Supplementary Material

First-Line Tislelizumab Plus Chemotherapy in Advanced Non-Squamous Non-Small Cell Lung Cancer: PD-L1 ≥ 50% Subgroup Analysis From the RATIONALE-304 Trial

Authors: Shun Lu · Jie Wang · Yan Yu · Xinmin Yu · Yanping Hu · Liao Wangjun · Xingya Li · Yuepeng Liu · Weidong Li · Xiaofei Qu · Yuanyuan Bao · Mengzhao Wang

Affiliations:

S. Lu

Department of Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China

J. Wang

Department of Medical Oncology, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China

Y. Yu

Department of Thoracic Oncology, Harbin Medical University Cancer Hospital, Harbin, China

X. Yu

Department of Thoracic Oncology, Zhejiang Cancer Hospital, Hangzhou, China

Y. Hu

Department of Thoracic Oncology, Hubei Cancer Hospital, Wuhan, China

L. Wangjun

Department of Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, China

Xi. Li

Department of Medical Oncology, The First Affiliated Hospital of Zhengzhou University/Henan Cancer Hospital, Zhengzhou, China

Y. Liu

Department of Medical Oncology, The First Hospital of China Medical University, Shenyang, China

W. Li

Department of Medical Oncology, Cancer Center of Guangzhou Medical University, Guangzhou, China

X. Qu*

Department of Clinical Development, BeOne Medicines, Ltd., Shanghai, China

Y. Bao

Department of Global Statistics and Data Science, BeOne Medicines, Ltd., Shanghai, China

M. Wang

Department of Pulmonary Medicine, Peking Union Medical College Hospital, Beijing, China

*This was Dr. Qu's affiliation during the time this study was conducted and manuscript developed.

Corresponding Author

Shun Lu, MD, PhD

E-mail: shun_lu@hotmail.com

Supplementary Table S1. List of EC/IRB approvals

Region name	Study site ID #	EC/IRB name	EC/IRB approval date or number
China	86001	The Ethics Committee of Beijing Cancer Hospital	2018YW09
China	86002	Ethics Committee of Pla No.906 Hospital	2018-002-01
China	86003	Ethics Committee of Fudan University Shanghai Cancer Center	1808189-2
China	86006	Ethics Committee of Henan Cancer Hospital	2018004
China	86007	Ethics Committee of The First Hospital of Nanjing Medical Hospital	2018-MD-079
China	86008	Ethics Committee of Nanfang Hospital of Southern Medical University	NFEC-2018-035
China	86009	Ethics Committee on Medicine Clinical Trial of Peking Union Medical College Hospital	HS2018073
China	86012	Ethics Committee of The First Hospital of Jilin University	18Y038-001
China	86015	Ethics Committee of The First Affiliated Hospital of Soochow University	No. 037 of 2018 EC review
China	86019	Ethics Committee of West China Hospital of Sichuan University	No. 77 of 2018 clinical trial review of western medicine
China	86022	Ethics Committee of Harbin Medical University Cancer Hospital	2018-18
China	86027	Ethics Committee of Zhejiang Cancer Hospital	No. 90 of IRB-[2018]
China	86029	Ethics Committee of Anhui Provincial Hospital	No. 140 of 2018 EC review
China	86036	Ethics Committee on Medicine Clinical Trial of Fujian Cancer Hospital	2018-027-01
China	86038	Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine	Medicine clinical trial 20180306-6
China	86039	Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University	XJTU1AF2018LSY-65
China	86042	Ethics Committee of Chinese PLA General Hospital	No. C2018-015-01 of EC review
China	86044	Ethics Committee of the National Cancer Center/Cancer Hospital of the Chinese Academy of Medical Science and Peking Union Medical College	18-024/1625
China	86045	Ethics Committee of Weifang People's Hospital	2018-004-01
China	86048	Ethics Committee of Tianjin Cancer Hospital	E2018081

