Supplementary Material

Supplementary Table 1. Overall PD-L1 IHC scoring and training summary by pathologist

Pathologist	SP142		SP263		22C3 (CPS)		22C3 (IC)	
	Scored SP142	SP142 training, indication (date)[a]	Scored SP263	SP263 training, indication (date)[b]	Scored 22C3 (CPS)	22C3 training, indication (date)[c]	Scored 22C3 (IC)	Training, indication (date)[d]
Pathologist 1	X	TNBC: IC 1% (May 13, 2016)	—[e]	—	—	—	X	TNBC: IC 1% (May 13, 2016)
Pathologist 2	X	TNBC: IC 1% (May 25, 2015)	X	RCC: IC 1% (Apr 11, 2018)	—	—	—	—
Pathologist 3	X	TNBC: IC 1% (May 25, 2015)	X	RCC: IC 1% (Mar 29, 2018)	X	Cervical: CPS 1 (Nov 6, 2018)	X	TNBC: IC 1% (May 25, 2015)
Pathologist 4	X	TNBC: IC 1% (May 25, 2015)	—	—	—	—	X	TNBC: IC 1% (May 25, 2015)
Pathologist 5	X	TNBC: IC 1% (Feb 7, 2017)	—	—	—	—	X	TNBC: IC 1% (Feb 7, 2017)
Pathologist 6	—	—	—	—	—	—	X	RCC: IC 1% (Mar 29, 2018)
Pathologist 7	—	—	X	RCC: IC 1% (Mar 29, 2018)	—	—	X	RCC: IC 1% (Mar 29, 2018)
Pathologist 8	—	—	—	—	X	See footnote c	—	—
Pathologist 9 (for training)	—	—	—	—	—	Esophageal: CPS 10 (Aug 1, 2017) RCC: CPS 1 (Aug 23, 2018) Gastric: CPS 10 (Sep 12, 2018) Cervical: CPS 1 (Nov 6, 2018)	—	—

[a] Official training provided by Ventana. CPS, combined positive score; IC, tumor-infiltrating immune cell; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

[b] Training provided by Ventana based on a different indication.

[c] Pathologists 3 and 9 were trained for CPS directly by Agilent based on different tumor indications indicated in the table. Pathologist 8 did not receive official assay vendor training for CPS on 22C3-stained slides and was trained internally at HistoGeneX (tumor type: gastric adenocarcinoma) by a senior Agilent-trained pathologist, Pathologist 9 who had received extensive, official assay vendor training for CPS on 22C3 in multiple indications. For quality assurance, following internal training, CPS scoring by pathologist 8 was monitored and compared with an officially trained pathologist to ensure that they were concordant at the CPS 1 cutoff. For this purpose, in total, 52 of 410 cases reported by pathologist 8 were randomly selected and re-read by pathologist 3. The overall percent agreement for these cases between pathologists 8 and 3 was 88% at the CPS 1 cutoff, which complies with the standard pass criteria applied in immunohistochemistry assay training programs.

[d] Official training by the medical device manufacturer for reading this algorithm on 22C3-stained slides does not exist. Samples were read by pathologists trained for scoring algorithm in either a different indication or using a different assay; dates correspond to official Ventana training for the IC algorithm in TNBC or SP263 analyzed with the same scoring algorithm in RCC.

