Supplementary Table S1. Representativeness of study participants.

Cancer type	Locally advanced/metastatic TNBC, no prior systemic therapy in the locally advanced/metastatic setting.
Sex	Breast cancer, including TNBC, is a predominantly female disease; approximately 0.5–1.0% of breast cancers occur in men. TNBC accounts for 10–15% of all breast cancers, but breast cancer in males is hormone receptor-positive in up to 95% of cases, thus male TNBC is particularly rare.
Age	TNBC is associated with younger age of onset than other subtypes. Women aged <40 years have the highest odds of diagnosis.
Race/ethnicity	TNBC disproportionately affects Black women. The prevalence of TNBC is higher in Black and Hispanic women than in Non-Hispanic White women. An analysis of real-world data from the US reported TNBC in 23% of breast cancers in African-American women vs 12% of White women.
Geography	Generally the incidence is highest in developed regions of the world and lower but increasing in less developed countries. Mortality shows less difference, due in part to earlier detection and improved treatment in more developed countries.
Other considerations	Populations enrolled in three large randomized phase 3 trials evaluating immunotherapy in the first-line metastatic TNBC setting enrolled populations comprising 4–7% Black/African-American and 17–30% Asian; however, these figures are strongly influenced by the demographics in participating countries. Underrepresentation in trials limits evaluation of the impact of racial/ethnic- or ancestry-based differences in efficacy and toxicity. The median age in these same three trials was 53–56 years.
Overall representativeness of this study	The ranges and percentages in the various small cohorts reported in the present paper are expected to be more diverse given the small patient numbers in each group. Although eligible, no males were enrolled. The age distribution across the various cohorts of our dataset (median 50-56 years) is similar to the average age distribution of TNBC in the literature. Across the various cohorts, the percentage of Black patients was ≤10%. Up to 28% of patients were of multiple/other/mixed race/ethnicity. Patients were enrolled in Europe and North America (plus Australia, South America, and Asia each for two studies).

Supplementary Table S2. Summary of baseline characteristics.

Characteristic	CO40151			IPATunity130, Cohort C			IPATunity170				
Treatment	Atezo + ipat + pac/nab-pac			Atezo + ipat + pac			Atezo + pac	Atezo + ipat + pac	Pac	Ipat + pac	Atezo + ipat + pac
PD-L1 status	+	–	Unknown	+	–	Unknown	+ (Cohort 2)		– or unknown (Cohort 1)		
PIK3CA/AKT1/PTEN status	Unselected			Not altered			Unselected				
No. of patients	51	45	18	40	25	37	57	58	41	43	43
Median age, years (range)	50 (29–84)	53 (27–79)	51 (29–87)	51 (30–83)	54 (36–72)	56 (22–83)	52 (30–82)	52 (28–84)	53 (29–78)	52 (25–72)	54 (30–81)
Race, %											
American Indian/Alaska Native	0	2	0	5	4	5	11	9	2	7	12
Asian	12	0	0	13	12	11	28	33	22	16	23
Black/African American	2	0	0	10	8	8	4	3	0	5	5
White	75	87	72	50	60	54	56	50	71	67	60
Multiple/other/unknown	12	11	28	23	16	22	2	5	5	5	0
ECOG PS status 0, %	45	53	61	58	60	62	74	53	63	67	60
Prior (neo)adjuvant chemotherapy, %	69	62	78	35	60	35	51	40	63	58	58
Anthracycline	57	49	56	33	52	27	40	31	32	44	51
Taxane	55	53	56	28	56	35	30	31	49	49	44
PIK3CA/AKT1/PTEN alteration, %[a]											
Altered	31			0	0	0	44	34	34	30	53
PIK3CA/AKT1				0	0	0	23	10	22	16	19

Characteristic	CO40151			IPATunity130, Cohort C			IPATunity170				
PTEN only				0	0	0	21	24	12	14	35
Not altered	39			100	100	100	47	59	41	51	30
Unknown	29			0	0	0	9	7	24	19	16
PD-L1 status, %											
Positive	100	0	0	100	0	0	100	100	0	0	0
Negative	0	100	0	0	100	0	0	0	95	98	86
Unknown	0	0	100	0	0	100	0	0	5	2	14
BRCA mutation status, %[b]											
Negative	NA	NA	NA	85	80	84	75	81	66	72	63
Positive	NA	NA	NA	15	20	16	16	12	10	9	21
Unknown	NA	NA	NA	0	0	0	9	7	24	19	16

[a]By central testing.
[b]By local testing before enrollment. Not collected in CO40151.
Abbreviations: atezo, atezolizumab; ipat, ipatasertib; NA, not available, pac, paclitaxel; PS, performance status.