China	86049	Ethics Committee of Hunan Cancer Hospital	No. 339 of 2018
China	86055	Ethics Committee of Hubei Cancer Hospital	No. 21 of 2018 EC review
China	86059	Ethics Committee of the Cancer Hospital of Shantou University Medical College	2018003
China	86060	Ethics Committee of Yunnan Cancer Hospital	No. YW201803 of EC review
China	86065	Ethics Committee of Hangzhou First People's Hospital	No. 013 of 2018 EC review -01
China	86068	Ethics Committee of The First Affiliated Hospital of Xiamen University	XMYY-2017Y014-01
China	86072	Clinical Medical Research Specialized Ethics Committee of The First Hospital of China Medical University	2018YL027
China	86075	Ethics Committee of Liaoning Cancer Hospital & Institute	20180626
China	86077	Human Research Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine	No. 156 of 2018 EC review
China	86082	Ethics Committee of Changsha Central Hospital	No. 003 of 2018 EC review
China	86085	Biomedical Research Ethics Committee of Xuzhou Central Hospital	XZXY-LY-20180315-006
China	86086	Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine	No. 61 of 2018 EC review
China	86087	Ethics Committee of the Cancer Center of Guangzhou Medical University	No. 2 of 2018 EC 1st review
China	86088	Ethics Committee of The Affiliated Hospital of Zunyi Medical College	No. 010 of 2018 EC review
China	86089	Ethics Committee of Hainan General Hospital	No. 52 of 2018 EC review
China	86094	Ethics Committee of Qilu Hospital of Shandong University	2018038
China	86100	Ethics Committee of Beijing Hospital	2018BJYYEC-052-02
China	86102	Ethics Committee of Shandong Cancer Hospital	SDZLEC2018-013-01
China	86103	Ethics Committee of The First Affiliated Hospital of Zhengzhou University	Medicine-2018-52
China	86120	Ethics Committee of Shanghai Chest Hospital	LS1818
China	86122	Ethics Committee of The People's Hospital of Guangxi Zhuang Autonomous Region	No. 2018-05(01) EC review
China	86124	Ethics Committee of People's Liberation Army Specialty Medical Center	No. 05 of 2018 EC review

China	86125	Ethics Committee of The Second Affiliated Hospital of Chongqing Medical University	No. 17 of 2018 EC review
China	86126	Ethics Committee of Chongqing Three Gorges Central Hospital	No. 010 of 2018 EC review
China	86127	Ethics Committee of Tianjin Medical University General Hospital	IRB2018-039-01
China	86140	Ethics Committee of Jinan Central Hospital	No. 2018-034-01
China	86144	Ethics Committee of Affiliated Hospital of Guilin Medical University	No. F2018006
China	86148	Ethics Committee of Guizhou Cancer Hospital	No. 2018-05-23 EC review

EC ethics committee, *IRB* institutional review board

Supplementary Table S2. Patient demographic and baseline characteristics in the PD-L1 ≥ 50% and ITT populations

	PD-L1 ≥ 50% population			ITT population		
Characteristics	**Tislelizumab plus chemotherapy (*n* = 74)**	**Chemotherapy alone (*n* = 36)**	**PD-L1 ≥ 50% total (*N* = 110)**	**Tislelizumab plus chemotherapy (*n* = 223)**	**Chemotherapy alone (*n* = 111)**	**ITT total (*N* = 334)**
Median age (range), years	61.0 (32−75)	64.5 (32−74)	62.0 (32−75)	60.0 (27−75)	61.0 (25−74)	61.0 (25−75)
Age group, *n* (%)						
< 65 years	48 (64.9)	18 (50.0)	66 (60.0)	163 (73.1)	74 (66.7)	237 (71.0)
≥ 65 years	26 (35.1)	18 (50.0)	44 (40.0)	60 (26.9)	37 (33.3)	97 (29.0)
Sex, *n* (%)						
Male	50 (67.6)	29 (80.6)	79 (71.8)	168 (75.3)	79 (71.2)	247 (74.0)
Female	24 (32.4)	7 (19.4)	31 (28.2)	55 (24.7)	32 (28.8)	87 (26.0)
Smoking status, *n* (%)						
Former	31 (41.9)	9 (25.0)	40 (36.4)	115 (51.6)	53 (47.7)	168 (50.3)
Current	14 (18.9)	4 (11.1)	18 (16.4)	32 (14.3)	13 (11.7)	45 (13.5)
Never	29 (39.2)	23 (63.9)	52 (47.3)	76 (34.1)	45 (40.5)	121 (36.2)
ECOG PS, *n* (%)						
0	14 (18.9)	7 (19.4)	21 (19.1)	54 (24.2)	24 (21.6)	78 (23.4)
1	60 (81.1)	29 (80.6)	89 (80.9)	169 (75.8)	87 (78.4)	256 (76.6)
Disease stage, *n* (%)						
Stage IIIB	14 (18.9)	6 (16.7)	20 (18.2)	40 (17.9)	21 (18.9)	61 (18.3)
Stage IV	60 (81.1)	30 (83.3)	90 (81.8)	183 (82.1)	90 (81.1)	273 (81.7)
Histology, *n* (%)						
Adenocarcinoma	71 (95.9)	34 (94.4)	105 (95.5)	215 (96.4)	107 (96.4)	322 (96.4)
Mixed adeno-squamous	1 (1.4)	2 (5.6)	3 (2.7)	1 (0.4)	2 (1.8)	3 (0.9)
Other	2 (2.7)	0	2 (1.8)	7 (3.1)	2 (1.8)	9 (2.7)
EGFR mutation status, *n* (%)						
Negative	72 (97.3)	35 (97.2)	107 (97.3)	218 (97.8)	109 (98.2)	327 (97.9)
Missing[a]	2 (2.7)	1 (2.8)	3 (2.7)	5 (2.2)	2 (1.8)	7 (2.1)
ALK rearrangement status, *n* (%)						
Negative	55 (74.3)	26 (72.2)	81 (73.6)	166 (74.4)	79 (71.2)	245 (73.4)
Unknown	19 (25.7)	10 (27.8)	29 (26.4)	57 (25.6)	32 (28.8)	89 (26.6)