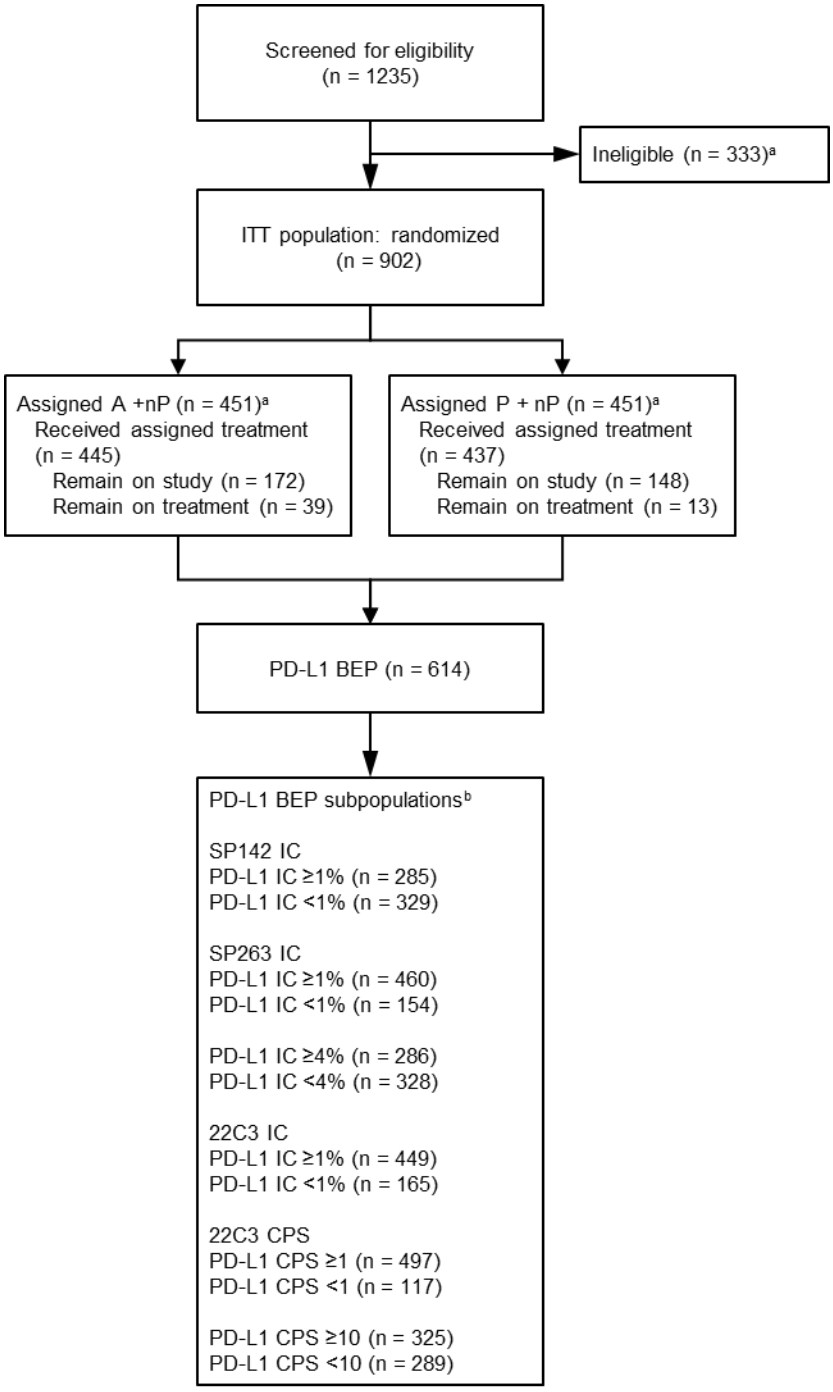
[e] Indicates scoring or training that was not undertaken by the given pathologist.

Supplementary Table 2. Select clinical and demographic characteristics for ITT and BEP populationsa

Characteristic	Patients	
	ITT (n=902)	BEP (n=614)
Disease status, %		
Locally advanced unresectable	9.8	8.6
Metastatic	90.0	91.2
Median age (range), years	55 (46–64)	55 (47–65)
ECOG PS	0 (0–1)	0 (0–1)
No. of metastatic sites, %		
0–3	74.6	73.1
>3	25.1	26.9
Metastatic sites, %		
Liver metastases	26.4	25.4
Brain metastases	6.8	6.8
Node-only disease	6.2	6.0
Time from last surgery to metastatic diagnosis, %		
Not applicable	37.4	36.2
<24 months	30.6	32.9
≥24 months	32.0	30.9
Prior taxane use, %	51.4	51.0
PD-L1 status IC ≥1% (SP142), %	40.9	46.4

[a]BEP, biomarker-evaluable population; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, tumor-infiltrating immune cells; ITT, intention-to-treat population; PD-L1, programmed death-ligand 1.