Supplementary Table S3. Summary of treatment exposure (triplet regimens shown in bold).

Characteristic	CO40151			IPATunity130, Cohort C			IPATunity170				
PD-L1 status	+	–	Unknown	+	–	Unknown	+		– or unknown		
PIK3CA/AKT1/PTEN status	Unselected			Not altered							
Treatment	**Atezo + ipat + pac/nab-pac**			**Atezo + ipat + pac**			**Atezo + pac**	**Atezo + ipat + pac**	**Pac**	**Ipat + pac**	**Atezo + ipat + pac**
No. of patients	**51**	**45**	**18**	40	25	37	57	**58**	41	43	**43**
Median treatment duration, months (range)											
Paclitaxel	**(*n* = 38) 5.1 (0–21)**	**(*n* = 40) 5.1 (1–17)**	**(*n* = 16) 4.7 (1–15)**	**6.1 (0–25)**			3.3 (0–20)	**4.9 (0–16)**	3.2 (0–17)	3.7 (0–15)	**4.7 (0–17)**
Nab-paclitaxel	**(*n* = 13) 5.1 (0–9)**	**(*n* = 5) 3.3 (<1–11)**	**(*n* = 2) 5.4 (5–6)**	**–**	**–**	**–**	–	**–**	–	–	**–**
Ipatasertib	**7.1 (0–42)**	**6.7 (1–44)**	**7.3 (0–37)**	**6.2 (0–28)**			–	**5.3 (0–19)**	–	3.5 (0–16)	**3.9 (0–18)**
Atezolizumab	**6.0 (0–38)**	**6.5 (0–43)**	**7.3 (0–38)**	**5.7 (0–27)**			3.3 (0–20)	**5.1 (0–19)**	–	–	**5.1 (0–18)**

Abbreviations: atezo, atezolizumab; ipat, ipatasertib; pac, paclitaxel.

Supplementary Table S4. Grade ≥3 AEs[a] in >5% of patients receiving the triplet regimen in any trial.

Trial	CO40151	IPATunity130, Cohort C	IPATunity170		All trials (*n* = 317)
Treatment	**Atezo + ipat +pac/nab-pac (*n* = 114)**	**Atezo + ipat + pac (*n* = 102)**	**Cohort 1, Atezo + ipat + pac (*n* = 43)**	**Cohort 2, Atezo + ipat + pac (*n* = 58)**	
Diarrhea	14 (12)	17 (17)	6 (14)	8 (14)	45 (14)
Rash	11 (10)	2 (2)	5 (12)	3 (5)	21 (7)
Neutropenia	12 (11)	6 (6)	5 (12)	5 (9)	28 (9)
Neutrophil count decreased	1 (1)	4 (4)	2 (5)	3 (5)	10 (3)
ALT increased	7 (6)	8 (8)	2 (5)	7 (12)	24 (8)
AST increased	4 (4)	8 (8)	1 (2)	6 (10)	19 (6)
Peripheral neuropathy	2 (2)	7 (7)	1 (2)	1 (2)	11 (3)
Lipase increased	6 (5)	3 (3)	0	2 (3)	11 (3)
Fatigue	0	3 (3)	2 (5)	3 (5)	8 (3)
Syncope	1 (1)	0	0	3 (5)	4 (1)

[a]AEs graded according to NCI CTCAE version 4.0 for CO40151 and IPATunity130 and version 5.0 for IPATunity170 and coded using MedDRA version 24.1.

Abbreviations: AE, adverse event; atezo, atezolizumab; ipat, ipatasertib; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; pac, paclitaxel.

Supplementary Table S5. Results of GSEA analysis with hallmark gene sets.

