Supplementary Material

Development of the Lunit SCOPE immuno-oncology (IO) artificial intelligence (AI)-powered tissue analyzer

The Lunit SCOPE IO model is composed of two convolutional neural networks, one of which performs segmentation of cancer areas (CA) and cancer stroma (CS), and the other of which performs cell detection. The current version of Lunit SCOPE IO used in this study contains updated versions of the cell detection AI model and the tissue segmentation AI model, compared to previous versions.[1] This section describes the differences in relation to the previous models.

Cell Detection Model

The cell detection model detects the location of lymphocytes and tumor cells. This model is based on a Convolutional Neural Network (CNN). In the previous model, a Faster R-CNN architecture was used.[2] In contrast, in the current version, a DeepLabV3+[3] architecture with a Resnet-34[6] backbone as feature extractor was employed. With this model, we posed the detection task as a dense pixel prediction problem. To train the network, a circle of radius 0.95 μm centered around the point annotation of each cell is drawn, with the class value associated with the cell at that location (lymphocyte or tumor cell). The training patches cover an area of 151,414 μm^2 (linearly resized to an image of 2048 x 2048 pixels). In each training step, a random portion of the images of size 1024 x 1024 is cropped; this image is passed through on-the-fly data augmentation. The model outputs probability maps of size 256 x 256, which are linearly interpolated to match the original input dimensions (1024 x 1024 pixels), therefore having a 1-to-1 pixel correspondence with the pixel annotations. Since the model predicts the likelihood of the cells being at each pixel, a post-processing stage is required to extract the locations of cells. In this stage, the likelihood maps are Gaussian filtered ($\sigma = 3$), followed by local maximum detection with a radius of 0.57 μm. The model was optimized using the Adam optimizer[7] with a learning rate of 0.002, decayed by a multiplicative factor of 0.2 when the validation loss did not decrease for a period of 5 epochs, and mini-batches of 24 samples. The performance of this model in detecting lymphocytes, tumor cells, and endothelial cells in terms of the F1-score, was 0.69, 0.74, and 0.39, respectively.

Tissue Segmentation Model

The AI model was similar to that in the previous version, except that the backbone for feature extraction was ResNet-34.[4] Similarly, it determines if a pixel belongs to cancer area, cancer stroma, or background regions. The model was trained with patches that covered an area of 605,657 μm^2, which were linearly resized to images of size 1024 x 1024 pixels. The model outputs probability maps of size 256 x 256, which are linearly interpolated to match the original input dimensions (1024 x 1024 pixels), therefore having a 1-to-1 pixel correspondence with the pixel annotations. In this case, there was no balanced sampling between patches from different types of organs. The segmentation model was optimized using the Adam optimizer[5] with a learning rate of 0.0001, decayed by a multiplicative factor of 0.5 when the validation loss did not decrease for a period of 5 epochs, and mini-batches of 32 samples. The performance of this model at segmenting Cancer Area and Cancer Stroma, in terms of the Intersection-over-Union metric, was 0.78 and 0.64, respectively.

Datasets for developing the AI models

The whole-slide images (WSIs) that composed the data used for developing the previously described AI models included more than 16 other primary tumor types and origins (Supplementary Table S7a-b). The *Cell Detection Model* was developed with patches extracted from 3,334 WSIs (*N*=2,485 for training and *N*=849 for tuning). From these WSIs, 5,698 and 1,925 patches of area 151,414 μm^2 per patch were extracted for training and tuning, respectively. The total number of annotated cells can be found in Supplementary Table S8. The *Tissue Segmentation Model* was developed with patches extracted from 14,969 WSIs (*N*=14,143 for training, and *N*=826 for tuning). From these WSIs, 56,545 and 2,971 patches of area 605,657 μm^2 per patch were extracted for training and validation, respectively. The total area of annotated tissues is presented in Supplementary Table S9.

Supplementary Table S1. Distribution of immune phenotype

	Overall (*N*=163)	**Atezolizumab plus bevacizumab (*N*=82)**	**Nivolumab or pembrolizumab (*N*=81)**
Immune phenotype, n (%)			
IIP	39(23.9%)	25 (30.5%)	14 (17.3%)
IEP	49(30.1%)	23 (28.0%)	26 (32.1%)
IDP	75(46.0%)	34 (41.5%)	41 (50.6%)

Abbreviations: IDP, Immune-Desert phenotype; IEP, Immune-Excluded phenotype; IIP, Inflamed immune phenotype

Supplementary Table S2. Summary of tumor microenvironment-related variables

	Overall (*N*=163)	**Atezolizumab plus bevacizumab (*N*=82)**	**Nivolumab or pembrolizumab (*N*=81)**
Intratumoral macrophage (iMP)			
Mean (SD)	14.4 (19.7)	11.3 (14.9)	17.6 (23.2)
Median (IQR)	5.9 (16.4)	5.5 (10.8)	7.7 (20.1)
Min, Max	0.8, 143.7	0.9, 76.2	0.8, 143.7
Stromal macrophage (sMP)			
Mean (SD)	72.0 (74.9)	62.9 (51.0)	81.3 (92.4)
Median (IQR)	48.6 (51.8)	47.2 (52.8)	49.2 (67.4)
Min, Max	0.0, 438.8	0.0, 306.8	0.0, 438.8
Intratumoral fibroblast (iFB)			
Mean (SD)	153.1 (181.8)	145.7 (127.5)	160.5 (224.4)
Median (IQR)	105.6 (112.4)	115.0 (92.6)	82.5 (121.0)
Min, Max	1.4, 1266.4	16.3, 657.0	1.4, 1266.4
Stromal fibroblast (sFB)			
Mean (SD)	1412.0 (526.5)	1408.5 (486.8)	1415.5 (566.8)
Median (IQR)	1443.7 (684.8)	1445.2 (591.2)	1407.7 (720.1)
Min, Max	0.0, 2785.2	339.4, 2616.1	0.0, 2785.2
Tumor endothelial cell (TEC)			
Mean (SD)	54.2 (42.9)	56.8 (42.3)	51.6 (43.8)
Median (IQR)	44.0 (53.7)	46.5 (52.3)	34.7 (49.8)
Min, Max	1.7, 223.7	1.7, 223.7	1.9, 194.9
Stromal endothelial cell (sEC)			
Mean (SD)	121.4 (114.3)	135.4 (107.4)	107.2 (119.8)
Median (IQR)	98.3 (114.9)	118.2 (116.5)	72.1 (101.8)
Min, Max	0.0, 860.8	0.0, 710.2	0.0, 860.8

Abbreviations: IQR, Inter quartile range; max, maximum; min, minimum; SD, Standard deviation

Supplementary Table S3. Objective response rate according to inflamed immune phenotype

	IIP (*N*=39)	**Non-IIP (*N*=124)**
Overall		
Patients evaluated	39	118
ORR, *n* (%)	14 (35.9%)	24 (20.3%)
***P*-value[1]**	0.0799	
Complete response	0 (0%)	5 (4.2%)
Partial response	14 (35.9%)	19 (16.1%)
Stable disease	19 (48.7%)	50 (42.4%)
Disease progression	6 (15.4%)	44 (37.3%)
Atezolizumab plus bevacizumab		
Patients evaluated	25	57
ORR, *n* (%)	10 (40.0%)	16 (28.1%)
***P*-value[1]**	0.4174	
Complete response	0 (0%)	2 (3.5%)
Partial response	10 (40.0%)	14 (24.6%)
Stable disease	10 (40.0%)	26 (45.6%)
Disease progression	5 (20.0%)	15 (26.3%)
Nivolumab or pembrolizumab		
Patients evaluated	14	61
ORR, *n* (%)	4 (28.6%)	8 (13.1%)
***P*-value[1]**	0.2202	
Complete response	0 (0%)	3 (4.9%)
Partial response	4 (28.6%)	5 (8.2%)
Stable disease	9 (64.3%)	24 (39.3%)
Disease progression	1 (7.1%)	29 (47.5%)

[1]*P*-values were calculated by chi-square test or Fisher's exact test.

Abbreviations: IIP, Inflamed immune phenotype; non-IIP, non-inflamed immune phenotype; ORR, objective response rate.

