancy test), and AE collection.

10.1. Oncology/Medical History and Demographic Data

Oncology/medical history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the patient's preexisting conditions, including primary oncology history, prior oncology treatment history, and significant medical history. Additional preexisting conditions present at the time when informed consent is given and up to the time of first dosing are to be regarded as concomitant. Medical history will include alcohol consumption and smoking history, if applicable.

Illnesses that first occur or are detected during the study, as well as worsening of a concomitant illness during the study, are to be documented as AEs on the eCRF in accordance with [Section 10.7](#). All changes that are not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Additionally, demographic data will be collected for all patients and include age, sex, race, and ethnicity.

10.2. Physical Examinations

A complete physical examination (head, eyes, ears, nose, and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and neurological and musculoskeletal systems) will be performed at the visits specified in the Schedule of Activities ([Table 5](#)) and when clinically indicated. Physical examinations will be performed by a qualified person.

Body weight (without shoes) will be recorded whenever physical examinations are performed; height (without shoes) will be recorded at screening only.

10.3. ECOG PS

ECOG PS will be assessed at the visits specified in the Schedule of Activities ([Table 5](#)) and when clinically indicated. Care will be taken to accurately score performance status, especially during screening of study eligibility purposes. Additional consideration should be given to borderline ECOG PS to avoid enrolling patients with significant impairment.

10.4. Vital Signs and Oxygen Saturation

Vital signs (SBP and DBP, pulse rate, respiratory rate, body temperature) and SpO₂ will be evaluated at the visits specified in the Schedule of Activities ([Table 5](#)) and when clinically indicated. All vital signs and SpO₂ will be measured after the patient has been at rest in a sitting position for at least 5 minutes. Blood pressure measurements will preferably be taken in the same arm for the duration of the study. SpO₂ measurements will be performed using pulse oximetry and on the location with the best pulsatile vascular bed (finger, earlobe). When matched with PK sampling, the vital sign and SpO₂ assessment should preferably be carried out before each PK sample drawing such that the PK sample is collected at the nominal time.

Vital signs and SpO₂ measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, pulse rate, or SpO₂ measurements will be repeated at the investigator's discretion. Any confirmed, clinically significant vital signs and SpO₂ measurements must be recorded as AEs.

10.5. Electrocardiograms

A 12-lead ECG will be performed at the visits specified in the Schedule of Activities ([Table 5](#)) and when clinically indicated. ECGs should be taken after the patient has been in a supine/semirecumbent position for at least 5 minutes.

At screening, the investigator will examine the ECG traces for signs of cardiac disease that could exclude the patient from the study. After study drug administration, any clinically significant changes in ECGs will be recorded as an AE and evaluated further, as clinically warranted. If the QTcF is prolonged (value of >500 ms), the ECGs should be re-evaluated by a qualified person at the institution for confirmation.

When matched with PK sampling, the ECG should preferably be carried out before or after each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections overrides the timing of the ECG collections).

10.6. Laboratory Assessments

Laboratory assessment ([Table 6](#)) will be performed at the visits specified in the Schedule of Activities ([Table 5](#)) and when clinically indicated. Laboratory assessment samples will be analyzed at local laboratories.

Table 6. Laboratory Assessments

Hematology	Biochemistry
Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Albumin ALT ALP AST BUN or urea Carbon dioxide Creatinine Creatine kinase and subtypes Electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT Glucose LDH Total bilirubin Direct bilirubin Total cholesterol Triglycerides
Coagulation	Urinalysis
Prothrombin time Activated partial thromboplastin time Thrombin time International normalized ratio Fibrinogen	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urobilinogen
Serology	Pregnancy test (for WOCBP only)
HBV (HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb). HBV DNA should be further tested for patients positive for HBsAg and/or HBcAb. HCV antibody. HCV RNA should be further tested for patients positive for HCV antibody. HIV antibody	Serum hCG should be tested at screening. After study drug administration, serum or urine hCG should be performed. A positive urine pregnancy will be confirmed using serum test.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGT, gamma-glutamyl transpeptidase; hCG, human chorionic gonadotropin; Hb, hemoglobin; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; Hct, hematocrit; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell; WOCBP, women of childbearing potential.

Urine samples will be analyzed by dipstick, and a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the patient's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention).

Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

10.7. Adverse Events

10.7.1. Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the patient enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the patient's medical history.

Patients will be instructed to report AEs at each study visit. All AEs are to be followed up until resolution or a stable clinical endpoint is reached.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the patient gives informed consent until the safety follow-up visit. Follow up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

The severity of AEs will be graded according to the NCI CTCAE version 5.0 (Grades 1 through 5).

Specific guidelines for classifying AEs by intensity and relationship to study drug are given in [Table 7](#) and [Table 8](#).

Table 7. Classification of Adverse Events by Intensity

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL ^a
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL ^b
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Abbreviations: ADL, activities of daily living; AE, adverse event.

^a Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^b Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Table 8. Classification of Adverse Events by Relationship to Study Drug

Unrelated	This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
Unlikely	This category applies to those AEs that are judged to be unrelated to the study drug but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the study drug; (2) it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it does not follow a known pattern of response to the study drug; or (4) it does not reappear or worsen when the drug is readministered.
Possibly	This category applies to those AEs for which a connection with the study drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; or (3) it follows a known pattern of response to the study drug.
Probably	This category applies to those AEs that the investigator feels with a high degree of certainty are related to the study drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the study drug.
Definitely	This category applies to those AEs that the investigator feels are incontrovertibly related to study drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose and recurs with reexposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the study drug.

Abbreviation: AE, adverse event.

10.7.2. Adverse Events of Special Interest

For the YL201 clinical program, based on the available preclinical data, review of the cumulative literature, reported toxicities for the same class of agents and biological plausibility, ILD/pneumonitis and infusion-related reactions are considered to be AEs of special interest (AESIs).

Additional relevant information regarding the AESIs for the YL201 clinical program regardless of seriousness is to be collected through the targeted questionnaires built within the applicable eCRFs in the clinical study database.

10.7.2.1. Interstitial Lung Disease/Pneumonitis

ILD/pneumonitis is considered an important identified risk based on a comprehensive cumulative review of the available safety information from drugs of similar class and biological plausibility. Refer to the current investigator's brochure (IB) for additional information.

ILD/pneumonitis should be ruled out if a patient develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the "Other Non-Laboratory Adverse Events, except Alopecia" dose modification section of the study protocol ([Section 8.3](#)).

If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include high-resolution CT, pulmonologist consultation, pulmonary function tests and pulse oximetry (SpO₂), arterial blood gases if clinically indicated, and 1 blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible. As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines.

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the "ILD/pneumonitis" dose modification section of the study protocol ([Section 8.3](#)).

All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

10.7.2.2. Infusion-Related Reactions

As with any therapeutic antibodies, there is a possibility of infusion-related reaction and immune responses causing allergic or anaphylactic reactions after the administration of YL201. Immune responses causing allergic or anaphylactic reactions are considered to be an AESI for YL201 clinical program.

Patients who receive YL201 should be monitored by means of vital signs, physical examination, and signs and symptoms of infusion-related reaction: fever, chills, nausea, vomiting, headache, cough, dizziness, rash, and/or lower back pain usually of mild to moderate severity and may lead to shortness of breath and severe lowering of blood pressure.

Patients will be carefully observed for a minimum of 3 hours after the commencement of the first administration (C1D1) for evidence of any infusion-related reactions, and a minimum of 2 hours after the commencement of subsequent infusions (C2D1 and beyond).

10.7.3. Serious Adverse Events

A serious AE (SAE) is any untoward medical occurrence, in the view of either the investigator or sponsor, that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with NCI CTCAE Grade 5.

Other important medical events that may not be immediately life threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. SAEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the sponsor's assessment. If the sponsor or the investigator believe that an event is serious, the event must be considered serious and evaluated by the sponsor for expedited reporting.

10.7.4. Serious Adverse Event Reporting

An SAE occurring from the time informed consent is obtained until the safety follow-up visit must be reported to the Syneos Health Safety and Pharmacovigilance group and will be communicated to the sponsor. Any such SAE due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the investigator becomes aware of the event. Notification can be made using the dedicated fax line or email for the Syneos Health Safety and Pharmacovigilance group:

- Fax number: +1-877-464-7787
- Email address: safetyreporting@syneoshealth.com

If the investigator contacts the Syneos Health pharmacovigilance group by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed to determine the etiology of the problem. The investigator must report all additional follow-up evaluations to the Syneos Health Safety and Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the investigator and sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the patient's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

10.7.5. Suspected Unexpected Serious Adverse Reactions

AEs that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (ie, the event is not consistent with the safety information in the IB)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The investigator will assess whether an event is causally related to study treatment. The sponsor (or designee) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life threatening must be reported to the regulatory authorities within 7 days after the sponsor (or designee) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities within 15 calendar days after the sponsor (or designee) first has knowledge of them.

The sponsor (or designee) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant independent ethics committees (IECs)/IRBs of reportable events within the applicable timeframes.

10.7.6. Pregnancy

WOCBP must have a negative pregnancy test at screening. After study drug administration, any known cases of pregnancy in female patients will be reported until the patient completes or withdraws from the study. The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the investigator will follow up with the patient until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The investigator should notify the sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or therapeutic abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly, the investigator will report the event by faxing/emailing a completed pregnancy report form to the sponsor (or designee) within 24 hours of knowledge of the event.

If the investigator becomes aware of a pregnancy occurring in the partner of a patient participating in the study, the pregnancy should be reported to the sponsor (or designee) within 24 hours of knowledge of the event. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Upon discontinuation from the study, only those procedures that would not expose the patient to undue risk will be performed. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a patient is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the sponsor after delivery.

10.7.7. Overdose

The investigator must immediately notify the sponsor of any occurrence of overdose with study drug.

11. EFFICACY ASSESSMENTS

11.1. Tumor Assessment

Tumor assessments will include all known or suspected disease sites. Imaging technique may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scans for patients with known or suspected brain metastases; bone scans for patients with PC and other patients with known or suspected bone metastases. For each patient, the same imaging technique used to characterize each identified and reported lesion at screening will be employed to follow the same lesion throughout the clinical study.

The screening scans must be performed within 28 days before enrollment and will be used as baseline. After the start of study treatment, scans will be performed every 2 cycles for the first 4 assessments and then every 3 cycles thereafter as specified in the Schedule of Activities ([Table 5](#)), with additional scans when clinically indicated (eg, symptomatic deterioration). Assessments will continue until PD is suggested in the image. For patients who discontinue the treatment for reasons other than imaging PD (eg, unacceptable toxicity), a tumor assessment should be carried out at the EOT visit and every 3 cycles (± 7 days) after treatment discontinuation until PD, starting a new anticancer treatment, withdrawal of consent by patients, or death, whichever occurs first.

Assessment of tumor response will be made by the investigator using RECIST version 1.1 ([Appendix 16.2](#)). For patients with PC, RECIST version 1.1 has been modified based on PCWG3 criteria ([Appendix 16.3](#)), which are specific for this patient population. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

All primary imaging data used for tumor assessments may be collected by the sponsor to enable the possibility of a centralized, independent review of response endpoints by an Independent Review Facility (IRF).

11.2. PSA Assessment (for Patients With PC)

For patients with PC, blood samples for PSA assessment will be collected at the time points specified in the Schedule of Activities ([Table 5](#)) and when clinically indicated.

The detailed instructions for blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual, if applicable.

12. PHARMACOKINETICS, IMMUNOGENICITY AND BIOMARKER ASSESSMENTS

12.1. Pharmacokinetics Assessments

Blood samples for PK analysis will be collected at the time points indicated in [Table 9](#). PK samples will be collected from the arm opposite from infusion site, or alternatively, infusion site will need to be flushed with 10 mL of saline.

Table 9. Schedule of Pharmacokinetic Sampling

Cycle	Day	Sampling Time Point
1	1	BI ^a
		EOI ^b
		3 h postdose (±15 min) ^c
		6 h postdose (±15 min) ^c
	2	24 h postdose (±2 h) ^c
	8	168 h postdose (±24 h) ^c
	15	336 h postdose (±24 h) ^c
2	1	BI ^a
		EOI ^b
3	1	BI ^a
		EOI ^b
		6 h postdose (±15 min) ^c
	8	168 h postdose (±48 h) ^c
4 and beyond (every 2 cycles)	1	BI ^a
		EOI ^b
Unscheduled ^d		Anytime

Abbreviations: BI, before infusion; EOI, end of infusion.

^a BI: Within 8 h before infusion start.

^b EOI: Within 15 min after end of infusion.

^c Sampling times are related to the end of infusion.

^d ¹ If the schedule on Day 1 of Cycle 2 is delayed for 3 days or more, or if the patient cannot continue into Cycle 2, collect blood sample at 504 h postdose (± 48 h) in Cycle 1.

² PK samples may be collected at other time points if clinically indicated (eg, at the time of other significant AE that are at least possibly related to YL201).

The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be adjusted during the study, dependent on emerging data, to ensure appropriate characterization of PK profile.

The detailed instructions for blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual.

The concentration of YL201-ADC, YL201-TAb and unconjugated payload (YL0010014) will be determined from the blood samples using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

12.2. Immunogenicity Assessments

Blood samples for ADA assessment will be collected at the time points indicated in [Table 10](#). For patients with a positive ADA status at the safety follow-up visit, additional blood ADA samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of the study drug, or if the patient's ADA status becomes negative, the ADA titer becomes less than baseline (applicable when preexisting ADAs are observed), the patient starts another therapy for cancer, or the patient withdraws consent from the study, whichever occurs first.

Table 10. Schedule of ADA Sampling

Cycle	Day	Sampling Time Point
1	1	BI ^a
	8	7 days after the EOI (± 1 day)
2 and beyond (every 2 cycles)	1	BI ^a
EOT	—	The date the investigator decides the discontinuation of study treatment (+7 days)
Safety Follow-up ^b	—	42 days (± 7 days) after the last study drug administration or until starting new anticancer treatment, whichever comes first.

Abbreviations: ADA, antidrug antibody; BI, before infusion; EOT, end of treatment.

^a BI: Within 8 h before infusion start.

^b For patients with a positive ADA status at the safety follow-up visit, additional blood ADA samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of the study drug, or if the patient's ADA status becomes negative, the ADA titer becomes less than baseline (applicable when preexisting ADAs are observed), the patient starts another therapy for cancer, or the patient withdraws consent from the study, whichever occurs first.

The timing of ADA samples may be adjusted during the study, dependent on emerging data, to ensure appropriate characterization of ADA profile.

The detailed instructions for blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual.

Samples will be analyzed using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

12.3. Exploratory Biomarker Assessments

Blood samples for sB7H3 analysis will be collected at the time points specified in [Table 11](#).

Table 11. Schedule of Blood Sampling for Soluble B7H3 Assessment

Cycle	Day	Sampling Time Point
Every cycle	1	BI ^a
EOT	—	The date the investigator decides the discontinuation of study treatment (+7 days)

Abbreviations: BI, before infusion; EOT, end of treatment.

^a BI: Within 8 h before infusion start.

The timing of sB7H3 samples may be adjusted during the study, dependent on emerging data, to ensure appropriate characterization of sB7H3 profile and its relationship to efficacy.

The detailed instructions for blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual.

Samples will be analyzed using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

13. STATISTICAL ANALYSIS

13.1. Determination of Sample Size

The study utilizes a standard 3+3 design and consists of 6 planned dose levels. Therefore, up to 36 DLT-evaluable patients are needed to reach an accurate estimate of the MTD/RED(s). The actual number of dose levels and patients enrolled at each dose level will depend upon tolerability and efficacy of YL201.

13.2. Analysis Sets

13.2.1. Full Analysis Set

The full analysis set will include all patients enrolled in this study.

13.2.2. Safety Analysis Set

The safety analysis set will include all patients who received at least 1 dose of YL201.

13.2.3. DLT-Evaluable Set

The DLT-evaluable set is a subset of the full analysis set and will include all patients who were enrolled and received at least 1 dose of YL201, with the exception of those patients for whom DLT evaluation could not be adequately conducted.

13.2.4. Efficacy Analysis Set

The efficacy analysis set is a subset of the full analysis set and will include all patients who received at least 1 dose of YL201 and had baseline and at least 1 postbaseline efficacy assessment.

13.2.5. Pharmacokinetic Analysis Set

The PK concentration analysis set is a subset of the full analysis set and will include all patients who received at least 1 dose of YL201 and had at least 1 postdose concentration measurement above the lower limit of quantitation (LLOQ) for YL201-ADC, YL201-TAb, or YL0010014, without major protocol deviations or events (eg, incomplete dosing, disallowed concomitant medications) affecting PK.

The PK parameter analysis set is a subset of the full analysis set and will include all patients who have at least 1 PK parameter of interest for YL201-ADC, YL201-TAb, or YL0010014, without major protocol deviations or events (eg, incomplete dosing, disallowed concomitant medications) affecting PK.

13.2.6. Immunogenicity Analysis Set

The immunogenicity analysis set is a subset of the full analysis set and will include all patients who received at least 1 dose of YL201 and had at least 1 ADA assessment.

13.2.7. Biomarker Analysis Set

The biomarker analysis set is a subset of the full analysis set and will include all patients who received at least 1 dose of YL201 and had baseline and, where applicable, at least 1 postbaseline assessment for biomarkers.

13.3. Statistical Methods

13.3.1. General Statistical Considerations

Descriptive statistics will be provided for selected demographic, safety, PK, efficacy and biomarker data by dose level/cohort within each part and time as appropriate. Descriptive statistics on continuous data will include the number of patients (N), mean, standard deviation, median, minimum and maximum (as well as geometric mean and geometric coefficient of variation for $C_{\max}$ and AUC PK parameters), while categorical data will be summarized using frequency count and percentage. All data will be listed, and summary tables will be provided. Graphical summaries of the data may be presented.

A statistical analysis plan (SAP) will be prepared after the protocol is approved and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS[®] software version 9.4 or higher (SAS Institute, Cary, North Carolina).

13.3.2. Patient Disposition and Baseline Characteristics

Patient disposition and reasons for treatment and study discontinuation will be summarized at each dose level and in total, if applicable, in the full analysis set and safety analysis data.

Demographic and baseline characteristics such as age, sex, race, ethnicity, baseline ECOG PS, medical history, cancer stage, lines of prior regimens, prior treatment type, and best response to prior anticancer therapy will be summarized for the full analysis set, safety analysis set and efficacy analysis set. If 2 or more analysis sets within a part of the study are identical to each other, the table will be presented only once.

13.3.3. Safety Analysis

The safety profile will be based on AEs, clinical laboratory measurements, vital signs and SpO₂ measurements, ECG recordings, physical examination findings, and ECOG PS assessments. AEs will be graded according to the NCI CTCAE version 5.0. In the dose-escalation part, the incidence of DLTs will also be evaluated.

Safety analysis in general will be descriptive and will be presented in tabular format with appropriate summary statistics. The number of DLTs identified among the DLT-evaluable patients in the DLT-evaluable set will be listed and summarized for each cohort of YL201.

13.3.3.1. Adverse Event Analysis

A TEAE is defined as an AE that emerges during the treatment period (from first dose until follow-up visit after the last dose of study drug), having been absent at pretreatment; or reemerges during treatment, having been present at baseline but stopped before treatment; or worsens in severity after starting treatment relative to the pretreatment state, when the AE is continuous.

The number and percentage of patients who report TEAEs will be tabulated by the worst NCI CTCAE grade, system organ class (SOC), and preferred term (PT).

Similarly, the number and percentage of patients who report treatment-emergent SAEs will be tabulated, as well as TEAEs/SAEs considered related to YL201.

The time interval from the date of first dose of study drug to the first onset date of AESIs will be summarized by AESI category.

A by-patient AE (including TEAE) data listing will be provided including, but not limited to, verbatim term, PT, SOC, NCI CTCAE grade, and relationship to study drug.

Deaths, other SAEs, and other significant AEs, including those leading to permanent discontinuation from YL201, will be listed.

13.3.3.2. Clinical Laboratory Evaluation Analysis

Descriptive statistics will be provided for selected clinical laboratory test results (hematology, biochemistry, coagulation, and urinalysis) and changes from baseline by scheduled time of evaluation, including the EOT visit. In addition, the change from baseline will be summarized for the maximum posttreatment value and minimum value.

Abnormal laboratory results for selected clinical laboratory tests will be graded according to the NCI CTCAE version 5.0, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst value according to NCI CTCAE grade, will be provided for selected clinical laboratory tests. Abnormal clinical laboratory test results that are deemed of clinical significance or of Grade 3 or 4 will be listed.

13.3.3.3. Vital Signs and Oxygen Saturation Analysis

Descriptive statistics will be provided for the vital signs and SpO₂ measurements and changes from baseline by scheduled time of evaluation, including the EOT visit. In addition, the change from baseline will be summarized for the maximum and minimum value.

13.3.3.4. Electrocardiogram Analysis

A shift table, presenting the 2-way frequency tabulation for baseline and each scheduled time, including the EOT visit according to the categories for ECG (normal and abnormal) will be provided. Other ECG data will be listed.

13.3.3.5. Physical Examination and ECOG PS Analysis

Physical examination findings and ECOG PS will be listed.

13.3.4. Efficacy Analysis

The efficacy analysis will be performed for the efficacy analysis set. All efficacy endpoints will be listed and summarized.

For patients with non-PC, the efficacy endpoints will include ORR, DCR, DoR, TTR, PFS, OS, and best tumor response.

For patients with PC, the efficacy endpoints will include PSA response rate at 12 weeks, best PSA response, PSA-PFS, rPFS, FFS, OS, ORR, DCR, DoR, TTR, and best tumor response. ORR, DCR, DoR, TTR, and best tumor response will be assessed in patients with PC with measurable soft tissue lesions at baseline only.

The efficacy endpoints are defined as follows:

- ORR: defined as the proportion of patients who achieved a best overall response of complete response (CR) or partial response (PR).
- DCR: defined as the proportion of patients who achieved a best overall response of CR, PR or stable disease (SD).
- DoR: defined as the time interval from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of PD. DoR will be assessed for patients with a response (CR or PR) only.
- TTR: defined as the time interval from the date of the first dose of study drug to the date of the first documentation of objective response (CR or PR).
- PFS: defined as the time interval from the date of the first dose of study drug to the date of first documentation of PD or death due to any cause, whichever occurs first.
- OS: defined as the time interval from the date of the first dose of study drug to the date of death due to any cause.
- Best tumor response: defined as the maximum percentage change in the sum of longest dimensions (SLD) of measurable lesion(s) at any time during the study.

For patients with PC only:

- PSA response:
 - PSA response rate: defined as the proportion of patients who achieved a $\geq 50\%$ decrease in PSA from baseline.
 - Best PSA response: defined as the maximum percentage change in PSA at any time during the study.
 - PSA-PFS: defined as the time interval from the date of the first dose of study drug to the date of the first documentation of PSA progression, based on PCWG3 criteria.
- rPFS: defined as the time interval from the date of the first dose of study drug to the date of the first documentation of radiographic tumor progression or death due to any cause, whichever occurs first, based on RECIST 1.1 and PCWG3 criteria.

- **FFS:** defined as the time interval from the date of the first dose of study drug to the date of the first documentation of radiographic tumor progression, unequivocal clinical progression, PSA progression or death due to disease progression, whichever occurs first.

For ORR, DCR and PSA response rate, the point estimates and 2-sided corresponding 95% exact binomial confidence interval (CI) will be provided.

Time-to-event variables, including DoR, TTR, PFS, OS, PSA-PFS, rPFS, and FFS, will be summarized descriptively using the Kaplan-Meier method to provide the median event time and 2-sided 95% CI. PFS rate at 3 and 6 months and OS rate at 6 and 12 months will be estimated by Kaplan-Meier method.

Descriptive statistics for best tumor response and best PSA response will be provided. A waterfall plot will be presented for each patient.

13.3.5. Pharmacokinetic Analysis

The PK analysis will be performed on the PK analysis set using actual sample times and noncompartmental methods.

The concentration-time data for YL201-ADC, YL201-TAb, and YL0010014 will be listed, plotted, and summarized using descriptive statistics by dose level/cohort within each part at each point.

Single- and multiple-dose PK parameters of YL201-ADC, YL201-TAb, and YL0010014 will be listed and summarized using descriptive statistics by dose level/cohort within each part.

The concentration data may be used to perform a population PK modeling. If performed, results of population PK analysis will be reported separately (ie, not in the clinical study report).

13.3.6. Immunogenicity Analysis

The immunogenicity analysis will be performed for the immunogenicity analysis set. The percentage of patients with a positive ADA status will be summarized by dose level/cohort within each part and time as appropriate. For patients with a positive ADA status, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit.

13.3.7. Biomarker Analysis

Explorative analysis for biomarkers will be listed and summarized using descriptive statistics.

13.4. Interim Analysis

No interim analysis is planned for this study.

13.5. Data Monitoring Committee

An external data monitoring committee will not be established for this study. For the purpose of this protocol, an internal SRC consisting of investigators and medical experts of the sponsor (or designee) will be established to assess the safety and tolerability of patients. This meeting

will be held regularly, after each cohort of patients have completed Cycle 1, and when necessary.

14. STUDY MANAGEMENT

14.1. Approval and Consent

14.1.1. Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations (CFR), in compliance with ICH and GCP guidelines and according to the appropriate regulatory requirements in the countries where the study was conducted.

14.1.2. Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and patient information sheets and other patient-facing material.

14.1.3. Informed Consent

For each study patient, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the principal investigator (PI) or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and guidelines for ICH. The PI will provide the sponsor or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

14.2. Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also [Section 14.3](#).

Clinical data will be entered by site personnel on eCRFs for transmission to the sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system. Access to the EDC system is available to only authorized users via the study's internet web site, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

14.3. Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

14.4. Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is longer.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the sponsor.

14.5. Monitoring

The study will be monitored according to the monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits and contacts will be made at appropriate times during the study. The PI will assure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each patient.

14.6. Quality Control and Quality Assurance

The sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the sponsor lies with the investigator generating the data.

The sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, SOP, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

14.7. Protocol Amendment and Protocol Deviation

14.7.1. Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of patients or the conduct of the study will be classed as administrative amendments and will be submitted to the appropriate regulatory authorities and the IECs/IRBs for information only. The sponsor will ensure that acknowledgement is received and filed.

Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

14.7.2. Protocol Deviations

Should a protocol deviation occur, the sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable regulatory authority mandates is an investigator responsibility.

14.8. Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR, and in compliance with GCP guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All patients are required to give written informed consent before participation in the study.

14.9. Financing and Insurance

Before the study commences, the sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

14.10. Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others

performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the sponsor or their designee. With respect to such rights, the sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. To facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the sponsor or its designee, as will be set forth in the clinical study agreement.

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16. APPENDIX

16.1. Eastern Cooperative Oncology Group Performance Status Scale

0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

16.2. Response Evaluation Criteria in Solid Tumors, Version 1.1

The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1, are described in [Eisenhauer et al 2009](#). A short summary is given below.

DEFINITIONS

- **Measurable Lesions**

- Tumor Lesions – Lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
 - 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan with slice thickness no greater than 5 mm. When slice thickness is greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness
 - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
 - 20 mm by chest X-ray
- Nodal Lesions – To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI (scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
- Irradiated Lesions – Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not measurable unless there has been demonstrated progression in the lesion prior to enrollment.

- **Non-Measurable Lesions** – All other lesions, including small lesions (tumor lesions with longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 to < 15 mm with scan slice thickness no greater than 5 mm) and truly non-measurable lesions (i.e., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cysts, and also abdominal masses that are not confirmed and followed by imaging techniques).

METHODS OF MEASUREMENT

- **Measurement of Lesions** – The longest diameter of selected lesions should be measured in the plane in which the images were acquired (axial plane). All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 4 weeks before study Day 1.
- **Methods of Assessment** – The same method of assessment and the same technique should be used to characterize each identified and reported lesion throughout the trial.

- **CT/MRI** – Contrast-enhanced CT or MRI should be used to assess all lesions. Optimal visualization and measurement of metastasis in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. CT and MRI should be performed with ≤ 5 mm thick contiguous slices.

BASELINE DOCUMENTATION OF “TARGET” AND “NON-TARGET” LESIONS

- **Target Lesions** – All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.
 - Target lesions should be selected on the basis of their size (lesions with the longest diameter) and suitability for accurate repeated measurements.
 - Pathologic lymph nodes (with short axis ≥ 15 mm) may be identified as target lesions. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions.
 - A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference by which to characterize objective tumor response.
- **Non-Target Lesions** – All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required and these lesions should be followed as “present”, “absent”, or in rare cases “unequivocal progression” throughout the study. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

RESPONSE CRITERIA

Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

• Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions ^a . The appearance of one or more new lesions is also considered progression.

^a To achieve “unequivocal progression” on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

EVALUATION OF OBJECTIVE RESPONSE

• Time Point Response: Patients with Target (+/- Non-Target) Disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable

• Time Point Response: Patients with Non-Target Disease Only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD ^a
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PD = progressive disease; NE = not evaluable

^a “Non-CR/non-PD” is preferred over “stable disease” for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

• Overall Response: Confirmation of CR and PR Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR ^a
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable

^a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes “CR” may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

• Special Notes on Response Assessment

- Nodal Lesions – Lymph nodes identified as target lesions should always have the actual short axis measurement recorded, even if nodes regress to below 10 mm on study. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and pharmacodynamics, the actual short axis measurement of the nodes is to be included in the sum of diameters.
- Target Lesions That Become “Too Small to Measure” – While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being “too small to measure”. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

- **New Lesion** – A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.
- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

CONFIRMATORY MEASUREMENTS / DURATION OF RESPONSE

- **Response Confirmation** – In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. To be assigned a status of confirmed PR or CR, measurements must have met the criteria for each again at least 4 weeks after initial documentation. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 to 8 weeks). **For this study, the next scheduled tumor assessment can meet this requirement.**
- **Duration of Overall Response** – The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented, taking as reference for PD the smallest measurements recorded on study.
- **Duration of Stable Disease** – SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study.