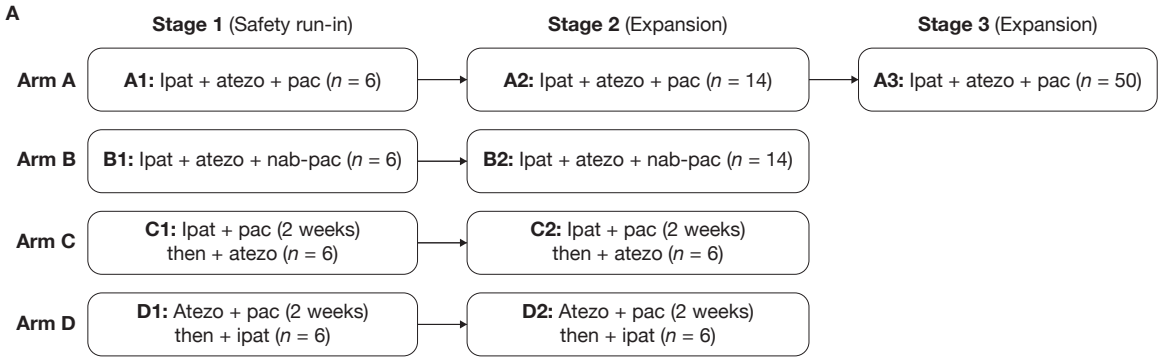
Gene set ID	No. of genes in the gene set	Median t statistics	Regulation direction of pathways	Enrichment score	Normalized enrichment score	*P* value	Adjusted *P* value
Hallmark E2F targets	200	-1.45	Down	-0.65	-3.09	3.6×10^{-35}	1.8×10^{-33}
Hallmark G2M checkpoint	200	-1.41	Down	-0.59	-2.8	5.5×10^{-25}	1.4×10^{-23}
Hallmark IFN gamma response	191	0.84	Up	0.55	2.93	9.7×10^{-24}	1.6×10^{-22}
Hallmark MYC targets V1	195	-1.06	Down	-0.58	-2.75	4.1×10^{-23}	5.2×10^{-22}
Hallmark TNFα signaling via NF-κB	190	0.6	Up	0.46	2.42	1.8×10^{-13}	1.8×10^{-12}
Hallmark IFN alpha response	95	0.91	Up	0.57	2.69	3.0×10^{-13}	2.5×10^{-12}
Hallmark epithelial–mesenchymal transition	195	0.65	Up	0.43	2.26	1.8×10^{-11}	1.3×10^{-10}
Hallmark oxidative phosphorylation	198	-0.61	Down	-0.45	-2.13	7.6×10^{-10}	4.8×10^{-9}
Hallmark allograft rejection	171	0.49	Up	0.41	2.14	1.3×10^{-8}	7.5×10^{-8}
Hallmark androgen response	97	0.8	Up	0.48	2.25	3.1×10^{-8}	1.6×10^{-7}
Hallmark complement	176	0.46	Up	0.38	1.99	1.4×10^{-7}	6.5×10^{-7}
Hallmark mitotic spindle	199	-0.55	Down	-0.41	-1.94	1.6×10^{-7}	6.9×10^{-7}
Hallmark inflammatory response	172	0.45	Up	0.37	1.89	6.5×10^{-7}	2.5×10^{-6}
Hallmark MYC targets V2	56	-1.09	Down	-0.57	-2.21	9.7×10^{-7}	3.5×10^{-6}
Hallmark protein secretion	94	0.41	Up	0.43	2.02	6.0×10^{-6}	2.0×10^{-5}
Hallmark apoptosis	156	0.45	Up	0.34	1.74	3.0×10^{-5}	9.4×10^{-5}
Hallmark IL2 STAT5 signaling	185	0.42	Up	0.33	1.73	3.9×10^{-5}	0.00012
Hallmark IL6 JAK STAT3 signaling	76	0.48	Up	0.42	1.89	0.00015	0.00043
Hallmark DNA repair	142	-0.47	Down	-0.38	-1.76	0.00023	0.00060
Hallmark UV response DN	142	0.24	Up	0.29	1.47	0.0051	0.013
Hallmark hypoxia	180	0.23	Up	0.27	1.39	0.011	0.025
Hallmark spermatogenesis	79	-0.52	Down	-0.38	-1.58	0.013	0.030
Hallmark glycolysis	179	-0.17	Down	-0.29	-1.37	0.030	0.065
Hallmark estrogen response late	180	-0.11	Down	-0.28	-1.34	0.037	0.077
Hallmark coagulation	105	0.45	Up	0.28	1.33	0.043	0.086
Hallmark xenobiotic metabolism	158	0.05	Up	0.25	1.25	0.051	0.098