Supplementary Figure 1. Study populations



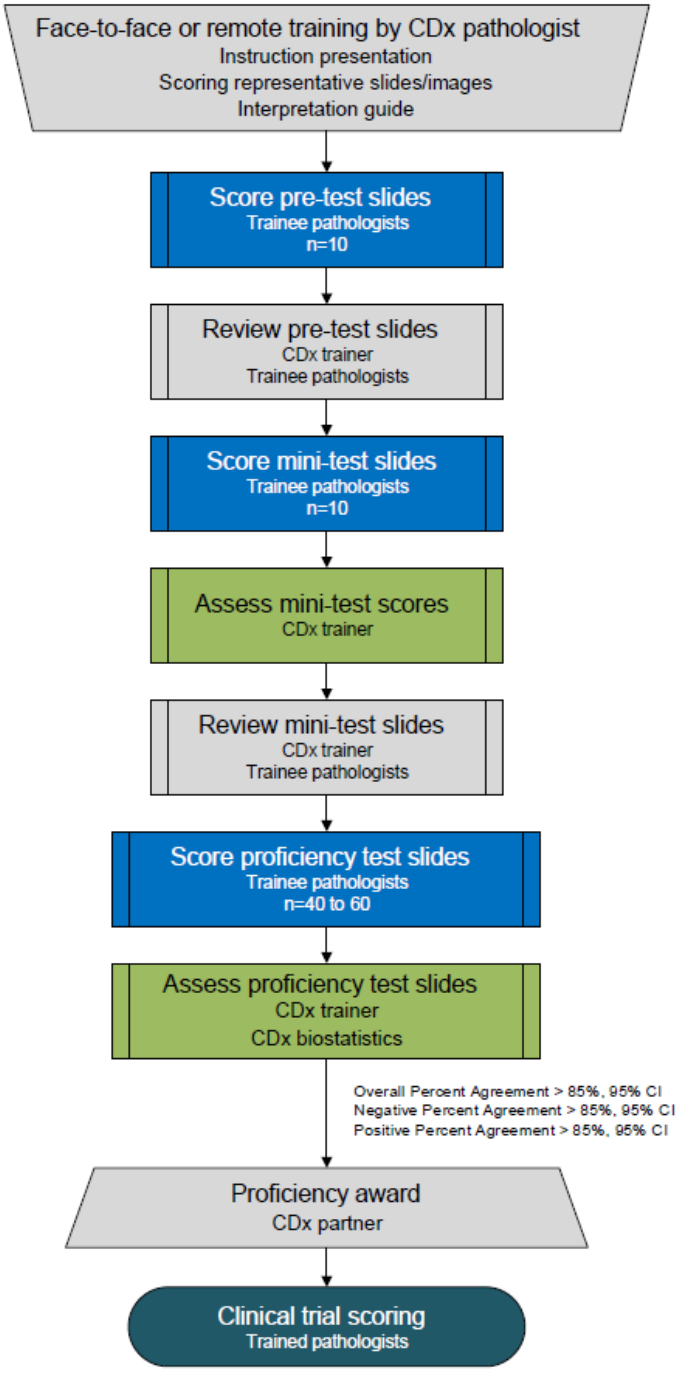
[a] Additional details on screening, treatment assignment, study and treatment discontinuation, death and loss to follow up were previously reported (Schmid P, et al. N Engl J Med.

2018;379(22): 2108-2121 and Schmid P, et al. Lancet Oncol. 2020;21(1):44-59. 2020 Jan;21(1):44-59).

[b] Biomarker-evaluable population (BEP) includes patients with evaluable tumor samples for the biomarker analysis.

[c] Patients may be included in more than one assay-defined subpopulation.