16.3. Criteria for Radiographic Progression per Prostate Cancer Working Group 3 (PCWG3)

The PCWG3 criteria are described in [Scher et al 2016](#). A short summary is given below.

Date Progression Detected ^a	Criteria for Progression	Criteria for Confirmation of Progression (requirement and timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 6	Bone lesions: Two or more new lesions compared with baseline bone scan by PCWG3	Timing: at least 6 weeks after progression identified or at Week 12 visit ^c	Two or more new bone lesions on bone scan (compared with Week 6 scan)
	Soft tissue lesions: Progressive disease on CT or MRI by modified RECIST version 1.1 ^b	No confirmatory scan required for soft tissue disease progression	NA
Week 12 or later	Bone lesions: Two or more new lesions on bone scan compared with Week 6 bone scan	Timing: at least 6 weeks after progression identified. Required for bone lesions observed on bone scan ^c	Persistent ^d or increase in number of bone lesions on bone scan compared with prior scan
	Soft tissue lesions: Progressive disease on CT or MRI by modified RECIST version 1.1 ^b	No confirmatory scan required for soft tissue disease progression	NA

Abbreviations; CT, computed tomography; MRI, magnetic resonance imaging; NA, not applicable; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumors.

^a Progression detected by bone scan at an unscheduled visit will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan. Progression detected by bone scan at an unscheduled visit prior to Week 12 will require a confirmatory scan at least 6 weeks later showing 2 or more new bone lesions on bone scan.

^b For RECIST version 1.1 see [Appendix 16.2](#).

^c Confirmation must occur at the next available scan.

^d For confirmation, at least 2 of the lesions first identified as new must be present at that next available scan

A Multi-Center, Open-Label, Phase 1b Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of YL201 in Patients with Selected Advanced Solid Tumors

Study Protocol

Protocol Number:	YL201-CN-101-01
Protocol Version:	3.0
Protocol Date:	06 December 2023
Investigational Product:	YL201
Development Phase:	Phase 1b
Indication Studied:	Advanced solid tumors
Sponsor Name and Address:	MediLink Therapeutics (Suzhou) Co., Ltd. Unit 101, B3, BioBAY, No. 218, Xinghu Street, Suzhou Industrial Park, Suzhou, China Telephone Number: +86 512 6285 8368

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of MediLink Therapeutics, and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable institutional review board or independent ethics committee. This information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You must not disclose any of the information to others without written authorization from MediLink Therapeutics, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

Protocol Signature Page

I have read this protocol thoroughly and have been familiar with it, confirm that it includes the necessary content for the implementation of the study, and clearly understand my responsibilities associated with this study protocol. I agree to and will strictly abide by Chinese laws and regulations, the Declaration of Helsinki, the Good Clinical Practice, and this study protocol in fulfilling our relevant responsibilities.

Name of Principal Investigator
Sun Yat-sen University Cancer Center

Date

Protocol Signature Page

I have read this protocol thoroughly and have been familiar with it, confirm that it includes the necessary content for the implementation of the study, and clearly understand my responsibilities associated with this study protocol. I agree to and will strictly abide by Chinese laws and regulations, the Declaration of Helsinki, the Good Clinical Practice, and this study protocol in fulfilling our relevant responsibilities.

Name of Investigator from the Sub-site
[Site Name]

Date

Protocol Signature Page

I have read this protocol thoroughly and have been familiar with it, confirm that it includes the necessary content for the implementation of the study, and clearly understand my responsibilities associated with this study protocol. I agree to and will strictly abide by Chinese laws and regulations, the Declaration of Helsinki, the Good Clinical Practice, and this study protocol in fulfilling our relevant responsibilities.

Sponsor Representative
MediLink Therapeutics (Suzhou) Co., Ltd.

Date

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Abbreviation

Abbreviations	Full Name
ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
anti-PD-(L)1	Anti-programmed death receptor (ligand) 1
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BI	Before infusion
BOR	Best overall response
BRCA	Breast cancer susceptibility gene
CAR-T	Chimeric antigen receptor T cell
CI	Confidence interval
CINV	Chemotherapy-induced nausea and vomiting
CL	Clearance
C _{max}	Maximum concentration
cPR	Confirmed partial response
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C _{trough}	Trough concentration
DAR	Drug-to-antibody ratio
DBP	Diastolic blood pressure
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DpR	Depth of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic case report form
EDC	Electronic Data Capture System
EGFR	Epidermal growth factor receptor
EOI	End of infusion
EOT	End of treatment
E-R	Exposure-response
ESCC	Esophageal squamous cell carcinoma
FAS	Full Analysis Set

Abbreviations	Full Name
GCP	Good Clinical Practice
GnRHa	Gonadotropin-releasing hormone analog
Hb	Hemoglobin
HBcAb	Hepatitis B core antibody
HBeAb	Hepatitis B e antibody
HBeAg	Hepatitis B e antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCT	Hematocrit
HCV	Hepatitis C virus
HER	Human epidermal growth factor receptor
HIV	Human immunodeficiency virus
ICF	Informed consent form
ILD	Interstitial lung disease
INR	International normalized ratio
IRR	Infusion related reaction
IV	Intravenous
LYM	Lymphocyte count
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
MRT _{last}	Mean residence time from time 0 to the last time point
NCI	National Cancer Institute
NEU	Neutrophil count
NMPA	National Medical Products Administration
NPC	Nasopharyngeal carcinoma
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PARP	Poly ADP-ribose polymerase
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PLT	Platelet count
PPS	Per Protocol Set
PR	Partial response
PT	Preferred term
Q3W	Once every 3 weeks
RBC	Red blood cell count
RED	Recommended expansion dose

Abbreviations	Full Name
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
ROS1	C-Ros oncogene 1
RP2D	Recommended Phase 2 dose
rPFS	Radiological progression-free survival
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sB7H3	Soluble B7H3
SBP	Systolic blood pressure
SCLC	Small cell lung cancer
SOC	Organ system class
SOP	Standard Operating Procedure
SpO2	Peripheral oxygen saturation
sqNSCLC	Non-small cell lung squamous cell carcinoma
SS	Safety Set
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TAb	Total antibody
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TTR	Time to response
UICC	Union for International Cancer Control
ULN	Upper limit of normal
uPR	Unconfirmed partial response
VALG	Veterans Administration Lung Study Group
V_d	Volume of distribution
WBC	White blood cell count

Synopsis

Protocol Number	YL201-CN-101-01
Study Drug	YL201 for Injection
Sponsor	MediLink Therapeutics (Suzhou) Co., Ltd.
Study Title	A Multi-Center, Open-Label, Phase 1b Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of YL201 in Patients with Selected Advanced Solid Tumors
Study Phase	Phase 1b
Indication Under Investigation	Advanced solid tumors, including but not limited to: Non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), nasopharyngeal carcinoma (NPC), esophageal squamous cell carcinoma (ESCC), etc.
Study Sites	Approximately 10 to 60 study sites in China
Study Objectives <u>Primary Objectives:</u> - To evaluate the safety and tolerability of YL201 in patients with selected advanced solid tumors - To evaluate the efficacy of YL201 in patients with selected advanced solid tumors based on the objective response rate (ORR). <u>Secondary Objectives:</u> - To evaluate other efficacy endpoints of YL201 in patients with selected advanced solid tumors - To evaluate the pharmacokinetic (PK) characteristics of YL201 - To evaluate the immunogenicity of YL201 <u>Exploratory Objectives:</u> - To explore biomarkers associated with YL201 efficacy - To explore the exposure-response (E-R) relationships for efficacy and safety endpoints of YL201	
Study Design This is a multi-center, open-label, Phase 1b study of YL201 conducted in China to evaluate the safety, efficacy, and PK characteristics of YL201 in patients with the following selected advanced solid tumors: - Cohort A: Patients with locally advanced or metastatic NSCLC without actionable genomic alterations who have progressed or are intolerant during or after standard of care (including platinum-based chemotherapy and anti-programmed death receptor (ligand) 1 (anti-PD-(L)1) therapy) - Cohort B: Patients with locally advanced or metastatic NSCLC with actionable genomic alterations who have progressed or are intolerant during or after standard of care (including targeted therapy for driver genes) - Cohort C: Patients with extensive-stage SCLC who have progressed or are intolerant during or after standard of care (including platinum-based chemotherapy and anti-PD-(L)1 therapy) - Cohort D: Patients with recurrent or metastatic NPC who have progressed or are intolerant during or after standard of care (including platinum-based chemotherapy and anti-PD-(L)1 therapy) - Cohort E: Patients with locally advanced unresectable or metastatic ESCC who have progressed or are intolerant during or after standard of care (including platinum, fluorouracil, or taxane-based chemotherapy and anti-PD-(L)1 therapy) - Cohort F: Patients with other solid tumors who have progressed or are intolerant during or after standard of care Subjects in each cohort are not required to confirm the expression level of B7H3 in tumor tissues before enrollment, but they need to provide archived or fresh tumor samples. Subjects who are not able to provide tumor samples or have inadequate samples may be eligible on a case-by-case basis after discussion with the sponsor. Based on the results of the YL201-INT-101-01 dose-escalation study, 2.0 mg/kg and 2.4 mg/kg will be selected as the recommended expansion dose (RED) of YL201. During the study, the sponsor and	

investigator will, based on the available data, decide whether and when to initiate or terminate a particular cohort or dose level, and whether to explore other dose levels or dosing regimens, based on a balance between subject risks and benefits.

Subjects will be treated with YL201 intravenous (IV) infusion at REDs once every 3 weeks (Q3W) as a treatment cycle. The number of treatment cycles is not fixed in this study. Subjects who can benefit from this study treatment may continue study treatment until progressive disease (PD), intolerable toxicity, or withdrawal of informed consent by subjects.

It is planned to enroll approximately 30-90 subjects in each cohort.

After the completion of study for each cohort, the recommended Phase 2 dose (RP2D) of YL201 in patients with selected advanced solid tumors will be determined based on the available safety, efficacy, and PK data.

Study Population

Inclusion Criteria

Subjects are eligible for the study if they meet all of the following inclusion criteria:

- 1) Have been informed of the study prior to initiation of the study and voluntarily sign and date the informed consent form (ICF).
- 2) Aged ≥ 18 to ≤ 75 years at the time of signing the ICF.
- 3) Subjects enrolled in Cohort A should meet the following criteria:
 - Have a histologically or cytologically confirmed diagnosis of NSCLC;
 - Have locally advanced (stage IIIB/IIIC) or metastatic (stage IV) disease (using the 8th edition of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) staging system) at study entry that is not amenable to radical surgery or radiotherapy;
 - For NSCLC with adenocarcinoma or mixed with adenocarcinoma components, there should be clear documentation showing no epidermal growth factor receptor (EGFR)-sensitizing mutations, no anaplastic lymphoma kinase (ALK) and C-Ros oncogene 1 (ROS1) fusions; for NSCLC with other pathological types such as squamous cell carcinoma, if the previous EGFR, ALK, and ROS1 gene status are unknown, corresponding testing is not required before enrollment.
 - Have received at least platinum-based chemotherapy and anti-PD-(L)1 therapy previously for locally advanced or metastatic disease, and have disease progression or are intolerant during or after treatment.

Subjects enrolled in Cohort B should meet the following criteria:

- Have a histologically or cytologically confirmed diagnosis of NSCLC;
- Have locally advanced (stage IIIB/IIIC) or metastatic (stage IV) disease (using the 8th edition of the UICC and the AJCC staging system) at study entry that is not amenable to radical surgery or radiotherapy;
- Have clear documentation of EGFR-sensitizing mutations, ALK fusions, or ROS1 fusions, or known positive for other actionable genomic alterations for which targeted therapy is already marketed in China;
- Have received at least corresponding targeted therapy previously for locally advanced or metastatic disease, and have disease progression or are intolerant during or after treatment.

Subjects enrolled in Cohort C should meet the following criteria:

- Have a histologically or cytologically confirmed diagnosis of SCLC. Combined SCLC is not eligible for this study.
- Have extensive-stage disease at study entry (using a combination of the Veterans Administration Lung Study Group (VALG) and the 8th edition of the AJCC TNM staging system. Extensive stage: AJCC 8th edition stage IV [any T, any N, M1a/b/c], or T3-4 that cannot be encompassed in a tolerable radiotherapy plan because of multiple pulmonary nodules or excessive tumor/nodule volume);
- Have received at least platinum-based chemotherapy and anti-PD-(L)1 therapy previously for extensive-stage SCLC, and have disease progression or are intolerant during or after treatment.

Subjects enrolled in Cohort D should meet the following criteria:

- Have a histologically or cytologically confirmed diagnosis of NPC;
- Have metastatic (stage IVB, using the 8th edition of the UICC and AJCC staging system) or recurrent disease that is not amenable to local or radical treatment at study entry;
- Have received at least platinum-based chemotherapy and anti-PD-(L)1 therapy previously for metastatic or recurrent disease, and have disease progression or are intolerant during or after treatment.

Subjects enrolled in Cohort E should meet the following criteria:

- Have a histologically or cytologically confirmed diagnosis of ESCC;
- Have locally advanced unresectable or metastatic disease at study entry. Subjects with direct invasion of adjacent organs (such as the aorta or trachea) (T4b disease) should be carefully evaluated before enrollment, and those at higher risk as deemed by the investigator should not be enrolled in this study;
- Have received at least platinum, fluorouracil, or taxane-based chemotherapy and anti-PD-(L)1 therapy previously for locally advanced or metastatic disease, and have disease progression or are intolerant during or after treatment.

Subjects enrolled in Cohort F should meet the following criteria:

- Have a histologically or cytologically confirmed diagnosis of advanced solid tumors (except SCLC, NSCLC, NPC, and ESCC);
- Have disease progression or are intolerant during or after prior standard of care, or no available standard treatment options.

Note: For all cohorts, if the subject has disease progression during or within 6 months after prior neoadjuvant therapy, adjuvant therapy, or radical radiochemotherapy, this regimen will be considered as first-line therapy for advanced/metastatic diseases.

- 4) At least one measurable extracranial lesion according to RECIST v1.1. Lesions previously treated with radiotherapy or other local therapies are not considered as target lesions unless there is clear evidence of progression.
- 5) Able to provide archived or fresh tumor samples. Subjects who are not able to provide tumor samples or have inadequate samples may be eligible on a case-by-case basis after discussion with the sponsor.
- 6) Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1.
- 7) Adequate organ and marrow function as defined below within 7 days prior to the first dose:
 - Haemoglobin (Hb) ≥ 9.0 g/dL (have not received blood transfusion or erythropoietin treatment within 14 days before the first dose)
 - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L (have not received granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor treatment within 14 days before the first dose);
 - Platelet count (PLT) $\geq 100 \times 10^9$ /L (have not received platelet transfusion, thrombopoietin, or interleukin-11 treatment within 14 days before the first dose);
 - Total bilirubin (TBIL) $\leq 1.5 \times$ upper limit of normal (ULN) in the absence of obvious metastases to liver, or $\leq 3 \times$ ULN in the presence of metastases to liver;
 - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3 \times$ ULN in the absence of obvious metastases to liver, or $\leq 5 \times$ ULN in the presence of metastases to liver;
 - Serum albumin ≥ 2.5 g/dL;
 - Creatinine clearance ≥ 50 mL/min (calculated according to Cockcroft-Gault formula);
 - Activated partial thromboplastin time (APTT) and international normalized ratio (INR) $\leq 1.5 \times$ ULN, except for subjects receiving anticoagulant therapy, who should have a stable anticoagulant therapy regimen and whose APTT and INR must be within a therapeutic range as deemed appropriate by the investigator.
- 8) Female subjects of childbearing potential must agree to use highly effective contraceptive measures from the time of screening throughout the study period and for at least 6 months after

the last dose of study drug. Male subjects must agree to use highly effective contraceptive measures from the time of screening and throughout the study period and for at least 6 months after the last dose of study drug.

- 9) Life expectancy of ≥ 3 months.
- 10) Able and willing to comply with protocol visits and procedures.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

- 1) Prior treatment with an agent targeting B7H3 (including antibody, antibody-drug conjugate (ADC), chimeric antigen receptor T cell (CAR-T), and other drugs);
- 2) Prior treatment with a topoisomerase I inhibitor or an ADC consisting of a topoisomerase I inhibitor;
- 3) Concurrent enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study.
- 4) Inadequate washout period for prior anti-tumor treatment before the first dose of study drug, defined as follows:
 - Chemotherapy or small molecule targeted therapy < 2 weeks or 5 half-lives, whichever is shorter
 - Antibody therapy < 3 weeks;
 - Hormone therapy < 3 weeks;
 - Treatment with Chinese herbal medicine with anti-tumor indications < 2 weeks;
 - Brain radiotherapy < 2 weeks;
 - Palliative radiation < 2 weeks, and radical radiotherapy < 4 weeks.
- 5) Undergone major surgery (not including diagnostic surgery) within 4 weeks before the first dose of study drug or intend to undergo major surgery during the study.
- 6) Prior allogeneic bone marrow transplantation or solid-organ transplantation.
- 7) Received systemic steroids (> 10 mg/day of prednisone or its equivalent) or other immunosuppressive therapy within 2 weeks before the first dose of study drug, except for:
 - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection)
 - Systemic steroids at physiological doses as replacement therapy (e.g., physiological corticosteroid replacement therapy for adrenal or pituitary insufficiency)
 - Steroids as preventive medication for hypersensitivity reactions (e.g., to CT contrast media) or chemotherapy-induced nausea and vomiting (CINV).
- 8) Received any live vaccine within 4 weeks before the first dose of study drug or intend to receive a live vaccine during the study.
- 9) A history of metastases to meninges or carcinomatous meningitis.
- 10) Brain metastasis or spinal cord compression, except for:
 - Asymptomatic brain metastasis subjects who do not require immediate local or systemic treatment (such as mannitol or corticosteroids) are allowed to be enrolled;
 - If the subject's brain metastasis is treated and stable (defined as that brain imaging at least 4 weeks prior to the first dose shows that the lesion is stable, there is no evidence of new neurological symptoms, and immediate local or systemic therapy is not required within 2 weeks prior to the first dose) and there is no evidence of new or original brain metastasis enlargement, enrollment is allowed.
- 11) Uncontrolled or clinically significant cardiovascular disorders, including but not limited to:
 - Medical history of symptomatic congestive cardiac failure (New York Heart Association (NYHA) class II to IV) or any arterial thromboembolic event (e.g., myocardial infarction, unstable angina, cerebrovascular accident, and transient ischaemic attack) within 6 months before the first dose.
 - Uncontrolled hypertension, defined as systolic blood pressure (SBP) > 160 mm Hg and/or diastolic blood pressure (DBP) > 100 mm Hg after antihypertensive therapy;

- Serious arrhythmia requiring treatment;
 - Corrected QT interval by Fridericia's formula (QTcF) prolongation to >450 ms (for males) or 470 ms (for females).
- 12) Clinically significant concomitant lung disorders, including but not limited to:
- A history of (noninfectious) interstitial lung disease (ILD)/pneumonitis that requires steroids, or currently having ILD/pneumonitis;
 - Pulmonary embolism occurring within 3 months prior to the first dose;
 - Any autoimmune, connective tissue, or inflammatory disorder (e.g., rheumatoid arthritis, Sjögren's syndrome, sarcoidosis) where there is documented or suspicion of pulmonary involvement at screening;
 - Prior pneumonectomy;
 - Other moderate to severe lung disorders that may interfere with the detection or management of drug-related pulmonary toxicity and seriously affect respiratory function.
- 13) Have a diagnosis of Gilbert's syndrome.
- 14) Uncontrolled third-space fluid (e.g., pleural effusions, ascites, pericardial effusions) that requires repeated drainage.
- 15) A history of gastrointestinal perforation and/or fistula within 6 months prior to first dose, or active gastric and duodenal ulcers, ulcerative colitis, or other gastrointestinal conditions that may cause haemorrhage or perforation at the investigator's discretion.
- 16) Subjects with serious infections (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade ≥ 3) within 4 weeks prior to the first dose, such as severe pneumonia requiring hospitalization, bacteraemia, or complicated infections, or active infections requiring systemic therapy within 2 weeks prior to the first dose. Subjects receiving prophylactic anti-infective therapy (e.g., for the prevention of urinary tract infection or chronic obstructive pulmonary disease exacerbation) may be eligible for enrollment after discussion with the sponsor.
- 17) Known human immunodeficiency virus (HIV) infection.
- 18) Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Active HBV infection is defined as hepatitis B core antibody (HBcAb) or hepatitis B surface antigen (HBsAg) positive, and HBV deoxyribonucleic acid (DNA) level > 200 IU/mL or 1000 copies/mL. Those with HBV infection should receive antiviral treatment according to local treatment guidelines and be willing to receive antiviral treatment throughout the study. Active HCV infection is defined as hepatitis C antibody positive and HCV ribonucleic acid (RNA) level above ULN at the study site.
- 19) Any other primary malignancy within 3 years before the first dose of study drug, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, or other curatively treated solid tumors.
- 20) Unresolved toxicities from previous anti-tumor therapy, defined as toxicities (other than alopecia and pigmentation) not yet resolved to NCI CTCAE Grade ≤ 1 or to the levels specified in the inclusion/exclusion criteria. Subjects with chronic Grade 2 toxicities may be eligible for enrollment after discussion with the sponsor if asymptomatic or adequately controlled with stable medication.
- 21) A history of severe hypersensitivity reactions to the drug substances, inactive ingredients in the drug product, or other monoclonal antibodies.
- 22) Women who are breastfeeding or pregnant as confirmed by pregnancy tests performed within 3 days before the first dose.
- 23) Any illness, medical condition, organ system dysfunction, or social situation, including but not limited to mental illness or alcohol abuse, deemed by the investigator to be likely to interfere with a subject's ability to sign ICF, adversely affect the subject's ability to cooperate and participate in the study, or compromise the interpretation of study results.

Study Drug and Route of Administration

YL201 product is a white to light yellow lyophilized powder with a specification of 200 mg/vial. YL201 should be stored at 2-8°C.

Each vial of YL201 should be reconstituted to 25 mg/mL before use. The total amount and volume of drug required should be determined based on the subject's body weight and dose, and then the required volume of

YL201 should be drawn for dilution to ensure a final drug concentration of 0.2-5.0 mg/mL for administration. The body weight of the subject prior to the first dose will be used to calculate the initial dose. If the subject's weight changes by more than 10% of baseline weight during treatment, the subject's dose will be recalculated based on the subject's updated weight.

YL201 will be administered via IV infusion, Q3W. The duration of IV infusion for each subject will be 60±10 minutes.

Sample Size

Approximately 30-90 subjects in each cohort

Study Endpoints

Primary Endpoints:

- Adverse events (AEs) as characterized by type, frequency, severity, time, and relationship to study treatment
- Laboratory test results, physical examination results, ECOG PS, vital signs, peripheral oxygen saturation (SpO₂), and electrocardiogram (ECG) parameters
- ORR assessed as per RECIST v1.1

Secondary Endpoints:

- Depth of response (DpR), disease control rate (DCR), duration of response (DoR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) assessed as per RECIST v1.1
- Single- and multiple-dose PK parameters of YL201 (including ADC, total antibody (TA_b), and unconjugated payload YL0010014), including but not limited to area under the curve (AUC), maximum concentration (C_{max}), trough concentration (C_{trough}), clearance (CL), volume of distribution (V_d), and half-life (t_{1/2})
- Metabolite profile of YL201
- Incidence of anti-YL201 antibodies

Exploratory Endpoints:

- Correlation between B7H3 expression level in tumor tissue and efficacy of YL201
- Correlation between the level of soluble B7H3 (sB7H3) in peripheral blood and efficacy of YL201
- Correlation between the efficacy and safety endpoints of YL201 and exposure

Statistical Analysis

Descriptive statistics will be provided for demographics and baseline characteristics, safety, PK, efficacy, and biomarker data by cohort, dose level, and visit (if applicable). Descriptive statistics for quantitative variables will include the number of subjects (N), mean, standard deviation, median, minimum, and maximum (as well as geometric mean and geometric coefficient of variation for PK parameters C_{max} and AUC), while qualitative variables will be summarized using N and percentage. For all summary figures and tables, the corresponding listings will be provided. All statistical analyses will be performed using SAS 9.4 or higher.

Safety Analysis:

Safety analyses will be based on safety set (SS), and safety data will be summarized by cohort and dose level, including AEs, clinical laboratory measurements, vital signs and SpO₂ measurements, ECG recordings, physical examination findings, and ECOG PS. Safety analyses will be descriptive and will be presented in tabular format with the appropriate summary statistics.

Efficacy Analysis:

Efficacy analyses will be based on the efficacy analysis set (EAS). For ORR and DCR, point estimates will be provided, and the two-sided 95% confidence intervals (CIs) for the corresponding indicators will be estimated using the exact (Clopper-Pearson) method.

DoR, TTR, PFS and OS will be summarized descriptively using the Kaplan-Meier method to estimate the median time to event, and its two-sided 95% CIs will be estimated using the Brookmeyer-Crowley method. PFS rate at 3 and 6 months and OS rate at 6 and 12 months will be estimated by Kaplan-Meier method, and the two-sided 95% CI of the PFS rate and OS rate will be estimated using the Greenwood formula.

In addition, descriptive statistics for DpR will be provided. A waterfall plot will be presented for each subject in the EAS.

PK Analysis:

The concentration-time data for YL201-ADC, YL201-TAb, and YL0010014 will be listed, plotted, and descriptively summarized by cohort and dose level at each time point.

Single- and multiple-dose PK parameters of YL201-ADC, YL201-TAb, and YL0010014 will be listed and descriptively summarized by cohort and dose level.

Immunogenicity Analysis:

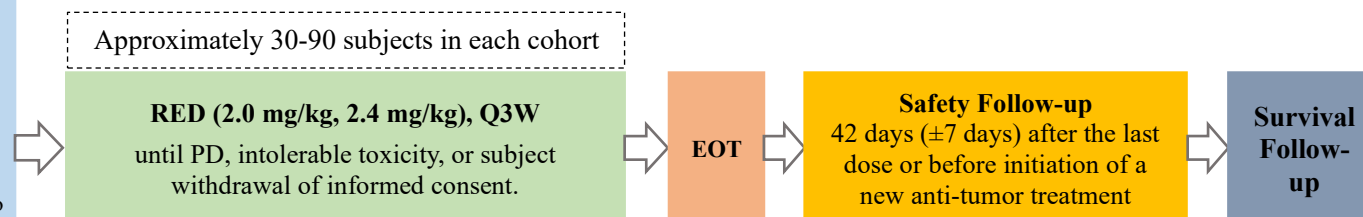
The percentage of anti-drug antibody (ADA)-positive subjects will be summarized by cohort, dose level, and visit (if applicable). For ADA-positive subjects, the extent (titer), onset, and duration of the ADA response will also be described if data permit.

Biomarker Analysis:

The exploratory analysis results of B7H3 expression level and sB7H3 level will be listed and descriptively summarized.

Study Flowchart

- **Cohort A:** Patients with locally advanced or metastatic NSCLC without actionable genomic alterations who have progressed or are intolerant during or after standard of care (including platinum-based chemotherapy and anti-programmed death receptor (ligand) 1 (anti-PD-(L)1) therapy)
- **Cohort B:** Patients with locally advanced or metastatic NSCLC with actionable genomic alterations who have progressed or are intolerant during or after standard of care (including targeted therapy for driver genes)
- **Cohort C:** Patients with extensive-stage SCLC who have progressed or are intolerant during or after standard of care (including platinum-based chemotherapy and anti-PD-(L)1 therapy)
- **Cohort D:** Patients with recurrent or metastatic NPC who have progressed or are intolerant during or after standard of care (including platinum-based chemotherapy and anti-PD-(L)1 therapy)
- **Cohort E:** Patients with locally advanced unresectable or metastatic ESCC who have progressed or are intolerant during or after standard of care (including platinum, fluorouracil, or taxane-based chemotherapy and anti-PD-(L)1 therapy)
- **Cohort F:** Patients with other solid tumors who have progressed or are intolerant during or after standard of care



Schedule of Assessments

	Screening Period ¹	Treatment Period												Post-treatment			
		Cycle 1						Cycle 2		Cycle 3			Cycle 4 and beyond		EOT ²	Safety Follow- up ³	Survival Follow- up ⁴
		D1		D2	D3	D8	D15	D1		D1		D8	D1				
		BI	EOI					BI	EOI	BI	EOI		BI	EOI			
Visit window	≤28 days	-		-	-	±1 day	±1 day	±2 days		±2 days		±2 days	±2 or ±4 days ⁵		+7 days	±7 days	±7 days
General Condition and Safety																	
Informed consent ⁶	X																
Demographic information ⁷	X																
Oncology/medical history ⁸	X																
Physical examination ⁹	X	X						X		X			X		X	X	
ECOG PS ¹⁰	X							X		X			X		X	X	
Height ¹¹	X																
Weight ¹²	X	X						X		X			X		X	X	
Vital signs ¹³	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
SpO ₂ ¹⁴	X	X						X		X			X		X	X	
12-lead ECG ¹⁵	X	X	X		X	X		X	X	X	X		X		X	X	
AE monitoring ¹⁶	←=====→																
Concomitant medications ¹⁷	←=====→																
New anti-tumor therapy															X	X	X
Survival status																	X
Laboratory Tests																	
Hematology ¹⁸	X					X	X	X		X		X	X		X	X	

	Screening Period ¹	Treatment Period												Post-treatment			
		Cycle 1						Cycle 2		Cycle 3			Cycle 4 and beyond		EOT ²	Safety Follow- up ³	Surviva Follow- up ⁴
		D1		D2	D3	D8	D15	D1		D1		D8	D1				
		BI	EOI					BI	EOI	BI	EOI		BI	EOI			
Visit window	≤28 days	-		-	-	±1 day	±1 day	±2 days		±2 days		±2 days	±2 or ±4 days ⁵		+7 days	±7 days	±7 days
Blood chemistry ¹⁹	X					X	X	X		X		X	X		X	X	
Coagulation ²⁰	X							X		X			X		X	X	
Urinalysis ²¹	X					X	X	X		X		X	X		X	X	
Pregnancy test ²²	X									X			X		X	X	
Serology ²³	X																
Efficacy Assessment																	
Tumor assessment ²⁴	X	Once every 6 weeks (±7 days) until Week 24, and then once every 9 weeks (±7 days) thereafter													X		
Administration																	
YL201 IV infusion ²⁵		X						X		X			X				
PK, ADA, and Biomarker Assessment																	
PK ²⁶		See Table 1 and Table 2															
ADA ²⁷		See Table 3															
Tumor tissue ²⁸	X																
sB7H3 ²⁹		See Table 4															

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BI = before infusion; CT = computed tomography; DBP = diastolic blood pressure; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EOT = end of treatment; HBcAb = hepatitis B core antibody; HBeAb = hepatitis B e antibody; HBeAg = hepatitis B e antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HER = human epidermal growth factor receptor; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IV = intravenous; MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = progressive disease; PK = pharmacokinetic; QTcF = corrected QT interval by Fridericia's formula; SBP = systolic blood pressure; SpO2 = peripheral oxygen saturation

1. **Screening period:** To be conducted within 28 days prior to the first dose.