	PD-L1 ≥ 50% population			ITT population		
Characteristics	**Tislelizumab plus chemotherapy (*n* = 74)**	**Chemotherapy alone (*n* = 36)**	**PD-L1 ≥ 50% total (*N* = 110)**	**Tislelizumab plus chemotherapy (*n* = 223)**	**Chemotherapy alone (*n* = 111)**	**ITT total (*N* = 334)**
Location of distant metastases, *n* (%)[b]						
Bone	28 (37.8)	15 (41.7)	43 (39.1)	75 (33.6)	41 (36.9)	116 (34.7)
Liver	8 (10.8)	6 (16.7)	14 (12.7)	20 (9.0)	17 (15.3)	37 (11.1)
Brain	7 (9.5)	3 (8.3)	10 (9.1)	11 (4.9)	7 (6.3)	18 (5.4)

Data cut-off: October 26, 2020

ALK anaplastic lymphoma kinase, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EGFR* epidermal growth factor receptor, *ITT* intent-to-treat, *PD-L1* programmed death-ligand 1

[a]Three patients in the tislelizumab plus chemotherapy arm and two patients in the chemotherapy alone arm had *EGFR* mutation status detected after enrollment; two patients in the tislelizumab plus chemotherapy arm had their *EGFR* status as indeterminate. All were reported as protocol deviations and assigned a missing value to *EGFR* status, as only negative or missing values were allowed in the data field

[b]Patients were counted only once within each category but may have been counted in multiple categories

Supplementary Table S3. Patient demographic and baseline characteristics in the PD-L1 50–89% and PD-L1 ≥ 90% subgroups (tislelizumab plus chemotherapy arm)

	Tislelizumab plus chemotherapy	
Characteristics	**PD-L1 50–89% subgroup (*n* = 39)**	**PD-L1 ≥ 90% subgroup (*n* = 35)**
Age group, *n* (%)		
< 65 years	25 (64.1)	23 (65.7)
≥ 65 years	14 (35.9)	12 (34.3)
Sex, *n* (%)		
Male	24 (61.5)	26 (74.3)
Female	15 (38.5)	9 (25.7)
Smoking status, *n* (%)		
Former	4 (10.3)	10 (28.6)
Current	15 (38.5)	14 (40.0)
Never	20 (51.3)	11 (31.4)
ECOG PS, *n* (%)		
0	5 (12.8)	9 (25.7)
1	34 (87.2)	26 (74.3)
Disease stage, *n* (%)		
Stage IIIB	5 (12.8)	9 (25.7)
Stage IV	34 (87.2)	26 (74.3)
ALK rearrangement status, *n* (%)		
Negative	27 (69.2)	28 (80.0)
Unknown	12 (30.8)	7 (20.0)

Data cut-off: April 26, 2023.