Supplementary Table S4. Patient characteristics according to immune phenotype and tumor endothelial cell density classification

	Immune phenotype				**TEC 3-group (Low/Middle/High)[1]**			
	Inflamed (*N*=39)	**Excluded (*N*=49)**	**Desert (*N*=75)**	***P*-value[2]**	**Low (*N*=41)**	**Middle (*N*=81)**	**High (*N*=41)**	***P*-value[2]**
Age group, *n* (%)								
≥ 60	26 (66.7%)	29 (59.2%)	38 (50.7%)	0.2453	22 (53.7%)	51 (63.0%)	20 (48.8%)	0.2876
< 60	13 (33.3%)	20 (40.8%)	37 (49.3%)		19 (46.3%)	30 (37.0%)	21 (51.2%)	
Gender, *n* (%)								
Male	34 (87.2%)	42 (85.7%)	61 (81.3%)	0.6707	31 (75.6%)	70 (86.4%)	36 (87.8%)	0.2289
Female	5 (12.8%)	7 (14.3%)	14 (18.7%)		10 (24.4%)	11 (13.6%)	5 (12.2%)	
Child-Pugh grade, *n* (%)								
Patients evaluated	38	49	75		41	81	40	
A	34 (89.5%)	35 (71.4%)	65 (86.7%)	0.0408	33 (80.5%)	69 (85.2%)	32 (80.0%)	0.7067
B	4 (10.5%)	14 (28.6%)	10 (13.3%)		8 (19.5%)	12 (14.8%)	8 (20.0%)	
BCLC stage, *n* (%)								
B	2 (5.1%)	5 (10.2%)	17 (22.7%)	0.0244	5 (12.2%)	9 (11.1%)	10 (24.4%)	0.1286
C	37 (94.9%)	44 (89.8%)	58 (77.3%)		36 (87.8%)	72 (88.9%)	31 (75.6%)	
HBV, *n* (%)								
Positive	27 (69.2%)	40 (81.6%)	52 (69.3%)	0.2664	35 (85.4%)	53 (65.4%)	31 (75.6%)	0.0585
HCV, *n* (%)								
Positive	4 (10.3%)	0 (0.0%)	3 (4.0%)	0.0454	2 (4.9%)	4 (4.9%)	1 (2.4%)	0.8922
ECOG, *n* (%)								
0	3 (7.7%)	3 (6.1%)	9 (12.0%)	0.4003	4 (9.8%)	7 (8.7%)	4 (9.8%)	1.0000
1	35 (89.7%)	46 (93.9%)	66 (88.0%)		37 (90.2%)	73 (90.1%)	37 (90.2%)	
2	1 (2.6%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (1.2%)	0 (0.0%)	
Treatment line, *n* (%)								
First-line	37 (94.9%)	32 (65.3%)	60 (80.0%)	0.0151	37 (90.2%)	66 (81.5%)	26 (63.4%)	0.0476
Second-line	1 (2.6%)	10 (20.4%)	7 (9.3%)		2 (4.9%)	7 (8.6%)	9 (22.0%)	

	Immune phenotype				TEC 3-group (Low/Middle/High)[1]			
	Inflamed (*N*=39)	**Excluded (*N*=49)**	**Desert (*N*=75)**	***P*-value[2]**	**Low (*N*=41)**	**Middle (*N*=81)**	**High (*N*=41)**	***P*-value[2]**
≥ Third-line	1 (2.6%)	7 (14.3%)	8 (10.7%)		2 (4.9%)	8 (9.9%)	6 (14.6%)	
Specimen type, n (%)								
Biopsy	18 (46.2%)	25 (51.0%)	49 (65.3%)	0.0965	27 (65.9%)	47 (58.0%)	18 (43.9%)	0.1236
Surgery	21 (53.9%)	24 (49.0%)	26 (34.7%)		14 (34.1%)	34 (42.0%)	23 (56.1%)	
Lymph node metastasis, *n* (%)								
Yes	21 (53.8%)	17 (34.7%)	18 (24.0%)	0.0063	18 (43.9%)	31 (38.3%)	7 (17.1%)	0.0220
No	18 (46.2%)	32 (65.3%)	57 (76.0%)		23 (56.1%)	50 (61.7%)	34 (82.9%)	
Number of metastasis, *n* (%)								
< 2	24 (61.5%)	37 (75.5%)	54 (72.0%)	0.3361	30 (73.2%)	51 (63.0%)	34 (82.9%)	0.0671
≥ 2	15 (38.5%)	12 (24.5%)	21 (28.0%)		11 (26.8%)	30 (37.0%)	7 (17.1%)	
Tissue harvest site, *n* (%)								
Patients evaluated	39	48	75		41	81	40	
Primary tumor	33 (84.6%)	46 (95.8%)	64 (85.3%)	0.3576	33 (80.5%)	73 (90.1%)	37 (92.5%)	0.3755
Lymph node	1 (2.6%)	0 (0.0%)	2 (2.7%)		2 (4.9%)	1 (1.2%)	0 (0.0%)	
Metastasis	5 (12.8%)	2 (4.2%)	9 (12.0%)		6 (14.6%)	7 (8.6%)	3 (7.5%)	
AFP								
Patients evaluated	37	49	75		40	81	40	
Mean (SD)	9356.0 (33743.6)	8405.7 (30064.4)	16539.3 (42353.9)	0.5734	9068.3 (18438.1)	15914.1 (45366.5)	8668.1 (31873.9)	0.7516
Median (IQR)	179.5 (2000.6)	113.9 (1278.3)	312.7 (7083.0)		225.4 (6438.4)	179.5 (3414.8)	256.1 (6266.6)	
Min, Max	2.4, 200000.0	0.7, 200000.0	1.3, 200000.0		1.3, 67610.2	0.7, 200000.0	1.3, 200000.0	
NLR								
Patients	38	49	73		39	81	40	

	Immune phenotype				TEC 3-group (Low/Middle/High)[1]			
	Inflamed (*N*=39)	**Excluded (*N*=49)**	**Desert (*N*=75)**	***P*-value[2]**	**Low (*N*=41)**	**Middle (*N*=81)**	**High (*N*=41)**	***P*-value[2]**
evaluated								
Mean (SD)	1.7 (1.4)	3.0 (4.1)	3.0 (3.12)		3.7 (3.4)	2.6 (2.8)	2.0 (3.5)	
Median (IQR)	1.3 (1.2)	1.2 (2.7)	1.9 (3.3)	0.1894	2.6 (3.7)	1.6 (2.7)	1.0 (0.8)	0.0021
Min, Max	0.4, 5.9	0.3, 21.7	0.2, 14.8		0.2, 15.3	0.3, 14.8	0.3, 21.7	
CRP								
Patients evaluated	27	33	59		30	60	29	
Mean (SD)	1.0 (1.7)	13.4 (61.6)	1.6 (2.4)		2.4 (3.4)	1.7 (2.6)	13.4 (65.9)	
Median (IQR)	0.3 (0.8)	0.8 (4.5)	0.5 (1.5)	0.0741	0.7 (2.4)	0.4 (1.6)	0.5 (0.9)	0.5505
Min, Max	0.0, 6.5	0.0, 356.0	0.0, 9.5		0.0, 10.8	0.0, 11.6	0.0, 356.0	

[1]TEC 3-group: Low=TEC<21.5/mm^2, Middle=21.5/mm^2≤TEC<75.2/mm^2, High=TEC≥75.2/mm^2

[2]*P*-values for categorical variables were calculated by chi-square test or fisher's exact test, and *p*-values for continuous variables were calculated by Kruskal-Wallis rank sum test.

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; TEC, tumor endothelial cell density; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; SD, standard deviation

Supplementary Table S5. Objective response rate according to tumor endothelial cell density classification

	Atezolizumab plus bevacizumab (*N*=82)			**Nivolumab or pembrolizumab (*N*=81)**		
TEC 2-group (Low/High)[1]						
Cutoff of 21.5/mm^2	Low (*n*=17)		High (*n*=65)	Low (*n*=23)		High (*n*=52)
ORR, *n* (%)	4 (23.5%)		22 (33.8%)	5 (21.7%)		7 (13.5%)
***P*-value[2]**	0.6023			0.4955		
TEC 3-group (Low/Middle/High)[3]						
Cutoffs of 21.5/mm^2 and 75.2/mm^2	Low (*n*=17)	Middle (*n*=42)	High (*n*=23)	Low (*n*=23)	Middle (*n*=35)	High (*n*=17)
ORR, *n* (%)	4 (23.5%)	14 (33.3%)	8 (34.8%)	5 (21.7%)	7 (20.00%)	0 (0.00%)
***P*-value[2]**	0.7129			0.1122		

[1]TEC 2-group: Low=TEC<21.5/mm^2, High=TEC≥21.5/mm^2

[2]*P*-values were calculated by chi-square test or fisher's exact test.

[3]TEC 3-group: Low=TEC<21.5/mm^2, Middle=21.5/mm^2≤TEC<75.2/mm^2, High=TEC≥75.2/mm^2

The cutoffs of 21.5/mm^2 and 75.2/mm^2 were determined according to 25th and 75th percentiles of the TEC, respectively.

Abbreviations: ORR, objective response rate; TEC, tumor endothelial cell density.