2. **EOT:** To be conducted within 7 days (+7 days) after confirmation/notification of subject discontinuation of treatment. If an EOT assessment has been performed within the last 7 days, this assessment can be considered as the EOT assessment and need not be repeated. For CT/MRI scans performed within 4 weeks, bone scans within 6 weeks, or subjects withdrawn from the study because of PD, no repeat examinations are required.
3. **Safety follow-up:** To be conducted 42 days (± 7 days) after the last dose of study drug or before starting a new anti-tumor treatment, whichever occurs first. Subjects will return to the study site for clinical and laboratory assessments, review of concomitant medications, and assessment of resolution of treatment-related toxicities. Subjects continuing to experience toxicity at this time point will continue to undergo follow-up at least every 4 weeks until the follow-up endpoint in 9.1. If an EOT assessment is performed during this period, this assessment can be considered as the safety follow-up assessment and need not be repeated.
4. **Survival follow-Up:** Telephone follow-up will be conducted every 12 weeks (± 7 days) after the last dose until death or loss to follow-up.
5. **Visit window for Cycle 4 and subsequent cycles:** ± 2 days for Cycle 4 to Cycle 8, and ± 4 days for Cycle 9 and every cycle thereafter.
6. **Informed consent:** Should be obtained before undergoing any study specific procedures.
7. **Demographic information:** Includes age, sex, race, and ethnicity.
8. **Oncology/medical history:** Includes oncology history and treatment history, other prior medical history and treatment history. Oncology history and treatment history: The oncology history and treatment history of the target indication at screening should be recorded. The medical history collection includes the date and results of diagnosis, clinical stage at the time of initial diagnosis and screening (clinical staging criteria corresponding to different disease types), etc., and all anti-tumor treatment history since the diagnosis of the target indication should be recorded. Other prior medical history and treatment history: Other significant medical history, including onset date and end date of disease, should be recorded at screening from 6 months prior to signing of ICF. If the subject has a history of other malignancy, epilepsy, psychiatric disorders, etc. within 5 years, it should be recorded in other important medical history. Additional pre-existing conditions present at the time of signing of ICF and up to the time of first dose are to be regarded as concomitant. The treatment history of other diseases, including prescription drugs, over-the-counter drugs, Chinese herbal medicines, other treatments (including surgery), within 28 days prior to the first dose, should be recorded. Allergy history, drug dependence history, alcohol consumption history, and smoking history (for NSCLC and SCLC cohorts only) of the subjects should also be obtained at screening.
9. **Physical examination:** Includes an assessment of all the major body systems (head, eyes, ears, nose, and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and neurological and musculoskeletal systems). The assessment will be performed by a physician at screening (within 7 days before the first dose), on Day 1 of every cycle (within 24 hours before infusion (BI)), at the EOT visit, the safety follow-up visit, and when clinically indicated.
10. **ECOG PS:** To be performed at screening (within 7 days before the first dose), on Day 1 of each cycle from Cycle 2 (within 3 days BI), at the EOT visit, the safety follow-up visit, and when clinically indicated.
11. **Height:** To be measured at screening (within 7 days prior to the first dose) only.
12. **Weight:** To be measured at screening (within 7 days before the first dose), on Day 1 of every cycle (within 24 hours BI), at the EOT visit, the safety follow-up visit, and when clinically indicated. If the weight at screening has been measured within 24 hours prior to the first dose, there is no need to repeatedly measure the weight within 24 hours BI on C1D1. The initial dose will be calculated using the subject's weight prior to the first dose. If the subject's weight changes by more than 10% of baseline weight during treatment, the subject's dose will be recalculated based on the subject's updated weight.
13. **Vital signs:** Includes SBP and DBP, pulse rate, respiratory rate, and body temperature. The assessment will be performed at screening (within 7 days before the first dose), each visit during study treatment, the EOT visit, the safety follow-up visit, and when clinically indicated. On C1D1, C2D1, and C3D1, vital signs should be collected BI and within 30 minutes after the EOI. Beginning at Cycle 4, only pre-dose assessments are required. The assessments should be performed after the subject has been at rest in a sitting position for at least 5 minutes. When matched with PK sampling, the vital sign assessment should preferably be carried out before each PK sampling such that the PK sample is collected at the nominal time.
14. **SpO₂:** To be measured at screening (within 7 days before the first dose), on Day 1 of each cycle (within 24 hours BI), at the EOT visit, the safety follow-up visit, and when clinically indicated. This assessment should be performed using pulse oximetry at the optimal pulsatile vascular bed (finger, earlobe) after the subject has been at

- rest in a sitting position for at least 5 minutes. When matched with PK sampling, the SpO₂ assessment should preferably be carried out before each PK sampling such that the PK sample is collected at the nominal time.
15. **12-lead ECG:** To be performed at screening (within 7 days before the first dose), on C1D1, C1D3, C1D8, C2D1, Day 1 of every cycle thereafter, at the EOT visit, the safety follow-up visit, and when clinically indicated. On C1D1, C2D1, and C3D1, all subjects should undergo ECG assessments within 24 hours BI and 30 minutes after the EOI; subjects receiving the PK intensive sampling should also undergo ECG assessments at 6 hours (± 15 minutes) after the EOI on C1D1 and C3D1. Beginning at Cycle 4, only pre-dose assessments (within 24 hours BI) are required for all subjects. The ECG assessment should be performed after the subject has been at rest in a supine/semirecumbent position for at least 5 minutes. When matched with PK sampling, the ECG assessment should preferably be carried out before each PK sampling such that the PK sample is collected at the nominal time. If QTcF prolongation (> 500 ms) is observed, the ECG should be re-evaluated by a qualified person at the institution for confirmation.
 16. **AE monitoring:** AEs should be recorded at each visit using NCI CTCAE version 5.0. The period of observation for collection of AEs extends from the time the subject signs the ICF until the safety follow-up visit. If an AE persists, the AE should be followed up (even after the safety follow-up visit) until the follow-up endpoint in 9.1.
 17. **Concomitant medications:** All concomitant medications from the time the subject signs the ICF until the safety follow-up visit should be recorded including supportive care drugs (e.g., anti-emetic treatment and prophylaxis), the drugs used to treat AEs or diseases, and non-drug supportive interventions (e.g., transfusions).
 18. **Hematology:** To be performed at screening (within 7 days before the first dose), on C1D8, C1D15, C2D1 and Day 1 of every cycle thereafter (within 3 days BI), C3D8, at the EOT visit, the safety follow-up visit, and when clinically indicated.
 19. **Blood chemistry:** To be performed at screening (within 7 days before the first dose), on C1D8, C1D15, C2D1 and Day 1 of every cycle thereafter (within 3 days BI), C3D8, at the EOT visit, the safety follow-up visit, and when clinically indicated.
 20. **Coagulation:** To be performed at screening (within 7 days before the first dose), on C2D1 and Day 1 of every cycle thereafter (within 3 days BI), at the EOT visit, the safety follow-up visit, and when clinically indicated.
 21. **Urinalysis:** To be performed at screening (within 7 days before the first dose), on C1D8, C1D15, C2D1, and Day 1 of every cycle thereafter (within 3 days BI), C3D8, at the EOT visit, the safety follow-up visit, and when clinically indicated. Urine samples will be analyzed by dipstick, and a microscopic analysis will be performed if dipstick abnormal.
 22. **Pregnancy test:** For women of childbearing potential (WOCBP), a serum hCG pregnancy test should be performed at screening (within 3 days before the first dose). After study drug administration, a serum or urine hCG pregnancy test should be performed on Day 1 of every 2 cycles from Cycle 3 (within 3 days BI), at the EOT visit, the safety follow-up visit, and when deemed necessary. A positive urine pregnancy should be confirmed using serum pregnancy test.
 23. **Serology:** Includes tests for HBV (HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb), HCV (HCV antibody), and HIV (HIV antibody). For HBsAg- or HBcAb-positive subjects, HBV DNA should be further tested; for HCV antibody-positive subjects, HCV RNA should be further tested. The tests will be performed at screening, and afterwards retest will be conducted only if deemed necessary by the investigator.
 24. **Tumor assessment:**
Imaging sites include all known or suspected disease sites. Screening scans should include at least head, chest, abdomen, pelvic CT or MRI scans and bone scans. For the NPC cohort, neck and nasopharyngeal CT or MRI scans should also be included, and for the ESCC cohort, neck CT or MRI scans should also be included. For patients with abnormal bone scans, appropriate CT or MRI should be additionally performed to confirm bone metastases at sites of suspected bone metastases (if the bone lesions are already within the range covered by routine CT/MRI scans, no additional scans are required). Screening scans should be performed within 28 days prior to the first dose (for bone scans performed at the study site within 3 months prior to the first dose and other examinations within 28 days prior to the first dose, no repeat examinations are required), and the results will serve as baseline data.
During the treatment period, at least chest, abdomen, and pelvic CT or MRI scans are included. For the NPC cohort, neck and nasopharyngeal CT or MRI scans should also be included, and for the ESCC cohort, neck CT or MRI scans should also be included. Subjects with brain metastases or bone metastases confirmed at screening should undergo head CT or MRI or bone scans at each tumor assessment during the treatment period. For subjects suspected of having brain metastases or bone

metastases during the treatment period, the investigator may decide, based on clinical indications, whether they should undergo head CT or MRI or bone scans. For patients with abnormal bone scans, appropriate CT or MRI should be additionally performed to confirm bone metastases at sites of suspected bone metastases (if the bone lesions are already within the range covered by routine CT/MRI scans, no additional scans are required). Assessments will be conducted every 6 weeks (± 7 days) after the study drug administration until Week 24, and then every 9 weeks (± 7 days) thereafter (i.e., Weeks 6, 12, 18, 24, 33, 42 and 51, etc.), and when clinically indicated.

Subjects who achieve a complete response (CR) or partial response (PR) should undergo confirmatory imaging at least 4 weeks later. Assessments will continue until PD is suggested in the image. For subjects who discontinue the treatment for reasons other than imaging PD (e.g., unacceptable toxicity), a tumor assessment should be carried out at the EOT visit every 9 weeks (± 7 days) after treatment discontinuation until PD, starting a new anti-tumor treatment, withdrawal of informed consent by subjects, or death, whichever occurs first. Throughout the clinical study, the same imaging techniques will be used to follow the same lesions in each subject to characterize each lesion identified and reported at screening.

25. **YL201 IV infusion:** YL201 will be administered via IV infusion, Q3W. The duration of YL201 IV infusion for each subject will be 60 ± 10 minutes.
26. **PK sampling:** Specific time points for collection of blood PK samples are shown in Table 1 and Table 2 below.
27. **ADA sampling:** Specific time points for collection of ADA samples are shown in Table 3 below.
28. **Tumor tissues:** Subjects should provide 6 to 10 slides of archived or fresh tumor samples before the first dose of study drug for exploratory assessment of B7H3 expression level. Subjects who are not able to provide tumor samples or have inadequate samples may be eligible on a case-by-case basis after discussion with the sponsor.
29. **sB7H3 sampling:** Specific time points of sB7H3 sample collection are shown in Table 4 below.

Schedule of Biological Sample Collection

Table 1 PK Sampling Schedule (Intensive Sampling)^a

Cycle	Day	Sampling Time Point
1	1	Within 3 h BI
		Within 30 min after the EOI
		3 h (± 15 min) after the EOI
		6 h (± 15 min) after the EOI
	2	24 h (± 2 h) after the EOI
	3	48 h (± 2 h) after the EOI
	8	168 h (± 24 h) after the EOI
15	336 h (± 24 h) after the EOI	
2	1	Within 3 h BI ^b
		Within 30 min after the EOI
3	1	Within 3 h BI
		Within 30 min after the EOI
		6 h (± 15 min) after the EOI
	8	168 h (± 48 h) after the EOI
4 and beyond (every 2 cycles)	1	Within 3 h BI
		Within 30 min after the EOI
Unscheduled ^c		Anytime

Abbreviations: BI = before infusion; EOI = end of infusion; h = hour(s); min = minute(s).

a: In the study, only 20-30 subjects at each dose level (regardless of the cohort) will undergo intensive PK sampling according to the above table for the analysis of plasma concentrations of ADC, TAb, uncoupled payload YL0010014 and the identification of drug metabolites.

b: If the dose on Day 1 of Cycle 2 is delayed for 3 days or more, or if the subject cannot continue into Cycle 2, collect an additional blood sample at 504 h (± 48 h) after the EOI in Cycle 1.

c: PK samples may be collected at other time points if clinically indicated (e.g., at the time of other significant AE that are at least possibly related to YL201).

Table 2 PK Sampling Schedule (Sparse Sampling)^a

Cycle	Day	Sampling Time Point
1	1	Within 3 h BI
		Within 30 min after the EOI
	8	168 h (±24 h) after the EOI
2 and beyond (every 2 cycles)	1	Within 3 h BI
		Within 30 min after the EOI
Unscheduled ^b		Anytime

Abbreviations: BI = before infusion; EOI = end of infusion; h = hour(s); min = minute(s).

a: The remaining subjects in the study will undergo PK sparse sampling according to the above table for the analysis of plasma concentrations of ADC, TAb, uncoupled payload YL0010014.

b: PK samples may be collected at other time points if clinically indicated (e.g., at the time of other significant AE that are at least possibly related to YL201).

Table 3 ADA Sampling Schedule

Cycle	Day	Sampling Time Point
1	1	Within 3 h BI
2 and beyond (every 2 cycles)	1	Within 3 h BI
EOT	—	Within 7 days after confirmation/notification of subject discontinuation of treatment.
Safety follow-up ^a	—	42 days (± 7 days) after the last dose of study drug or before starting a new anti-tumor treatment, whichever occurs first.

Abbreviations: ADA = antidrug antibody; BI = before infusion; EOI = end of infusion; EOT = end of treatment; h = hour(s).

a: For subjects with a positive ADA status at the safety follow-up visit, additional ADA blood samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of the study drug, or if the subject's ADA status becomes negative, the ADA titer becomes less than baseline (applicable when preexisting ADAs are observed), the subject starts another anti-tumor therapy, or the subject withdraws consent from the study, whichever occurs first.

Table 4 sB7H3 Sampling Schedule

Cycle	Day	Sampling Time Point
1	1	Within 3 h BI
2 and beyond (every 2 cycles)	1	Within 3 h BI
EOT	-	Within 7 days after confirmation/notification of subject discontinuation of treatment.

Abbreviations: BI = before infusion; EOT = end of treatment.

1 Introduction

1.1 Study Rationale

Cancer, also known as malignancy, is a disease caused by the abnormal regulation of mechanisms that control cell growth and proliferation. In recent years, the incidence of cancer has been increasing year by year, seriously threatening human health and social development. Global cancer statistics show that in 2020, there were about 19.29 million new cancer cases worldwide, and about 9.96 million people died of cancer^[1]. China is a concentrated area of cancer outbreak. According to the "Analysis of the Epidemiological Characteristics of Malignancies in China in 2015"^[2] reported by the National Cancer Center in 2019, it is estimated that there were about 3.929 million new cases of malignancy in China in 2015, with an incidence rate of 285.83/100,000 (305.47/100,000 for males and 265.21/100,000 for females). There were about 2.338 million deaths from malignancy, with a death rate of 170.05/100,000 (210.10/100,000 for males and 128.00/100,000 for females). The common malignancies in China are lung cancer, gastric cancer, colorectal cancer, hepatic cancer and breast cancer female, etc., and the incidences of top 10 account for about 76.7% of the total new cases of malignancy. The overall cancer burden in China shows a continuous upward trend, with significant differences in cancer burden between urban and rural areas and between men and women, and the cancer prevention and control situation remains grim.

B7-H3 is a 316 amino-acid long type I transmembrane protein encoded by a gene in chromosome 9 in mice and 15 in humans^[3]. B7H3 serves as a member of B7 superfamily, which shares 20% - 27% amino-acid identity with other B7 family ligands^[4]. Recent studies have shown that B7-H3 is a crucial player in tumor growth and metastasis beyond the immune regulatory roles^[5]. The function of B7-H3 needs to be fully explored to better reveal its important role in immune responses and tumor evasion.

B7-H3 is considered as a promising target for cancer treatment. B7-H3 protein has a very limited expression in normal tissues because of its post-transcriptional regulation by micro-ribonucleic acids (microRNAs)^[6]. In contrast, the messenger ribonucleic acid (mRNA) expression and protein level of B7-H3 are up-regulated in malignant tumor tissues. Furthermore, high expression levels of B7-H3 have been found to be associated with PD and poor prognosis in cancer patients^{[6]-[7][8][9]}.

Regardless of the negative prognostic association with B7-H3 in cancer, the biological role of B7-H3 remains unclear and controversial due to the lack of a known B7-H3 receptor^[5]. Recent advances in molecular biology and antibody engineering have enabled the development of antibody-based targeting agents that exploit the overexpression of B7-H3 in tumors. Most of these strategies have been tested in early clinical studies and have yielded encouraging safety and/or efficacy data, including monoclonal antibodies (mAbs), bispecific antibodies, chimeric antigen receptor T cell (CAR-T) therapies, and antibody-drug conjugate (ADC) therapies^{[10]-[11][12]}. Among all the approaches tested in clinical study, MGC018 and DS-7300, as two of the most progressed investigational ADCs targeting B7-H3, exhibit most promising efficacy and favorable safety results^{[13]-[14]}.

MediLink Therapeutics (Suzhou) has developed a new B7-H3-targeted ADC (named YL201) with novel linker and payload of topoisomerase I inhibitor. The YL201 was well tolerated, and suppressed pre-existing tumor growth in a dose-dependent manner in various cancer cells or patient derived (solid tumor) xenograft models, including non-small cell lung cancer, castration-resistant prostate cancer, esophageal squamous cell carcinoma, and colorectal carcinoma.

1.2 Overview of Clinical Studies

1.2.1 Pharmacology Studies

YL201 and YL0010014 toxin payload have been characterized in a panel of *in vitro* and *in vivo* studies.

In vitro, YL201 and YL201-mAb specifically bound to cell surface B7-H3. After binding, the high affinity complex was internalized into the cell, released cytotoxic YL0010014, induced cell cycle arrest at G2/M or S stage and induced apoptosis in various tumor cells, subsequently suppressed cancer cell proliferation. YL201 imparted cytotoxic activity to target cells via ADC internalization of the tumor cell, whereas YL201-mAb had no contribution on the bioactivity of YL201 except selectively targeting the cognate B7-H3 receptor.

In vivo anti-tumor efficacy was determined in various human cancer xenograft models in the immune-deficient mice. The results indicated that YL201 was well tolerated, and YL201 suppressed pre-existing tumor growth in a dose-dependent manner in various cancer cells or patient derived (solid tumor) xenograft models, including non-small cell lung cancer, castration-resistant prostate cancer, esophageal squamous cell carcinoma and colorectal carcinoma. Following administration of YL201 in tumor-bearing mice, pharmacokinetic (PK)/pharmacodynamic (PD) results suggested that YL201 was stable in the circulation, and the cytotoxic payload YL0010014 was mainly detected in the tumor tissues in a YL201 dose-dependent manner.

In safety pharmacology studies, instead of using the payload YL0010014 which is not soluble itself, the prodrug YL0010033, which is rapidly converted to YL0010014, was used. YL0010014 did not show any effects on central nervous system and respiratory system in rat at a single dose of 1.5 mg/kg prodrug. YL201 did not have any significant effects on blood pressure, heart rate, electrocardiogram (ECG) parameters or body temperature in conscious and unrestrained telemetered male cynomolgus monkeys following a single dose of 15 mg/kg.

The toxic payload YL0010014 has moderate toxicity. By design, it aims to limit potential damage to normal tissue expressing low-level B7-H3. The *in vitro* half maximal effective concentration (EC₅₀) of cell proliferation was about 1.1-61.6 nM and the safe tolerated dose (STD10) was 4.25 mg/kg for YL0010014 when treated weekly, for a total of 5 doses in rat.

Overall, YL0010014 was well tolerated by animals in *in vivo* efficacy studies as well as in safety pharmacology studies.

1.2.2 Pharmacokinetic Studies

Pharmacokinetics of YL201-ADC (all the form of YL201 with a drug-to-antibody ratio [DAR] $\geq$ 1), YL201-total antibody (TA_b) (all the form of YL201 with a DAR $\geq$ 0) and YL0010014 were

evaluated following a single- or repeat- intravenous (i.v.) injection of YL201 in cynomolgus monkeys.

Following a single i.v. injection of YL201 at 0.5, 2, and 6 mg/kg in monkeys, there was no test article-related clinical signs and no significant sex difference were observed in all groups during the study. The systemic exposure area under the curve from time 0 to infinity (AUC_{inf}) (152, 1130, and 6940 h· μ g/mL) increased in a greater than dose-proportional (0.5, 2, and 6 mg/kg) manner. The clearance (CL) decreased from 3.64 mL/h/kg to 0.939 mL/h/kg with the dose ranged from 0.5 mg/kg to 6 mg/kg. The half-life ($T_{1/2}$) and mean residence time from time 0 to the last measurable concentration (MRT_{last}) were longer at 6 mg/kg ($T_{1/2}$: 153 h; MRT_{last} : 57.7 h) than at 0.5 and 2 mg/kg ($T_{1/2}$: 122 and 138 h; MRT_{last} : 28.9 h and 30.4 h).

The PK parameters of YL201-TAb were similar to that of YL201-ADC, indicating the relative stability of YL201 in systemic circulation following administration of YL201 in monkey. Positive anti-B7-H3 mAb ADA was detected in 15/18 (83.3%) of monkeys.

In the repeat i.v. injection in cynomolgus monkey study (accomplished with repeated-dose toxicity study), 10 monkeys (5/sex) received 2 mg/kg of YL201 via i.v. infusion over 30 min once every 3 weeks (Q3W) for 3 doses in 6 weeks. After repeat i.v. injection, no sex differences in the area under the curve from zero to the last time point (AUC_{last}) of ADC (YL201-ADC), total antibody (YL201-TAb), and YL0010014 (toxin of YL201) were observed after the first dose in all YL201 treated groups or the last dose in 10 and 15 mg/kg groups. In addition, no marked accumulation of YL201-ADC and YL201-TAb was noticed after repeated doses of YL201 at 10 and 15 mg/kg, and no marked accumulation of YL0010014 was noticed after all repeated doses.

ADAs were generated in monkey serum after several administrations, which caused significant reduction in the exposure for YL201-ADC and YL201-TAb in 2 mg/kg group. Therefore, it was impossible to accurately determine the relationship between exposure ratio and dose ratio, sex difference and accumulation in this group. ADA was detected in 7/10 monkeys. Systemic exposure accumulation could not be estimated due to ADA formation.

Elimination of YL201 was studied in rats. Following a single intravenous dose of [^{3} H-YL0010014] YL201 at 4 mg/200 μ Ci/kg in Sprague-Dawley rats, 82.83% of the total administered dose was recovered during 0-840 h post-dose period from rats, with 49.87% in feces, 14.14% in urine, 1.83% in cage rinse/wash, and 16.99% in the carcass. The YL0010014-derived radioactivity was slowly excreted via urine and feces. Approximately 92.68% of the administered dose was recovered from BDC rats within 0 - 72 h, with 9.98% in bile, 6.11% in urine, 3.54% in feces, and 0.63% in cage rinse/wash, indicating that excretion from feces via bile was the main excretion route for [^{3} H-YL0010014] YL201.

1.2.3 Toxicological Studies

Selection of the cynomolgus monkey for toxicology evaluation was based on the results of B7-H3 binding potency and tissue cross-reactivity. Similar binding affinity of YL201 to human and monkey B7-H3, whereas no binding affinity of YL201 to mouse or rat B7-H3 was observed. The tissue cross-reactivity patterns of YL201 in human and monkey were generally similar. With the similar binding affinity and potency of YL201 against human and monkey B7-H3, monkey was

selected as the appropriate model for the assessment of YL201 toxicity. Rats were selected to evaluate toxicity profile of the toxin (YL0010014).

The single-dose toxicity of YL201 was addressed by the first dose of a 6-week repeat dose study in monkeys to evaluate the potential toxicity. The maximum tolerated dose (MTD) was considered to be 15 mg/kg for YL201 in this study.

In the 6-week repeat-dose i.v. toxicity study with YL201 in cynomolgus monkeys with a 4-week recovery period, animals were administered either vehicle control (0.9% NaCl injection) or YL201 (ADC: 2, 10, or 15 mg/kg) by i.v. infusion Q3W, for a total of 3 doses. The presence of the anti-YL201 antibody was detected in 10/10, 7/10, and 2/10 animals after i.v. injection at 2, 10, 15 mg/kg of YL201 in monkeys. The presence of ADA was detected on Day 22 during the second dosing period. No test article-related mortality or moribundity were noted in all treated groups.

Test article-related changes in body weight were noted in the 10 mg/kg and 15 mg/kg groups. Body weight loss or decreased body weight gains were noted in animals from Day 10. The body weight loss was partially recovered in 10 mg/kg group at the end of the recovery period.

There were no test article-related findings in food consumption, serum chemistry ophthalmology examinations, safety pharmacology (ECG, blood pressure, heart rate, and respiration examinations), immunology, or urinalysis.

Decreases in white blood cell count (WBC) (neutrophil count [NEU] and lymphocyte count [LYM]), red blood cell count (RBC), haemoglobin (Hb), and haematocrit (HCT) were observed in both male and female animals at 10 mg/kg and 15 mg/kg of YL201. Test article-related histopathological changes were found in ovary, thymus, spleen, lymph nodes (axilla, neck, groin, mesentery), site of administration and skin. Changes in 15 mg/kg group were noted in skin (mild to moderate hyperpigmentation), ovary (severe reduction of ovarian follicles), thymus (mild to moderate reduction of lymphocyte), spleen (mild to moderate reduction of white pulp lymphocyte), lymph nodes (mild to moderate reduction of secondary follicles). The above changes were also noted in the 2 mg/kg and/or 10 mg/kg groups with lower incidence or severity. All of these histopathological lesions were not observed at the end of recovery period, except the lesions in skin and ovary (partially recovered).

Tissue cross reactivity was tested in human and cynomolgus monkey tissues. Biotin-YL201 staining was observed in normal fresh frozen human and cynomolgus monkey tissues.

The tissue expression pattern of B7-H3 observed in both human and monkey tissues, including bladder, breast, colon, fallopian tube, gastrointestinal tract, skin (human only), liver, lymph node, ovary, placenta, prostate, spleen, thymus, tonsil, testis, ureter, uterus (cervix with endometrium), was nearly identical.

In addition, YL0010014 was clastogenic in an *in vitro* Chinese hamster lung chromosomal aberration assay. However, neither mutagenicity in an *in vitro* bacterial reverse mutation assay nor clastogenicity in an *in vivo* rat bone marrow micronucleus assay was observed. No significant cytokine release was observed for YL201 exposed in peripheral blood mononuclear cell (PBMC) up to 72 h, indicating the low risk of systemic inflammatory response *in vivo*.

1.2.4 Metabolic Information

Stability and metabolic profile of YL0010014 was examined separately and intensively, including liver cell/microsomal stability and metabolites identification both in hepatocytes of 5 species and *in vivo* following i.v. injection in tumor-bearing mice and SD rats. Potential drug-drug interaction caused by YL0010014 was studied in a panel of *in vitro* studies including cytochrome P450 enzymes induction, inhibition, and time dependent interaction (TDI). In cytochrome P450 inhibition study, the IC₅₀ of YL0010014 was greater than 3 μM, YL0010014 resulted in no inhibition of CYP enzyme at concentrations below 3 μM and had no time-dependence inhibition of CYP. YL0010014 was not an inducer of CYP1A2, CYP2B6 and CYP3A4.

1.3 Overview of Clinical Studies

1.3.1 Clinical Studies of YL201

YL201 was investigated in an open-label, multicenter, Phase 1 dose-escalation clinical study in patients with advanced solid tumors to evaluate its safety, tolerability, pharmacokinetics, and efficacy in China and the United States. The study number is YL201-INT-101-01.