ALK anaplastic lymphoma kinase, *ECOG PS* Eastern Cooperative Oncology Group performance status, *PD-L1* programmed death-ligand 1.

Supplementary Table S4. Overall summary of TEAEs in the safety population

n (%)	Tislelizumab plus chemotherapy (*n* = 74)	Chemotherapy alone (*n* = 35)
Patients with ≥ 1 TEAE	74 (100.0)	35 (100.0)
Grade ≥ 3 TEAEs	56 (75.7)	17 (48.6)
Serious TEAEs	32 (43.2)	10 (28.6)
TEAEs leading to death	3 (4.1)	1 (2.9)
TEAEs leading to discontinuation		
Any study treatment component	21 (28.4)	2 (5.7)
Tislelizumab	8 (10.8)	NA
Carboplatin/cisplatin	6 (8.1)	0
Pemetrexed	17 (23.0)	2 (5.7)
TEAEs leading to treatment modification		
Any study treatment component[a,b]	61 (82.4)	20 (57.1)
Tislelizumab[a]	55 (74.3)	NA
Carboplatin/cisplatin[b]	39 (52.7)	15 (42.9)
Pemetrexed	55 (74.3)	19 (54.3)

Data cut-off: October 26, 2020. Adverse event grades were evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

NA not applicable, *TEAE* treatment-emergent adverse event

[a]Treatment modification of tislelizumab included dose delay, infusion interruption, and infusion rate decrease

[b]Treatment modification of carboplatin/cisplatin/pemetrexed included dose reduction, infusion interruption, dose delay, and infusion rate decrease

Supplementary Table S5. Incidence of TEAEs occurring in ≥ 20% of patients in the safety population

	Tislelizumab plus chemotherapy (*n* = 74)		Chemotherapy alone (*n* = 35)	
***n* (%)**	**Grade 1–2**	**Grade ≥ 3**	**Grade 1–2**	**Grade ≥ 3**
Patients with ≥ 1 TEAE	74 (100.0)	56 (75.7)	35 (100.0)	17 (48.6)
Anemia	56 (75.7)	11 (14.9)	24 (68.6)	4 (11.4)
Leukopenia	52 (70.3)	13 (17.6)	24 (68.6)	3 (8.6)
ALT increased	39 (52.7)	4 (5.4)	11 (31.4)	1 (2.9)
Thrombocytopenia	37 (50.0)	16 (21.6)	13 (37.1)	7 (20.0)
AST increased	35 (47.3)	3 (4.1)	12 (34.3)	0
Nausea	35 (47.3)	0	15 (42.9)	0
Fatigue	32 (43.2)	2 (2.7)	13 (37.1)	2 (5.7)
Decreased appetite	29 (39.2)	1 (1.4)	11 (31.4)	2 (5.7)
Neutropenia	29 (39.2)	35 (47.3)	19 (54.3)	8 (22.9)
Vomiting	22 (29.7)	0	8 (22.9)	0
Cough	20 (27.0)	0	4 (11.4)	0
Hypoproteinemia	20 (27.0)	0	8 (22.9)	0
Blood creatinine increased	17 (23.0)	0	0	0
Constipation	16 (21.6)	0	8 (22.9)	0

Data cut-off: October 26, 2020

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *TEAE* treatment-emergent adverse event

Supplementary Table S6. Incidence of TEAEs related to any component of study treatment occurring in ≥ 20% of patients in the safety population

	Tislelizumab plus chemotherapy (*n* = 74)		Chemotherapy alone (*n* = 35)	
***n* (%)**	**Grade 1–2**	**Grade ≥ 3**	**Grade 1–2**	**Grade ≥ 3**
Patients with ≥ 1 TEAE	74 (100.0)	50 (67.6)	34 (97.1)	13 (37.1)
Anemia	53 (71.6)	9 (12.2)	21 (60.0)	3 (8.6)
Leukopenia	52 (70.3)	13 (17.6)	24 (68.6)	3 (8.6)
Thrombocytopenia	38 (51.4)	15 (20.3)	13 (37.1)	7 (20.0)
ALT increased	36 (48.6)	4 (5.4)	10 (28.6)	1 (2.9)
Nausea	35 (47.3)	0	15 (42.9)	0
AST increased	33 (44.6)	3 (4.1)	11 (31.4)	0
Fatigue	30 (40.5)	1 (1.4)	11 (31.4)	1 (2.9)
Neutropenia	29 (39.2)	35 (47.3)	19 (54.3)	8 (22.9)
Decreased appetite	27 (36.5)	1 (1.4)	9 (25.7)	1 (2.9)
Vomiting	22 (29.7)	0	8 (22.9)	0
Blood creatinine increased	15 (20.3)	0	0	0