Gene set ID	No. of genes in the gene set	Median t statistics	Regulation direction of pathways	Enrichment score	Normalized enrichment score	*P* value	Adjusted *P* value
Hallmark estrogen response early	189	0.17	Up	0.24	1.25	0.057	0.11
Hallmark mTORC1 signaling	196	-0.3	Down	-0.27	-1.27	0.067	0.12
Hallmark KRAS signaling up	170	0.24	Up	0.23	1.2	0.078	0.13
Hallmark TGF BETA signaling	52	0.09	Up	0.3	1.23	0.14	0.23
Hallmark WNT BETA catenin signaling	38	-0.17	Down	-0.35	-1.26	0.16	0.26
Hallmark heme metabolism	173	0.09	Up	0.22	1.12	0.18	0.29
Hallmark angiogenesis	28	0.25	Up	0.32	1.14	0.27	0.38
Hallmark apical surface	35	0.03	Up	0.3	1.13	0.27	0.38
Hallmark bile acid metabolism	87	0.02	Down	-0.26	-1.11	0.27	0.38
Hallmark apical junction	177	0.13	Up	0.2	1.06	0.29	0.40
Hallmark NOTCH signaling	32	0.37	Down	-0.33	-1.12	0.30	0.40
Hallmark myogenesis	156	0.1	Up	0.21	1.04	0.33	0.43
Hallmark unfolded protein response	110	0.04	Up	0.22	1.05	0.34	0.44
Hallmark UV RESPONSE UP	143	-0.19	Down	-0.23	-1.04	0.35	0.44
Hallmark adipogenesis	191	-0.03	Down	-0.22	-1.04	0.38	0.46
Hallmark pancreas beta cells	17	-0.48	Down	-0.31	-0.94	0.55	0.65
Hallmark P53 pathway	192	-0.03	Down	-0.2	-0.94	0.58	0.67
Hallmark peroxisome	93	-0.05	Down	-0.21	-0.92	0.64	0.73
Hallmark cholesterol homeostasis	71	0.11	Up	0.19	0.86	0.78	0.85
Hallmark fatty acid metabolism	138	0.04	Down	-0.19	-0.85	0.79	0.85
Hallmark HEDGEHOG signaling	31	0.08	Up	0.21	0.76	0.86	0.90
Hallmark KRAS signaling DN	117	0.05	Down	-0.19	-0.82	0.86	0.90
Hallmark reactive oxygen species pathway	47	0	Down	-0.19	-0.72	0.91	0.91
Hallmark PI3K AKT mTOR signaling	98	-0.12	Down	-0.18	-0.77	0.91	0.91

Abbreviations: DGE, differential gene expression; JAK, Janus kinase.