As of the data cutoff date of October 16, 2023, a total of 49 subjects (receiving a dose of 0.8-3.0 mg/kg) were enrolled, including 19 with non-small cell lung cancer (NSCLC), 12 with small cell lung cancer (SCLC), 7 with nasopharyngeal carcinoma (NPC), 2 with metastatic castration-resistant prostate cancer (mCRPC), and 9 with other solid tumors. Efficacy data showed that among the 40 efficacy-evaluable subjects, 32 (80%) had varying degrees of tumor shrinkage, of whom 16 achieved objective response, with an objective response rate (ORR) of 40%; safety data showed that the most common treatment-emergent adverse events (TEAEs) (incidence ≥15% in all subjects, regardless of severity and causality) included: nausea (59.2%), white blood cell count decreased (53.1%), anaemia (49.0%), neutrophil count decreased (46.9%), vomiting (44.9%), decreased appetite (42.9%), weight decreased (38.8%), fatigue (36.7%), lymphocyte count decreased (36.7%), platelet count decreased (32.7%), alopecia (26.5%), rash (22.4%), diarrhoea (20.4%), hypokalaemia (20.4%), constipation (16.3%) and hyponatraemia (16.3%); among them, common (incidence > 5% in all patients) National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥ 3 TEAEs included: neutrophil count decreased (28.6%), anaemia (26.5%), white blood cell count decreased (26.5%), lymphocyte count decreased (26.5%), platelet count decreased (14.3%), hypokalaemia (8.2%), and PD (6.1%). No interstitial lung disease (ILD) occurred in all subjects; infusion related reaction (IRR) was observed in 3 subjects, all with CTCAE Grade ≤ 2.

1.3.2 Clinical Studies of Similar Products

MGC018 developed by MacroGenics and DS-7300 developed by Daiichi Sankyo are the two most advanced ADC drugs targeting B7-H3, and their published results are as follows:

MGC018

At the 2021 American Society of Clinical Oncology (ASCO) and the 2021 European Society for Medical Oncology (ESMO), MacroGenics announced the preliminary results of a Phase 1/2 dose-escalation and cohort-expansion study (NCT03729596) of MGC018 in patients with advanced solid tumors ^{[15]-[16]}, showing preliminary anti-tumor activity.

Efficacy: In the dose-escalation study, the RP2D was 3 mg/kg, IV, Q3W. Three melanoma patients had target lesion shrinkage of 24%, 28%, and 36%, respectively (confirmed partial response [cPR], currently treated for 6 months); preliminary data from the mCRPC expansion cohort showed that 11 of 22 patients had a $\geq 50\%$ decrease in PSA level, and 7 of 13 patients with evaluable lesions underwent their first 9-week imaging assessment, of whom 4 had target lesion shrinkage of 13%, 21%, 27%, and 35%, respectively (unconfirmed partial response [uPR]). In the cohort expansion study, a total of 32 treated patients underwent their first 9-week imaging assessment and were evaluable for tumor response (16 mCRPC and 16 NSCLC), with 8 (25%) having a $>30\%$ reduction in target lesion size from baseline (PR), including 4 mCRPC patients (2 cPR and 2 uPR) and 4 NSCLC patients (4 uPR), and one additional NSCLC patient had a 30% reduction in target lesion size, but non-target lesions were not evaluable due to bronchial obstruction, making the overall response not evaluable. The best overall response rates (BOR) were 25% (4/16) in both the mCRPC and NSCLC cohorts.

Safety: 83/86 (96.5%) patients in the cohort expansion experienced at least 1 TEAE, of which 78 (90.7%) were treatment-related; 29 (33.7%) patients experienced at least 1 serious adverse event (SAE), of which 24 were treatment-related. The most common treatment-related adverse events (TRAEs) (incidence $\geq 20\%$) were fatigue (37%), neutropenia (34%), palmar-plantar erythrodysesthesia syndrome (31%), pleural effusion (23%), nausea (22%) and asthenia (20%), with no febrile neutropenia reported. Serious TRAEs that occurred in at least 2 subjects included pyrexia (4%), pleural effusion (4%), dyspnea (2%), anemia (2%), and thrombocytopenia (2%).

Additionally, two clinical studies of MGC018 are ongoing: a Phase 1 study of MGC018 in combination with lorigerlimab (MGD019, a PD-1 $\times$ CTLA-4 bispecific antibody) in patients with advanced solid tumors (NCT05293496) and a Phase 2 study comparing two dose levels of MGC018 in patients with mCRPC (NCT05551117).

DS-7300

As of June 30, 2022, a total of 147 patients had been enrolled in the Phase 1/2 dose-escalation and dose-expansion study (NCT04145622) ^[17] of DS-7300 in patients with advanced solid tumors (receiving a therapeutic dose of 4.8 - 16.0 mg/kg), including SCLC (20 patients), mCRPC (73 patients), ESCC (26 patients), and squamous non-small cell lung cancer (sqNSCLC) (9 patients).

Efficacy: Among the 118 patients evaluable for efficacy, the overall tumor response rate was 32%, and the confirmed ORR was 28%. Notably, in the two subgroups of patients with advanced lung cancer, the ORRs for SCLC (n=19) and sqNSCLC (n=5) were 58% and 40%, respectively, with median DORs of 5.5 months and 4.3 months, respectively. The ORR was 33% and 23% in the mCRPC subgroup and the ESCC subgroup, respectively.

Safety: The most common TEAEs (incidence $\geq 10\%$) were nausea (63%), anaemia (33%), infusion related reaction (32%), decreased appetite (31%), fatigue (30%), vomiting (30%), diarrhoea (16%), pyrexia (16%), constipation (14%), chills (13%), and dehydration (11%). The most common Grade ≥ 3 TEAEs were anaemia (19%), neutropenia (4%), nausea (3%), pneumonia (3%), and neutrophil count decreased (3%). Drug-related ILD was determined in 7 patients, including 2 with Grade 1 and 4 with Grade 2 in the 12 mg/kg dose group and 1 with

Grade 5 in the 16 mg/kg dose group (this dose group has been discontinued), and 2 cases are pending.

In addition, a Phase 2 clinical study of DS-7300 in previously treated patients with ES-SCLC is ongoing (NCT05280470).

1.4 Risk-Benefit Assessment

Known Potential Risks

Results from the YL201 preclinical study showed that the toxic and effective payload YL0010014 has moderate toxicity. By design, it aims to limit potential damage to normal tissue expressing low-level B7-H3. In addition, YL201 may also produce ADA, leading to weight loss, decreased WBC (NEU and LYM), RBC, Hb, and HCT, and histopathological changes in the ovaries, thymus, spleen, lymph nodes (axillary, cervical, inguinal, mesenteric), administration site, and skin. YL0010014 was clastogenic in an *in vitro* Chinese hamster lung chromosomal aberration assay. However, neither mutagenicity in an *in vitro* bacterial reverse mutation assay nor clastogenicity in an *in vivo* rat bone marrow micronucleus assay was observed. No significant cytokine release was observed, suggesting a low risk of systemic inflammatory response to YL201 *in vivo*.

The results of the YL201 clinical study showed that the most common TEAEs (incidence $\geq 15\%$ in all patients, regardless of severity and causality) included: nausea (59.2%), white blood cell count decreased (53.1%), anaemia (49.0%), neutrophil count decreased (46.9%), vomiting (44.9%), decreased appetite (42.9%), weight decreased (38.8%), fatigue (36.7%), lymphocyte count decreased (36.7%), platelet count decreased (32.7%), alopecia (26.5%), rash (22.4%), diarrhoea (20.4%), hypokalaemia (20.4%), constipation (16.3%), and hyponatraemia (16.3%); among them, common (incidence $> 5\%$ in all patients) NCI CTCAE Grade ≥ 3 TEAEs included: neutrophil count decreased (28.6%), anaemia (26.5%), white blood cell count decreased (26.5%), lymphocyte count decreased (26.5%), platelet count decreased (14.3%), hypokalaemia (8.2%), and PD (6.1%). No ILD occurred in all subjects; IRR was observed in 3 subjects, all with CTCAE Grade ≤ 2 .

Among 86 patients with advanced solid tumors treated with the similar product MGC018, the most common TRAEs (incidence $\geq 20\%$) were fatigue (37%), neutropenia (34%), palmar-plantar erythrodysesthesia syndrome (31%), pleural effusion (23%), nausea (22%), and asthenia (20%), with no febrile neutropenia reported. Serious TRAEs that occurred in at least 2 subjects included pyrexia (4%), pleural effusion (4%), dyspnea (2%), anemia (2%), and thrombocytopenia (2%). The most common TEAEs (incidence $\geq 10\%$) in 147 patients with advanced solid tumors who received DS-7300 were nausea (63%), anaemia (33%), infusion related reaction (32%), decreased appetite (31%), fatigue (30%), vomiting (30%), diarrhoea (16%), pyrexia (16%), constipation (14%), chills (13%), and dehydration (11%).

Known Potential Benefits

The results of preclinical studies for YL201 showed that YL201 suppressed the pre-existing tumor growth in a dose-dependent manner in various cancer cells or patient-derived (solid tumor) xenograft models, including non-small cell lung cancer, castration-resistant prostate

cancer, esophageal squamous cell carcinoma, and colorectal carcinoma. The cytotoxic payload YL0010014 was mainly detected in tumor tissues in a YL201 dose-dependent manner.

The Phase 1 dose-escalation clinical study of YL201 showed preliminary efficacy in patients with various solid tumors, including NSCLC, NPC, SCLC, mCRPC, and other solid tumors. Of the 40 subjects evaluable for efficacy, 32 (80%) had varying degrees of tumor shrinkage, of whom 16 achieved objective response, with an ORR of 40%.

Among 32 patients treated with the similar product MGC018 at the RP2D, the BORs for the mCRPC and NSCLC cohorts were both 25% (4/16 patients). Among 118 evaluable patients treated with DS-7300, the ORRs for SCLC (n = 19) and sqNSCLC (n = 5) were 58% and 40%, respectively, with median DORs of 5.5 months and 4.3 months, respectively. The ORR was 33% and 23% in the mCRPC subgroup and the ESCC subgroup, respectively.

Assessment of Potential Risks and Benefits

In summary, preclinical and current clinical study data shows that YL201 monotherapy is generally safe and well-tolerated in the treatment of solid tumors and shows preliminary clinical benefits. Combined with the safety and efficacy results of similar B7-H3 ADC drugs in clinical studies, the benefits of this product for the treatment of patients with advanced solid tumors (NSCLC, SCLC, NPC, ESCC, mCRPC, and other solid tumors) outweigh the risks, which is sufficient to support the planned clinical studies.

2 Study Objectives and Endpoints

2.1 Study Objectives

Primary Objectives:

- To evaluate the safety and tolerability of YL201 in patients with selected advanced solid tumors
- To evaluate the efficacy of YL201 in patients with selected advanced solid tumors based on the objective response rate (ORR).

Secondary Objectives:

- To evaluate other efficacy endpoints of YL201 in patients with selected advanced solid tumors
- To evaluate the PK characteristics of YL201
- To evaluate the immunogenicity of YL201

Exploratory Objectives:

- To explore biomarkers associated with YL201 efficacy
- To explore the exposure-response (E-R) relationships for efficacy and safety endpoints of YL201

2.2 Study Endpoints

Primary Endpoints:

- Adverse events (AEs) as characterized by type, frequency, severity, time, and relationship to study treatment
- Laboratory test results, physical examination results, ECOG PS, vital signs, peripheral oxygen saturation (SpO₂), and electrocardiogram (ECG) parameters
- ORR assessed as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)

Secondary Endpoints:

- Depth of response (DpR), disease control rate (DCR), duration of response (DoR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) assessed as per RECIST v1.1
- Single- and multiple-dose PK parameters of YL201 (including ADC, total antibody (TAb), and unconjugated payload YL0010014), including but not limited to area under the curve (AUC), maximum concentration (C_{max}), trough concentration (C_{trough}), clearance (CL), volume of distribution (V_d), and half-life (t_{1/2})
- Metabolite profile of YL201
- Incidence of anti-YL201 antibodies

Exploratory Endpoints:

- Correlation between B7H3 expression level in tumor tissue and efficacy of YL201
- Correlation between the level of soluble B7H3 (sB7H3) in peripheral blood and efficacy of YL201
- Correlation between the efficacy and safety endpoints of YL201 and exposure

3 Study Design

3.1 Overall Design

This is a multi-center, open-label, Phase 1b study of YL201 conducted in China to evaluate the safety, efficacy, and PK characteristics of YL201 in patients with the following selected advanced solid tumors:

- Cohort A: Patients with locally advanced or metastatic NSCLC without actionable genomic alterations who have progressed or are intolerant during or after standard of care (including platinum-based chemotherapy and anti-programmed death receptor (ligand) 1 (anti-PD-(L)1) therapy)
- Cohort B: Patients with locally advanced or metastatic NSCLC with actionable genomic alterations who have progressed or are intolerant during or after standard of care (including targeted therapy for driver genes)
- Cohort C: Patients with extensive-stage SCLC who have progressed or are intolerant during or after standard of care (including platinum-based chemotherapy and anti-PD-(L)1 therapy)
- Cohort D: Patients with recurrent or metastatic NPC who have progressed or are intolerant during or after standard of care (including platinum-based chemotherapy and anti-PD-(L)1 therapy)
- Cohort E: Patients with locally advanced unresectable or metastatic ESCC who have progressed or are intolerant during or after standard of care (including platinum, fluorouracil, or taxane-based chemotherapy and anti-PD-(L)1 therapy)
- Cohort F: Patients with other solid tumors who have progressed or are intolerant during or after standard of care

Subjects in each cohort are not required to confirm the expression level of B7H3 in tumor tissues before enrollment, but they need to provide archived or fresh tumor samples. Subjects who are not able to provide tumor samples or have inadequate samples may be eligible on a case-by-case basis after discussion with the sponsor.

Based on the results of the YL201-INT-101-01 dose-escalation study, 2.0 mg/kg and 2.4 mg/kg will be selected as the recommended expansion dose (RED) of YL201. During the study, the sponsor and investigator will, based on the available data, decide whether and when to initiate or terminate a particular cohort or dose level, and whether to explore other dose levels or dosing regimens, based on a balance between subject risks and benefits.

Subjects will be treated with YL201 intravenous (IV) infusion at REDs once every 3 weeks (Q3W) as a treatment cycle. The number of treatment cycles is not fixed in this study. Subjects who can benefit from this study treatment may continue study treatment until PD, intolerable toxicity, or withdrawal of informed consent by subjects.

It is planned to enroll approximately 30-90 subjects in each cohort.

After the completion of study for each cohort, the recommended Phase 2 dose (RP2D) of YL201 in patients with selected advanced solid tumors will be determined based on the available safety, efficacy, and PK data.

3.2 Rationale for Study Design

YL201 was investigated in an open-label, multicenter, Phase 1b dose-escalation clinical study in patients with advanced solid tumors to evaluate its safety, tolerability, pharmacokinetics, and efficacy in China and the United States (Study No.: YL201-INT-101-01). Based on the currently accumulated data and under the guidance of the “Technical Guidelines for First-in-Human Dose Escalation and Expansion Studies of Anti-tumor Drugs” and the “Technical Guidelines for Clinical Research and Development of Antibody-drug Conjugates”, a Phase 1b clinical study is proposed to further evaluate the safety, efficacy, and pharmacokinetic characteristics of YL201 in patients with selected advanced solid tumors. The comprehensive data in multiple cohorts at REDs (2.0 mg/kg and 2.4 mg/kg), including safety, efficacy, PK characteristics, will be evaluated to provide data support for the design of future studies.

3.3 Rationale for Selected Doses

In the Phase 1 dose-escalation study of YL201, the safety, tolerability, and efficacy of YL201 were investigated at doses of 0.8 mg/kg, 1.6 mg/kg, 2.0 mg/kg, 2.4 mg/kg, 2.8 mg/kg, and 3.0 mg/kg. The results showed that the MTD of YL201 monotherapy was 2.8 mg/kg, Q3W. In addition, YL201 showed preliminary efficacy in patients with advanced solid tumors at doses of 1.6 mg/kg and above, with a total of 16 (40.0%) subjects achieving objective response after receiving YL201.

Based on the above data, this study intends to select 2.0 mg/kg and 2.4 mg/kg for the dose expansion study of YL201 to further evaluate the efficacy and safety of YL201.

3.4 Rationale for Selected Endpoints

This study is a dose-expansion Phase 1b study designed to further evaluate the safety, efficacy, and pharmacokinetic characteristics of YL201 in advanced solid tumors, to provide a reasonable basis for the design of dosing regimens for subsequent studies. Therefore, the primary endpoints are safety and tolerability, and ORR. The secondary endpoints are other efficacy endpoints, PK parameters, and immunogenicity characteristics. In addition, exploratory analyses will be conducted to investigate the expression level of biomarker B7H3 and its correlation with YL201 efficacy, as well as the correlation between YL201 efficacy and safety endpoints and exposure.

3.5 Randomization and Blinding

Not applicable in this study.

3.6 End of Study

The end of the study is defined as the last subject completes the last visit, withdraws informed consent, dies, discontinues from the study, or is lost to follow-up, whichever comes first.

4 Study Subjects

4.1 Inclusion Criteria

Subjects are eligible for the study if they meet all of the following inclusion criteria:

- 1) Have been informed of the study prior to initiation of the study and voluntarily sign and date the informed consent form (ICF).
- 2) Aged ≥ 18 to ≤ 75 years at the time of signing the ICF.
- 3) Subjects enrolled in Cohort A should meet the following criteria:
 - Have a histologically or cytologically confirmed diagnosis of NSCLC;
 - Have locally advanced (stage IIIB/IIIC) or metastatic (stage IV) disease (using the 8th edition of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) staging system) at study entry that is not amenable to radical surgery or radiotherapy;
 - For NSCLC with adenocarcinoma or mixed with adenocarcinoma components, there should be clear documentation showing no epidermal growth factor receptor (EGFR)-sensitizing mutations, no anaplastic lymphoma kinase (ALK) and C-Ros oncogene 1 (ROS1) fusions; for NSCLC with other pathological types such as squamous cell carcinoma, if the previous EGFR, ALK, and ROS1 gene status are unknown, corresponding testing is not required before enrollment.
 - Have received at least platinum-based chemotherapy and anti-PD-(L)1 therapy previously for locally advanced or metastatic disease, and have disease progression or are intolerant during or after treatment.

Subjects enrolled in Cohort B should meet the following criteria:

- Have a histologically or cytologically confirmed diagnosis of NSCLC;
- Have locally advanced (stage IIIB/IIIC) or metastatic (stage IV) disease (using the 8th edition of the UICC and the AJCC staging system) at study entry that is not amenable to radical surgery or radiotherapy;
- Have clear documentation of EGFR-sensitizing mutations, ALK fusions, or ROS1 fusions, or known positive for other actionable genomic alterations for which targeted therapy is already marketed in China;
- Have received at least corresponding targeted therapy previously for locally advanced or metastatic disease, and have disease progression or are intolerant during or after treatment.

Subjects enrolled in Cohort C should meet the following criteria:

- Have a histologically or cytologically confirmed diagnosis of SCLC. Combined SCLC is not eligible for this study.

- Have extensive-stage disease at study entry (using a combination of the Veterans Administration Lung Study Group (VALG) and the 8th edition of the AJCC TNM staging system. Extensive stage: AJCC 8th edition stage IV [any T, any N, M1a/b/c], or T3-4 that cannot be encompassed in a tolerable radiotherapy plan because of multiple pulmonary nodules or excessive tumor/nodule volume);
- Have received at least platinum-based chemotherapy and anti-PD-(L)1 therapy previously for extensive-stage SCLC, and have disease progression or are intolerant during or after treatment.

Subjects enrolled in Cohort D should meet the following criteria:

- Have a histologically or cytologically confirmed diagnosis of NPC;
- Have metastatic (stage IVB, using the 8th edition of the UICC and AJCC staging system) or recurrent disease that is not amenable to local or radical treatment at study entry;
- Have received at least platinum-based chemotherapy and anti-PD-(L)1 therapy previously for metastatic or recurrent disease, and have disease progression or are intolerant during or after treatment.

Subjects enrolled in Cohort E should meet the following criteria:

- Have a histologically or cytologically confirmed diagnosis of ESCC;
- Have locally advanced unresectable or metastatic disease at study entry. Subjects with direct invasion of adjacent organs (such as the aorta or trachea) (T4b disease) should be carefully evaluated before enrollment, and those at higher risk as deemed by the investigator should not be enrolled in this study;
- Have received at least platinum, fluorouracil, or taxane-based chemotherapy and anti-PD-(L)1 therapy previously for locally advanced or metastatic disease, and have disease progression or are intolerant during or after treatment.

Subjects enrolled in Cohort F should meet the following criteria:

- Have a histologically or cytologically confirmed diagnosis of advanced solid tumors (except SCLC, NSCLC, NPC, and ESCC);
- Have disease progression or are intolerant during or after prior standard of care, or no available standard treatment options.

Note: For all cohorts, if the subject has disease progression during or within 6 months after prior neoadjuvant therapy, adjuvant therapy, or radical radiochemotherapy, this regimen will be considered as first-line therapy for advanced/metastatic diseases.

- 4) At least one measurable extracranial lesion according to RECIST v1.1. Lesions previously treated with radiotherapy or other local therapies are not considered as target lesions unless there is clear evidence of progression.

- 5) Able to provide archived or fresh tumor samples. Subjects who are not able to provide tumor samples or have inadequate samples may be eligible on a case-by-case basis after discussion with the sponsor.
- 6) Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1.
- 7) Adequate organ and marrow function as defined below within 7 days prior to the first dose:
 - Haemoglobin (Hb) ≥ 9.0 g/dL (have not received blood transfusion or erythropoietin treatment within 14 days before the first dose)
 - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L (have not received granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor treatment within 14 days before the first dose);
 - Platelet count (PLT) $\geq 100 \times 10^9$ /L (have not received platelet transfusion, thrombopoietin, or interleukin-11 treatment within 14 days before the first dose);
 - Total bilirubin (TBIL) $\leq 1.5 \times$ upper limit of normal (ULN) in the absence of obvious metastases to liver, or $\leq 3 \times$ ULN in the presence of metastases to liver;
 - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3 \times$ ULN in the absence of obvious metastases to liver, or $\leq 5 \times$ ULN in the presence of metastases to liver;
 - Serum albumin ≥ 2.5 g/dL;
 - Creatinine clearance ≥ 50 mL/min (calculated according to Cockcroft-Gault formula);
 - Activated partial thromboplastin time (APTT) and international normalized ratio (INR) $\leq 1.5 \times$ ULN, except for subjects receiving anticoagulant therapy, who should have a stable anticoagulant therapy regimen and whose APTT and INR must be within a therapeutic range as deemed appropriate by the investigator.
- 8) Female subjects of childbearing potential must agree to use highly effective contraceptive measures from the time of screening throughout the study period and for at least 6 months after the last dose of study drug. Male subjects must agree to use highly effective contraceptive measures from the time of screening and throughout the study period and for at least 6 months after the last dose of study drug.
- 9) Life expectancy of ≥ 3 months.
- 10) Able and willing to comply with protocol visits and procedures.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

- 1) Prior treatment with an agent targeting B7H3 (including antibody, antibody-drug conjugate (ADC), chimeric antigen receptor T cell [CAR-T], and other drugs);

- 2) Prior treatment with a topoisomerase I inhibitor or an ADC consisting of a topoisomerase I inhibitor.
- 3) Concurrent enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study.
- 4) Inadequate washout period for prior anti-tumor treatment before the first dose of study drug, defined as follows:
 - Chemotherapy or small molecule targeted therapy < 2 weeks or 5 half-lives, whichever is shorter;
 - Antibody therapy < 3 weeks;
 - Hormone therapy < 3 weeks;
 - Treatment with Chinese herbal medicine with anti-tumor indications < 2 weeks;
 - Brain radiotherapy < 2 weeks;
 - Palliative radiation < 2 weeks, and radical radiotherapy < 4 weeks.
- 5) Undergone major surgery (not including diagnostic surgery) within 4 weeks before the first dose of study drug or intend to undergo major surgery during the study.
- 6) Prior allogeneic bone marrow transplantation or solid-organ transplantation.
- 7) Received systemic steroids (> 10 mg/day of prednisone or its equivalent) or other immunosuppressive therapy within 2 weeks before the first dose of study drug, except for:
 - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection)
 - Systemic steroids at physiological doses as replacement therapy (e.g., physiological corticosteroid replacement therapy for adrenal or pituitary insufficiency)
 - Steroids as preventive medication for hypersensitivity reactions (e.g., to CT contrast media) or chemotherapy-induced nausea and vomiting (CINV).
- 8) Received any live vaccine within 4 weeks before the first dose of study drug or intend to receive a live vaccine during the study.
- 9) A history of metastases to meninges or carcinomatous meningitis.
- 10) Brain metastasis or spinal cord compression, except for:
 - Asymptomatic brain metastasis subjects who do not require immediate local or systemic treatment (such as mannitol or corticosteroids) are allowed to be enrolled;
 - If the subject's brain metastasis is treated and stable (defined as that brain imaging at least 4 weeks prior to the first dose shows that the lesion is stable, there is no evidence of new neurological symptoms, and immediate local or systemic therapy

is not required within 2 weeks prior to the first dose) and there is no evidence of new or original brain metastasis enlargement, enrollment is allowed.

- 11) Uncontrolled or clinically significant cardiovascular disorders, including but not limited to:
 - Medical history of symptomatic congestive cardiac failure (New York Heart Association (NYHA) class II to IV) or any arterial thromboembolic event (e.g., myocardial infarction, unstable angina, cerebrovascular accident, and transient ischaemic attack) within 6 months before the first dose;
 - Uncontrolled hypertension, defined as systolic blood pressure (SBP) > 160 mm Hg and/or diastolic blood pressure (DBP) > 100 mm Hg after antihypertensive therapy;
 - Serious arrhythmia requiring treatment;
 - Corrected QT interval by Fridericia's formula (QTcF) prolongation to > 450 ms (for males) or 470 ms (for females).
- 12) Clinically significant concomitant lung disorders, including but not limited to:
 - A history of (noninfectious) interstitial lung disease (ILD)/pneumonitis that requires steroids, or currently having ILD/pneumonitis;
 - Pulmonary embolism occurring within 3 months prior to the first dose;
 - Any autoimmune, connective tissue, or inflammatory disorder (e.g., rheumatoid arthritis, Sjögren's syndrome, sarcoidosis) where there is documented or suspicion of pulmonary involvement at screening;
 - Prior pneumonectomy;
 - Other moderate to severe lung disorders that may interfere with the detection or management of drug-related pulmonary toxicity and seriously affect respiratory function.
- 13) Have a diagnosis of Gilbert's syndrome.
- 14) Uncontrolled third-space fluid (e.g., pleural effusions, ascites, pericardial effusions) that requires repeated drainage.
- 15) A history of gastrointestinal perforation and/or fistula within 6 months prior to first dose, or active gastric and duodenal ulcers, ulcerative colitis, or other gastrointestinal conditions that may cause haemorrhage or perforation at the investigator's discretion.
- 16) Subjects with serious infections (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade $\geq$ 3) within 4 weeks prior to the first dose, such as severe pneumonia requiring hospitalization, bacteraemia, or complicated infections, or active infections requiring systemic therapy within 2 weeks prior to the first dose. Subjects receiving prophylactic anti-infective therapy (e.g., for the prevention of urinary tract infection or chronic obstructive pulmonary disease exacerbation) may be eligible for enrollment after discussion with the sponsor.

- 17) Known human immunodeficiency virus (HIV) infection.
- 18) Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Active HBV infection is defined as hepatitis B core antibody (HBcAb) or hepatitis B surface antigen (HBsAg) positive, and HBV deoxyribonucleic acid (DNA) level >200 IU/mL or 1000 copies/mL. Those with HBV infection should receive antiviral treatment according to local treatment guidelines and be willing to receive antiviral treatment throughout the study. Active HCV infection is defined as hepatitis C antibody positive and HCV ribonucleic acid (RNA) level above ULN at the study site.
- 19) Any other primary malignancy within 3 years before the first dose of study drug, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, or other curatively treated solid tumors.
- 20) Unresolved toxicities from previous anti-tumor therapy, defined as toxicities (other than alopecia and pigmentation) not yet resolved to NCI CTCAE Grade ≤ 1 or to the levels specified in the inclusion/exclusion criteria. Subjects with chronic Grade 2 toxicities may be eligible for enrollment after discussion with the sponsor if asymptomatic or adequately controlled with stable medication.
- 21) A history of severe hypersensitivity reactions to the drug substances, inactive ingredients in the drug product, or other monoclonal antibodies.
- 22) Women who are breastfeeding or pregnant as confirmed by pregnancy tests performed within 3 days before the first dose.
- 23) Any illness, medical condition, organ system dysfunction, or social situation, including but not limited to mental illness or alcohol abuse, deemed by the investigator to be likely to interfere with a subject's ability to sign ICF, adversely affect the subject's ability to cooperate and participate in the study, or compromise the interpretation of study results.

4.3 Screening Failure

Subjects are required to sign the informed consent form before undergoing any study-related procedures and then enter the screening period. During this period, the eligibility of the subjects will be reviewed, and various examinations, including imaging and laboratory tests, will be completed. Before a subject is confirmed as a screening failure, the laboratory assessments that determine the subject's eligibility can be repeated once during the screening period. Subjects who fail screening may be re-screened once at the discretion of the investigator. Screening numbers cannot be reused. Each subject entering the study will be assigned a unique screening number during the screening period. If the subject fails the screening, the screening number will be invalidated. If the subject re-participates in the screening of this study, a new screening number needs to be assigned.

5 Study Drug

5.1 Information of Investigational Product

Name	YL201 for Injection
Strength	200 mg/vial
Storage Conditions	2-8°C
Supplier	MediLink Therapeutics (Suzhou) Co., Ltd.

5.2 Treatment with Investigational Product

5.2.1 Dosing Regimen

2.0 mg/kg, or 2.4 mg/kg, intravenous infusion, Q3W as a treatment cycle. The number of treatment cycles is not fixed in this study. Subjects who can benefit from this study treatment may continue study treatment until PD, intolerable toxicity, or withdrawal of informed consent by subjects.

Each vial of YL201 should be reconstituted to 25 mg/mL before use. The total amount and volume of drug required should be determined based on the subject's body weight and dose, and then the required volume of YL201 should be drawn for dilution to ensure a final drug concentration of 0.2-5.0 mg/mL for administration. The body weight of the subject prior to the first dose will be used to calculate the initial dose. If the subject's weight changes by more than 10% of baseline weight during treatment, the subject's dose will be recalculated based on the subject's updated weight.