Data cut-off: October 26, 2020

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *TEAE* treatment-emergent adverse event

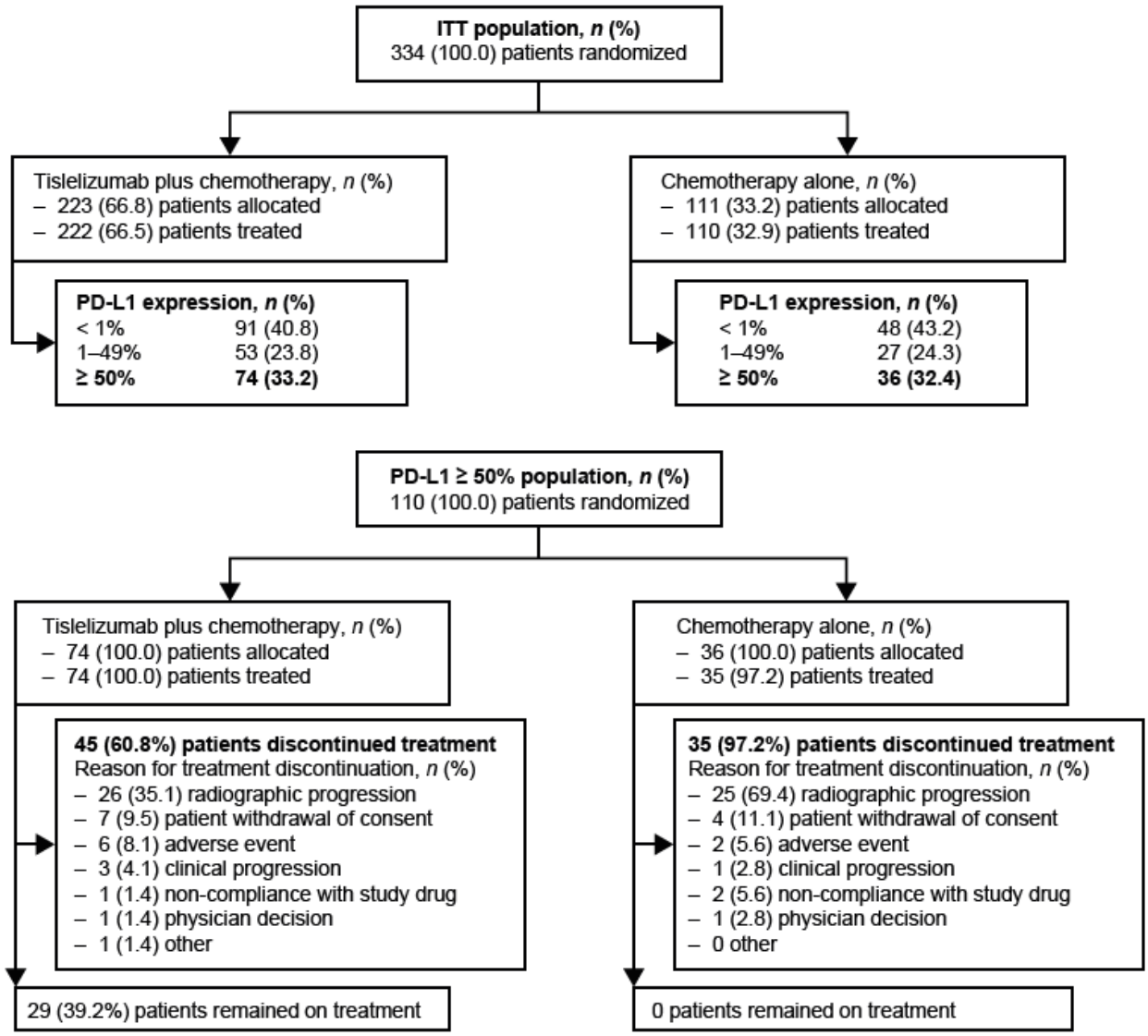
Supplementary Table S7. Summary of immune-mediated TEAEs in the safety population