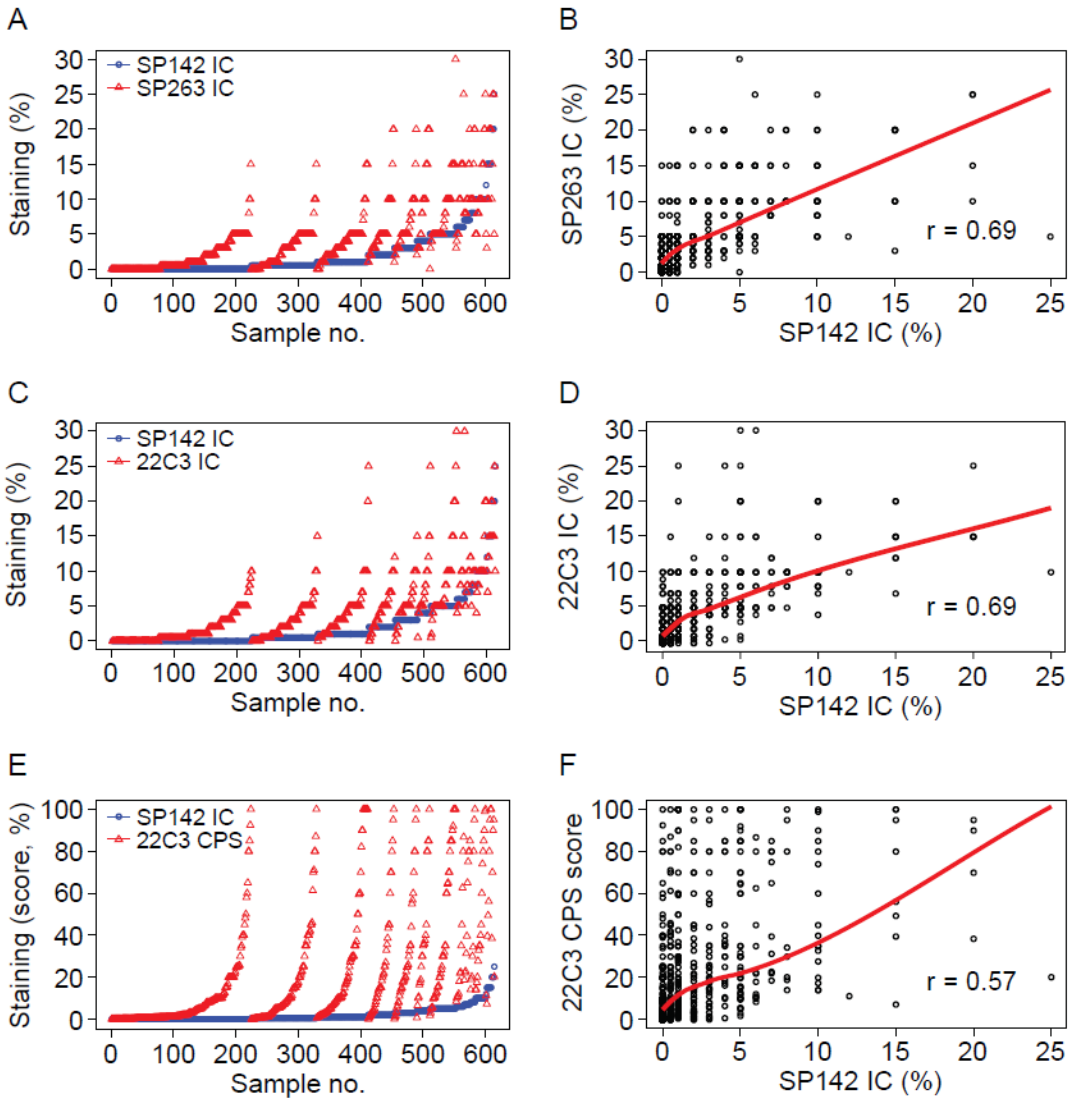
Supplementary Figure 2 Companion diagnostic pathologist training workflow



Overview of a typical pathologist training program for scoring of PD-L1 immunohistochemistry assays. The flow chart represents a typical training program that pathologists must complete in order to be qualified to read histological slides for a companion diagnostic immunohistochemical

assay in a clinical trial. The manufacturer provides face-to-face or remote training to site pathologists according to the official assay interpretation and scoring guide. All case collections used during the training are provided by the manufacturer. The trainer pathologist demonstrates the scoring method using an instructional case set. Trainee pathologists first score a small self-study case collection and check their results with the instructor and case consensus scores. Proficiency test case collections can be arranged in a small and large case set or a single large case set. Raw scores are used to determine a case status relative to a predefined cutoff and the overall percent agreement (OPA), the positive percent agreement (PPA) and the negative percent agreement (NPA) with consensus scores relative to this cutoff must typically be > 85%. The manufacturer provides documentation that each individual pathologist is certified competent to apply the scoring algorithm in accordance with the interpretation guide and may score clinical trial samples.