Supplementary Table S6a. Subgroup survival analysis by treatment regimen, based on 2-group IP

		Median (months)		PFS	Median (months)		OS
		IIP	Non-IIP	HR (95% CI), P-value	IIP	Non-IIP	HR (95% CI), P-value
Atezolizumab plus bevacizumab							
Age	≥ 60 (n=50)	9	6.3	0.78 (0.35−1.76), 0.5549	NE	NE	0.60 (0.19−1.88), 0.3778
	< 60 (n=32)	3.3	4	1.33 (0.51−3.48), 0.5570	8.9	NE	1.29 (0.33−5.05), 0.7127
Gender	Male (n=73)	6.8	6.3	0.92 (0.49−1.75), 0.8006	14.7	NE	0.80 (0.33−1.91), 0.6109
	Female (n=9)	1.3	5.5	1.17 (0.12−11.28), 0.8912	NE	12.5	0.00 (0.00−Inf), 0.4795
Child-Pugh grade	A (n=65)	4.1	6.9	1.29 (0.66−2.53), 0.4607	NE	NE	1.21 (0.41−3.56), 0.7233
	B (n=16)	1.3	1.1	0.33 (0.07−1.58), 0.1479	11.4	3	0.33 (0.07−1.53), 0.1360
BCLC	B (n=12)	11.1	11	0.68 (0.08−5.93), 0.7272	NE	NE	0.00 (0.00−Inf), 0.5024
	C (n=70)	4.1	4.5	0.93 (0.49−1.78), 0.8298	NE	12.5	0.79 (0.33−1.91), 0.6022
HBV	Positive (n=57)	4.1	4	1.03 (0.52−2.04), 0.9410	14.7	12.5	1.01 (0.41−2.48), 0.9844
	Negative (n=25)	NR	NR	0.73 (0.19−2.83), 0.6477	NE	NE	0.00 (0.00−Inf), 0.1413
HCV	Positive (n=1)	2.4	-	NA	NE	-	NA
	Negative (n=81)	6.8	6.2	0.87 (0.47−1.63), 0.6686	NE	NE	0.81 (0.34−1.92), 0.6286

		Median (months)		PFS	Median (months)		OS
		IIP	Non-IIP	HR (95% CI), P-value	IIP	Non-IIP	HR (95% CI), P-value
ECOG	0 (n=9)	2.5	6.3	5.11 (0.68−38.58), 0.0818	NE	NE	0.00 (0.00−Inf), 0.5930
	≥ 1 (n=73)	9	5.5	0.84 (0.43−1.62), 0.5982	NE	NE	0.74 (0.30−1.79), 0.4950
Treatment line	1st line (n=82)	6.8	6.2	0.92 (0.50−1.69), 0.7774	NE	NE	0.78 (0.33−1.85), 0.5640
	≥ 2nd line (n=0)	-	-	-	-	-	-
Specimen type	Biopsy (n=33)	6.8	3.3	0.58 (0.19−1.75), 0.3306	NE	8.8	0.41 (0.09−1.83), 0.2254
	Surgery (n=49)	4.1	9.7	1.19 (0.56−2.55), 0.6544	NE	NE	1.36 (0.43−4.28), 0.6022
LN metastasis	Yes (n=28)	4.1	3.3	0.63 (0.25−1.58), 0.3220	NE	9	0.76 (0.21−2.70), 0.6651
	No (n=54)	9	6.9	0.94 (0.40−2.20), 0.8840	NE	NE	0.62 (0.18−2.20), 0.4581
Number of metastasis	< 2 (n=65)	6.8	6.3	1.00 (0.49−2.02), 0.9943	14.7	NE	0.77 (0.28−2.13), 0.6181
	≥ 2 (n=17)	4.1	3.1	0.77 (0.22−2.65), 0.6809	NE	12.4	0.79 (0.14−4.35), 0.7814
Tissue harvest	Primary (n=75)	6.8	5.5	0.91 (0.48−1.74), 0.7750	NE	NE	0.75 (0.30−1.89), 0.5440
	Non-primary (n=7)	2.6	NR	2.11 (0.19−23.76), 0.5375	11.4	NE	Inf (0.00−Inf), 0.4795
Nivolumab or pembrolizumab							
Age	≥ 60 (n=43)	12.2	2.4	0.53 (0.22−1.28), 0.1522	18.2	9.3	0.52 (0.18−1.53), 0.2280

		Median (months)		PFS	Median (months)		OS
		IIP	Non-IIP	HR (95% CI), P-value	IIP	Non-IIP	HR (95% CI), P-value
	< 60 (n=38)	4.7	1.5	0.48 (0.17−1.38), 0.1630	9.1	5	0.56 (0.17−1.85), 0.3311
Gender	Male (n=64)	4.7	2.3	0.51 (0.24−1.10), 0.0799	18.2	6.5	0.49 (0.19−1.26), 0.1301
	Female (n=17)	4.2	1.3	0.45 (0.10−2.09), 0.2999	8.7	3.8	0.38 (0.08−1.77), 0.2013
Child-Pugh grade	A (n=69)	4.7	2.5	0.57 (0.28−1.13), 0.1007	9.1	7.1	0.60 (0.27−1.35), 0.2109
	B (n=12)	-	0.9	NA	-	1.4	NA
BCLC	B (n=12)	-	2.5	NA	-	22.5	NA
	C (n=69)	4.7	2.1	0.49 (0.24−0.97), 0.0368	9.1	5	0.43 (0.19−0.96), 0.0341
HBV	Positive (n=62)	4.7	2.1	0.41 (0.18−0.92), 0.0256	9.1	5.1	0.39 (0.15−0.99), 0.0408
	Negative (n=19)	6.5	2.6	0.96 (0.27−8.33.48), 0.9564	8.3	8.3	1.07 (0.22−5.18), 0.9284
HCV	Positive (n=6)	11.7	2.1	0.25 (0.03−2.43), 0.1966	8.6	3.5	0.20 (0.02−2.03), 0.1375
	Negative (n=75)	4.7	2.2	0.52 (0.25−1.09), 0.0795	9.1	5.2	0.54 (0.23−1.27), 0.1542
ECOG	0 (n=6)	1.3	1.2	1.07 (0.11−10.57), 0.9526	8.3	36.5	1.67 (0.15−19.23), 0.6777
	≥ 1 (n=75)	4.7	2.2	0.42 (0.21−0.87), 0.0155	9.1	5.1	0.44 (0.19−1.03), 0.0511
Treatment line	1st line (n=47)	4.7	2.5	0.42 (0.18−0.97), 0.0372	9.1	7.1	0.49 (0.18−1.30), 0.1416
	≥ 2nd line (n=34)	6.6	1.4	0.76 (0.18−3.24), 0.7080	1	3.8	0.36 (0.05−2.75), 0.3085

		Median (months)		PFS	Median (months)		OS
		IIP	Non-IIP	HR (95% CI), P-value	IIP	Non-IIP	HR (95% CI), P-value
Specimen type	Biopsy (n=59)	11.7	2.4	0.45 (0.19−1.07), 0.0631	7.9	5.2	0.68 (0.27−1.74), 0.4194
	Surgery (n=22)	4.2	1.4	0.60 (0.20−1.81), 0.3598	9.1	5.2	0.36 (0.08−1.62), 0.1677
LN metastasis	Yes (n=28)	11.7	2.2	0.25 (0.07−0.86), 0.0178	9.1	5.4	0.27 (0.08−0.96), 0.0304
	No (n=53)	4.2	2.1	0.64 (0.25−1.64), 0.3541	7.9	5	0.80 (0.28−2.26), 0.6703
Number of metastasis	< 2 (n=50)	10	2.3	0.51 (0.18−1.45), 0.2014	18.2	5.1	0.54 (0.17−1.79), 0.3081
	≥ 2 (n=31)	4.7	2.1	0.37 (0.14−1.00), 0.0417	9.1	5.2	0.51 (0.17−1.51), 0.2150
Tissue harvest	Primary (n=68)	4.2	2.1	0.55 (0.27−1.12), 0.0945	8.3	4.2	0.47 (0.20−1.11), 0.0767
	Non-primary (n=12)	15.8	3.9	0.00 (0.00−Inf), 0.0709	18.2	9.9	0.00 (0.00−Inf), 0.1154

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; LN, Lymph node; NA, not applicable; NE, not evaluable; TEC, tumor endothelial cell density.

Supplementary Table S6b. Subgroup survival analysis by treatment regimen, based on 2-group TEC

		Median (months)		PFS	Median (months)		OS
		High	Low	HR (95% CI), p-value	High	Low	HR (95% CI), p-value
Atezolizumab plus bevacizumab							
Age	≥ 60 (n=50)	11.1	3.2	0.52 (0.21−1.29), 0.1517	NE	12.5	0.73 (0.25−2.11), 0.5572
	< 60 (n=32)	4	4.1	0.55 (0.22−1.39), 0.2009	NE	11.2	0.92 (0.19−4.34), 0.9139
Gender	Male (n=73)	6.7	4.1	0.57 (0.28−1.13), 0.1042	NE	NE	0.88 (0.35−2.20), 0.7762
	Female (n=9)	5.5	1.6	0.28 (0.04−2.02), 0.1797	NE	12.5	0.00 (0.00−Inf), 0.1573
Child-Pugh grade	A (n=65)	9.7	4.3	0.60 (0.28−1.29), 0.1860	NE	NE	0.69 (0.22−2.19), 0.5275
	B (n=16)	1.3	1.1	0.49 (0.14−1.78), 0.2723	6.5	2.1	0.24 (0.04−1.48), 0.0978
BCLC	B (n=12)	15.7	1.1	0.00 (0.00−Inf), 0.0009	NE	2.1	0.00 (0.00−Inf), 0.0009
	C (n=70)	6.7	3.9	0.62 (0.31−1.21), 0.1550	NE	14.7	0.80 (0.32−2.03), 0.6400
HBV	Positive (n=57)	4.1	2.6	0.57 (0.28−1.17), 0.1198	12.5	8.9	0.49 (0.20−1.22), 0.1178
	Negative (n=25)	NE	3.9	0.47 (0.10−2.22), 0.3291	NE	NE	0.00 (0.00−Inf), 0.4613
HCV	Positive (n=1)	2.4	-	NA	NE	-	NA
	Negative (n=81)	6.9	3.9	0.50 (0.26−0.95), 0.0311	NE	14.7	0.59 (0.25−1.42), 0.2375
ECOG	0 (n=9)	11	2.6	0.32 (0.05−1.99), 0.2015	NE	NE	0.35 (0.02−5.89), 0.4504
	≥ 1 (n=73)	6.7	4.1	0.57 (0.28−1.17), 0.1219	NE	14.7	0.58 (0.23−1.49), 0.2544