YL201 will be administered via IV infusion, Q3W. The duration of IV infusion for each subject will be 60±10 minutes.

5.2.2 Dose Modification Scheme

Dose modification and interruption are allowed during the study. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed (graded according to NCI CTCAE version 5.0).

The specific criteria for dose adjustment and interruption of YL201 are shown in Table 5. These criteria provide guidance for clinical judgment, and the investigator can also adjust it based on the actual situation of the subject during the study.

If the next cycle of administration is delayed due to a continuous pause in treatment, the date of resumption of treatment will be counted as Day 1 of the next cycle. Resumption of administration for the next cycle can only be delayed by a maximum of 28 days. Therefore, unless discussed and agreed with the sponsor, the subject should discontinue treatment.

If the subject still cannot tolerate the treatment after the investigator adjusts the dose, the investigator needs to determine whether the subject is suitable to continue receiving the investigational product.

Table 5 Dose Modification Principles

Worst Toxicity (NCI CTCAE version 5.0)	Management Guideline for YL201
Grades 1 or 2 toxicity, unless otherwise specified	Maintain dose and schedule
Infusion related reaction	
Grade 1 Transient and mild reactions; no infusion interruption required; no treatment required	- If infusion related reaction is observed during administration, the infusion speed should be reduced by 50% and patient should be closely monitored. - If no other reactions appear, the subsequent infusion speed could be resumed at the initial planned speed.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	- Administration of YL201 should be interrupted briefly. - If the event resolves or improves to Grade ≤ 1, infusion can be restarted at a 50% reduced infusion speed. - Subsequent administrations should be conducted at the reduced speed.
Grade 3 Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Administration of YL201 should be discontinued immediately and permanently.
Grade 4 Life-threatening consequences; urgent intervention indicated.	Administration of YL201 should be discontinued immediately and permanently.
Hematologic toxicity	
Neutrophil count decreased	
Grade 3 ($< 1.0 \times 10^9/L$ to $0.5 \times 10^9/L$)	Delay dose until resolved to Grade ≤ 2 , then maintain dose
Grade 4 ($< 0.5 \times 10^9/L$)	Delay dose until resolved to Grade ≤ 2 , then reduce dose by 1 level
Febrile neutropenia (ANC $< 1.0 \times 10^9/L$, with pyrexia $> 38.3^\circ C$ or a sustained body temperature of $\geq 38^\circ C$ for more than 1 hour)	Delay dose until resolved, then reduce dose by 1 level
Lymphocyte count decreased	
Grade 1 to Grade 3 lymphopenia	No dose modification
Grade 4 ($< 0.2 \times 10^9/L$)	Delay dose until resolved to Grade ≤ 2 , then: - If resolved in ≤ 14 days from day of onset, maintain dose - If resolved in > 14 days from day of onset, reduce dose by 1 level
Anemia	
Grade 3 (hemoglobin < 8.0 g/dL) Transfusion indicated	Delay dose until resolved to Grade ≤ 2 , then maintain dose
Grade 4 Life-threatening consequences; urgent intervention indicated.	Delay dose until resolved to Grade ≤ 2 , then reduce dose by 1 level
Platelet count decreased	
Grade 3 (platelet count $< 50 \times 10^9/L$ to $25 \times 10^9/L$)	Delay dose until resolved to Grade ≤ 1 , then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level

Worst Toxicity (NCI CTCAE version 5.0)	Management Guideline for YL201
Grade 4 (platelet count < 25×10 ⁹ /L)	Delay dose until resolved to Grade ≤ 1, then reduce dose by 1 level
Pulmonary toxicity	
ILD/pneumonitis	
Grade 3	Delay dose until resolved to Grade ≤ 1, then: - If resolved in ≤ 28 days from day of onset, maintain dose - If resolved in > 28 days from day of onset, reduce dose by 1 level
Grade 4	Permanently discontinue patient from study treatment
Hepatotoxicity	
ALT or AST concurrent with TBIL increased	
ALT or AST > 3.0 × ULN, concurrent with TBIL > 2.0 × ULN	Delay study medication until drug-induced liver injury can be ruled out. If drug-induced liver injury is ruled out, the patient should be treated accordingly, and resumption of study drug may occur after discussion between the investigator and the sponsor. If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment.
ALT or AST increased	
Grade 3 (> 5.0 to 20.0 × ULN, for patients without metastases to liver and patients with metastases to liver with baseline levels ≤ 3 × ULN)	Repeat testing within 3 days. Delay dose until resolved to Grade ≤ 1 if baseline ≤ 3 × ULN; otherwise, delay dose until resolved to ≤ baseline level, then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level
Grade 3 (> 8.0 to 20.0 × ULN, for patients with metastases to liver with baseline levels >3 × ULN)	Repeat testing within 3 days. Delay dose until resolved to ≤ baseline level, then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level
Grade 4 (> 20.0 × ULN)	Permanently discontinue patient from study treatment
TBIL increased	
Grade 2 (> 1.5 to 3.0 × ULN)	If no liver lesions at baseline, delay dose until resolved to Grade ≤ 1, then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level If documented liver lesions at baseline, continue study treatment.
Grade 3 (> 3.0 to 10.0 × ULN)	If no liver lesions at baseline, repeat testing within 3 days. Delay dose until resolved to Grade ≤ 1, then: - If resolved in ≤ 7 days from day of onset, reduce dose by 1 level - If resolved in > 7 days from day of onset, discontinue YL201 If liver lesions at baseline, repeat testing within 3 days. Delay dose until resolved to Grade ≤ 2, then: - If resolved in ≤ 7 days from day of onset, reduce dose by 1 level - If resolved in > 7 days from day of onset, discontinue YL201
Grade 4 (> 10.0 × ULN)	Permanently discontinue patient from study treatment
Gastrointestinal toxicity	

Worst Toxicity (NCI CTCAE version 5.0)	Management Guideline for YL201
Nausea	
Grade 3	Delay dose until resolved to Grade ≤ 1 , then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level
Diarrhea/colitis	
Grade 3	Delay dose until resolved to Grade ≤ 1 , then: - If resolved in ≤ 3 days from day of onset, maintain dose - If resolved in > 3 days from day of onset, reduce dose by 1 level
Grade 4	Permanently discontinue patient from study treatment
Other laboratory adverse events with signs or symptoms	
Grade 3	Delay dose until resolved to Grade ≤ 1 or baseline level, then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level
Grade 4	Permanently discontinue patient from study treatment
Other non-laboratory adverse events, excluding alopecia	
Grade 3	Delay dose until resolved to Grade ≤ 1 or baseline level, then: - If resolved in ≤ 7 days from day of onset, maintain dose - If resolved in > 7 days from day of onset, reduce dose by 1 level
Grade 4	Permanently discontinue patient from study treatment

The dose reduction scheme is shown in Table 6. During the study, the investigator will decide the number of dose reductions based on the subject's actual situation. If the subject is still unable to tolerate the treatment and it is assessed that the dose cannot be further reduced, the study treatment should be discontinued.

Table 6 Dose Reduction Scheme

Current Dose (mg/kg, Q3W)	First Dose Reduction (mg/kg, Q3W)	Second Dose Reduction (mg/kg, Q3W)	Third Dose Reduction (mg/kg, Q3W)
2.4	2.0	1.6	/
2.0	1.6	/	/

5.3 Drug Management

5.3.1 Packaging and Labeling of Drugs

The sponsor will package and label the investigational product.

The label content includes: drug name, drug number, packaging strength, dosage and administration, production batch number, expiration date, storage requirements, manufacturer, drug supplier, precautions, etc., and marked "For clinical study use only".

5.3.2 Transportation, Storage and Distribution of Study drug

The sponsor shall establish procedures for the supply and management of study drug, including receipt, storage, dispensing, use and retrieval of study drug. The study drug will be uniformly

distributed by the sponsor, and a dedicated person will deliver the study drug directly to the study site. The study site should establish sound procedures for receiving the study drug, and a dedicated person is required to receive the study drug and sign the drug receipt form.

The study site should establish a strict drug management system with dedicated personnel (dedicated personnel, dedicated cabinets, locked storage) in accordance with the management procedures to be responsible for the storage and distribution of the study drug, and establish a registration system (recording content includes date, quantity, batch number/serial number, expiration date, assigned code, signature, etc.). The study site should ensure that the storage environment conditions (temperature, light, humidity, etc.) of the study drug meet the regulations, and record and save them. If it is found that the storage conditions exceed the specified range, the sponsor should be contacted immediately.

The study drug manager at the study site will distribute the study drug to the study nurse based on the subject's grouping information, and the study nurse will administer the study drug to the subject. The dispensing and retrieval of each dose should be recorded in the special record sheet in a timely manner.

After use, put the empty vial back into the study drug box, and count the study drug before and after daily administration. If the study drug is lost, scattered, or misused, detailed records should be made. After the study, all study drugs delivered to the investigator (including all unused, partially used study drugs and all returned empty drug vials, together with the complete and signed drug return record form) should be returned to the sponsor, and the sponsor will recycle and destroy them (or destroy them by the clinical institution after being authorized by the sponsor), and they are not allowed to flow into the market.

5.4 Concomitant Treatments

All concomitant drug therapy/non-drug therapy used during the study should be recorded in detail on the Concomitant Drug Therapy/Non-drug Therapy page of the electronic Case Report Form (eCRF), including the reason for drug use/therapy, the method of administration/therapy, and the start and end dates.

5.4.1 Permitted Concomitant Treatments

Concomitant therapy is permitted in this study, except for those expected to interfere with the evaluation of the study treatment (or interact with it). Drugs or therapies allowed during the study are as follows:

1. Symptomatic treatment or treatment for complications or AEs (including blood products, infusion, transfusion, granulocyte colony-stimulating factor, erythropoietin, thrombopoietin, analgesics, antiemetics, and antidiarrheal drugs, etc.);
2. Routine infection prophylaxis (including antibiotics, antiviral drugs, anti-pneumocystis drugs, and antifungal drugs) for the occurrence of opportunistic infections or viral diseases, according to the investigator's assessment;
3. To prevent infusion reactions caused by YL201, the investigator may use acetaminophen or other analgesics, diphenhydramine or other antihistamines, as appropriate;

4. To prevent vomiting caused by YL201, the investigator may use antiemetics (such as dexamethasone 5-HT₃ receptor antagonists [e.g., palonosetron, ondansetron] or NK₁ receptor antagonists [e.g., aprepitant]) as appropriate. For patients with diarrhoea, supportive treatment with antidiarrheal drugs (such as loperamide, probiotics, and montmorillonite powder) should be given in a timely manner;
5. Subjects with bronchopneumopathy are allowed to use bronchodilators (such as salbutamol) intermittently;
6. Nutritional support;
7. Medications or therapies required for pre-existing diseases.

Use e-cigarettes with caution, and use medications not prescribed by the investigator and alternative/complementary therapies with caution.

5.4.2 Prohibited Concomitant Treatments

1. Tumor surgery, systemic chemotherapy, radiotherapy, immunotherapy, biotherapy, molecular targeted therapy, and hormone therapy with any anti-tumor effects, modern Chinese medicine preparations approved for marketing by the National Medical Products Administration (NMPA) for anti-tumor treatment, or immunomodulators with auxiliary anti-tumor effects, etc. Palliative or supportive care for symptoms related to advanced tumors is allowed, such as palliative local radiotherapy (limited scope) and bisphosphonates or denosumab for pain relief, but these treatments cannot be used for target lesions and are not considered tumor treatments;
2. Vaccination with live or live attenuated vaccines is prohibited, including but not limited to: herpes zoster vaccine, varicella vaccine, live influenza vaccine, BCG (tuberculosis) vaccine, measles vaccine, rubella vaccine, yellow fever vaccine, except for seasonal influenza vaccines that do not contain live viruses;
3. Any other investigational drugs.

5.5 Treatment Compliance

Accurate records of the subjects' medication use will be kept during the study. The investigator must check the subjects' medication use, and unused medications must be returned and checked.

The investigator should record the name, date, time, actual dose, and administration schedule of each drug administration in the eCRF to determine the subject's medication compliance. The reasons for discontinuation or dose reduction must be recorded in the eCRF.

6 Discontinuation of Treatment and Subject Withdrawal

6.1 Criteria for Subject Withdrawal from the Study

- 1) The subject or legal representative withdraws informed consent;
- 2) The subject is lost to follow-up;
- 3) The subject dies;

Subjects may choose to withdraw from the clinical study at any time. If a subject or the subject's legal representative withdraws informed consent, the subject must withdraw from the study and will no longer receive study treatment. If the subject withdraws informed consent but is still willing to undergo end-of-treatment visits, safety follow-up, and/or survival follow-up, the investigator will confirm the follow-up procedures with the subject and record them in the original medical record. Data collected during follow-up will be recorded in the original medical record and/or the electronic data capture (EDC) system.

Subjects may also discontinue treatment for the following reasons:

- 1) The compliance of the subject is poor, and affects the efficacy and safety assessment, which is ineffective after communication by the investigator;
- 2) The subject experiences an AE or SAE that requires discontinuation of treatment judged by the investigator;
- 3) There is evidence of definite PD or deterioration in the subject;
- 4) Pregnancy;
- 5) Initiation of new anti-tumor therapy;
- 6) Serious protocol deviations that may affect the study results;
- 7) Other reasons for which the investigator believes that discontinuation of the study drug is in the subject's best interest.

Discontinuation of study treatment does not mean withdrawal from the study, as some data after treatment discontinuation may be important for the study. Therefore, subjects are required to complete the end-of-treatment visit and other scheduled follow-up visits after the end of treatment.

For each subject who discontinues treatment, the investigator should record all required details in the eCRF, including the date of treatment discontinuation and the reason.

6.2 Replacement of Subjects

Subjects who are lost to follow-up are generally not replaced.

7 Study Procedures

7.1 Examinations and Assessments During the Study

7.1.1 Informed Consent

The investigator will explain all study procedures to the subject prior to screening. Written informed consent must be obtained from the subject (or his/her guardian) voluntarily before any study-specific procedures are performed.

Subjects who are re-screened will need to re-sign the informed consent form.

7.1.2 Demographic Information

Demographic data, including age, sex, ethnicity, and race, will be collected from subjects during the screening period.

7.1.3 Oncology/Medical History

Oncology history and treatment history: The oncology history and treatment history of the target indication at screening should be recorded. The medical history collection includes the date and results of diagnosis, clinical stage at the time of initial diagnosis and screening (clinical staging criteria corresponding to different disease types), etc., and all anti-tumor treatment history since the diagnosis of the target indication should be recorded.

Other prior medical history and treatment history:

Other significant medical history, including onset date and end date of disease, should be recorded at screening from 6 months prior to signing of ICF. If the subject has a history of other malignancy, epilepsy, psychiatric disorders, etc. within 5 years, it should be recorded in other important medical history. Additional pre-existing conditions present at the time of signing of ICF and up to the time of first dose are to be regarded as concomitant. The treatment history of other diseases, including prescription drugs, over-the-counter drugs, Chinese herbal medicines, other treatments (including surgery), within 28 days prior to the first dose, should be recorded.

Allergy history, drug dependence history, alcohol consumption history, and smoking history (for NSCLC and SCLC cohorts only) of the subjects should also be obtained at screening.

The investigator will verify the subject's eligibility based on the medical history review.

7.1.4 Physical Examination

Physical examination includes an assessment of all the major body systems (head, eyes, ears, nose, and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and neurological and musculoskeletal systems). The assessment will be performed by the investigator at screening (within 7 days before the first dose), Day 1 of every cycle (within 24 hours before infusion (BI)), the EOT visit, the safety follow-up visit, and when clinically indicated.

7.1.5 ECOG PS Score

ECOG PS score will be performed at screening (within 7 days before the first dose), Day 1 of each cycle from Cycle 2 (within 3 days BI), the EOT visit, the safety follow-up visit, and when clinically indicated.

7.1.6 Height

Height will be measured only at screening (within 7 days before the first dose).

7.1.7 Body Weight

Body weight will be measured at screening (within 7 days before the first dose), Day 1 of every cycle (within 24 hours BI), the EOT visit, the safety follow-up visit, and when clinically indicated. If the weight at screening has been measured within 24 hours prior to the first dose, there is no need to repeatedly measure the weight within 24 hours BI on C1D1. The initial dose will be calculated using the subject's weight prior to the first dose. If the subject's weight changes by more than 10% of baseline weight during treatment, the subject's dose will be recalculated based on the subject's updated weight.

7.1.8 Vital Signs

Vital signs examination includes SBP and DBP, pulse rate, respiratory rate, and body temperature. The assessment will be performed at screening (within 7 days before the first dose), each visit during study treatment, the EOT visit, the safety follow-up visit, and when clinically indicated. On C1D1, C2D1, and C3D1, vital signs should be collected BI and within 30 minutes after the EOI (post-dose). Beginning at Cycle 4, only pre-dose assessments are required. The assessments should be performed after the subject has been at rest in a sitting position for at least 5 minutes. When matched with PK sampling, the vital sign assessment should preferably be carried out before each PK sampling such that the PK sample is collected at the nominal time.

The investigator will verify the subject's eligibility based on the examination results.

7.1.9 SpO₂

SpO₂ will be measured at screening (within 7 days before the first dose), Day 1 of every cycle (within 24 hours BI), the EOT visit, the safety follow-up visit, and when clinically indicated. This assessment should be performed using pulse oximetry at the optimal pulsatile vascular bed (finger, earlobe) after the subject has been at rest in a sitting position for at least 5 minutes. When matched with PK sampling, the SpO₂ assessment should preferably be carried out before each PK sampling such that the PK sample is collected at the nominal time.

7.1.10 12-Lead ECG

Record heart rate, PR interval, RR interval, QRS, QT interval, QTcF, and electrocardiogram diagnostic results.

Examinations will be performed at screening (within 7 days before the first dose), C1D1, C1D3, C1D8, C2D1, and Day 1 of every cycle thereafter, the EOT visit, safety follow-up visit, and when clinically indicated. On C1D1, C2D1, and C3D1, all subjects should undergo ECG assessments within 24 hours BI and 30 minutes after the EOI; subjects receiving the PK intensive sampling should also undergo ECG assessments at 6 hours (± 15 minutes) after the EOI on C1D1 and C3D1. Beginning at Cycle 4, only pre-dose assessments (within 24 hours BI) are required for all subjects.

The ECG assessment should be performed after the subject has been at rest in a supine/semirecumbent position for at least 5 minutes. When matched with PK sampling, the

ECG assessment should preferably be carried out before each PK sampling such that the PK sample is collected at the nominal time. If QTcF prolongation (>500 ms) is observed, the ECG should be re-evaluated by a qualified person at the institution for confirmation.

7.1.11 AE Monitoring

AEs should be recorded at each visit using NCI CTCAE version 5.0. The period of observation for collection of AEs extends from the time the subject signs the ICF until the safety follow-up visit. If an AE persists, the AE should be followed up (even after the safety follow-up visit) until the follow-up endpoint in 9.1.

7.1.12 Concomitant Medications

All concomitant medications from the time the subject signs the ICF until the safety follow-up visit should be recorded including supportive care drugs (e.g., anti-emetic treatment and prophylaxis), the drugs used to treat AEs or diseases, and non-drug supportive interventions (e.g., transfusions).

The investigator will verify the subject's eligibility based on the subject's medication.

7.1.13 New Anti-Tumor Therapy

Collect the name of the new anti-cancer treatment (trade name of the drug/name of the surgery, etc.), the administration method (if applicable), the start and end dates of the treatment.

7.1.14 Laboratory Tests

Item	Test Parameters
Hematology	WBC, RBC, Hb, PLT, HCT, NEU, neutrophil percentage (NEUT%), LYM, lymphocyte percentage (LYMPH%), eosinophil count (EO#), eosinophil percentage (EO%), basophil count (BASO#), basophil percentage (BASO%), monocyte count (MONO#), monocyte percentage (MONO%) Examination will be performed at screening (within 7 days before the first dose), C1D8, C1D15, C2D1 and Day 1 of every cycle thereafter (within 3 days BI), C3D8, the EOT visit, the safety follow-up visits, and when clinically indicated.
Blood chemistry	Total protein (TP), albumin (ALB), globulin (GLO), total bilirubin (TBIL), direct bilirubin (DBIL), alanine transaminase (ALT), aspartate transaminase (AST), urea (Urea)/blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), glucose (GLU), triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), potassium (K), sodium (Na), chloride (Cl), magnesium (Mg), calcium (Ca), phosphorus (P) Examination will be performed at screening (within 7 days before the first dose), C1D8, C1D15, C2D1 and Day 1 of every cycle thereafter (within 3 days BI), C3D8, the EOT visit, the safety follow-up visits, and when clinically indicated.
Coagulation function	Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), international normalized ratio (INR) Examination will be performed at screening (within 7 days before the first dose), C2D1 and Day 1 of every cycle thereafter (within 3 days BI), the EOT visit, the safety follow-up visits, and when clinically indicated.
Urine analysis	Urobilinogen, bilirubin urine, ketone bodies, occult blood, protein, glucose, pH, leukocytes, erythrocytes Examination will be performed at screening (within 7 days before the first dose), C1D8, C1D15, C2D1 and Day 1 of every cycle thereafter (within 3 days BI), C3D8, the EOT visit, the safety follow-up visits, and when clinically indicated. Urine samples will be

Item	Test Parameters
	analyzed by dipstick, and a microscopic analysis will be performed if dipstick abnormal.
Pregnancy test	For women of childbearing potential (WOCBP), a serum hCG pregnancy test should be performed at screening (within 3 days before the first dose). After study drug administration, a serum or urine hCG pregnancy test should be performed on Day 1 of every 2 cycles from Cycle 3 (within 3 days BI), at the EOT visit, the safety follow-up visit, and when deemed necessary. A positive urine pregnancy should be confirmed using serum pregnancy test.
Serology	Serology examination includes tests for HBV (HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb), HCV (HCV antibody), and HIV (HIV antibody). For HBsAg- or HBcAb-positive subjects, HBV DNA should be further tested; for HCV antibody-positive subjects, HCV RNA should be further tested. The tests will be performed at screening, and afterwards retest will be conducted only if deemed necessary by the investigator.

7.1.15 Tumor Assessment

Imaging sites include all known or suspected disease sites. Screening scans should include at least head, chest, abdomen, pelvic CT or MRI scans and bone scans. For the NPC cohort, neck and nasopharyngeal CT or MRI scans should also be included, and for the ESCC cohort, neck CT or MRI scans should also be included. For patients with abnormal bone scans, appropriate CT or MRI should be additionally performed to confirm bone metastases at sites of suspected bone metastases (if the bone lesions are already within the range covered by routine CT/MRI scans, no additional scans are required). Screening scans should be performed within 28 days prior to the first dose (for bone scans performed at the study site within 3 months prior to the first dose and other examinations within 28 days prior to the first dose, no repeat examinations are required), and the results will serve as baseline data.

During the treatment period, at least chest, abdomen, and pelvic CT or MRI scans are included. For the NPC cohort, neck and nasopharyngeal CT or MRI scans should also be included, and for the ESCC cohort, neck CT or MRI scans should also be included. Subjects with brain metastases or bone metastases confirmed at screening should undergo head CT or MRI or bone scans at each tumor assessment during the treatment period. For subjects suspected of having brain metastases or bone metastases during the treatment period, the investigator may decide, based on clinical indications, whether they should undergo head CT or MRI or bone scans. For patients with abnormal bone scans, appropriate CT or MRI should be additionally performed to confirm bone metastases at sites of suspected bone metastases (if the bone lesions are already within the range covered by routine CT/MRI scans, no additional scans are required). Assessments will be conducted every 6 weeks (± 7 days) after the study drug administration until Week 24, and then every 9 weeks (± 7 days) thereafter (i.e., Weeks 6, 12, 18, 24, 33, 42 and 51, etc.), and when clinically indicated.

Subjects who achieve a complete response (CR) or partial response (PR) should undergo confirmatory imaging at least 4 weeks later. Assessments will continue until PD is suggested in the image. For subjects who discontinue the treatment for reasons other than imaging PD (e.g., unacceptable toxicity), a tumor assessment should be carried out at the EOT visit every 9 weeks (± 7 days) after treatment discontinuation until PD, starting a new anti-tumor treatment, withdrawal of informed consent by subjects, or death, whichever occurs first. Throughout the

clinical study, the same imaging techniques will be used to follow the same lesions in each subject to characterize each lesion identified and reported at screening.

The investigator will assess the tumor imaging according to RECIST v1.1 (the frequency of tumor assessment can be increased by the investigator based on clinical needs).

7.1.16 Collection of Biological Samples [PK/ADA/sB7H3/Tumor Tissues]

PK/ADA/sB7H3

See the biological sample collection schedule for PK/ADA/sB7H3 blood sample collection times. After each venous blood sample collection, record the exact time of sampling (accurate to the minute), as well as the actual time of dosing (start and end time of dosing) and dose, which must be accurately recorded in the eCRF for each sample. If there is any deviation from the above protocol due to technical difficulties, the details of the deviation should be recorded in the eCRF.

For the convenience of the study site, the PK, ADA, and sB7H3 blood collections at the same scheduled sampling time point can be combined. The collected blood samples will be used for PK (including ADC, TAB, unconjugated payload YL0010014 blood concentration analysis and drug metabolite identification), ADA, and sB7H3 analysis.

If multiple procedures are scheduled at the same time point, perform vital signs, SpO₂, 12-lead ECG, and PK sampling in sequence.

PK samples may be collected at other time points if clinically indicated (e.g., at the time of other significant AE that are at least possibly related to YL201).

The timing of PK samples may be adjusted during the study, dependent on emerging data, to acquire a relatively complete blood concentration-time curve as much as possible.

For subjects with a positive ADA status at the safety follow-up visit, additional ADA blood samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of the study drug, or if the subject's ADA status becomes negative, the ADA titer becomes less than baseline (applicable when preexisting ADAs are observed), the subject starts another anti-tumor therapy, or the subject withdraws consent from the study, whichever occurs first.

Tumor Tissues

Subjects in each cohort are not required to confirm the expression level of B7H3 in tumor tissues before enrollment, but they need to provide archived or fresh tumor samples. Subjects should provide 6 to 10 slides of archived or fresh tumor samples before the first dose of study drug for exploratory assessment of B7H3 expression level. Subjects who are not able to provide tumor samples or have inadequate samples may be eligible on a case-by-case basis after discussion with the sponsor.

In this study, the subjects' serum samples need to be sent to Frontage Laboratories (Shanghai) Co., Ltd. for PK, ADA, and sB7H3 testing, and the subjects' tumor sections need to be sent to MEDx Translational Medicine (Suzhou) Co., Ltd. for B7H3 testing.

The remaining sections will be stored at MEDx Translational Medicine (Suzhou) Co., Ltd. for 5 years after the end of the study and then destroyed. The remaining serum samples in test tubes

and backup serum samples in tubes will be stored at Frontage Laboratories (Shanghai) Co., Ltd. for 5 years after the drug is marketed, and then transferred to Shanghai Solid Waste Disposal Co., Ltd. for destruction, and it is promised that the study samples will only be used for this clinical study and will not be used for other purposes.

For details on the collection and processing of biological samples, please refer to the laboratory operation manual.

7.2 Visit Schedule

7.2.1 Screening Period (≤ 28 Days)

Subjects are required to sign the ICF on a voluntary basis before participating in the screening. The subjects who meet all inclusion criteria and none of the exclusion criteria are eligible to participate in the study.

- Signing of ICF
- Collection of demographic information
- Collection of oncology/medical history
- Physical examination
- ECOG PS
- Height
- Body weight
- Vital signs
- SpO₂
- 12-lead ECG
- AE monitoring
- Recording concomitant medications
- Laboratory tests: hematology, blood chemistry, coagulation function, urine analysis, serum pregnancy test, serology
- Tumor assessment
- Collection of tumor tissues
- Confirmation of eligibility (Subjects who are not able to provide tumor samples or have inadequate samples may be eligible on a case-by-case basis after discussion with the sponsor)

7.2.2 Treatment Period

Only 20 - 30 subjects (regardless of cohort) at each dose level will undergo intensive PK sampling, while the remaining subjects will undergo sparse PK sampling, as detailed in Table 1 and Table 2.