Supplementary Figure 3. Analytical correlation between SP142, SP263 and 22C3 raw values



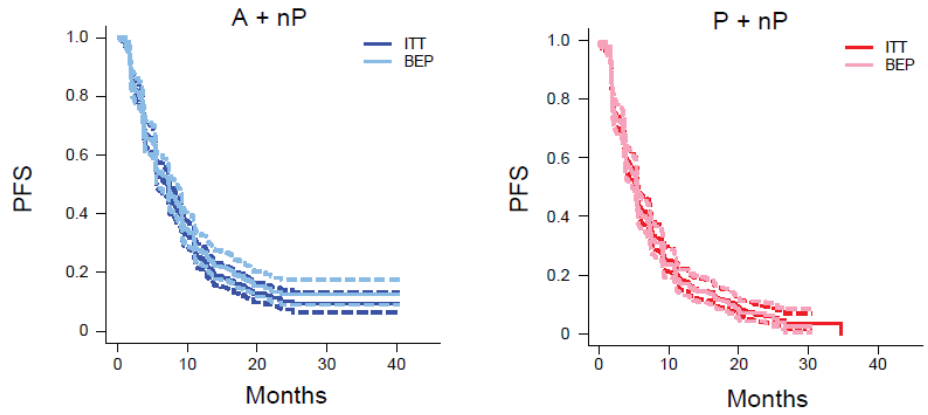
CPS, Combined Positive Score; IC, tumor-infiltrating immune cells; *r*, Spearman correlation index.

Sample level expression and correlation between SP142 IC and SP263 IC (A–B), 22C3 IC (C–D) and 22C3 CPS (E–F). In panels A, C and E, raw PD-L1 scores are plotted (y-axis) per individual sample (x-axis). Most samples displayed higher scores for SP263 and 22C3 (red

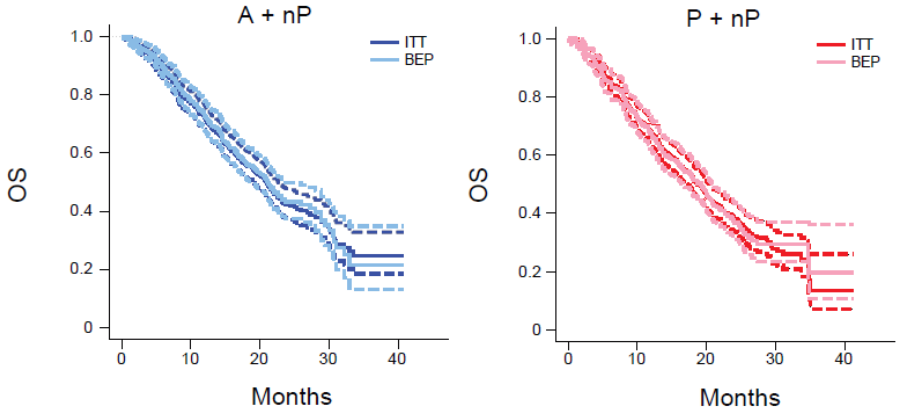
symbols) compared with SP142 (blue symbols), while a smaller number of cases had higher SP142 scores compared with the other assays. For samples with the same staining scores for two given assays, overlapping data points are visualized as red. The plots in panels B, D and F show the correlation (Spearman correlation index) between the raw values from the SP142 IC (x-axis) and the SP263 or 22C3 assays (y-axis).