		Median (months)		PFS	Median (months)		OS
		High	**Low**	**HR (95% CI), p-value**	**High**	**Low**	**HR (95% CI), p-value**
Treatment line	1st line (n=82)	6.7	3.9	0.51 (0.27−0.97), 0.0365	NE	14.7	0.59 (0.25−1.40), 0.2236
	≥ 2nd line (n=0)	-	-	-	-	-	-
Specimen type	Biopsy (n=33)	5.5	2.6	0.35 (0.13−0.94), 0.0290	NE	6.3	0.36 (0.11−1.20), 0.0836
	Surgery (n=49)	9.7	4.3	0.61 (0.26−1.45), 0.2595	NE	NE	0.86 (0.23−3.21), 0.8186
LN metastasis	Yes (n=28)	3.9	4.1	1.24 (0.40−3.79), 0.7071	12.4	8.9	0.87 (0.18−4.22), 0.8626
	No (n=54)	15.7	2.6	0.35 (0.16−0.78), 0.0071	NE	14.7	0.51 (0.17−1.48), 0.2048
Number of metastasis	< 2 (n=65)	9.7	3.9	0.39 (0.19−0.79), 0.0068	NE	14.7	0.53 (0.20−1.38), 0.1872
	≥ 2 (n=17)	3.3	2.6	1.61 (0.20−12.70), 0.6492	12.4	6.3	0.83 (0.09−7.29), 0.8667
Tissue harvest	Primary (n=75)	6.7	3.9	0.55 (0.28−1.07), 0.0747	NE	14.7	0.59 (0.24−1.41), 0.2296
	Non-primary (n=7)	NE	2.6	0.18 (0.01−2.93), 0.1768	NE	NE	NA
Nivolumab or pembrolizumab							
Age	≥ 60 (n=43)	3.4	2.7	0.77 (0.36−1.66), 0.4995	9.3	7.9	0.84 (0.32−2.19), 0.7172
	< 60 (n=38)	1.3	2.8	1.49 (0.69−3.24), 0.3103	3.6	8.3	2.06 (0.93−4.57), 0.0713
Gender	Male (n=64)	2.6	2.8	0.98 (0.52−1.87), 0.9621	5.1	9.5	1.06 (0.52−2.19), 0.8679

		Median (months)		PFS	Median (months)		OS
		High	Low	HR (95% CI), p-value	High	Low	HR (95% CI), p-value
	Female (n=17)	1.3	2.8	1.47 (0.48−4.48), 0.5002	3.6	6.7	1.67 (0.54−5.18), 0.3664
Child-Pugh grade	A (n=69)	2.6	2.8	1.04 (0.57−1.89), 0.9037	6.5	9.1	1.07 (0.54−2.11), 0.8557
	B (n=12)	0.9	0.4	0.44 (0.11−1.81), 0.2429	1.5	0.7	0.45 (0.11−1.83), 0.2516
BCLC	B (n=12)	3	1.6	0.32 (0.08−1.31), 0.0959	22.5	5.1	0.44 (0.07−2.75), 0.3697
	C (n=69)	2.1	3	1.23 (0.67−2.25), 0.5046	3.9	8.3	1.28 (0.67−2.44), 0.4508
HBV	Positive (n=62)	1.5	2.8	1.36 (0.75−2.47), 0.3131	4.2	7.9	1.41 (0.73−2.71), 0.3080
	Negative (n=19)	4.6	1.2	0.28 (0.07−1.11), 0.0533	13.2	8.3	0.41 (0.09−2.02), 0.2605
HCV	Positive (n=6)	6.9	1.6	0.38 (0.05−2.76), 0.3209	8.3	4.4	0.41 (0.06−2.93), 0.3573
	Negative (n=75)	2.3	2.8	1.13 (0.64−2.00), 0.6695	4.2	7.9	1.23 (0.65−2.33), 0.5312
ECOG	0 (n=6)	1.3	1.2	0.39 (0.03−4.35), 0.4263	8.3	NE	Inf (0.00−Inf), 0.5024
	≥ 1 (n=75)	2.3	2.8	1.09 (0.62−1.91), 0.7608	5	8.3	1.09 (0.59−2.02), 0.7748
Treatment line	1st line (n=47)	3.4	3	0.99 (0.50−1.95), 0.9818	7.1	9.1	1.25 (0.58−2.71), 0.5693
	≥ 2nd line (n=34)	1.4	1.2	0.49 (0.17−1.45), 0.1876	4	1.8	0.43 (0.15−1.27), 0.1164
Specimen type	Biopsy (n=59)	2.4	2.8	1.05 (0.56−1.98), 0.8799	4	7.9	1.49 (0.74−3.03), 0.2634
	Surgery (n=22)	1.4	2.4	0.76 (0.25−2.35), 0.6313	8.3	5.6	0.44 (0.13−1.42), 0.1553
LN metastasis	Yes (n=28)	1.3	4.2	1.62 (0.62−4.22), 0.3177	2.7	5.4	1.42 (0.55−3.70), 0.4655

		Median (months)		PFS	Median (months)		OS
		High	**Low**	**HR (95% CI), p-value**	**High**	**Low**	**HR (95% CI), p-value**
	No (n=53)	2.6	2.4	0.65 (0.33−1.27), 0.2028	5	8.3	0.93 (0.42−2.08), 0.8674
Number of metastasis	< 2 (n=50)	2.4	2.7	1.15 (0.57−2.32), 0.7050	4.2	5.4	1.14 (0.50−2.57), 0.7588
	≥ 2 (n=31)	2.2	2.8	0.82 (0.34−1.96), 0.6494	5.1	8.3	1.18 (0.48−2.93), 0.7149
Tissue harvest	Primary (n=68)	2.4	2.5	0.78 (0.42−1.45), 0.4268	4.2	5.4	0.96 (0.48−1.91), 0.9067
	Non-primary (n=12)	1.3	7.5	1.60 (0.42−6.10), 0.4893	14.4	12.6	0.84 (0.18−3.86), 0.8251

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; IP, immune phenotype; IIP, inflamed immune phenotype; LN, Lymph node; NA, not applicable; NE, not evaluable.

Supplementary Table S7a. Primary tumor types in the training set

	Total (*N* = 16,628)	**SMC (*n* = 5,704)**	**Aurora dx (*n* = 5,145)**	**Curelin e (*n* = 3,021)**	**SuperBi oChips (*n* = 931)**	**TCGA (*n* = 672)**	**PLCO (*n* = 213)**	**iSpecim en (*n* = 221)**	**CPTAC (*n* = 150)**	**NLST (*n* = 92)**	**GTEx (*n* = 465)**
Urothelial carcinoma	1509	316	582	489	67	55	0	0	0	0	0
Gastric carcinoma	1770	905	0	294	89	17	0	0	0	0	465
Colorectal carcinoma	1346	457	585	92	108	26	78	0	0	0	0
Non-small cell lung carcinoma	1035	187	284	41	69	77	64	221	0	92	0
Breast carcinoma	1415	546	238	503	61	67	0	0	0	0	0
Melanoma	1102	78	595	181	10	194	0	0	44	0	0
Prostate carcinoma	1002	246	579	95	45	37	0	0	0	0	0
Renal cell carcinoma	1004	181	585	91	57	82	0	0	8	0	0
Uterine corpus carcinoma	922	150	572	95	13	60	0	0	32	0	0
Pancreatic carcinoma	825	430	249	73	9	16	0	0	48	0	0

	Total (*N* = 16,628)	**SMC (*n* = 5,704)**	**Auroradx (*n* = 5,145)**	**Cureline (*n* = 3,021)**	**SuperBioChips (*n* = 931)**	**TCGA (*n* = 672)**	**PLCO (*n* = 213)**	**iSpecimen (*n* = 221)**	**CPTAC (*n* = 150)**	**NLST (*n* = 92)**	**GTEx (*n* = 465)**
Head and neck carcinoma	643	112	236	204	59	14	0	0	18	0	0
Esophageal carcinoma	550	235	0	245	68	2	0	0	0	0	0
Hepatocellular carcinoma	435	105	141	80	102	7	0	0	0	0	0
Biliary tract carcinoma	482	113	45	304	17	3	0	0	0	0	0
Uterine cervical carcinoma	556	194	128	149	58	13	0	0	0	0	0
Ovarian carcinoma	742	159	326	85	99	2	71	0	0	0	0
Other cancers[a]	1290	1290	0	0	0	0	0	0	0	0	0

Abbreviations: PLCO, Prostate, Lung, Colorectal, and Ovarian; CPTAC, Clinical Proteomic Tumor Analysis Consortium; GTEx, Genotype-Tissue Expression; NLST, National Lung Screening Trial; SMC, Samsung Medical Center.