C1D1 (BI)

- Physical examination
- Body weight
- Vital signs
- SpO₂
- 12-lead ECG
- AE monitoring
- Recording concomitant medications
- PK sampling
- ADA sampling
- sB7H3 sampling

C1D1 (EOI)

- Vital signs
- 12-lead ECG
- AE monitoring
- Recording concomitant medications
- PK sampling

C1D2

- Vital signs
- AE monitoring
- Recording concomitant medications
- PK sampling

C1D3

- Vital signs
- 12-lead ECG
- AE monitoring
- Recording concomitant medications
- PK sampling

C1D8 (±1 day)

- Vital signs

- 12-lead ECG
- AE monitoring
- Recording concomitant medications
- Laboratory tests: hematology, blood chemistry, urine analysis
- PK sampling

C1D15 (±1 day)

- Vital signs
- AE monitoring
- Recording concomitant medications
- Laboratory tests: hematology, blood chemistry, urine analysis
- PK sampling

C2D1 (±2 days, BI)

- Physical examination
- ECOG PS
- Body weight
- Vital signs
- SpO₂
- 12-lead ECG
- AE monitoring
- Recording concomitant medications
- Laboratory tests: hematology, blood chemistry, coagulation function, urine analysis
- PK sampling
- ADA sampling
- sB7H3 sampling

C2D1 (±2 days, EOI)

- Vital signs
- 12-lead ECG
- AE monitoring
- Recording concomitant medications
- PK sampling

C3D1 (±2 days, BI)

- Physical examination
- ECOG PS
- Body weight
- Vital signs
- SpO₂
- 12-lead ECG
- AE monitoring
- Recording concomitant medications
- Laboratory tests: hematology, blood chemistry, coagulation function, urine analysis, pregnancy test
- Tumor assessment
- PK sampling

C3D1 (±2 days, EOI)

- Vital signs
- 12-lead ECG
- AE monitoring
- Recording concomitant medications
- PK sampling

C3D8 (±2 days)

- Vital signs
- AE monitoring
- Recording concomitant medications
- Laboratory tests: hematology, blood chemistry, urine analysis
- PK sampling

CnD1 (visit window for Cycle 4 to Cycle 8 is ±2 days, and ±4 days for Cycle 9 and every cycle thereafter, BI)

- Physical examination
- ECOG PS
- Body weight
- Vital signs

- SpO₂
- 12-lead ECG
- AE monitoring
- Recording concomitant medications
- Laboratory tests: hematology, blood chemistry, coagulation function, urine analysis, pregnancy test (pregnancy test will be performed on Day 1 of every 2 cycles from Cycle 3 [within 3 days BI])
- Tumor assessment (every 6 weeks [± 7 days] after study drug administration until Week 24, and then every 9 weeks [± 7 days] thereafter [i.e., Weeks 6, 12, 18, 24, 33, 42, and 51, etc.]
- PK sampling (once every 2 cycles starting from Cycle 4)
- ADA sampling (once every 2 cycles starting from Cycle 4)
- sB7H3 sampling (once every 2 cycles starting from Cycle 4)

CnD1 (visit window for Cycle 4 to Cycle 8 is ± 2 days, and ± 4 days for Cycle 9 and every cycle thereafter, EOI)

- AE monitoring
- Recording concomitant medications
- PK sampling (once every 2 cycles starting from Cycle 4)

7.2.3 End-of-Treatment (EOT) Visit

The EOT visit will be conducted within 7 days after confirmation/notification of subject discontinuation. If an EOT assessment has been performed within the last 7 days, this assessment can be considered as the EOT assessment and need not be repeated. For CT/MRI scans performed within 4 weeks, bone scans within 6 weeks, or subjects withdrawn from the study because of PD, no repeat examinations are required.

- Physical examination
- ECOG PS
- Body weight
- Vital signs
- SpO₂
- 12-lead ECG
- AE monitoring
- Recording concomitant medications
- Recording new anti-tumor treatment

- Laboratory tests: hematology, blood chemistry, coagulation function, urine analysis, pregnancy test
- Tumor assessment
- ADA sampling
- sB7H3 sampling

7.2.4 Follow-up Period

Safety follow-up

The safety follow-up will be conducted 42 days (± 7 days) after the last dose of study drug or before starting a new anti-tumor treatment, whichever occurs first. Subjects will return to the study site for clinical and laboratory assessments, review of concomitant medications, and assessment of resolution of treatment-related toxicities. Subjects continuing to experience toxicity at this time point will continue to undergo follow-up at least every 4 weeks until the follow-up endpoint in 9.1. If an EOT assessment is performed during this period, this assessment can be considered as the safety follow-up assessment and need not be repeated.

- Physical examination
- ECOG PS
- Body weight
- Vital signs
- SpO₂
- 12-lead ECG
- AE monitoring
- Recording concomitant medications
- Recording new anti-tumor treatment
- Laboratory tests: hematology, blood chemistry, coagulation function, urine analysis, pregnancy test
- ADA sampling

Survival follow-up

Telephone follow-up will be conducted every 12 weeks (± 7 days) after the last dose until death or loss to follow-up.

- Recording new anti-tumor treatment
- Recording survival status

For subjects who discontinue the treatment for reasons other than imaging PD (e.g., unacceptable toxicity), a tumor assessment should be carried out every 9 weeks (± 7 days) after treatment

discontinuation until PD, starting a new anti-tumor treatment, withdrawal of informed consent by subjects, or death, whichever occurs first.

8 Evaluation Endpoints

8.1 Safety Endpoints

Safety evaluation will include monitoring and recording all AEs, laboratory test results, physical examination results, ECOG PS, vital signs, SpO₂ and ECG parameters, etc., and determining the RP2D of YL201 in selected patients with advanced solid tumors.

8.2 Efficacy Endpoints

Primary endpoints:

- ORR: defined as the proportion of subjects who achieve a best overall response of CR or PR from the first dose of study drug.

Secondary endpoints:

- DpR: defined as the maximum percentage change in the sum of longest dimensions (SLD) of measurable lesion(s) at any time during the study.
- DCR: defined as the proportion of subjects who achieve a best overall response of CR or PR or stable disease [SD] from the first dose of study drug.
- DoR: defined as the time from the first documentation of response (CR or PR in subjects with a best overall response of CR or PR) to the first documentation of PD or death, whichever occurs first.
- TTR: defined as the time from the first study drug administration to the first documentation of response (CR or PR) in subjects with a best overall response of CR or PR.
- PFS: defined as the time from the first study drug administration to the first documentation of PD or death, whichever occurs first.
- OS: defined as the time from the first study drug administration to death from any cause.

8.3 Pharmacokinetic Parameters

Single- and multiple-dose PK parameters of YL201 (including ADC, TAb, and unconjugated payload YL0010014), including but not limited to AUC, C_{max}, C_{trough}, CL, V_d, and t_{1/2}, and the metabolite profile of YL201.

8.4 Immunogenicity Indicators

Immunogenicity indicators include the incidence of anti-YL201 antibodies.

8.5 Exploratory Endpoints

Exploratory endpoints include B7H3 expression level in tumor tissue and the correlation with YL201 efficacy, sB7H3 level in peripheral blood and the correlation with YL201 efficacy, and the correlation between the YL201 efficacy and safety endpoints and the exposure.

9 Adverse Events and Serious Adverse Events

9.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All pre-existing medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history eCRF. During the study period outside the screening period, changes in these conditions and new symptoms, signs, syndromes, or diseases should be recorded in the AE eCRF. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgeries planned for known medical conditions prior to the subject's enrollment in the study are not considered AEs; these medical conditions should be reported in the subject's medical history.

Subjects will be instructed to report AEs at each study visit. All AEs (including laboratory abnormalities) must be followed up until any of the following:

- 1) The event is resolved;
- 2) The event is stable;
- 3) The event returns to baseline;
- 4) The event can be attributed to medications other than the study drug or is unrelated to the study procedures;
- 5) No more information is available (the subject refuses to provide further information, or there is evidence that the subject is still lost to follow-up given the greatest possible efforts that have been made).

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or non-serious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the subject signs the ICF until the safety follow-up visit. Follow up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the event on that day should be recorded. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

The severity of AEs will be graded according to NCI CTCAE version 5.0 (Grade 1 to 5).

Specific guidelines for classifying AEs by severity and relationship to study drug are shown in 7 and Table 8.

Table 7 Adverse Events Classified by Severity

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL ^a
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL ^b
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

Abbreviations: ADL = activities of daily living; AE = adverse event.

^a Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^b Self-care ADL refers to bathing, dressing, feeding self, using the toilet, taking medications, etc., and not being bedridden.

Table 8 Classification of Adverse Events by Relationship to Study Drug

Not Related	This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
Unlikely Related	This category applies to those AEs that are judged to be unrelated to the study drug but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the study drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the study drug; or (4) it does not reappear or worsen when the drug is readministered.
Possibly Related	This category applies to those AEs for which a connection with the study drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related to study drug if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it follows a known pattern of response to the study drug.
Probably Related	This category applies to those AEs that the investigator feels with a high degree of certainty are related to the study drug. An AE may be considered probably related to study drug if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the study drug.
Definitely Related	This category applies to those AEs that the investigator feels are incontrovertibly related to study drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the study drug.

Abbreviation: AE = adverse event.

9.2 Adverse Events of Special Interest (AESIs)

Based on the safety data from preclinical studies of YL201 and early clinical studies of similar ADC products, AESIs include ILD of any grade, IRR $\geq$ Grade 3, and platelet count decreased $\geq$ Grade 3.

Whether it is the first report or an updated report, the investigator must complete the "Adverse Event of Special Interest Report Form", sign and date it, and immediately report it (no later than 24 hours after becoming aware of the AESI or updated information) to the sponsor's pharmacovigilance team, the sponsor, or an authorized representative. The information to be collected and the reporting pathway for AESIs shall refer to the handling requirements for SAEs. The investigator should ensure that sufficiently detailed event description information is submitted within the above timeframe to allow for a comprehensive medical assessment of the case.

9.3 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence, in the view of either the investigator or sponsor, that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of PD should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with NCI CTCAE Grade 5.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. SAEs are critically important for the identification of significant safety problems; therefore, it is necessary to take into account both the investigator's and the sponsor's assessment. If the sponsor or the investigator believe that an event is serious, the event must be considered serious and evaluated by the sponsor for expedited reporting.

9.4 Reporting of Serious Adverse Events

An SAE occurring from the time informed consent is obtained until the safety follow-up visit must be reported to the Pharmacovigilance Department of R&G Pharma Studies Co., Ltd. (hereinafter referred to as R&G) and will be communicated to the sponsor. Any such SAE due to any cause, whether or not related to the study drug, must be reported within 24 hours of

occurrence or when the investigator becomes aware of the event. If the investigator contacts the Pharmacovigilance Department of R&G by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the study drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed to determine the etiology of the problem. The investigator must report all additional follow-up evaluations to the Pharmacovigilance Department of R&G within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs should be followed up until the investigator and sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study should be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

See Pharmacovigilance Management Plan (PVMP) for details.

9.5 Suspected unexpected serious adverse reactions

AEs that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- Serious
- Unexpected (i.e., the event is not consistent with the safety information in the Investigator's Brochure)
- There is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The investigator will assess whether an event is causally related to study treatment. The sponsor (or designee) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7- or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities within 7 days after the sponsor (or designee) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities within 15 calendar days after the sponsor (or designee) has first knowledge of them.

The sponsor (or designee) is responsible for reporting SUSARs and any other events requiring expedited reporting to regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators

will notify the relevant independent ethics committees (IECs)/institutional review boards (IRBs) of reportable events within the applicable timeframes.

9.6 Pregnancy

Pregnancy test must be negative for women of childbearing potential (WOCBP) at screening. Any known cases of pregnancy in female subjects from the time of screening and throughout the study and for at least 6 months after the last dose of study drug will be reported until the subject completes or withdraws from the study. The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the sponsor (or designee) within 24 hours of becoming aware of the pregnancy. The pregnancy will not be processed as an SAE; however, the investigator will follow up with the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The investigator should notify the sponsor (or designee) of the pregnancy outcome by submitting a pregnancy follow-up report. If the pregnancy outcome involves spontaneous abortion or therapeutic abortion (any congenital anomaly detected in the aborted fetus should be recorded), stillbirth, neonatal death, or congenital anomaly, the investigator should report the event by faxing/emailing a completed pregnancy report form to the sponsor (or designee) within 24 hours of becoming aware of the event.

If the investigator becomes aware of a pregnancy occurring in the partner of a subject participating in the study, the pregnancy should be reported to the sponsor (or designee) within 24 hours of knowledge of the event. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the potential effects on the fetus.

After the study is terminated, subjects will only undergo procedures that do not expose them to excessive risk. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the sponsor after delivery.

9.7 Overdose

The investigator should immediately notify the sponsor of any overdose events of the study drug.

10 Data Management

10.1 Database Establishment

This study uses an eCRF remote data entry method to collect data in clinical study. The data manager designs the database and tests it with simulated data or real eCRF data to ensure that the database is accurate.

10.2 Database Verification

The data verification methods during data management include: data logic checks, manual checks, medical checks, and statistical pre-analysis checks. Data queries will be reflected in the EDC system in the form of electronic queries for the study site to resolve. If the resolution is satisfactory, the query will be closed. If the data query is still not resolved or a new query is generated after updating the database based on the resolution to the previous data query, the investigator or clinical research coordinator (CRC) needs to resolve again after confirmation with the investigator. The above process will be repeated until all data in the database is confirmed to be correct.

10.3 Database Lock

The data manager will write a data review report based on the study protocol, data review standards, and database. The project manager will convene a data review meeting attended by the sponsor, principal investigator, statistician, and data manager to review the data, and the representatives of all parties will sign the data review resolution. After all parties approve the data lock, the data manager will organize and execute the data lock. The locked data will be submitted to the statistician for statistical analysis.

The database can be locked when the following conditions are met.

- 1) All data has been collected into the database
- 2) All coding has been verified and confirmed
- 3) All data queries have been resolved (including queries raised during data review)
- 4) Data review has been completed
- 5) Source data verification has been completed
- 6) Verification of serious adverse events has been completed
- 7) Signatures of all investigators have been obtained
- 8) Analyzable cases have been defined and saved in the final analysis database.

11 Statistical Analysis and Sample Size

Detailed methods for the summarization and statistical analysis of the data collected in this study will be described in the Statistical Analysis Plan (SAP). The plan presented in this protocol may be appropriately modified in the SAP, but major revisions involving the primary endpoint need to be reflected in the protocol amendment.

11.1 Statistical Hypothesis

There is no statistical hypothesis for this study.

11.2 Sample Size Calculation

It is planned to enroll approximately 30-90 subjects in each cohort.

11.3 Statistical Analysis Datasets

Full Analysis Set (FAS): Includes all subjects enrolled in this study.

Safety Set (SS): Includes all subjects who have received at least one dose of study drug treatment. The SS population will be the analysis population for safety evaluation in this study.

Efficacy Analysis Set (EAS): Includes all subjects who have received at least one dose of study drug treatment and have baseline and at least one post-dose efficacy assessment. The EAS population will be the analysis population for efficacy evaluation in this study.

Pharmacokinetic Concentration Analysis Set (PKCS): Includes all subjects who have received at least one dose of study drug treatment and have at least one quantifiable plasma concentration collected after dosing, without major protocol deviations/violations or events that will significantly affect the PK profile.

Pharmacokinetic Parameter Analysis Set (PKPS): Includes all subjects who have at least 1 PK parameter of interest for YL201-ADC, YL201-TAb, or YL0010014, without major protocol deviations/violations or events that will significantly affect the PK profile.

Immunogenicity Set (IMGS): Includes all subjects who have received at least one dose of study drug treatment and have at least one evaluable immunogenicity data.

11.4 Statistical Analytical Method

11.4.1 General Principles of Statistical Analysis

Descriptive statistics will be provided for demographics and baseline characteristics, safety, PK, efficacy, and biomarker data by cohort, dose level, and visit (if applicable). Descriptive statistics for quantitative variables will include the number of subjects (N), mean, standard deviation, median, minimum, and maximum (as well as geometric mean and geometric coefficient of variation for PK parameters C_{max} and AUC), while qualitative variables will be summarized using N and percentage. For all summary figures and tables, the corresponding listings will be provided. All statistical analyses will be performed using SAS 9.4 or higher.

In general, any change from baseline, baseline values used in listings/summaries/figures, or baseline values as covariates in statistical analyses refer to the last available value prior to the

first dose. If necessary, specific parameters or baselines for assessments will be defined in detail in the SAP.

11.4.2 Demographic and Baseline Characteristics Analysis

Demographic data and baseline characteristics of subjects, including demographics, medical history, diagnosis and treatment history, concomitant medications, prior therapies (surgery, neoadjuvant/adjuvant therapy, radiotherapy, systemic therapy, etc.), tumor stage and number of metastatic organs, etc., will be summarized by cohort and dose level. Medical coding of drug names for prior therapies and concomitant medications will be performed based on the latest version of the WHO Drug Dictionary.

11.4.3 Safety Analysis

Safety analyses will be based on SS, and safety data will be summarized by cohort and dose level, including AEs, clinical laboratory measurements, vital signs and SpO₂ measurements, ECG recordings, physical examination findings, and ECOG PS. Safety analyses will be descriptive and will be presented in tabular format with the appropriate summary statistics.

All adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and graded for severity according to NCI CTCAE v5.0. The number and percentage of AEs occurring during or after the first study drug administration, including TEAEs, SAEs, TEAEs related to study drug, SAEs related to study drug, Grade 3 or higher TEAEs and TEAEs leading to discontinuation of treatment, TEAEs leading to death, AESIs, will be summarized by System Organ Class (SOC) and Preferred Term (PT). In addition, the severity of TEAEs and their relationship to the study drug will also be summarized by SOC and PT. Multiple occurrences of the same AE in the same subject will be recorded as 1 AE by the maximum severity in the summary.

Deaths reported during study treatment and during the follow-up period after treatment completion/discontinuation will be summarized. Values of safety indicators such as clinical laboratory measurements, vital signs and SpO₂ measurements, ECG recordings, physical examination findings, and ECOG PS, and their changes from baseline will be summarized at each scheduled visit. Where applicable, the changes in clinical significance of each safety indicator before and after dosing will be summarized using a crossover classification table.

11.4.4 Efficacy Analysis

Efficacy analyses will be based on the EAS. For ORR and DCR, point estimates will be provided, and the two-sided 95% confidence interval (CI) for the corresponding indicators will be estimated using the exact (Clopper-Pearson) method.

DoR, TTR, PFS and OS will be summarized descriptively using the Kaplan-Meier method to estimate the median time to event, and its two-sided 95% CIs will be estimated using the Brookmeyer-Crowley method. PFS rate at 3 and 6 months and OS rate at 6 and 12 months will be estimated by Kaplan-Meier method, and the two-sided 95% CI of the PFS rate and OS rate will be estimated using the Greenwood formula.

In addition, descriptive statistics for DpR will be provided. A waterfall plot will be presented for each subject in the EAS.

11.4.5 Pharmacokinetic Analysis

The concentration-time data for YL201-ADC, YL201-TAb, and YL0010014 will be listed, plotted, and descriptively summarized by cohort and dose level at each time point.

Single- and multiple-dose PK parameters of YL201-ADC, YL201-TAb, and YL0010014 will be listed and descriptively summarized by cohort and dose level.

11.4.6 Immunogenicity Analysis

The percentage of ADA-positive subjects will be summarized by cohort, dose level, and visit (if applicable). For ADA-positive subjects, the extent (titer), onset, and duration of the ADA response will also be described if data permit.

11.4.7 Exploratory Endpoint Analysis

The exploratory analysis results of B7H3 expression level and sB7H3 level will be listed and descriptively summarized.

11.5 Interim Analysis

No interim analysis will be performed in this study.

12 Study Management

12.1 Ethics

12.1.1 Ethical Requirements

This study will be conducted in strict accordance with Good Clinical Practice (GCP), the Declaration of Helsinki, relevant laws and regulations, and the review comments of the ethics committee.

The investigator should ensure that this study is reviewed and approved by a qualified ethics committee that meets the requirements of the GCP. Prior to the initiation of the study, the investigator should submit the protocol, ICF and other necessary materials to the EC for review and approval. The sponsor can only provide the study drug after receiving approval from the ethics committee. The EC must also be informed of subsequent protocol addendum and SAEs occurring during the study that may affect the safety of subjects and continued participation in the study. The investigator will be responsible for reporting the progress of the study to the EC. In addition, the investigator must promptly provide the sponsor with copies of all communications with the EC. For protocol review and approval, the EC must confirm the protocol title and protocol number, and indicate the reviewed protocol documents and the review date. During the study, if there are any new amendments to the study protocol, informed consent form, etc., written approval must be obtained again from the relevant regulatory authorities in accordance with regulations.

12.1.2 Informed Consent

The informed consent form (along with the study protocol) must be reviewed and approved by the EC.

The investigator must inform the subjects of the information about this study both verbally and in writing. It is the responsibility of the investigator or his/her designee to explain the contents of the informed consent form to the subject (or his/her guardian or witness) in a manner and language that the subject (or his/her guardian or witness) can understand. If there is any new information that may affect the subject's continuous participation in the study, the investigator should promptly inform the subject (or his/her guardian) and record accordingly.

The final text of ICF and other information provided to the subjects should include the following contents: the study overview, objectives, process and duration, study procedures to be followed by the subjects, the obligations of the subjects, the expected possible benefits (including the possibility of no benefit) and risks for the subjects, and notification to subjects that they may be assigned to different study groups and may be assigned to each group; treatment and corresponding compensation available to subjects in the event of study-related damages; compensation for subjects participating in the clinical study; willingness of study participation; confidentiality of the subjects' personal data, etc.

Prior to signing the ICF, the investigator or his/her designee should give subjects (or their guardian) adequate time and opportunity to understand the details of the clinical study. The subject (or their guardian) and the investigator obtaining informed consent should sign and date the ICF separately (relationship with subjects should be indicated if it is not personally signed by

subjects). Both the Investigator and the subject should keep one copy of the ICF. If important new information about the study drug is available, the ICF must be revised in writing and submitted to the EC for approval before obtaining the consent of subjects (or their guardian) again.

12.1.3 Subject Confidentiality

The investigator is responsible for maintaining the anonymity of the subjects. Subjects should be identified only by initials, numbers, and/or codes on case report forms or other documents, not by their names. The investigator must keep the subject enrollment form, which records the subject's code, name, and home address, confidential. The investigator must keep confidential any documents that could reveal the identity of the subject.

12.2 Responsibilities of All Parties

12.2.1 Investigator's Responsibilities

The investigator's responsibilities mainly include but are not limited to:

- 1) The investigator should hold a joint discussion with the sponsor to finalize and sign the protocol, which will be implemented after approval by the EC.
- 2) The investigator must read and understand the contents of the study protocol in detail and conduct the study strictly in accordance with the protocol.
- 3) The investigator should understand and be familiar with the nature, effects, efficacy, and safety of the study drug (including relevant information from preclinical studies of the drug), and should also be aware of all new information related to the drug discovered during the clinical study.
- 4) The investigator must conduct the clinical study in a medical institution equipped with good medical facilities, laboratory equipment, and medical staff. The institution should have all the facilities to handle emergencies to ensure the safety of the subjects. Laboratory test results should be accurate and reliable.
- 5) The investigator should obtain approval from the medical institution or the regulatory authority, and ensure that there is sufficient time to take charge of and complete the clinical study within the period specified in the protocol. The investigator should ensure that the study personnel fully understand the study protocol and the study drug, clarify their respective roles and responsibilities in the study, supervise all study personnel in implementing the study protocol, and take measures to implement quality management of the clinical study to ensure that a sufficient number of subjects who meet the study protocol are enrolled in the clinical study.
- 6) Before the implementation of the clinical study, the investigator should explain to the subject the details of the study approved by the ethics committee and obtain written informed consent.
- 7) The investigator or his/her delegated clinician shall be responsible for making medical decisions related to the clinical study, such as ensuring that subjects receive appropriate treatment for adverse events during the study. The investigator, as a clinician or delegated clinician, shall be responsible for all medical decisions related to the clinical study.

- 8) The investigator has the obligation to take necessary measures for the safety of subjects, and make due records. If a subject experiences an adverse event related to the study drug, the investigator should ensure that the subject receives proper medical care and truthfully inform the subject of the relevant conditions. If an SAE occurs during the clinical study, the investigator should give appropriate treatment to the subject promptly, and submit the signed and dated reports to the drug regulatory authorities, health administrative departments, sponsor and EC in the meantime.
- 9) The investigator shall submit an annual report of the clinical study to the EC, or submit progress reports in accordance with the requirements of the EC. The investigator shall report in writing to the sponsor, the EC, and the clinical trial institution as soon as possible if any event occurs that may significantly affect the conduct of the study or increase the risk to the subjects.
- 10) The investigator should guarantee that the data will be recorded on the medical record and case report form correctly, accurately, completely, timely and legally.
- 11) The investigator should accept the monitoring and auditing by the monitor or auditor appointed by the sponsor, as well as the auditing and inspection by the drug regulatory authorities, to ensure the quality of the clinical study.
- 12) The investigator should negotiate with the sponsor regarding the cost of the clinical study, and specify the agreed amount in the contract. The investigator must not charge the subjects for the study drug during the clinical study.
- 13) After the completion of the clinical study, the investigator should write a summary report, sign and date it prior to sending it to the sponsor.

12.2.2 Sponsor's Responsibilities

The sponsor's responsibilities mainly include but are not limited to:

- 1) The sponsor is responsible for initiating and applying for this clinical study and providing research funding.
- 2) The sponsor should provide the Investigator's Brochure, which includes chemical, pharmaceutical, toxicological, pharmacological, and clinical (including previous and ongoing studies) information and data of the study drug.
- 3) The sponsor and the investigator shall jointly design the clinical study protocol, and sign the study protocol and contract agreed upon by both parties.
- 4) The sponsor should provide the investigator with the study drug and control drug that are easy to identify, correctly coded, specially labeled, and have acceptable quality. The study drug should be properly packaged and stored as required by the study protocol. The sponsor should establish management and documentation systems for the study drug.
- 5) The sponsor should appoint qualified monitors who are acceptable to the investigator.
- 6) The sponsor should establish a quality management system for the clinical study and fulfill the management responsibilities, including the design, implementation, documentation, evaluation, reporting of results, and archiving of documents of the clinical study. The sponsor may organize audits of the clinical study to ensure quality.

- 7) The sponsor should conduct risk-based quality management to identify risks that affect critical steps and data of the clinical study. The sponsor should promptly scrutinize the SAEs with the investigator, take necessary actions to ensure the safety, rights and interests of subjects, and report to the drug regulatory authorities and health administrative departments in a timely manner.
- 8) The sponsor is responsible for submitting the summary report of this study to the NMPA.
- 9) The sponsor should provide drug clinical research liability insurance for this study. The sponsor should provide comprehensive medical insurance for subjects participating in the clinical study. For subjects who suffer from study-related damage or death, the sponsor should reimburse their cost of treatment and offer appropriate financial compensation. The sponsor should provide the investigator with legal and economic guarantees, except for events caused by medical malpractice.

12.3 Protocol Amendments

Any necessary changes to the protocol should be made in the form of protocol amendments and submitted to the EC for approval or filing after obtaining the signed consent of the sponsor and the principal investigator.

12.4 Training

According to GCP guidelines, the CRA should have qualifications recognized by the sponsor. Prior to initiation of the clinical study, the investigator should be trained by the study site director to familiarize and understand the protocol, comprehend GCP guidelines, use consistent recording methods and interpretation criteria, and to strictly carry out the study as specified in the protocol.

12.5 Standard Operation

The sponsor shall comply with the GCP (2020) and the Drug Registration Regulation (2020). The study drug is in compliance with the relevant requirements of Good Manufacturing Practices and is subjected to strict quality inspection.

Laboratory tests will be performed by the study site in accordance with SOPs.

The laboratory testing methods and quality control of the study site should be standardized. The clinical laboratories at the study site must conduct internal quality control as required and obtain a quality evaluation certificate from the National Center for Clinical Laboratories.

12.6 Quality Control and Assurance

- 1) SOPs will be established for all study procedures.
- 2) Site qualification: A clinical study site is a clinically qualified site for drug clinical studies identified by NMPA.
- 3) Qualification of study personnel: The study personnel must be trained on clinical studies and work under the guidance of senior professionals. Investigators and other study personnel will be trained on GCP and the study protocol.
- 4) Laboratory quality control measures: The laboratories should establish SOPs and quality control procedures for the study indicators.

- 5) **Monitoring:** All monitors will be trained on the GCP and study protocol, etc., and have the knowledge required for clinical study monitoring such as medicine, pharmacy, etc. Monitors will conduct regular monitoring during the course of the study. The monitor needs to verify that the clinical facilities of the study site meet the requirements, verify that the investigators follow the study protocol and accurately record the study results. During each monitoring visit, the monitor must also review the eCRF and source documents, and check the storage conditions of the drugs and the drug use records.
- 6) **Auditing:** The study site must also be audited by auditors appointed by the sponsor, as required by the GCP. The auditor will conduct a systematic audit for study-related activities and documents to evaluate whether the study has been performed in accordance with the protocol, SOPs, and applicable laws and regulations, as well as whether the study data have been recorded in a timely, truthful, accurate and complete manner. Audits should be conducted by personnel not directly involved in the clinical study.

12.6.1 Monitoring

A monitoring plan should be developed, and SOPs for monitoring should be established for the clinical study. The monitoring plan should comply with relevant laws and regulations, including monitoring strategies, monitoring responsibilities of all parties involved in the study, monitoring methods, and reasons for using different monitoring methods. It should emphasize the protection of the rights and interests of subjects, ensure the authenticity of data, and ensure that various risks in the clinical study are addressed.

The specific contents of monitoring include:

- 1) Confirm before initiation of the study that the study site has appropriate conditions, including staffing and training, well-equipped and well-functioning laboratories, various study-related testing capacities, a sufficient estimated number of subjects, and that the study personnel is familiar with the requirements of the protocol;
- 2) Verify that the study drugs are supplied, stored, dispensed and recovered in accordance with relevant regulations, and recorded accordingly;
- 3) Monitor the investigator's implementation of the study protocol, verify whether the investigator has fulfilled the responsibilities stipulated in the protocol and contract, and whether these responsibilities are delegated to unauthorized personnel during the study; ensure that the investigator receives the latest version of the Investigator's Brochure, all study-related documents, and study essential supplies, and implement them in accordance with the requirements of relevant laws and regulations.
- 4) Confirm the eligibility of enrolled subjects and report the enrollment rate and progress of the clinical study.
- 5) Confirm the accuracy and completeness of the CRF entries and their consistency with the source documents; verify whether there is any follow up, test or examination not performed by the investigator, whether errors and omissions are corrected by the investigator, and whether the above information is recorded in the CRF; verify that the withdrawal and loss to follow-up of enrolled subjects have been recorded and explained in the CRF; and ensure that any corrections,

additions, or deletions are made by the investigator or authorized personnel, and are signed and dated by the modifier, with reasons for modification provided if necessary.

- 6) Confirm that all AEs are reported within the specified timeframe in accordance with relevant laws and regulations, the study protocol, the EC, and the sponsor's requirements.
- 7) Communicate with the investigator in a timely manner regarding deviations from the study protocol, SOPs, and relevant laws and regulations, and take appropriate measures to prevent recurrence of the deviation.
- 8) Assist the investigator in necessary notification and application procedures, and report study data and results to the sponsor.
- 9) Prepare a written monitoring report after each monitoring visit, which should include the date, time, name of the monitor, and names of the investigators and other personnel contacted by the monitor. The sponsor should review and follow-up the issues in the monitoring reports, and make documentations for filing.