Supplementary Figure 4. Clinical activity in ITT and BEP populations

A



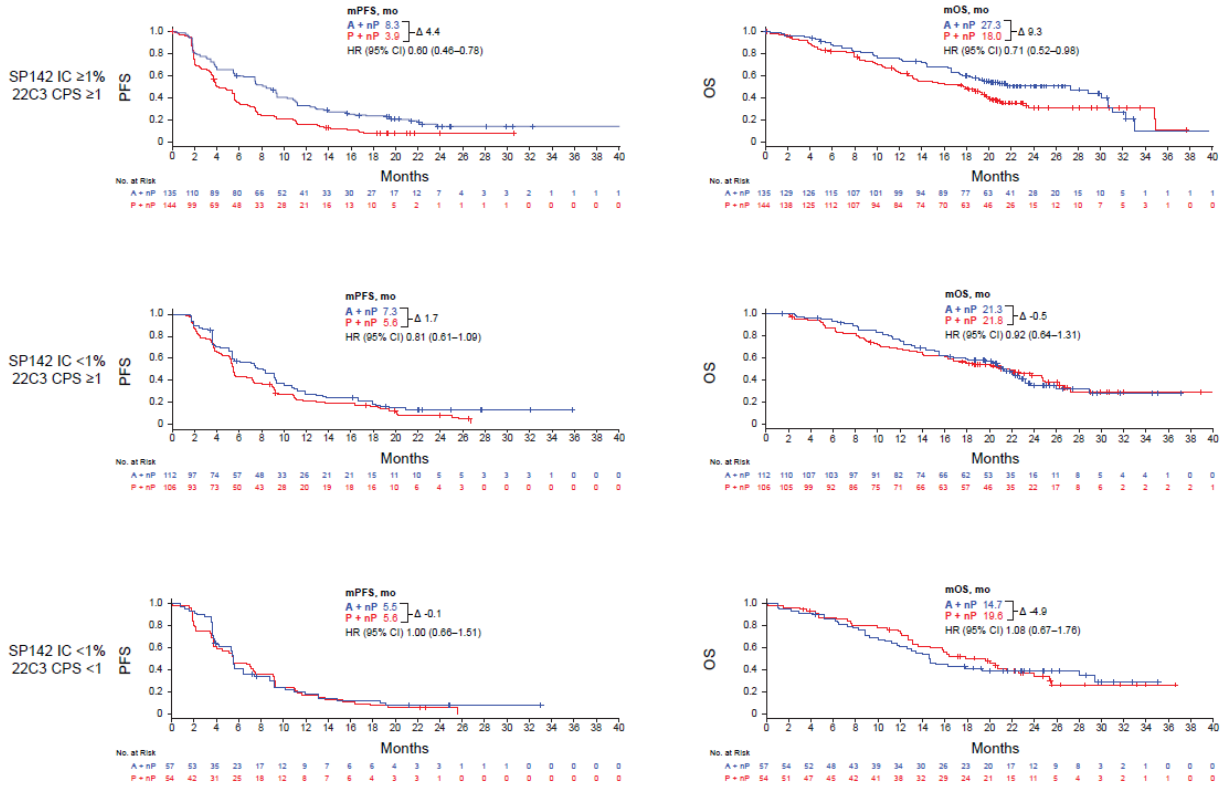
B



BEP, biomarker-evaluable population; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

Kaplan-Meier plots of (A) PFS and (B) OS in ITT vs BEP populations by treatment arm.

Supplementary Figure 5. Clinical outcomes in BEP double-selected populations for SP142 IC and 22C3 CPS assay combinations

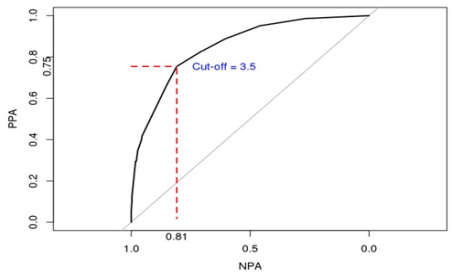


A, atezolizumab; BEP, biomarker-evaluable population; CPS, Combined Positive Score; IC, tumor-infiltrating immune cells; nP, *nab*-paclitaxel; OS, overall survival; P, placebo; PFS, progression-free survival.

Kaplan-Meier plots of PFS and OS in BEP double-selected populations defined by SP142 IC 1% and 22C3 CPS 1 cutoffs.

Supplementary Figure 6. Identification of model-derived optimized cutoffs for 22C3 IC that maximizes analytical concordance with SP142 IC 1% and its clinical activity

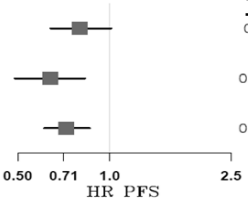
A



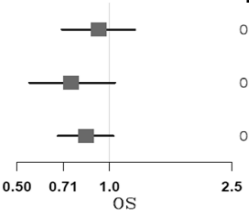
Prevalence, n (%)		22C3	
		IC <4%	IC ≥4%
SP142	IC <1%	266 (43.3)	63 (10.3)
	IC ≥1%	70 (11.4)	215 (35.0)
Agreement, % (95% CI)			
PPA	% (95% CI)	215/285	
		75.4 (70.4-80.4)	
NPA	% (95% CI)	266/329	
		80.9 (76.6-85.1)	
OPA	% (95% CI)	481/614	
		78.3 (75.1–81.6)	