[a]Other cancers included carcinoma of unknown primary, anal carcinoma, soft tissue tumors, thymic carcinoma, lymphomas, mediastinal carcinoma, and others.

Supplementary Table S7b. Primary tumor types in the tuning set

	Total (*N* = 849)	**SMC (*n* = 210)**	**Auroradx (*n* = 116)**	**Cureline (*n* = 217)**	**SuperBioChips (*n* = 39)**	**TCGA (*n* = 187)**	**PLCO (*n* = 17)**	**iSpecimen (*n* = 8)**	**CPTAC (*n* = 51)**	**NLST (*n* = 4)**
Non-small cell lung carcinoma	92	6	12	15	3	27	17	8	0	4
Melanoma	81	9	0	10	1	44	0	0	17	0
Breast carcinoma	62	18	9	19	3	13	0	0	0	0
Urothelial carcinoma	58	16	17	10	2	13	0	0	0	0
Colorectal carcinoma	55	25	10	6	4	10	0	0	0	0
Renal cell carcinoma	57	10	13	9	1	21	0	0	3	0
Head and neck carcinoma	49	5	10	14	3	11	0	0	6	0
Gastric carcinoma	44	15	0	17	3	9	0	0	0	0
Hepatocellular carcinoma	36	6	5	16	6	3	0	0	0	0
Prostate carcinoma	46	14	15	5	2	10	0	0	0	0
Uterine corpus carcinoma	44	3	9	3	1	11	0	0	17	0
Pancreatic carcinoma	44	6	0	20	1	9	0	0	8	0

	Total (*N* = 849)	**SMC (*n* = 210)**	**Auroradx (*n* = 116)**	**Cureline (*n* = 217)**	**SuperBioChips (*n* = 39)**	**TCGA (*n* = 187)**	**PLCO (*n* = 17)**	**iSpecimen (*n* = 8)**	**CPTAC (*n* = 51)**	**NLST (*n* = 4)**
Esophageal carcinoma	40	14	0	22	3	1	0	0	0	0
Uterine cervical carcinoma	36	9	3	20	1	3	0	0	0	0
Ovarian carcinoma	32	3	9	13	5	2	0	0	0	0
Biliary tract carcinoma	31	9	4	18	0	0	0	0	0	0
Other cancers[a]	42	42	0	0	0	0	0	0	0	0

Abbreviations: PLCO, Prostate, Lung, Colorectal, and Ovarian; CPTAC, Clinical Proteomic Tumor Analysis Consortium; NLST, National Lung Screening Trial; SMC, Samsung Medical Center.

[a]Other carcinomas included carcinoma of unknown primary, non-melanoma skin carcinoma, thyroid carcinoma, neuroendocrine tumor, small bowel carcinoma, anal carcinoma, thymic carcinoma, and others.

Supplementary Table S8. Numbers of annotated cells in the training and tuning sets

	Lymphocytes	**Tumor cells**	**Macrophages**	**Fibroblasts**	**Endothelial cells**
Training	466,000	1,640,000	9,685	91,325	18,831
Tuning	150,000	568,000	2,521	28,899	6,686

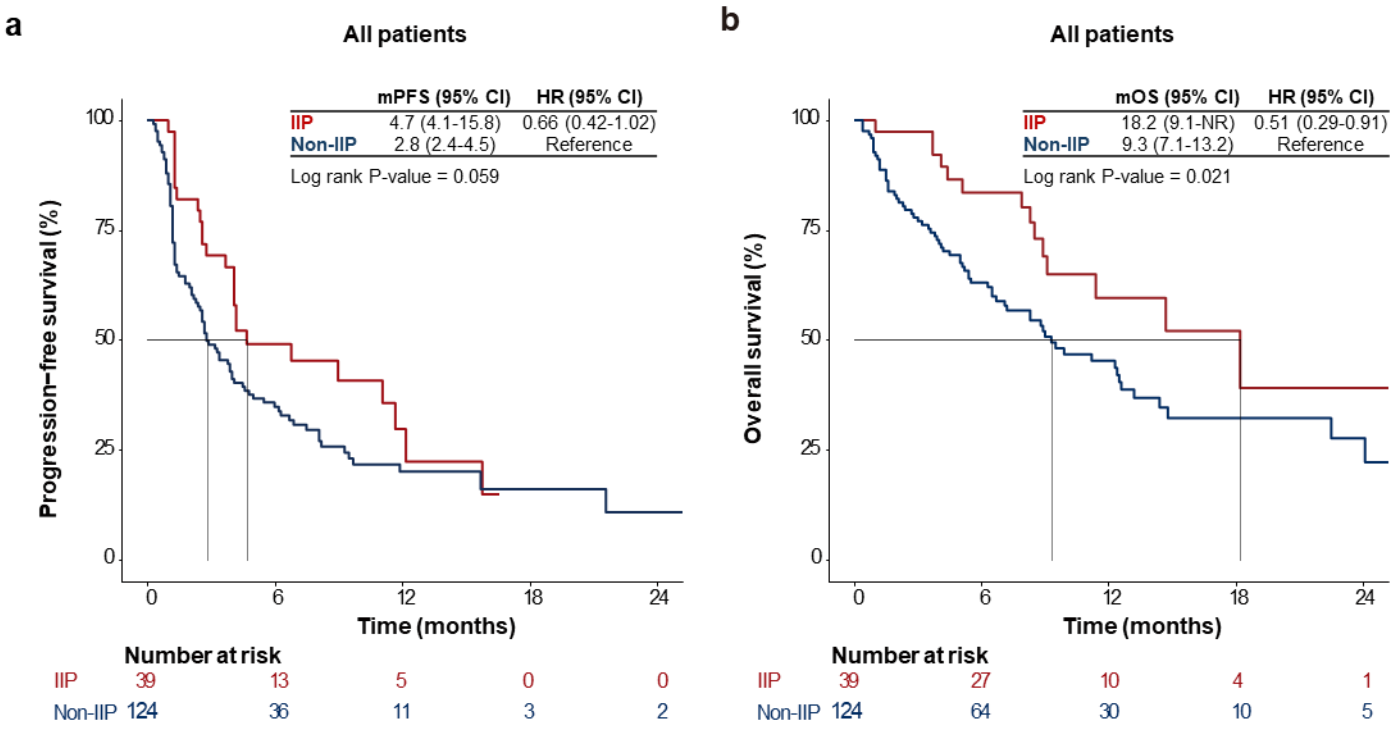
Supplementary Table S9. Areas of annotated tissue regions in the training and tuning sets

	Area (mm^2)		
	Cancer Area	**Cancer Stroma**	**Background non-tumor tissue**
Training	7,586	5,419	22,782
Tuning	517	418	950

Supplementary References

1. Park, S. et al. Artificial intelligence–powered spatial analysis of tumor-infiltrating lymphocytes as complementary biomarker for immune checkpoint inhibition in non–small-cell lung cancer. J. Clin. Oncol. 40, 1916–1928 (2022). https://doi.org/10.1200/JCO.21.02010
2. Ren, S., He, K., Girshick, R. & Sun, J. Faster R-CNN: Towards real-time object detection with region proposal networks. IEEE Trans. Pattern Anal. Mach. Intell. 39, 1137–1149 (2017). https://doi.org/10.1109/TPAMI.2016.2577031
3. Chen, L.C., Zhu, Y., Papandreou, G., Schroff, F. & Adam, H. Encoder-decoder with atrous separable convolution for semantic image segmentation. In Proc. Eur. Conf. Comput. Vis. 801–818 (2018).
4. He, K., Zhang, X., Ren, S. & Sun, J. Deep residual learning for image recognition. In Proc. IEEE Conf. Comput. Vis. Pattern Recognit. 770–778 (2016).
5. Kinga, D. & Adam, J.B. A method for stochastic optimization. In Int. Conf. Learn. Represent. arXiv preprint arXiv:1412.6980 (2014).