	Tislelizumab plus chemotherapy (*n* = 74)		Chemotherapy alone (*n* = 35)	
***n* (%)**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Patients with ≥ 1 imAE	29 (39.2)	7 (9.5)	2 (5.7)	1 (2.9)
Immune-mediated endocrinopathies (hypothyroidism)	10 (13.5)	0	0	0
Immune-mediated pneumonitis	10 (13.5)	2 (2.7)	1 (2.9)	1 (2.9)
Immune-mediated skin adverse reaction	10 (13.5)	0	1 (2.9)	0
Immune-mediated endocrinopathies (hyperthyroidism)	8 (10.8)	0	0	0
Immune-mediated colitis	2 (2.7)	1 (1.4)	0	0
Immune-mediated endocrinopathies (diabetes mellitus)	2 (2.7)	2 (2.7)	0	0
Immune-mediated myocarditis/pericarditis	2 (2.7)	2 (2.7)	0	0
Immune-mediated nephritis and renal dysfunction	2 (2.7)	1 (1.4)	0	0

Data cut-off: October 26, 2020. Adverse event grades were evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Patients with multiple events for a given category and preferred term were counted only once at the maximum grade for each category and preferred term, respectively. Medical Dictionary for Regulatory Activities version 23.0. imAE identified based on imAE Company Custom Queries version 2.3