B

22C3 IC	A+nP Patients, n	P+nP Patients, n	A+nP Events, n	P+nP Events, n	A+nP Median PFS, mo	A+nP (95% CI)		P+nP Median PFS, mo	P+nP (95% CI)		HR	(95% CI)		P value
<4%	171	165	144	149	5.68	5.45	8.28	5.49	4.53	6.93	0.8	0.64	1.01	0.06
>=4%	135	143	108	127	8.18	7.2	9.59	5.39	3.94	5.68	0.64	0.49	0.83	<=.005
All	306	308	252	276	7.36	5.55	8.34	5.39	4.83	5.59	0.72	0.61	0.86	<=.005

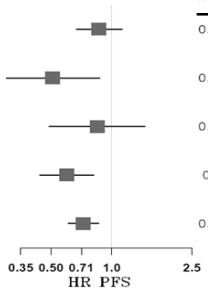


22C3 IC	A+nP Patients, n	P+nP Patients, n	A+nP Events, n	P+nP Events, n	A+nP Median OS, mo	A+nP (95% CI)		P+nP Median OS, mo	P+nP (95% CI)		HR	(95% CI)		P value
<4%	171	165	102	97	19.55	16.43	22.01	18.04	14.65	22.64	0.92	0.7	1.21	0.55
>=4%	135	143	68	86	27.27	20.21	31.08	19.22	16.53	22.67	0.75	0.55	1.04	0.08
All	306	308	170	183	21.13	19.02	23.72	19.22	16.53	20.8	0.84	0.68	1.03	0.1

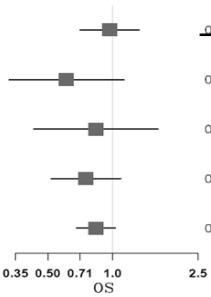


C

22C3 IC and SP142 IC	A+nP Patients, n	P+nP Patients, n	A+nP Events, n	P+nP Events, n	A+nP Median PFS, mo	A+nP (95% CI)		P+nP Median PFS, mo	P+nP (95% CI)		HR	(95% CI)		P value
22C3.IC<4% SP142.IC<1%	133	133	112	119	5.55	5.39	8.28	5.59	5.32	7.49	0.86	0.67	1.12	0.27
22C3.IC<4% SP142.IC>=1%	38	32	32	30	7.36	3.78	10.87	3.68	2.56	5.55	0.51	0.3	0.87	0.01
22C3.IC>=4% SP142.IC<1%	36	27	31	26	7.2	5.06	9.46	5.49	5.32	9.23	0.85	0.49	1.46	0.56
22C3.IC>=4% SP142.IC>=1%	99	116	77	101	9.23	7.23	11.07	5.29	3.81	5.68	0.6	0.44	0.81	<=.005
All	306	308	252	276	7.36	5.55	8.34	5.39	4.83	5.59	0.72	0.61	0.86	<=.005



22C3 IC and SP142 IC	A+nP Patients, n	P+nP Patients, n	A+nP Events, n	P+nP Events, n	A+nP Median OS, mo	A+nP (95% CI)		P+nP Median OS, mo	P+nP (95% CI)		HR	(95% CI)		P value
22C3.IC<4% SP142.IC<1%	133	133	80	76	20.53	15.44	23.16	20.5	15.87	25	0.97	0.71	1.33	0.85
22C3.IC<4% SP142.IC>=1%	38	32	22	21	19.12	16.79		13.63	9.82		0.61	0.33	1.13	0.11
22C3.IC>=4% SP142.IC<1%	36	27	19	18	21.36	14.29		21.03	17.84		0.84	0.43	1.63	0.61
22C3.IC>=4% SP142.IC>=1%	99	116	49	68	28.85	21.55	32.2	18.69	13.31	23.06	0.75	0.52	1.09	0.13
All	306	308	170	183	21.13	19.02	23.72	19.22	16.53	20.8	0.84	0.68	1.03	0.1



IC, tumor-infiltrating immune cells; NPA, negative percentage agreement; OPA, overall positive agreement; PPA, positive percentage agreement; ROC, receiver-operator curve.

(A) ROC curve analysis (area under the-curve) of optimal OPA based on NPA and PPA values for 22C3 IC using SP142 IC 1% as the reference standard. Prevalence and percentage agreement values are shown (right). (B) Forest plots of PFS and OS in BEP subpopulations defined by the exploratory cutoff of 22C3 IC 4%. (C) Forest plots of PFS and OS in BEP subpopulations defined by SP142 IC 1% and 22C3 IC 4%. Note: IC 3.5% from panel A ROC curve is rounded to IC 4% elsewhere in the figure.