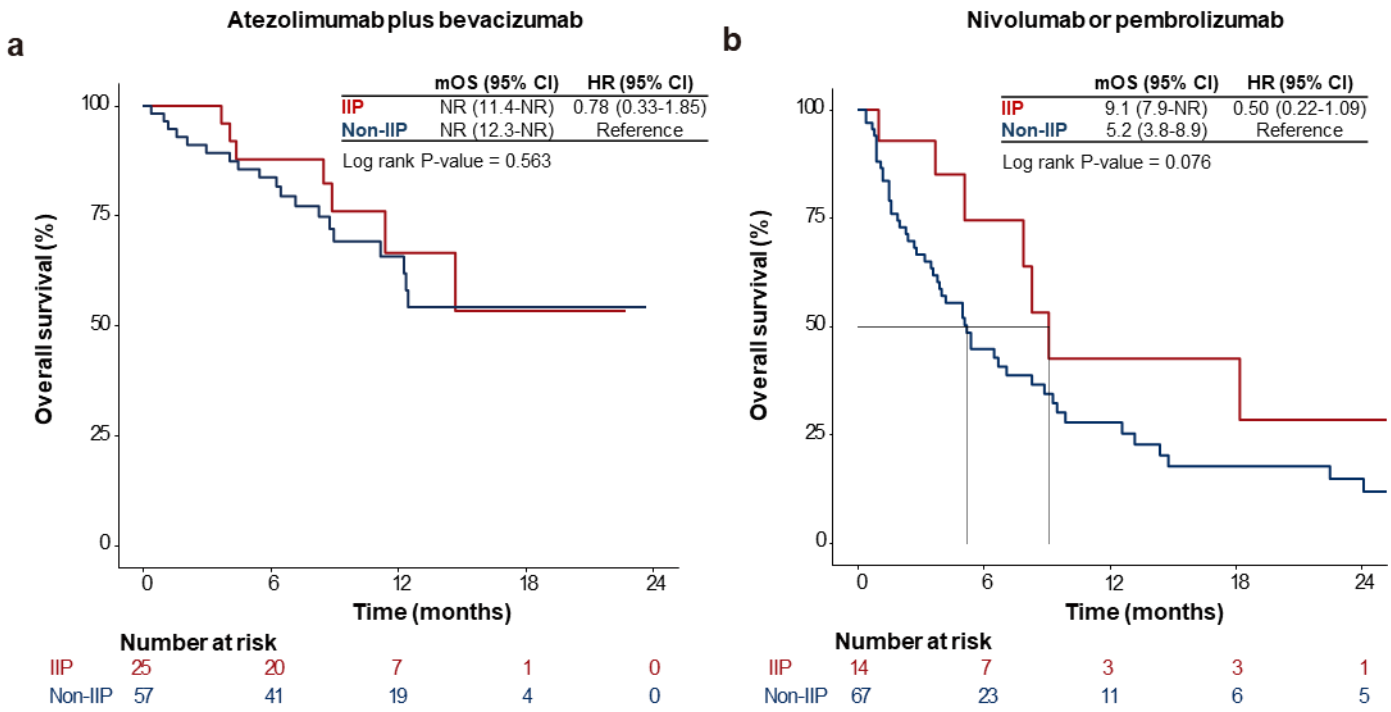
Supplementary Figure S1



Kaplan-Meier curves in the overall cohort, based on immune phenootypes
a. PFS after atezolizumab plus bevacizumab or monotherapies of nivolumab or pembrolizumab, according to immune phenotypes (IIP/non-IIP). **b.** OS after atezolizumab plus bevacizumab or monotherapies of nivolumab or pembrolizumab, according to immune phenotypes (IIP/non-IIP).

(Abbreviations: CI, confidence interval; HR, hazard ratio; IIP, inflamed immune phenotype; NR, not reached; OS, overall survival; PFS, progression-free survival)

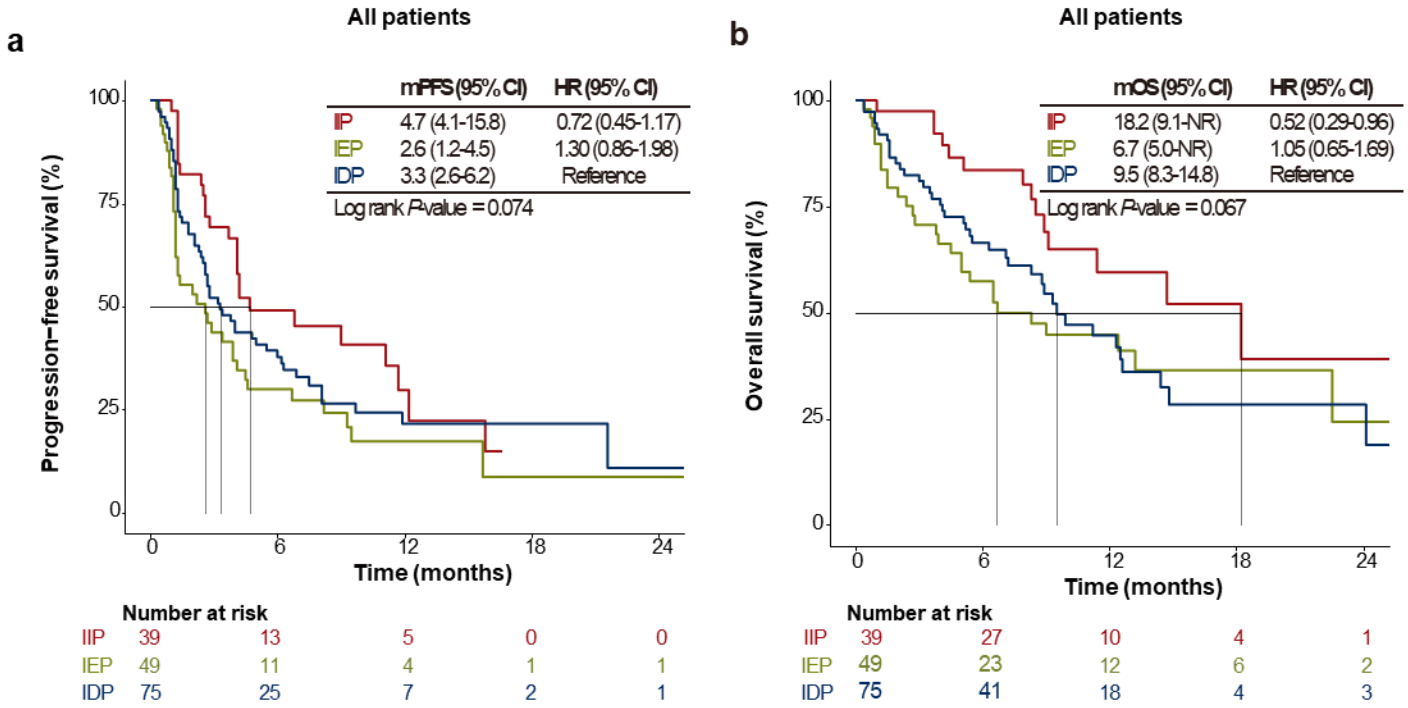
Supplementary Figure S2



Kaplan-Meier curves of OS by treatment regimen, based on immune phenotypes
a. OS after atezolizumab plus bevacizumab, according to immune phenotypes (IIP/non-IIP). **b.** OS after monotherapies of nivolumab or pembrolizumab, according to immune phenotypes (IIP/non-IIP).

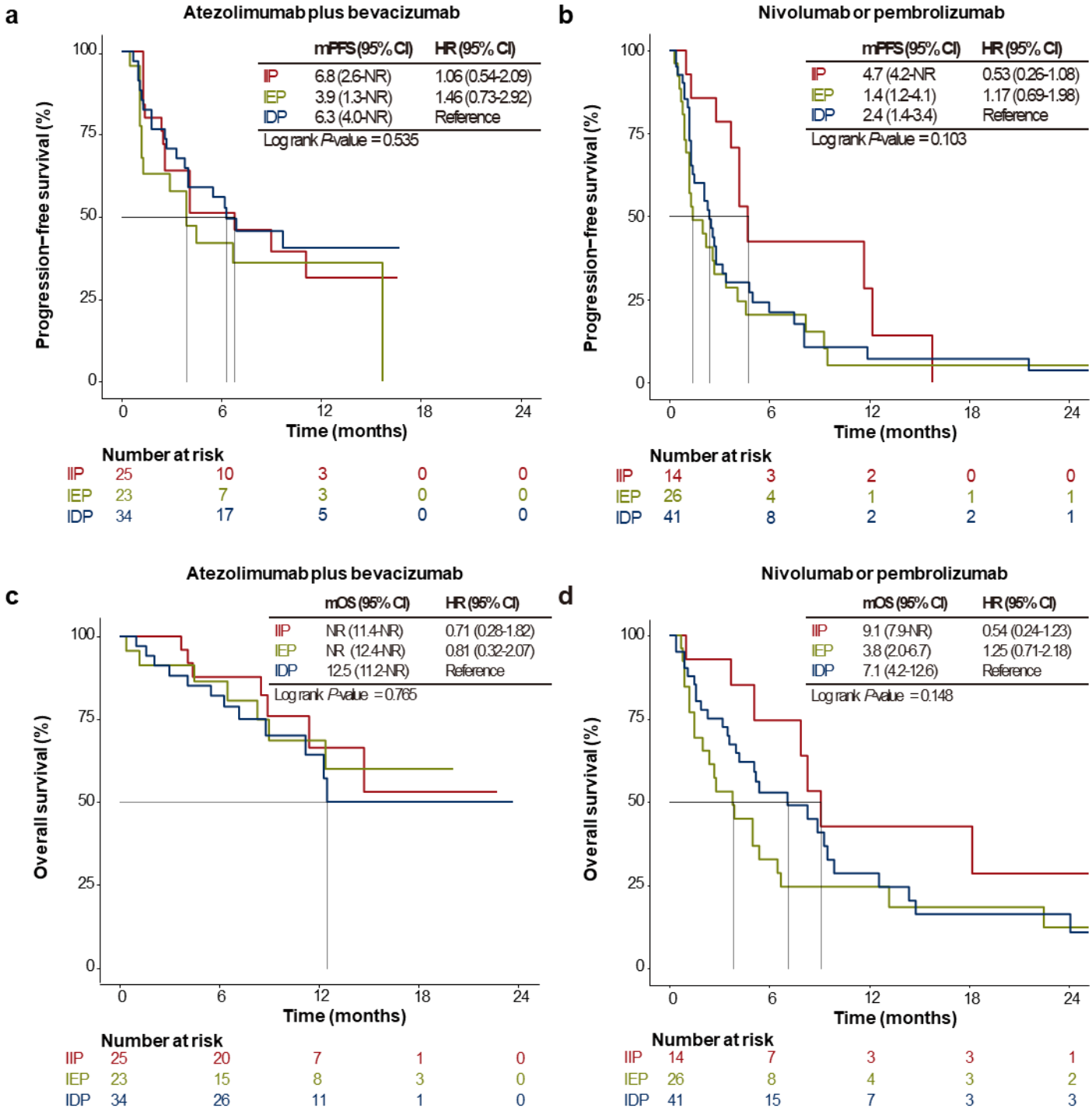
(Abbreviations: CI, confidence interval; HR, hazard ratio; IIP, inflamed immune phenotype; NR, not reached; OS, overall survival)