12.6.2 Audit and Inspection

The sponsor shall establish audit procedures for the clinical study and the study quality management system to ensure the implementation of audit procedures during the clinical trial. The sponsor or designated auditors should conduct audits of the clinical trial facility, including systematic and independent inspections of clinical study-related activities and documents.

Upon reasonable notice, the investigator should allow study-related audits by an auditor commissioned by the sponsor, as well as inspections by the regulatory authorities. The primary objective of the audits or inspections is to assess the compliance with the protocol, SOPs, and relevant laws and regulations for the conduct of clinical study-related activities, as well as the recording, analysis and reporting of study data. The investigator should provide direct access to all study documents, original records, and original data. Any problems observed and discovered by the auditor during the audit process should be documented in writing.

The drug regulatory authority may request the sponsor to provide audit reports based on work needs.

12.7 Early Termination or Suspension of the Study

Requested by the Investigator

The investigator may not be able to continue the study due to certain reasons. According to GCP requirements, if the investigator terminates or suspends a clinical trial without prior agreement of the sponsor, the investigator should inform the clinical trial institution, the sponsor and the EC immediately, and should provide them a detailed written explanation of the termination or suspension.

Requested by the Sponsor

The sponsor requests a premature discontinuation of the study or premature discontinuation of the study at a certain site for the following reasons:

- 1) Financial reasons;

- 2) Management reasons;
- 3) The investigator's failure to comply with the protocol, GCP, etc.;
- 4) The investigator's inability to recruit enough subjects;
- 5) Safety considerations.

According to GCP requirements, if the sponsor terminates or suspends the clinical study, the sponsor should notify the investigator and the drug regulatory authority. The investigator should report to the clinical trial institution and the EC, and provide a detailed written explanation.

Ethics Committee

If the EC terminates or suspends an approved clinical study, the investigator should inform the clinical trial institution and the sponsor immediately with providing a detailed written explanation of the termination or suspension.

Requested by Competent Authorities

According to the Provisions for Drug Registration, NMPA may order the sponsor to modify the clinical study protocol, suspend or early terminate the clinical study in any of the following cases during clinical study:

- 1) Failure of the EC to perform its duties;
- 2) Inability to ensure the safety of the subjects;
- 3) Failure of the sponsor to submit development safety update report as required;
- 4) Failure of the sponsor to timely address and report suspected and unexpected serious adverse reactions;
- 5) Evidence showing the clinical study drug is ineffective;
- 6) Quality problems of clinical study drugs;
- 7) Data falsification in clinical study;
- 8) Other GCP violations.

12.8 Recording and Preservation of Study Data

According to GCP requirements, for clinical studies used to apply for drug registration, essential documents should be kept for at least 5 years after the study drug is approved for marketing.

12.9 Confidentiality and Publication of Study Results

All information related to this study (including but not limited to the following documents: protocol, Investigator's Brochure) must be kept strictly confidential. The investigator must recognize that the scientific or medical information derived from this study may have commercial value to the sponsor. The investigator should keep confidential the information and data related to this study. If the investigator intends to publicly disclose information related to this study or conclusions drawn from the study, the investigator should consult with the sponsor in advance and obtain the sponsor's written consent. In order to protect its own rights and

interests, the sponsor may request the investigator not to publish information about the study before the study product is approved for marketing.

The sponsor has the right to publish or disseminate information or data related to this study, or to submit it to the drug regulatory authority. If the sponsor needs to include the investigator's name in the publication, dissemination, or advertising content, the sponsor should obtain the consent of the investigator.

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14 Appendices

14.1 Appendix 1: Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

1 Measurability of Tumor at Baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized into measurable or non-measurable as follows:

1.1.1 Measurable Lesions

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness not more than 5 mm)
- 10 mm by clinical routine examination equipment (tumor lesions that cannot be accurately measured with a caliper should be recorded as not measurable)
- 20 mm by chest X-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short diameter when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2 Non-Measurable Lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short diameter) as well as truly non-measurable lesions. Non-measurable lesions include meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, lymphangitis carcinomatosa of the skin/lung, abdominal masses that cannot be confirmed or followed up by imaging, and cystic lesions.

1.1.3 Special Considerations for Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comments:

Bone lesions:

- Bone scans, PET scans, or plain scans are not considered adequate imaging techniques to measure bone lesions, but can be used to confirm the presence or disappearance of bone lesions;
- Lytic bone lesions or mixed lytic-osteoblastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above;

- Osteoblastic lesions are non-measurable

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts;
- If it is a cystic metastatic lesion and meets the above definition of measurability, it can be considered a measurable lesion. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. The study protocol should describe in detail the criteria for these lesions to be considered measurable lesions.

1.2 Description of Measurement Methods

1.2.1 Lesion Measurement

All tumor measurements should be recorded in metric units at the time of clinical evaluation. All baseline tumor lesion should be measured at a time as close as possible to treatment initiation and should be completed within 28 days (4 weeks) prior to the start of the treatment.

1.2.2 Evaluation Methods

The same techniques and methods should be used for baseline assessment and subsequent measurements of lesions. All lesions must be assessed using imaging, except for lesions that cannot be assessed by imaging and can only be assessed by clinical investigation.

Clinical lesions: Clinical lesions are considered measurable only if they are superficial and ≥ 10 mm in diameter at the time of measurement (e.g., skin nodules). For patients with skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be assessed by both imaging and clinical examination, imaging should be used whenever possible, as imaging is more objective and can be reviewed repeatedly at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. Chest X-ray is applicable only when the lesions are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If the CT slice thickness is greater than 5 mm, the minimum measurable lesion should be twice the slice thickness. MRI is also acceptable in some cases (e.g., for whole body scan).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review on a later date due to their operational dependence, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are found using ultrasound during the study, they should be confirmed by CT or MRI. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers cannot be used alone to assess objective tumor response. However, if the marker level exceeds the upper limit of normal at baseline, it must return to normal for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytological/histological techniques: In specific situations stipulated by the protocol, these techniques can be used to identify PR and CR (such as the common presence of residual benign tumor tissue in germ cell tumor lesions). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and PD.

2 Tumor Response Assessment

2.1 Assessments of All Tumors and Measurable Lesions

In order to evaluate objective response or possible future progression, it is necessary to assess the overall tumor burden of all tumor lesions at baseline and use this as a reference for subsequent measurements. In clinical protocols where objective response is the primary endpoint, only patients with measurable lesions at baseline can be enrolled. A measurable lesion is defined as the presence of at least one measurable lesion. In studies where the primary treatment endpoint is PD (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2.2 Baseline Documentation of Target and Non-target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means

for subjects have only one or two accumulative organs, a maximum of two and four lesions respectively will be selected as the baseline measurement lesions).

Target lesions must be selected on the basis of their size (the longest diameter), be representative of all involved organs, and the measurement must have well repeatability. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes require special attention because they are normal tissues and can be detected by imaging even in the absence of tumor metastases. Pathological lymph nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short diameter of ≥ 15 mm by CT scan. Only the short diameter needs to be measured at baseline. Radiologists usually use the short diameter of a nodule to determine whether the nodule has metastasized. The size of nodules is generally expressed in terms of two-dimensional data from image detection (for CT scan, this is always the axial plane; for MRI, a plane will be chosen from the axial, sagittal, or coronal plane). The minimum value is the short diameter. For example, an abdominal node which is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm is the measurement of the nodule. Nodules with a diameter ≥ 10 mm but < 15 mm should not be considered target lesions. Nodules < 10 mm are not considered pathological nodules and do not need to be recorded or followed up.

The sum of the diameters (longest diameters for non-nodal lesions, short diameters for nodal lesions) for all target lesions will be calculated as the baseline sum diameters and reported. If lymph node diameters are included, as mentioned above, only the short diameters are included in the calculation. The baseline sum of diameters will serve as the reference value for the baseline level of the disease.

All remaining lesions, including pathological lymph nodes, may be considered non-target lesions and do not require measurement but should be recorded at baseline assessment. For example, recorded as "present", "missing" or in rare cases "unequivocal progression". In addition, target lesions that are widespread may be recorded with the target organ (e.g., massive pelvic lymphadenopathy or extensive liver metastases).

2.3 Response Criteria

2.3.1 Target Lesion Assessment

Complete response (CR): All target lesions disappear, and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters.

Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an absolute increase of at least 5 mm (the appearance of one or more new lesions is also considered progression).

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD in target lesions, taking the smallest value of sum of diameters while on study as reference.

2.3.2 Considerations for Target Lesion Assessment

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short diameter measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes shrinkage to below 10 mm on study. This means that if a lymph node is a target lesion, it cannot be said that the lesion has completely disappeared even if the criteria for complete response are met, since a normal lymph node is defined as having a short diameter of <10 mm. CRFs or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that are too small to measure: in clinical studies, all lesions (nodal or non-nodal) recorded at baseline should have their actual measurements recorded again at subsequent assessments, even if the lesions are very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". In this case, it is important to record the previous value on the CRF. If the radiologist believes that the lesion may have disappeared, it should also be recorded as 0 mm. If the lesion does exist but is relatively blurred and an accurate measurement cannot be given, it can be defaulted to 5 mm. (Note: This is unlikely to occur in lymph nodes, as they are usually of measurable size under normal circumstances, or are often surrounded by adipose tissue, such as in the retroperitoneal space; however, if this situation also occurs where no measurement can be given, it is also defaulted to 5 mm). The default value of 5 mm is derived from the slice thickness of the CT scan (this value does not change with different CT slice thicknesses). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce: When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

2.3.3 Assessment of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Although some non-target lesions are actually measurable, they do not need to be measured, but only need to be qualitatively assessed at the time points specified in the protocol.

Complete response (CR): All non-target lesions disappear and tumor markers return to normal levels. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: One or more non-target lesions are present and/or tumor marker levels are persistently maintained above the normal limit.

PD: There is clear progression of existing non-target lesions. Note: The appearance of one or more new lesions is also considered PD.

2.3.4 Special Considerations for the Assessment of Progression of Non-Target Lesions

The concept of progression of non-target lesions requires additional explanation as follows: when the patient also has measurable lesions: in this setting, to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions such that, even in presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR of target lesions will therefore be extremely rare.

When the patient has only non-measurable lesion: This circumstance arises in some phase 3 trials when it is not a criterion of study entry to have measurable lesion. The same general concepts apply here as noted above; however, in this instance, there is no measurable data of lesion. Because worsening in non-target lesions cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable lesion is comparable in magnitude to the increase that would be required to declare PD for measurable lesion: i.e. an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from "localized" to "widespread", or may be described in protocols as "sufficient to require a change in therapy". Examples also include peritoneal exudates from trace to large; lymphangitic lesions from in situ to distant; or possibly described in protocols as "sufficient to change treatment". If unequivocal progression is noted, the patient should be considered to have had overall PD at that point. It is preferable to have objective criteria applicable to the assessment of unmeasurable lesions, noting that the criteria for increase must be reliable.

2.3.5 New Lesions

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning techniques, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a new cystic lesion, but in fact, it is not.

A lesion identified on a follow-up visit but not scanned at baseline is considered as a new lesion and will indicate PD. An example of this is a patient who has visceral disease at baseline and the brain CT or MRI performed during study reveals metastases. This patient's brain metastases are considered to be evidence of PD even if he/she does not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents a truly new lesion. If a repeat examination confirms a new lesion, the time to PD should be calculated from the time it is first identified.

Lesions undergoing FDG-PET assessment generally require additional testing for confirmatory supplementation. It is reasonable to evaluate the progression by combining the results of the FDG-PET examination with supplementary CT scans, especially in the case of new suspected diseases. For new lesions that can be determined by FDG-PET imaging, the assessment should be performed according to the following procedures:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD, it is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study until the end of the study taking into account any requirement for confirmation. On occasion, a response may not be documented until after the end of therapy, so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. The protocol must specify how any new treatment prior to progression affects the best response. The patient's best overall response assignment will depend on the findings of both target and non-target lesions and will also take into consideration the appearance of new lesions. In addition, it depends on the nature of the study, the protocol requirements, and the outcome measures. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to determine which one is the BOR.

2.4.1 Time Point Response

It is assumed that a response occurs at the specific time point defined for each protocol. Appendix 1, Table 1 will provide a summary of the overall therapeutic response at each time point in a population of patients with measurable disease at baseline.

If the patient has no measurable lesions (no target lesions), the assessment can refer to Appendix 1, Table 2.

2.4.2 Explanation of Missing and Unevaluable Assessments

If lesion imaging or measurement cannot be performed at a particular time point, the patient is not evaluable at that time point. If only a portion of the lesions can be assessed in an evaluation, this is generally considered not evaluable at that time point unless there is evidence that the missing lesions will not affect the response evaluation at the designated time point. This is most likely to occur in the setting of PD. For example, if a patient has a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions are assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3 Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient is known.

Assessment of best overall response when the study does not require confirmation of complete or partial response: The best response in the study is the best response at all time points (e.g., a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best overall response, it must also meet the protocol specified minimum time from baseline. If the minimum time criterion is not met, even if the best overall response assessment is SD, it is not recognized, and the patient's best overall response will depend on subsequent assessments. For example: a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment will be considered not evaluable.

In the dose expansion stage, the assessment of BOR in the study where confirmation of complete or partial response is required: CR or PR may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. In this case, the best overall response is described in Appendix 1, Table 3. Confirmation is not required during the dose escalation stage.

2.4.4 Special Considerations for Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the CRF.

In studies where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of response. For example, in most studies, it is reasonable to consider a subject with time point responses of PR-NE-PR as a confirmed response.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as 'symptomatic deterioration'. Every effort should be made to assess for objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason

for stopping study therapy. The objective response status of such subjects will be assessed by the status of target and non-target lesions as shown in Appendix 1, Tables 1 to 3.

Conditions that define early progression, early death and inevaluability are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some situations, it is difficult to discriminate local residual disease from normal tissue. When the assessment of complete response is based on such a definition, it is recommended that a biopsy be performed prior to efficacy assessment of CR at that local site. FDG-PET is used as an assessment criterion similar to biopsy for confirming tumor response in some subjects when abnormal imaging findings of local lesions are considered to represent fibrosis or scarring of the lesion. In this case, the use of FDG-PET should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Appendix 1 Table 1 Time Point Response: Subjects with Target (+/- Non-target) Lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	Non-	CR
CR	Non-CR/Non-PD	Non-	PR
CR	NE	Non-	PR
PR	Non-PR or not all evaluable	Non-	PR
SD	Non-PR or not all evaluable	Non-	SD
Not all evaluable	Non-PD	Non-	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR=Complete response	PR=Partial response	SD=Stable disease	PD=Progressive disease NE=Not evaluable

Appendix 1 Table 2 Time Point Response - Subjects with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	Non-	CR
Non-CR or Non-PD	Non-	Non-CR or Non-PD
Not all evaluable	Non-	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Note: "Non-CR/non-PD" is preferred over SD for non-target lesions. Since SD is increasingly used as endpoint for assessment of response in some trials so to assign this category when no lesions can be measured is not advised.

For equivocal findings of progression (e.g. very small and undefined new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression is suspected.

Appendix 1 Table 3 Best Overall Response when Confirmation of CR and PR is Required

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR ^a
CR	SD	SD, if SD lasts long enough, otherwise, PD
CR	PD	SD, if SD lasts long enough, otherwise, PD
CR	NE	SD, if SD lasts long enough, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, if SD lasts long enough, otherwise, PD
PR	NE	SD, if SD lasts long enough, otherwise, NE
NE	NE	NE

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable. "a": If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response depends on whether minimum duration for SD is met. However, sometimes CR may be evaluated at first assessment, but subsequent scans suggest that small lesions are likely still present, and in fact, the subject has PR, not CR at the first time point. In this case, the original CR should be changed to PR and the best response is PR.

2.5. Frequency of Tumor Re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase 2 studies where the beneficial effect of therapy is not known, follow-up every 6-8 weeks (timed to coincide with the end of a cycle) is reasonable and the length of the interval can be adjusted in special regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target lesions should be evaluated at each assessment. In certain selectable situations, the frequency of evaluation for some non-target lesions can be reduced. For example, a repeat bone scan is only necessary when the efficacy evaluation of the target disease is confirmed as CR or when there is suspicion of progression in osseous lesions.

After the end of the treatment, the need for repetitive tumor evaluation depends on whether the study has as a goal the response rate or the time to an event (progression/death). If "time to an event" (e.g. TTP/DFSFS) is the primary endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative studies in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6-8 weeks on treatment or every 3-4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6. Efficacy Evaluation/Confirmation of DOR

2.6.1. Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has been traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomized studies (phase 2 or 3) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6-8 weeks) that is defined in the study protocol.

2.6.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent disease or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease or PD is objectively documented.

2.6.3. Duration of Stable Disease

The time from the start of treatment to PD (in randomized studies, starting from the time of randomization), with the smallest sum in the study as the reference (if the baseline sum is the smallest, it is used as the reference for calculating PD). The clinical relevance of the duration of SD varies in different studies and diseases. If, in a specific study, the proportion of patients maintaining the shortest stable period is used as the study endpoint, the protocol should specifically state the minimum time interval between two measurements in the definition of SD.

Note: The duration of response and SD as well as PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

14.2 Appendix 2: Eastern Cooperative Oncology Group (ECOG) - Performance Status

Score	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Death.

14.3 Appendix 3: Cockcroft and Gault Formula

Creatinine clearance will be calculated using the measured value of serum creatinine (in $\mu\text{mol/L}$):

$$\text{Female: } \frac{(140 - \text{Age} \times \text{Weight (kg)} \times 1.23 \times 0.85}{\text{Creatinine } (\mu\text{mol/L})}$$

$$\text{Male: } \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times 1.23}{\text{Creatinine } (\mu\text{mol/L})}$$

Creatinine clearance will be calculated using the measured value of serum creatinine (in mg/dL):

$$\text{Female: } \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} \times 0.85$$

$$\text{Male: } \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72}$$

Cited from:

[1]. Siersbaek NK, et al. Lancet. 1971, 1(7709): 1133-1134.

[2]. Kampmann J, et al. Acta Med Scand. 1974, 196(6): 517-520.

14.4 Appendix 4: New York Heart Association (NYHA) Classification of Heart Failure

NYHA Class	Criteria
I	Without symptoms and restrictions in ordinary physical activities. Experiencing tachypnoea while walking, climbing stairs, etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation of activities due to symptoms, even during less-than-ordinary activity (e.g., walking short distances, ~ > 20 to 100 m). Asymptomatic at rest only.
IV	Severe limitations. With symptoms even at rest, mainly for bedridden subjects.

Statistical Analysis Plan for Phase I/II Oncology Studies

SAP Version No.: V1.0

Sponsor Name: MediLink Therapeutics (Suzhou) Co., Ltd.

Protocol Name & Version: **YL201-INT-101-01 (Dose-escalation Study)**
A Phase 1, Multicenter, Nonrandomized, Open-Label, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of YL201 in Patients with Advanced Solid Tumors
Version 4.0, 13 April 2023

YL201-CN-101-01 (Dose-expansion Study)
A Multi-Center, Open-Label, Phase 1b Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of YL201 in Patients with Selected Advanced Solid Tumors
Version 3.0, 06 December 2023

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I confirm that I have reviewed this document and agree with the content.

Approvals		
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

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1. Glossary of Abbreviations

Abbreviation or specialist term	Description
ADA	Anti-drug antibody
ADC	Antibody-drug Conjugate
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
B7H3	B7 homolog 3
BI	Before Infusion
BLQ	Below the limit of quantitation
CI	Confidence interval
CL	Clearance rate
C _{max}	Maximum concentration
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
C _{trough}	Trough concentration
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic case report form
EOI	End of infusion
ESCC	Esophageal squamous cell carcinoma
FFS	Failure-free survival
ICF	Informed consent form
IV	Intravenous (ly)
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung carcinoma
ORR	Objective response rate
OS	Overall survival
PC	Prostate cancer
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetic
PSA	Prostate-specific antigen
PT	Preferred term
Q3W	Once every 3 weeks
QTc	Corrected QT interval
QTcF	Fridericia correction of QT interval

Abbreviation or specialist term	Description
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RED	Recommended expansion dose
rPFS	Radiological progression-free survival
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCLC	Small cell lung cancer
SD	Stable disease
SOC	System organ class
SpO ₂	Peripheral oxygen saturation
t _{1/2}	Half-life time
TAb	Total antibody
TEAE	Treatment-emergent adverse event
TTR	Time to response
WHO	World Health Organization

2. Introduction

Antibody-drug conjugates (ADCs) are being developed to improve the therapeutic index of cytotoxic anticancer agents. The strategy makes use of an immunoconjugate in which a cytotoxic agent is chemically linked to an antibody that selectively binds to an internalizing tumor-associated antigen. This strategy allows the delivery of the cytotoxic agent to the tumor site while minimizing the exposure to normal tissues. YL201 is an ADC that targets B7H3. YL201 consists of an anti-B7H3 antibody component and a drug component, bound via a novel tripeptide linker. The drug component ("YL0010014" hereafter) is a topoisomerase I inhibitor, which is derived from the antitumor agent camptothecin with an innovative structure.

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

3. Study Objectives

3.1 Dose-Escalation Study (YL201-INT-101-01 Study)

Primary Objectives:

- To assess the safety and tolerability of YL201 in patients with advanced solid tumors
- To determine the maximum tolerated dose (MTD) and select the recommended expansion dose(s) (RED(s)) of YL201 in patients with advanced solid tumors

Secondary Objectives:

- To characterize the pharmacokinetics (PK) of YL201 antibody-drug conjugate (YL201-ADC), YL201 total antibody (YL201-TAb), and unconjugated payload YL0010014
- To evaluate immunogenicity as measured by the presence of anti-drug antibodies (ADAs) in patients treated with YL201
- To document any preliminary evidence of YL201 efficacy in patients with advanced solid tumors

Exploratory Objectives:

- To evaluate the level of soluble B7 homolog 3 (B7H3) in peripheral blood before and after treatment and its relationship with efficacy

3.2 Dose-Expansion Study (YL201-CN-101-01 Study)

Primary Objectives:

- To evaluate the safety and tolerability of YL201 in patients with selected advanced solid tumors
- To evaluate the efficacy of YL201 in patients with selected advanced solid tumors based on the objective response rate (ORR)

Secondary Objectives:

- To evaluate other efficacy endpoints of YL201 in patients with selected advanced solid tumors
- To evaluate the pharmacokinetic (PK) characteristics of YL201
- To evaluate the immunogenicity of YL201

Exploratory Objectives:

- To explore biomarkers associated with YL201 efficacy
- To explore the exposure-response (E-R) relationships for efficacy and safety endpoints of YL201

4. Study Design

4.1 Dose-Escalation Study (YL201-INT-101-01 Study)

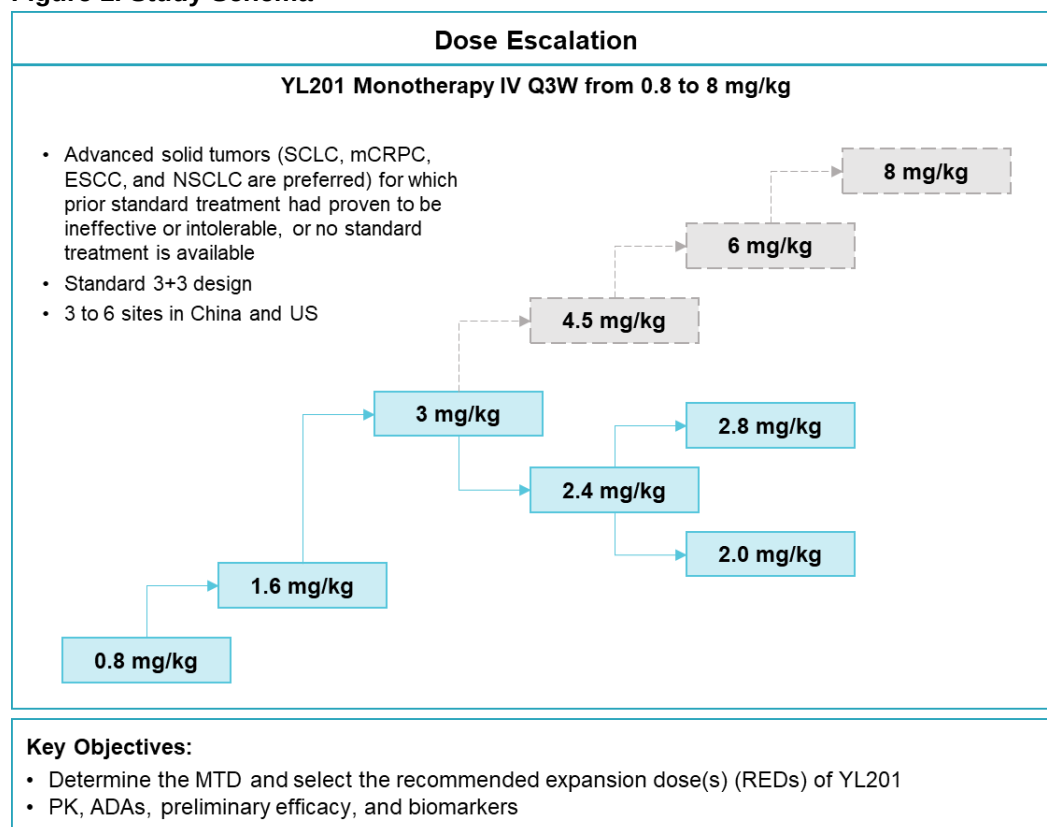
This is a phase 1, multicenter, nonrandomized, open-label, first-in-human study of YL201 conducted in China and the United States. The study will estimate the MTD/RED(s) in dose escalation cohorts of patients with advanced solid tumors unresponsive to currently available therapies or for whom no standard therapy is available.

Dose escalation will begin in patients with advanced solid tumors (SCLC, mCRPC, ESCC, and NSCLC are preferred). The proposed human starting dose of YL201 is 0.8 mg/kg, based on one sixth of the HED of the HNSTD in monkeys (15 mg/kg). Six dose levels are initially planned and include 0.8, 1.6, 3, 4.5, 6, and 8 mg/kg (Table 1). After observing two DLTs at 3.0 mg/kg, which were deemed intolerable, three intermediate dose levels including 2.4, 2.8, and 2.0 mg/kg are added after discussion with the SRC according to the toxicity data accrued in preceding dose levels. The study schema is shown in Figure 1.

Table 1. Proposed Dose-Escalation Scheme

Dose level	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6
Dose (mg/kg, Q3W)	0.8	1.6	3	4.5	6	8
Dosage increment	—	100%	88%	50%	33%	33%

Figure 1. Study Schema



To better estimate the MTD/RED(s) and characterize the safety, PK parameters, and efficacy of YL201, additional patients with preferred tumor types (SCLC, mCRPC, ESCC, and NSCLC) or other tumor types agreed upon after discussion with the sponsor may be enrolled in 1 or more dose levels that have been deemed to be safe and tolerable, defined as backfill enrollment. This backfill enrollment may be concurrent with dose escalation to estimate the MTD/RED(s), and are not included in the total number of DLT-evaluable patients.

Patients will be treated with YL201 IV infusion Q3W as a cycle. The number of treatment cycles is not fixed in this study. Patients who continue to derive clinical benefit from this study treatment in the absence of unacceptable toxicity, progressive disease (PD), or withdrawal of consent may continue the study treatment.

After completing the end-of-treatment (EOT) visit, patients will be followed up via a telephone call or site visit to confirm survival status and new cancer treatments every 3 months (± 7 days) until death or lost to follow up.

If the dose is interrupted because of toxicities, dose reduction may need to be conducted on the next administration when treatment is resumed. A maximum of 2 dose reductions are permitted, and the dose level will not be below 0.8 mg/kg. After 2 dose reductions, further dose reduction should not be conducted and the study treatment should be discontinued unless discussed and agreed with the sponsor.

The study is expected to be completed in approximately 3 years from the time the first patient is enrolled to the time the last patient is off the study.

4.2 Dose-Expansion Study (YL201-CN-101-01 Study)

This is a multi-center, open-label, Phase 1b study of YL201 conducted in China to evaluate the safety, efficacy, and PK characteristics of YL201 in patients with the following selected advanced solid tumors:

- Cohort A: Patients with locally advanced or metastatic NSCLC without actionable genomic alterations who have progressed or are intolerant during or after standard of care (including platinum-based chemotherapy and anti-programmed death receptor (ligand) 1 (anti-PD-(L)1) therapy)
- Cohort B: Patients with locally advanced or metastatic NSCLC with actionable genomic alterations who have progressed or are intolerant during or after standard of care (including targeted therapy for driver genes)
- Cohort C: Patients with extensive-stage SCLC who have progressed or are intolerant during or after standard of care (including platinum-based chemotherapy and anti-PD-(L)1 therapy)
- Cohort D: Patients with recurrent or metastatic NPC who have progressed or are intolerant during or after standard of care (including platinum-based chemotherapy and anti-PD-(L)1 therapy)
- Cohort E: Patients with locally advanced unresectable or metastatic ESCC who have progressed or are intolerant during or after standard of care (including platinum, fluorouracil, or taxane-based chemotherapy and anti-PD-(L)1 therapy)

- Cohort F: Patients with other solid tumors who have progressed or are intolerant during or after standard of care

Patients in each cohort are not required to confirm the expression level of B7H3 in tumor tissues before enrollment, but they need to provide archived or fresh tumor samples. Patients who are not able to provide tumor samples or have inadequate samples may be eligible on a case-by-case basis after discussion with the sponsor.

Based on the results of the YL201-INT-101-01 dose-escalation study, 2.0 mg/kg and 2.4 mg/kg will be selected as the recommended expansion dose (RED) of YL201. During the study, the sponsor and investigator will, based on the available data, decide whether and when to initiate or terminate a particular cohort or dose level, and whether to explore other dose levels or dosing regimens, based on a balance between subject risks and benefits.