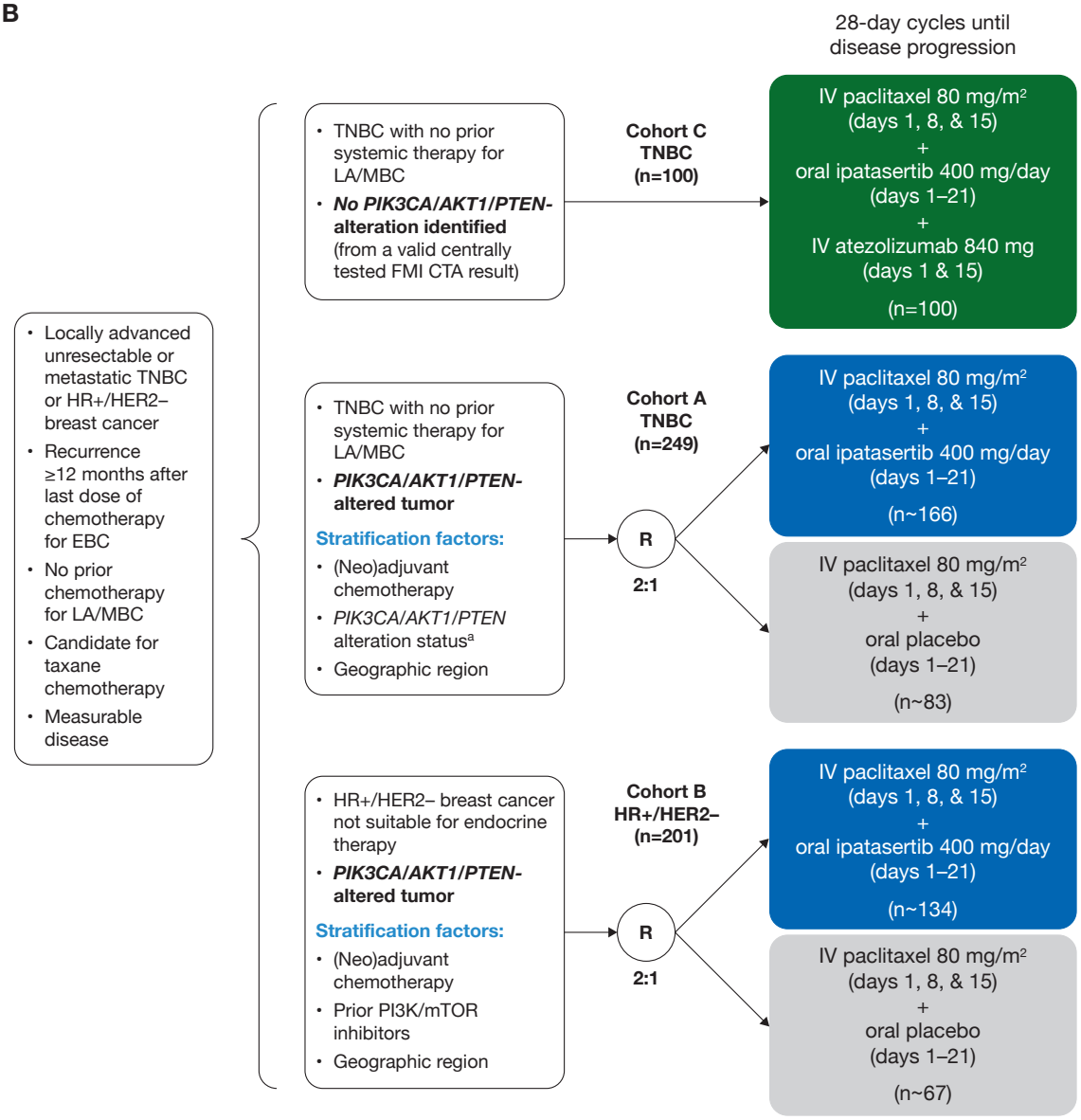
Supplementary Figure S1.
Trial designs of **A,** CO40151; **B,** IPATunity130; **C,** IPATunity170.

atezo, atezolizumab; CBR, clinical benefit rate; CIT, cancer immunotherapy; CTA, clinical trial assay; D, day; DoR, duration of response; EBC, early breast cancer; FMI, Foundation Medicine, Inc.; GHS/HRQoL, global health status/health-related quality of life; ipat, ipatasertib; HR+, hormone receptor positive; ITT, intent-to-treat; IV, intravenous; LA/MBC, locally advanced/metastatic breast cancer; pac, paclitaxel; PRO, patient-reported outcome; R, randomization.



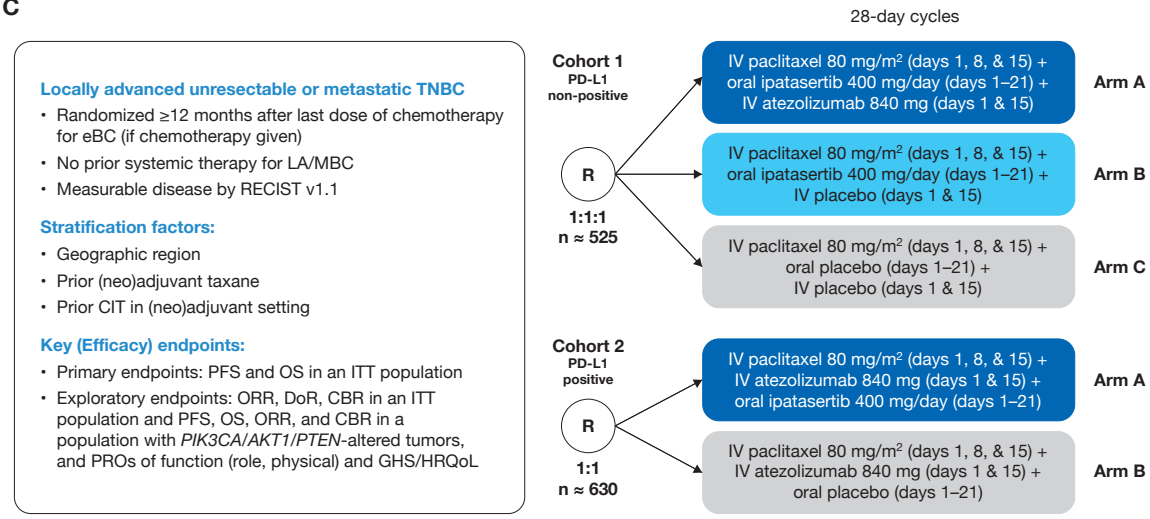
Patients were enrolled in the following order: A1 → B1 → A2 → B2/C1 → D1 → C2 → D2 → A3. Both Arms B2 and Arms C or D were open simultaneously, but priority for filling of arms went to Arms C and D. Arms C and D included a 2-week run-in period during which patients received a doublet, with the third agent added at week 3.