Supplementary Figure S3



Kaplan-Meier curves of OS by treatment regimen, based on 3-group immune phenotypes
a. PFS after atezolizumab plus bevacizumab or monotherapies of pembrolizumab or nivolumab, according to 3-group immune phenotypes (IIP/IEP/IDP). **b.** OS after atezolizumab plus bevacizumab or monotherapies of pembrolizumab or nivolumab, according to 3-group immune phenotypes (IIP/IEP/IDP). All analyses used IDP as a reference, comparing it to each IIP and IEP.
(Abbreviations: CI, confidence interval; HR, hazard ratio; IDP, immune-desert immune phenotype; IEP, immune-excluded immune phenotype; IIP, inflamed immune phenotype; NR, not reached; PFS, progression-free survival; OS, overall survival)

Supplementary Figure S4

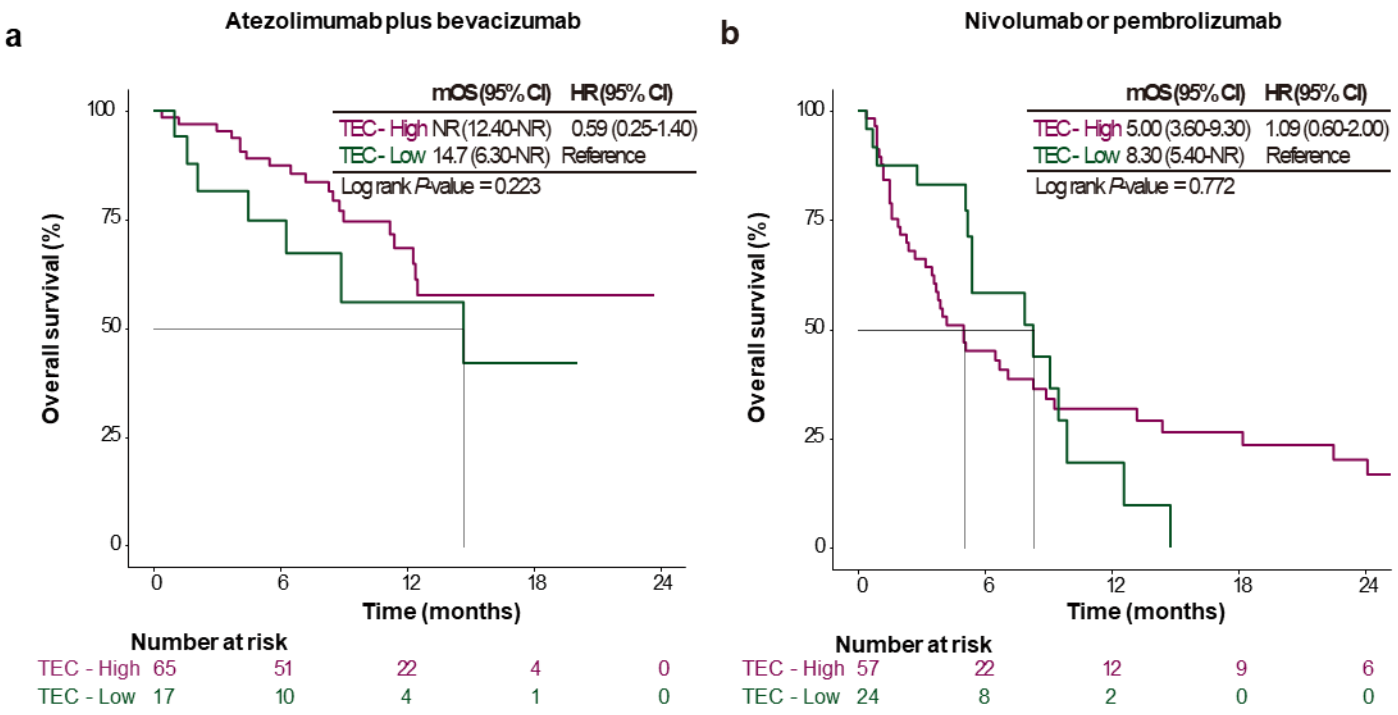


Kaplan-Meier curves by treatment regimen, based on 3-group immune phenotypes
a. PFS after atezolizumab plus bevacizumab, according to 3-group immune phenotypes (IIP/IEP/IDP). **b.** PFS after monotherapies of nivolumab or pembrolizumab, according to 3-

group immune phenotypes (IIP/IEP/IDP). **c.** OS after atezolizumab plus bevacizumab, according to 3-group immune phenotypes (IIP/IEP/IDP). **d.** OS after monotherapies of nivolumab or pembrolizumab, according to 3-group immune phenotypes (IIP/IEP/IDP). All analyses used IDP as a reference, comparing it to each IIP and IEP.

(Abbreviations: CI, confidence interval; HR, hazard ratio; IDP, immune-desert immune phenotype; IEP, immune-excluded immune phenotype; IIP, inflamed immune phenotype; NR, not reached; PFS, progression-free survival; OS, overall survival)

Supplementary Figure S5



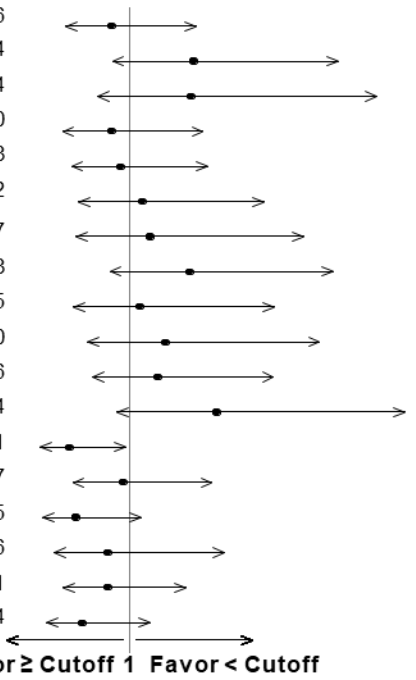
Kaplan-Meier curves of OS by treatment regimen, based on endothelial cell densities
a. OS after atezolizumab plus bevacizumab, according to TEC (high/low). **b.** OS after nivolumab or pembrolizumab monotherapy, according to TEC (high/low). The cutoff of 21.5/mm² was determined according to 25th percentile of the TEC.