Patients will be treated with YL201 IV infusion at REDs Q3W as a treatment cycle. The number of treatment cycles is not fixed in this study. Patients who can benefit from this study treatment may continue study treatment until PD, intolerable toxicity, or withdrawal of consent.

5. Study Endpoints

5.1 Dose-Escalation Study (YL201-INT-101-01 Study)

Primary Endpoints:

- Occurrence of DLTs during the first cycle

Secondary Endpoints:

- AEs as characterized by type, frequency, severity, timing, seriousness and relationship to study treatment
- Laboratory abnormalities as characterized by type, frequency, severity and timing
- Physical examination findings, ECOG PS, vital signs and peripheral oxygen saturation (SpO₂) measurements, and electrocardiogram (ECG) parameters
- Single- and multiple-dose PK parameters of YL201-ADC, YL201-TAb, and unconjugated payload YL0010014, including but not limited to area under the curve (AUC), maximum concentration (C_{max}), trough concentration (C_{trough}), clearance rate (CL), volume of distribution (V_d), and half-life time (t_{1/2})
- Incidence of anti-YL201 antibodies
- For patients with prostate cancer (PC): Prostate-specific antigen (PSA) response rate, best PSA response, PSA progression-free survival (PFS), radiological PFS (rPFS), failure-free survival (FFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), duration of response (DoR), time to response (TTR), and best tumor response, assessed using RECIST version 1.1 modified based on Prostate Cancer Working Group 3 (PCWG3) criteria
- For patients with non-PC: ORR, DCR, DoR, TTR, PFS, OS, and best tumor response, assessed using RECIST version 1.1

Exploratory Endpoints:

- The level of sB7H3 in peripheral blood before and after treatment

5.2 Dose-Expansion Study (YL201-CN-101-01 Study)

Primary Endpoints:

- Adverse events (AEs) as characterized by type, frequency, severity, time, and relationship to study treatment
- Laboratory test results, physical examination results, ECOG PS, vital signs, peripheral oxygen saturation (SpO₂), and electrocardiogram (ECG) parameters
- ORR assessed as per RECIST v1.1

Secondary Endpoints:

- Depth of response (DpR), disease control rate (DCR), duration of response (DoR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) assessed as per RECIST v1.1
- Single- and multiple-dose PK parameters of YL201 (including ADC, total antibody (TAb), and unconjugated payload YL0010014), including but not limited to area under the curve (AUC), maximum concentration (C_{max}), trough concentration (C_{trough}), clearance (CL), volume of distribution (V_d), and half-life ($t_{1/2}$)
- Metabolite profile of YL201
- Incidence of anti-YL201 antibodies

Exploratory Endpoints:

- Correlation between B7H3 expression level in tumor tissue and efficacy of YL201
- Correlation between the level of soluble B7H3 (sB7H3) in peripheral blood and efficacy of YL201
- Correlation between the efficacy and safety endpoints of YL201 and exposure

6. Analysis Sets

The following subject populations (i.e., analysis sets) will be evaluated and used for presentation of the data:

Full Analysis Set: Include all patients enrolled in this study.

Safety Analysis Set: Includes all patients who received at least 1 dose of YL201.

DLT-Evaluable Set: A subset of the full analysis set and includes all patients who were enrolled in the dose escalation study and received at least 1 dose of YL201, with the exception of those patients for whom DLT evaluation could not be adequately conducted.

Efficacy Analysis Set: A subset of the full analysis set and includes all patients who received at least 1 dose of YL201 and had baseline and at least 1 post-baseline efficacy assessment.

Pharmacokinetic Concentration Analysis Set: A subset of the full analysis set and includes all patients who received at least 1 dose of YL201 and had at least 1 post-dose concentration measurement above the lower limit of quantitation (LLOQ) for YL201-ADC, YL201-TAb, or YL0010014, without major protocol deviations or events (e.g., incomplete dosing, disallowed concomitant medications) affecting PK. This population will be used for PK analyses.

PK Parameter Analysis Set: A subset of the full analysis set and includes all patients who have at least 1 PK parameter of interest for YL201-ADC, YL201-TAb, or YL0010014, without major protocol deviations or events (e.g., incomplete dosing, disallowed concomitant medications) affecting PK.

Immunogenicity Analysis Set: A subset of the full analysis set and includes all patients who received at least 1 dose of YL201 and had at least 1 ADA assessment.

Biomarker Analysis Set: A subset of the full analysis set and includes all patients who received at least 1 dose of YL201 and had baseline and, where applicable, at least 1 post-baseline assessment for biomarkers.

7. Statistical Methodology

7.1 Statistical and Analytical Issues

7.1.1 Statistical Methods

Tabulations will be produced for selected demographic, baseline, safety, PK, efficacy parameters and biomarker data by dose level and time as appropriate. Continuous variables will be summarized by reporting the number of observations, mean, standard deviation, median, minimum, and maximum (as well as geometric mean and geometric coefficient of variation for C_{max} and AUC PK parameters).

Categorical variables will be summarized using frequency tables showing the number and percentage of subjects within a particular category, where the denominator is the number of non-missing values within category at applicable time point (unless otherwise specified). Time-to-event data will be summarized using the Kaplan-Meier method to present time-to-event data.

By-subject data listings will be produced for data collected through the study (e.g., CRF, PK, lab). All data listings that contain an evaluation date will contain a relative study day (Study Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study drug, which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. Unless otherwise specified, a baseline will be defined as the last evaluable/non-missing observation/assessment on or before the first dose of study drug on Cycle 1, Day 1.

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

When summarizing categorical variables, patients with non-missing data are included in the denominator to calculate percentages unless otherwise specified. When needed, the category of "Missing" is created and the number of patients with missing data is presented. When summarizing continuous variables, patients with missing data are not included in calculations.

As these are Phase 1/IIb, dose-escalation and dose-expansion trials, formal statistical hypothesis testing will not be performed. Although exploratory Confidence Intervals (CIs) will be presented as described below, these data will be used for exploratory conclusions only.

Statistical analyses will be carried out by using SAS Version 9.4 or higher. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the clinical study report.

Adverse events will be graded by the Investigator based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, and will be coded for summarization using the Medical Dictionary for Regulatory Activities (MedDRA® Version 25.0 or later). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2022 version or later).

7.1.1.1 Visit Windows

All data will be tabulated per the evaluation visit as recorded on the eCRF, even if the assessment is outside of the visit window. Unless otherwise stated in the analysis sections below, unscheduled visits will be included in data listings only.

7.1.1.2 Dose Level, Study Part, and Cohort Assignment

Analyses will be presented separately for subjects enrolled into dose escalation and dose expansion studies, and will also be presented for the two studies combined. Assignment of these 3 attributes (dose level, study part, cohort assignment) will be captured on the initial subject disposition electronic case report form (eCRF).

7.1.2 Handling of Dropouts and Missing Data

Unless indicated otherwise, summary statistics will be reported for observed data only and missing data will not be imputed.

7.1.3 Pooling of Investigational Sites

No by-site analyses are planned.

7.1.4 Determination of Sample Size

7.1.4.1 Dose-Escalation Study (YL201-INT-101-01 Study)

The dose-escalation study utilizes a standard 3+3 design and consists of 6 planned dose levels. Therefore, up to 36 DLT-evaluable patients are needed to reach an accurate estimate of the MTD/RED(s). The actual number of dose levels and patients enrolled at each dose level will depend upon tolerability and efficacy of YL201.

7.1.4.2 Dose-Expansion Study (YL201-CN-101-01 Study)

The dose-expansion study will evaluate the efficacy and safety of YL201 at two RED levels. The sample size was determined by practical consideration according to conventional sample size setting of those one arm phase Ib or phase II trials, in order to sufficiently evaluate the preliminary efficacy and observe wider range toxicities. So, the sample size for each indication was set at 30-90 and adjusted based on the emerging efficacy and safety data.

7.2 Subject Characteristics

7.2.1 Subject Disposition

Subject disposition will be presented by dose level for each study, each indication and overall. Tabulation will include the following:

- Number of subjects screened (i.e., who signed the informed consent)
- Number of subjects failed screening
- Number of enrolled subjects
- Number (%) in each subject population for analysis
- Number (%) of subjects who discontinued from treatment and reason(s)
- Number (%) of subjects who remain in study

Subjects excluded from the various analysis populations will be listed. Subjects who discontinue will be listed with reason for discontinuation.

7.2.2 Protocol Deviations

Major protocol deviations, as determined by a review of the data prior to database lock, will result in the removal of a subject from the PK population. Before the final database lock, the Non-compliance

Workbook, containing the cumulative and complete extracts of protocol deviations (PDs) and non-compliances (NCs) from all systems of record, will be generated by the project team.

Information from the final Non-compliance Workbook will be extracted and summarized. The number and percentage of subjects with a major deviation by type of deviation category will be presented by dose level for safety analysis set. In addition, all protocol deviations will be provided in a by-subject listing.

7.2.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be presented by dose level for each study, each indication and overall.

Demographic and baseline characteristics including but not limited to age, sex, race, ethnicity, baseline ECOG PS will be summarized for the full analysis set, safety analysis set and efficacy analysis set. If 2 or more analysis sets are identical to each other, the table will be presented only once. The above variables will be listed and summarized using both continuous and categorical descriptive statistics.

7.2.4 Prior and Concomitant Medications

Prior medication will be defined as any medication started and ended before the date of first treatment. Concomitant medication is defined as any medication that starts before, on or after the date of first treatment and stop on or after the date of first treatment or are still ongoing at the end of study. Medications missing both start and stop dates, or having a start date prior to the ICF date and missing the stop date, or having a stop date on or after the last dose of study drug and missing start date will be counted as concomitant.

For partial dates, the following approach will be taken:

- If the start day is missing but the start month and year are complete, a medication will be excluded as being concomitant only if the start month/year is before the month/year of first treatment obtained and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before first treatment obtained.
- If the start day and month are missing but the start year is complete, a medication will be excluded as concomitant only if the start year is before the year of first treatment signed and if the stop date (either: full date, month and year if missing day, or year if missing month and day) is before first treatment signed.

Prior and concomitant will be coded using the WHO Drug Dictionary, and subject incidence will be tabulated by Anatomic Therapeutic Class (ATC) category level 2 and preferred term, overall and by dose level for the Safety analysis set. Subjects will be counted only once for each ATC or preferred term in the event that they have multiple records of the same ATC or preferred term in the database.

All prior and concomitant medications will be included in a by-subject listing.

7.2.5 Medical Histories (Non-Cancer Related)

Medical history will be coded using MedDRA (version 25.0 or higher) and will be presented in a data listing by dose level and subject. The number of patients with at least one recorded medical history or current medical condition will be presented using frequency counts and percentages as well as an incidence table by SOC and PT. The safety population will be used for this summary. Additional preexisting conditions present at the time when informed consent is given and up to the time of first

dosing are to be regarded as concomitant. Medical history will include alcohol consumption and smoking history.

7.2.6 Cancer-Related Medical History

Descriptive statistics on diagnosis of solid tumor cancer-related medical history characteristics will be presented by dose level for each study, each indication and overall for the following:

- Line and type of prior anti-cancer therapy
- Cancer Stage
- Anatomical location of Primary tumor
- Cancer Histology
- Location and number of metastases
- Time since cancer diagnosis (months) = (Date of informed consent – Date of initial diagnosis)/30.4375.

Above will be presented by dose level in each indication and overall for the full analysis set, safety analysis set and efficacy analysis set. If 2 or more analysis sets are identical to each other, the table will be presented only once. All medical histories will be presented in data listings by dose level and subject.

For the time calculation, if only month and year are provided, the day=15 will be assumed. If only year is provided, month=6 and day=15 will be assumed.

7.2.7 Treatment Exposure and Compliance

The YL201 drug will be administered Q3W. In dose-escalation study, the initial dose of YL201 will be infused IV into each patient for 90±10 minutes. If there is no infusion-related reaction after the initial dose, the second and subsequent doses of YL201 will be infused IV into each patient for 60±10 minutes. In dose-expansion study, YL201 will be infused IV into each patient for 60±10 minutes.

The patient's weight at screening (baseline) will be used to calculate the initial dose. If, during the course of the treatment, the patient's weight changes by more than 10% of the baseline weight, the patient's dose will be recalculated based on the patient's updated weight.

All dose interruption and dose modification will be summarized. Study drug exposure will be presented cumulatively. The number of cycles received will be summarized using descriptive statistics. The number of infusions given will be presented in summary tables. In addition, the total cumulative dose (mg) received and the duration of treatment will be summarized. Total planned dose will be recorded on CRF. If missing, it will be re-calculated programmatically based on the protocol.

Total planned dose (mg) = Planned Dose Level (mg/kg) * Weight (kg) at screening/current visit. If, during the course of the treatment, the patient's weight changes by more than 10% of the baseline weight, the patient's dose will be recalculated based on the patient's updated weight. If dose reduced during the study, total planned dose (mg) will be the reduced dose level (mg/kg) * Weight(kg) at screening/current visit.

Dose Intensity and treatment compliance, which is synonymous with relative dose intensity, will be calculated as follows:

- Total treatment duration in weeks for dose intensity calculation = (Date of last cycle Day 1 - Date of Cycle 1 Day 1 + 21)/7.
- Weekly Dose Intensity (mg/week) = Total dose administered in mg / total treatment duration in weeks.
- Cycle-specific Relative Dose Intensity (%) = (Total dose taken by a subject during the cycle / total planned dose for the subject in this cycle) * 100. The Relative Dose Intensity will be expressed in percentage.

Relative Dose intensity will be summarized by categories:

- Less than 80%
- 80% ~ 120%
- Greater than 120%

Compliance with the study drug regimen will also be measured and summarized by the number of dose reductions.

These analyses will be presented by dose level for each study, each indication and overall. All dosing data will be presented in a data listing.

7.3 Safety Analysis

The safety profile will be based on AEs, clinical laboratory measurements, vital signs and SpO₂ measurements, ECG recordings, physical examination findings, and ECOG PS assessments. AEs will be graded according to the NCI CTCAE version 5.0. In the dose escalation study, the incidence of DLTs will also be evaluated.

Safety analysis in general will be descriptive and will be presented in tabular format with appropriate summary statistics. In the dose escalation study, the number of DLTs identified among the DLT-evaluable patients in the DLT-evaluable set will be listed and summarized for each dose level of YL201.

For both dose-escalation and dose-expansion studies, the primary objectives for this study involve safety. All safety analyses will be performed using the safety analysis set.

7.3.1 Adverse Events

Adverse events will be graded according to the NCI CTCAE Version 5.0, coded using the MedDRA coding system, and displayed in tables and data listings by system organ class (SOC) and preferred term (PT).

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as an AE that emerges during the treatment period (from first dose until safety follow-up visit after the last dose of study drug), having been absent at pretreatment; or reemerges during treatment, having been present at baseline but stopped before treatment; or worsens in severity after starting treatment relative to the pretreatment state, when the AE is continuous.

A condition present at baseline that worsens after initiation of study treatment will be captured as an AE with the onset date as the date the event worsened. A treatment-emergent SAE is defined as a TEAE classified as serious. AEs will be considered as drug-related if they are definitely/probably/possibly

related to study drug as eCRF recorded. Missing relationship will be considered definitely related to study drug. Missing severity will be considered as Grade 5.

If the start date of an AE is partially or completely missing, the date will be compared as far as possible with the date of the start of administration of study drug. The AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). The following general rules will be used:

- If the start day is missing but the start month and year are complete, an AE will be excluded as being treatment-emergent only if the start month/year is before the month/year of study drug administration or if the stop date/time is before study drug administration
- If the start day and month are missing but the start year is complete, an AE will be excluded as being treatment-emergent only if the start year is before the year of study drug administration or if the stop date/time is before study drug administration
- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date is before study drug administration

Adverse events are summarized by subject incidence rates; therefore, in any tabulation, a subject contributes only once to the count for a given SOC or PT (i.e., the most related occurrence or the most intense occurrence).

An overall of TEAE incidence summary table, including the number and percentage of patients with any TEAE, treatment-related TEAE (TRAE), adverse event of special interest (AESI), DLT, grade 3 or higher TEAE, grade 3 or higher TRAE, serious TEAE, serious TRAE, TEAE leading to dose interruption, TRAE leading to dose interruption, TEAE leading to dose reduction, TRAE leading to dose reduction, TEAE leading to study discontinuation, TRAE leading to study discontinuation, TEAE leading to death, and TRAE leading to death will be provided.

Additionally, the following tabulations by SOC and PT, sorted by decreasing frequency, will be produced by dose level for each study, each indication, and overall:

- TEAEs
- TRAEs
- DLTs
- Serious SAEs
- Serious TRAEs
- Grade 3 or higher TEAEs
- Grade 3 or higher TRAEs
- TEAEs leading to dose interruption
- TRAEs leading to dose interruption
- TEAEs leading to dose reduction
- TRAEs leading to dose reduction
- TEAEs leading to study discontinuation
- TRAEs leading to study discontinuation

- TEAEs leading to death
- TRAEs leading to death

In some circumstances, the time interval from the date of first dose of study drug to the first onset date of specific AEs will be summarized. The first onset date of an AE is defined as the date of AE to be identified as TEAE. For an AE that worsens in severity after starting treatment relative to the pretreatment state, the first onset date will be the grade change date.

No formal hypothesis-testing analysis of AE incidence rates will be performed. All AEs occurring on-study will be provided in data listings. By-subject listings also will be provided for the following: SAEs, DLTs, AEs leading dose interruption, AEs leading dose reduction, AEs leading to study discontinuation, and AEs leading to death.

7.3.2 Laboratory Parameters

Clinical laboratory evaluations will include the tests of hematology, biochemistry, coagulation and urinalysis.

Descriptive statistics will be provided for selected clinical laboratory test results (hematology, biochemistry, coagulation, and urinalysis) and changes from baseline by scheduled time of evaluation, including the EOT visit and safety F/U visit. In addition, the change from baseline will be summarized for the maximum post-treatment value and minimum value.

Abnormal laboratory results for selected clinical laboratory tests will be graded according to the NCI CTCAE version 5.0, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the maximum post-baseline grade according to NCI CTCAE, will be provided for selected clinical laboratory tests. All laboratory data will be reported in listings. Abnormal clinical laboratory test results that are deemed of clinical significance or of Grade 3 or 4 will also be listed.

7.3.3 Vital Signs and Oxygen Saturation Analysis

Vital signs will include the following items: Systolic blood pressure (mmHg) and Diastolic blood pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), and body temperature (°C).

The actual value and change from baseline to each visit will be descriptively summarized by visit/assessment, including EOT visit and safety F/U visit. In addition, the change from baseline will be summarized for the maximum and minimum value.

Vital sign and SpO₂ measurements will be presented in data listing separately.

7.3.4 Electrocardiogram

ECGs will include following parameters: Heart Rate (bpm), PR Interval (msec), RR Interval (msec), QRS Duration (msec), QT Interval (msec), QTC Interval (msec).

The actual value and change from baseline to each visit will be descriptively summarized by visit/assessment for ECG parameters, including EOT visit and safety F/U visit. QTc interval will be calculated using Fridericia [$QTcF = QT/(RR)^{1/3}$] corrections; and if RR is not available, it will be replaced with 60/HR in the correction formula.

These summary tables will be presented by timepoint by dose level and overall. A shift table, presenting the 2-way frequency tabulation for baseline and each scheduled time, according to the categories for ECG (normal and abnormal) will be provided.

Electrocardiogram data will be provided in a by-subject listing.

7.3.5 Physical Examination

Following examinations will be performed for the physical examinations: head, eyes, ears, nose, and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and neurological and musculoskeletal systems.

Body weight (without shoes) will be recorded whenever physical examinations are performed; height (without shoes) will be recorded at screening only.

The actual value and change from baseline to each visit will be descriptively summarized for body weight. A shift table for physical examination results from baseline to each visit will be presented.

Physical examination results and findings, including body weight and height, will be reported in a by-subject listing.

7.3.6 Eastern Cooperative Oncology Group Performance Status (ECOG PS)

A shift table from baseline to worst post-baseline ECOG performance score will be summarized by cohort and overall for the Safety Analysis Set. ECOG PS scores and assessment date will be reported in a by-subject listing.

7.4 Efficacy Analysis

Efficacy analyses will be performed by dose level for each study, each indication, and overall for the Efficacy Analysis Set. All efficacy endpoints will be listed and summarized.

For patients with non-PC, the efficacy endpoints will include ORR, DCR, DoR, TTR, PFS, OS, and best tumor response.

For patients with PC, the efficacy endpoints will include PSA response rate, best PSA response, PSA-PFS, rPFS, FFS, OS, ORR, DCR, DoR, TTR, and best tumor response. ORR, DCR, DoR, TTR, and best tumor response will be assessed in patients with PC with measurable soft tissue lesions at baseline only.

7.4.1 Best Tumor Response

Tumor response will be assessed according to RECIST 1.1 (Eisenhauer et al, 2009) by the Investigator according to the schedule of assessments. For patients with PC, RECIST version 1.1 has been modified based on PCWG3 criteria (Scher et al 2016), which are specific for the patient population.

Classification of best overall response is done according to the following hierarchy and rules:

1. CR: requires two consecutive CR response assessments with a minimum of 4 weeks apart
2. PR: requires two consecutive PR response assessments OR a PR response immediately followed by a CR response assessment (a minimum of 4 weeks apart)
3. SD: requires only one SD response assessment at least 6 weeks after the first dose

4. PD: requires only one PD response assessment

As part of RECIST 1.1, the sum of the diameters of all target measurable lesions is recorded. The sum will be used to calculate each subject's maximum percent decrease in target lesions, and waterfall plots of maximum tumor shrinkage (best change from baseline in percentage) per patient will be presented for each indication, and the best response after baseline will be highlighted in different colors for each patient.

7.4.2 Objective Response Rate (ORR)

Objective response rate (ORR) is defined as the proportion of patients who achieved a best overall response of complete response (CR) or partial response (PR). Both confirmed and pending ORR will be presented.

7.4.3 Disease Control Rate (DCR)

Disease control rate (DCR) is defined as the proportion of patients who achieved a best overall response of CR, PR or stable disease (SD).

7.4.4 Progression-Free Survival (PFS)

Progression-free survival (PFS) is defined as the time (months) from the date of the first dose of study drug to the date the progression is observed (i.e., recorded as 'progressive disease' on eCRF) or death due to any cause, whichever comes first.

Refer to Table 2 below for the censoring rules for PFS.

Table 2 Censoring rules for PFS

Hierarchy	Situation	Date of Event/Censoring	Outcome
1	Objectively documented PD	Date of radiological assessment showing PD	Event
2	Death due to any cause (if no documented PD)	Date of death	Event
3	No baseline radiological assessments	Date of first dose of study drug	Censor
4	Treatment discontinuation for clinical (no formal tumor assessment) progression	Date of last adequate radiological assessment prior to discontinuation due to clinical progression	Censor
5	Treatment discontinuation for toxicity or reason other than PD, clinical progression, or death	Date of last adequate radiological assessment	Censor
6	New anticancer treatment started with no PD beforehand	Date of last adequate radiological assessment prior to anticancer therapy	Censor
7	No death, PD, clinical progression, anticancer therapy or discontinuation	Date of last adequate radiological assessment	Censor

7.4.5 Duration of Response (DOR)

Duration of response (DOR) is defined as the months from the first documented CR or PR to the date of the first documentation of PD or death due to any cause, whichever occurs first. The censoring rules for

DOR are the same with PFS except that the situation of 'No baseline radiological assessments' will not apply to DOR.

7.4.6 Time to Response (TTR)

Time to response (TTR) is defined as the time interval from the date of the first dose of study drug to the date of the first documentation of objective response (CR or PR).

7.4.7 Overall Survival (OS)

Overall survival (OS) is defined as the time from the date of the first dose of study treatment to the date of death due to any cause. Subjects who remain alive before data cutoff or discontinued study due to reason other than death will be censored at the time of data cutoff or the last date the patient was known to be alive. Subjects who are not known to have died are censored at the time of data cutoff or the date last known to be alive.

7.4.8 Best PSA Response

Best PSA response is defined as the maximum percentage change in PSA at any time during the study. A waterfall plot of maximum PSA change (best change from baseline in percentage) per patient will be presented.

7.4.9 PSA Response Rate

PSA Response rate is defined as the proportion of patients who achieved a $\geq 50\%$ decrease in PSA from baseline. This is for patients with PC only.

7.4.10 PSA progression-free survival (PSA-PFS)

PSA-PFS is defined as the time interval from the date of the first dose of study drug to the date of the first documentation of PSA progression, based on PCWG3 criteria. The censoring rule for PSA-PFS is similar with PFS. This is for patients with PC only.

7.4.11 Radiological progression-free survival (rPFS)

rPFS is defined as the time interval from the date of the first dose of study drug to the date of the first documentation of radiographic tumor progression or death due to any cause, whichever occurs first, based on RECIST 1.1 and PCWG3 criteria. The censoring rule for rPFS is similar with PFS. This is for patients with PC only.

7.4.12 Failure-free Survival (FFS)

Failure-free survival (FFS) is defined as the time interval from the date of the first dose of study drug to the date of the first documentation of radiographic tumor progression, unequivocal clinical progression, PSA progression or death due to disease progression, whichever occurs first. The censoring rule for FFS is similar with PFS. This is for patients with PC only.

For the analysis of ORR, DCR, and PSA response rate, summary tables presenting the number and proportion of responders and non-responders, together with the 2 sided corresponding 95% exact binomial confidence interval (CI) for response rates will be presented. Summary of each response category of the best overall response (Complete Response [CR], Partial Response [PR], Stable Disease [SD], Progressive Disease [PD] or Not Evaluable [NE]) will be presented as well.

The time-to-event endpoints, including DOR, PFS, OS, PSA-PFS, rPFS and FFS will be analyzed by Kaplan-Meier methods (Kaplan & Meier, 1958). The survival functions of the time-to-event endpoints will be summarized for the 25th percentile (Q1), median, and 75th percentile (Q3) and 2-sided 95% CIs. The PFS rate at 3 and 6 months and OS rate at 6 and 12 months and their 95% CIs will be derived based on Kaplan-Meier estimates. In addition, the graphs of Kaplan-Meier estimates of survival functions will be presented. Additionally, descriptive statistics for TTR will be provided.

These analyses will be performed by dose level for each indication and overall. The date of first dose, disease progression, death, last tumor assessment, last contact, and PFS, OS, PSA-PFS, rPFS, FFS, PSA Progression and Clinical Progression will be reported in a by-subject listing.

7.5 Pharmacokinetics and Immunogenicity Analysis

7.5.1 Pharmacokinetic Analysis

One of the secondary objectives of this study is to evaluate the PK profile of the study drug after single and multiple doses. These analyses will be performed with the PK population. The third-party laboratory designated by the sponsor will be responsible for PK Analysis.

The concentration of YL201-ADC, YL201-TAb and unconjugated payload (YL0010014) will be determined from the blood samples using a validated analytical method.

7.5.1.1 PK Sampling Schedule

In dose-escalation study, serial PK blood samples will be collected from all patients.

In dose-expansion study, serial PK blood samples will be collected from approximately 20-30 patients at each dose level. For the remaining patients, sparse PK blood sample collection will be performed.

The PK analysis will be performed on the PK concentration analysis set using actual sample times and noncompartmental methods. The concentration-time data for YL201-ADC, YL201-TAb, and YL0010014 will be listed, plotted, and summarized using descriptive statistics by dose level at each point. Single- and multiple-dose PK parameters of YL201-ADC, YL201-TAb, and YL0010014 will be listed and summarized using descriptive statistics by dose level. The concentration data may be used to perform a population PK modeling. If performed, results of population PK analysis will be reported separately (i.e., not in the clinical study report).

7.5.2 Immunogenicity Analysis

The immunogenicity analysis will be performed for the immunogenicity analysis set.

The percentage of patients with a positive ADA status will be summarized by dose level and time as appropriate. For patients with a positive ADA status, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit.

7.6 Exploratory Biomarker Analysis

7.6.1.1 B7H3 Expression in Tumor Tissues

For patients in dose-expansion study, 6 to 10 slides of archival or fresh tumor tissue samples are required at screening for assessment of B7H3 expression level. If a patient is not able to provide adequate tumor samples, the investigator should discuss with the sponsor whether this patient can be enrolled or not.

Tumor tissue B7H3 expression level result will be listed and used as a baseline covariate in exploratory subgroup analysis to explore the correlation with response.

7.6.1.2 Soluble B7H3 Expression in Blood

For all patients in dose-escalation and dose-expansion studies, blood samples for soluble B7H3 analysis will be collected.

Descriptive statistics (mean, median, standard deviation, and range) for actual values, and change from baseline for soluble B7H3 will be tabulated by dose level and overall. All biomarker results will be presented in by-subject listings.

7.7 Subgroup Analysis

Subgroup analyses will be performed in an exploratory manner in order to investigate consistency of the treatment effect across different subgroups. Subgroup categories will include demographic characteristics (e.g., age and sex), baseline characteristics (e.g., ECOG PS, sites of metastases, and prior lines of treatment), and other subgroups as appropriate. Biomarker data may be incorporated in additional exploratory subgroup analysis.

Subgroup analyses will use similar methods as those used for the study population as a whole. Results for efficacy parameters in subgroups will be presented in descriptive summary tables and Forest plots, if needed.

7.8 Interim Analysis

Standard interim analysis is not applicable to this study. As this is an open-label study, appropriate analyses will be conducted on an ongoing basis. Analysis provided for review at Safety Review Committee meetings will be specified outside of this SAP.

7.9 Data Monitoring Committee

An external data monitoring committee will not be established for this study. For the purpose of this protocol, an internal safety review team consisting of investigators and medical experts of the sponsor (or designee) will be established to assess the safety and tolerability of patients. This meeting will be held regularly, after each cohort of patients in dose-escalation study have completed Cycle 1, and when necessary. A separate charter will further detail the role and responsibilities of the SRC.

7.10 Changes to Methods Planned in the Protocol

Not applicable.

8. References

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45(2):228-247.

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