B



[a]*PIK3CA/AKT1* mutant versus *PTEN* altered (and non-*PIK3CA/AKT1* mutant).

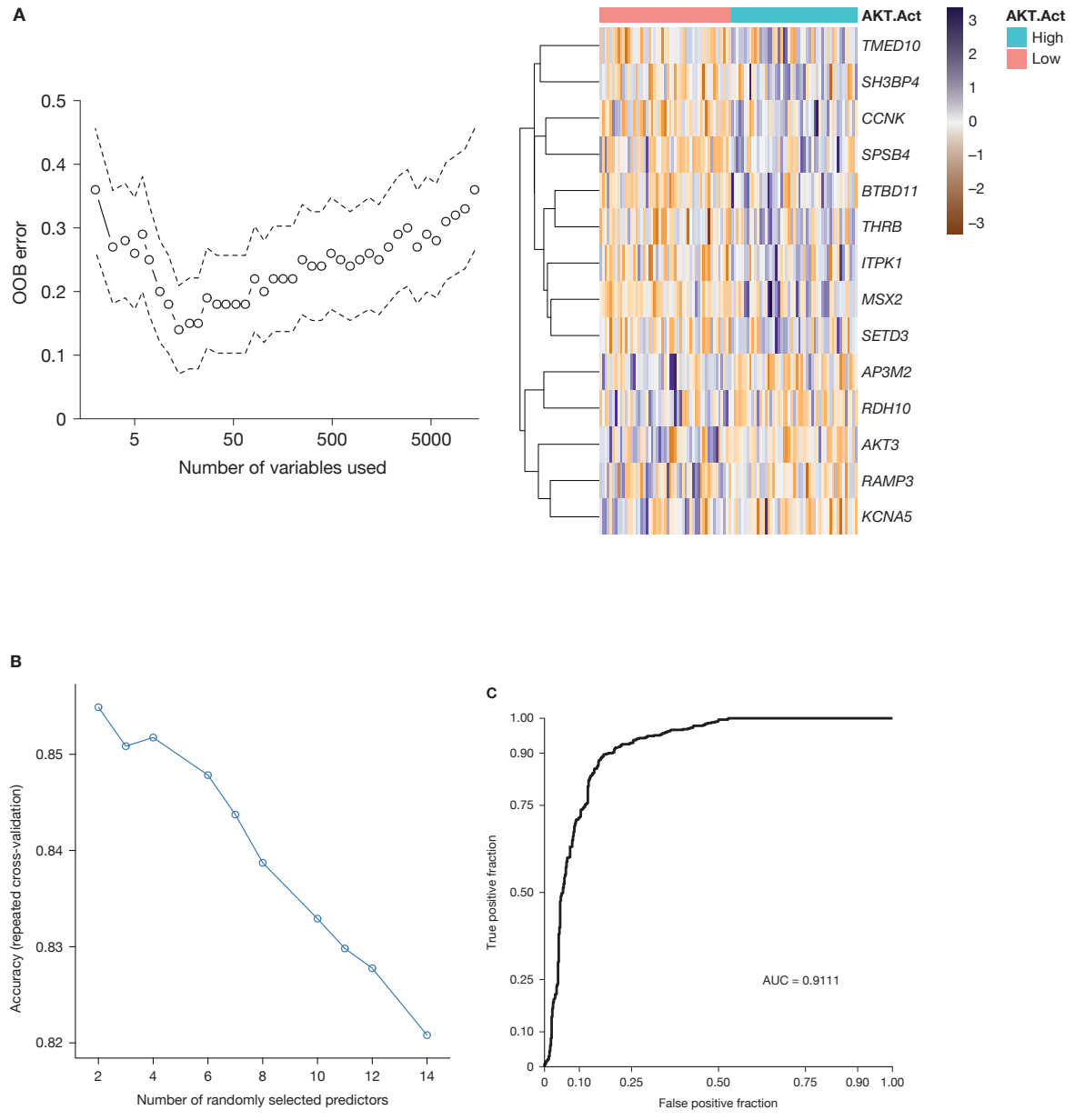
C



After unblinding of treatment assignments, patients in Arm B of Cohort 2 no longer received placebo for ipatasertib, patients in Arm B of Cohort 1 no longer received placebo for atezolizumab, and patients in Arm C of Cohort 1 no longer received placebo for ipatasertib nor placebo for atezolizumab.