(Abbreviations: CI, confidence interval; HR, hazard ratio; TEC, tumor endothelial cell density; NR, not reached; OS, overall survival)

Supplementary Figure S6

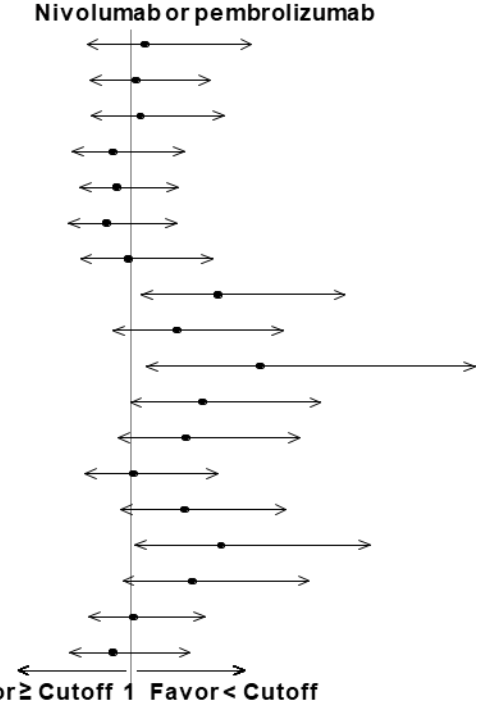
a

Variable	Quantile	Cuoff	N	n	mPFS ≥ Cutoff	mPFS < Cutoff	HR (95% CI), *p*-value
iMP density	0.25	3.0	82	56	5.5	6.2	0.86 (0.48−1.54), 0.6046
	0.5	5.9	82	35	3.9	6.9	1.53 (0.86−2.70), 0.1404
	0.75	19.4	82	15	3.3	6.3	1.50 (0.74−3.02), 0.2534
sMP density	0.25	28.7	82	59	6.7	4.0	0.85 (0.45−1.60), 0.6180
	0.5	48.6	82	40	6.9	5.5	0.93 (0.53−1.64), 0.7868
	0.75	80.5	82	20	6.8	5.5	1.11 (0.58−2.10), 0.7592
iFB density	0.25	56.5	82	66	5.5	7.6	1.17 (0.56−2.42), 0.6687
	0.5	105.6	82	46	3.9	9.0	1.49 (0.84−2.66), 0.1728
	0.75	168.9	82	18	6.8	5.5	1.08 (0.54−2.18), 0.8245
sFB density	0.25	1047.1	82	61	4.5	9.0	1.30 (0.66−2.55), 0.4470
	0.5	1443.7	82	41	4.1	6.7	1.23 (0.70−2.17), 0.4696
	0.75	1731.8	82	18	3.8	6.8	1.71 (0.90−3.25), 0.0954
TEC density	0.25	21.5	82	65	6.7	3.9	0.51 (0.27−0.97), 0.0371
	0.5	44.0	82	45	6.2	5.5	0.95 (0.53−1.67), 0.8397
	0.75	75.2	82	23	15.7	4.1	0.56 (0.29−1.09), 0.0835
sEC density	0.25	47.1	82	69	6.7	5.5	0.83 (0.38−1.77), 0.6176
	0.5	98.3	82	48	6.9	5.5	0.82 (0.46−1.46), 0.4851
	0.75	162.0	82	24	11.1	4.1	0.62 (0.32−1.17), 0.1354



b

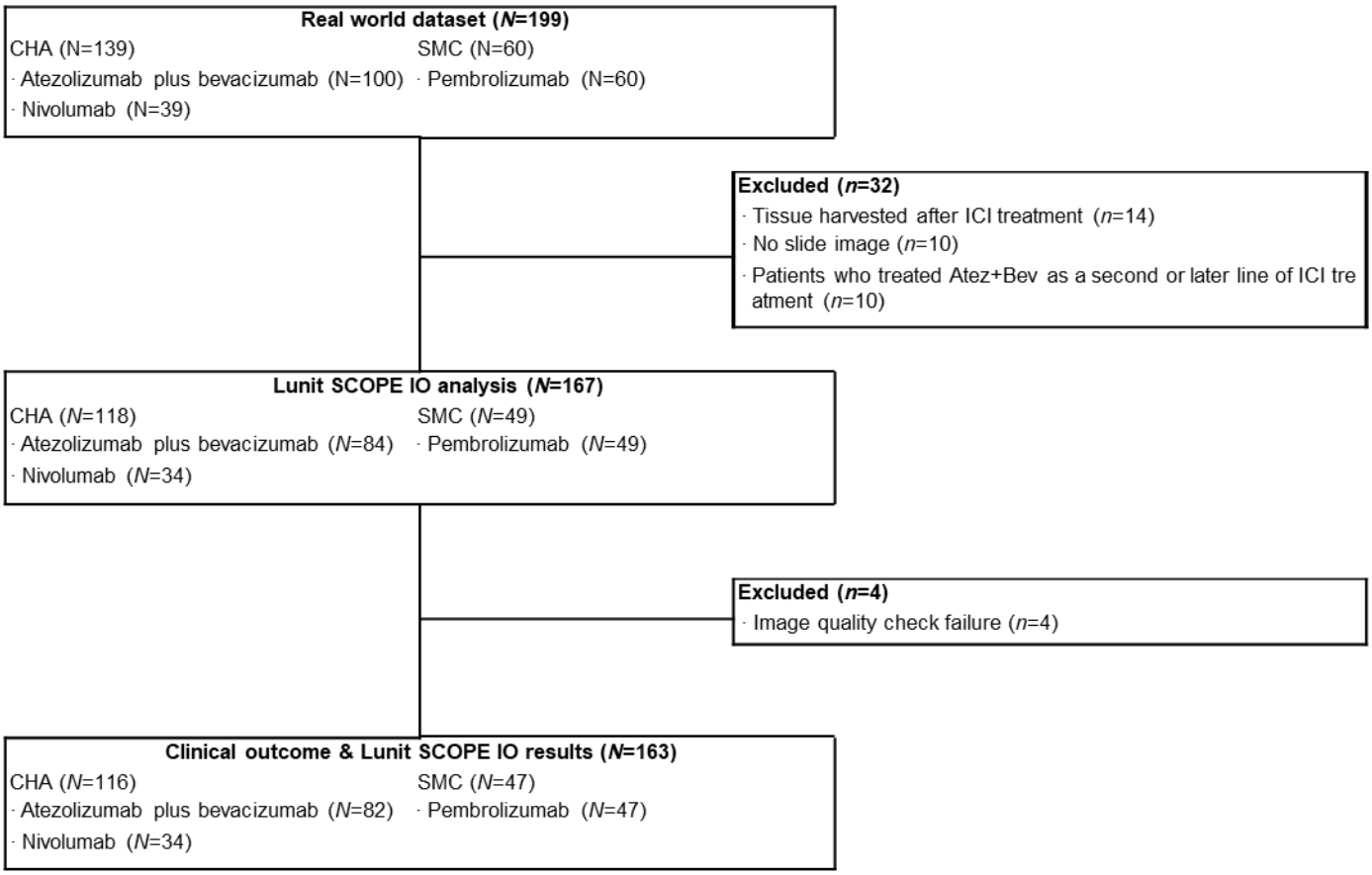
Variable	Quantile	Cuoff	N	n	mPFS ≥ Cutoff	mPFS < Cutoff	HR (95% CI), *p*-value
iMP density	0.25	3.0	81	66	2.7	2.6	1.12 (0.61−2.06), 0.7161
	0.5	5.9	81	46	2.8	2.5	1.04 (0.64−1.70), 0.8525
	0.75	19.4	81	26	3.1	2.5	1.08 (0.64−1.82), 0.7480
sMP density	0.25	28.7	81	63	2.6	2.6	0.84 (0.48−1.47), 0.5401
	0.5	48.6	81	42	2.6	2.6	0.88 (0.54−1.42), 0.5904
	0.75	80.5	81	21	2.8	2.6	0.79 (0.44−1.40), 0.4166
iFB density	0.25	56.5	81	56	2.7	2.3	0.98 (0.55−1.72), 0.9368
	0.5	105.6	81	35	1.4	2.7	1.77 (1.09−2.89), 0.0191
	0.75	168.9	81	23	2.2	2.6	1.41 (0.84−2.35), 0.1860
sFB density	0.25	1047.1	81	61	2.3	3.0	2.14 (1.14−4.03), 0.0158
	0.5	1443.7	81	40	2.2	2.8	1.63 (0.99−2.68), 0.0509
	0.75	1731.8	81	23	2.1	2.8	1.49 (0.89−2.49), 0.1264
TEC density	0.25	21.5	81	57	2.3	2.8	1.02 (0.59−1.77), 0.9352
	0.5	44.0	81	37	1.5	2.8	1.47 (0.91−2.37), 0.1140
	0.75	75.2	81	18	1.5	2.8	1.80 (1.04−3.11), 0.0338
sEC density	0.25	47.1	81	53	2.0	3.4	1.54 (0.93−2.57), 0.0941
	0.5	98.3	81	33	2.6	2.8	1.02 (0.63−1.65), 0.9562
	0.75	162.0	81	17	2.0	2.7	0.84 (0.46−1.52), 0.5451



Forest plot of PFS by treatment regimen, baesd on TME-related variable
a. Forest plot of PFS after atezolizumab plus bevacizumab with the comparison between the subgroup greater or equal to cutoffs and the subgroup less than cutoffs**. b.** Forest plot of PFS after monotherapies of nivolumab or pembrolizumab with the comparison of PFS between the subgroup greater or equal to cutoffs and the subgroup less than cutoffs. The number of patients greater or equal to cutoffs were listed as n.The cutoffs were defined as the 25th, 50th, and 75th percentiles of each variable.

(Abbreviations: CI, confidence interval; HR, hazard ratio; TEC, tumor endothelial cell density; iFB, intratumoral fibroblast density; iMP, intratumoral macrophage density; PFS, progression-free survival; sEC, stromal endothelial cell; sFB, stromal fibroblast; sMP, stromal macrophage; TME, tumor microenvironment)

Supplementary Figure S7



CONSORT diagram

Study samples were collected from two sites in South Korea, and 163 samples were analyzed in the current study in total.

(Abbreviations: CHA, CHA Bundang Medical Center; CONSORT, consolidated standards of reporting trials; ICI, immune checkpoint blockade; SMC, Samsung Medical Center)