imAE immune-mediated adverse event, *TEAE* treatment-emergent adverse event

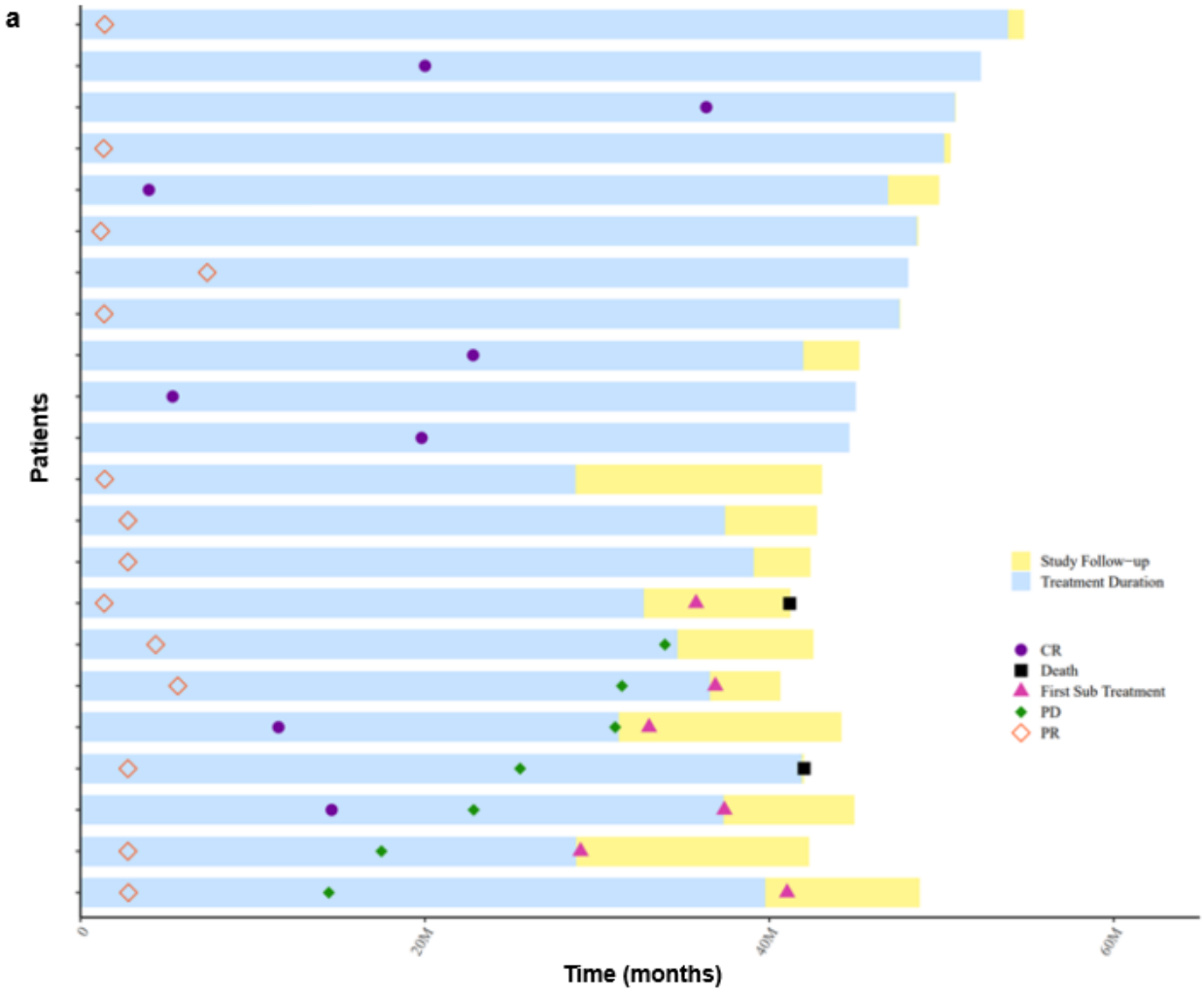
Supplementary Fig. S1. CONSORT diagram

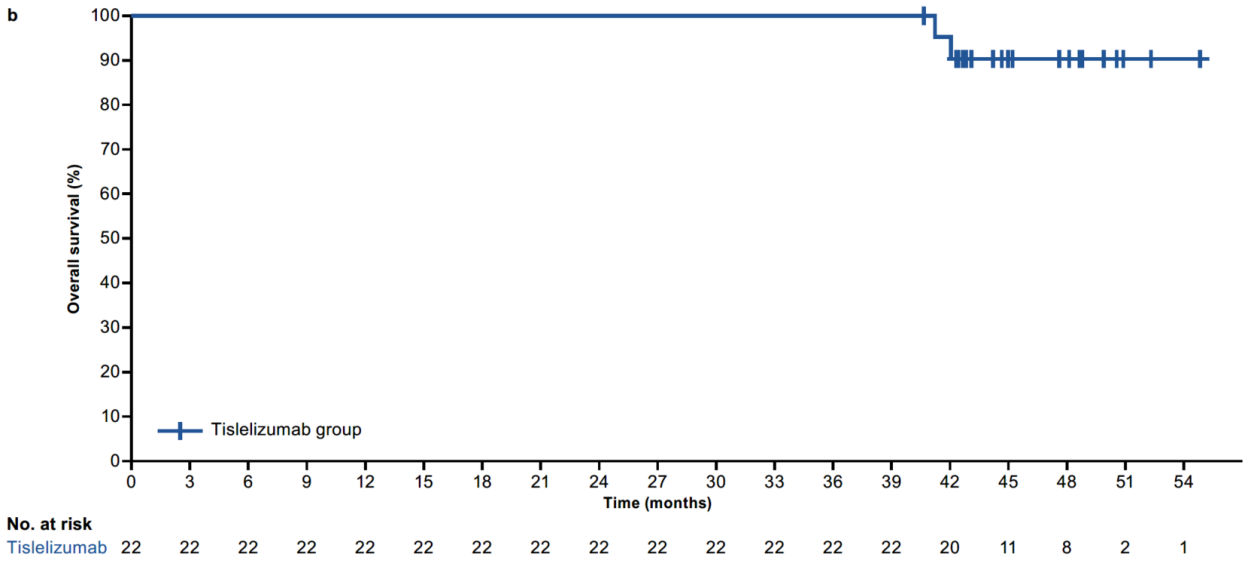


Data cut-off: October 26, 2020

ITT intent-to-treat, *PD-L1* programmed death-ligand 1

Supplementary Fig. S2. Objective response rate and overall survival in patients receiving long-term (≥ 35 cycles) treatment of tislelizumab (PD-L1 ≥ 50% population; *N* = 22). (A) Swimmer plot of patient treatment durations and response outcomes. (B) Kaplan–Meier plot of overall survival





CR complete response, *PD* progressive disease, *PD-L1* programmed death-ligand 1, *PR* partial response