Supplementary Figure S2.
Development and validation of pAKT model using FAIRLANE and LOTUS datasets. **A,** Selection of variables. **B,** Accuracy against the number of genes included in the model. **C,** True positive against false positive fractions. **D,** Representative example of a random forest tree from which pAKT was scored according to gene expression level. **E,** Validation using a subset of data from FAIRLANE. **F,** Validation applying the model to the LOTUS dataset in the control arm (paclitaxel plus placebo; left graph) and the experimental arm (ipatasertib plus paclitaxel; right graph).

atezo, atezolizumab; AUC, area under the curve; ipat, ipatasertib; OOB, out-of-bag; pac, paclitaxel.



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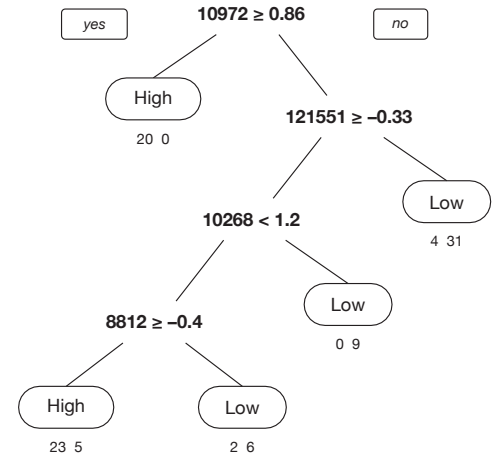

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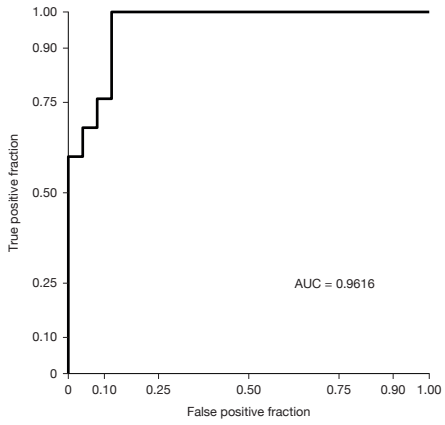
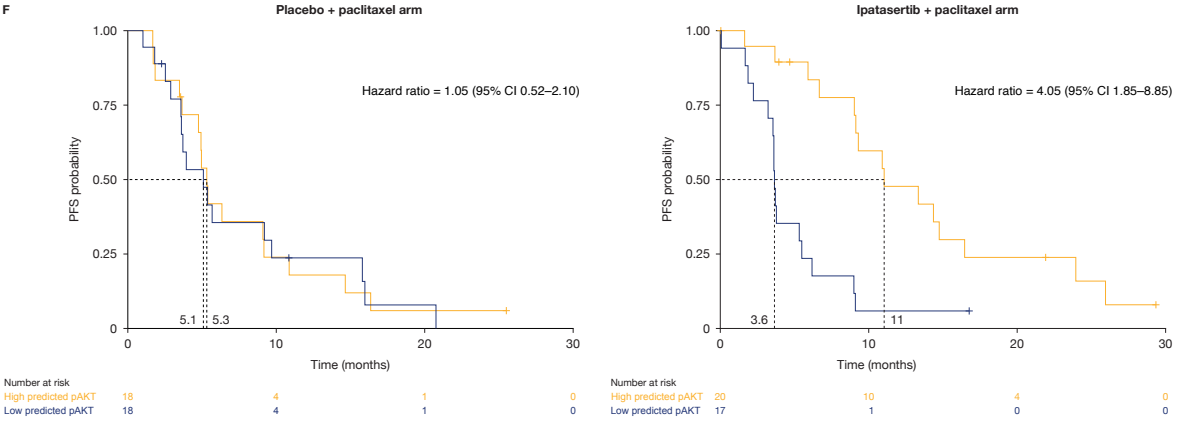
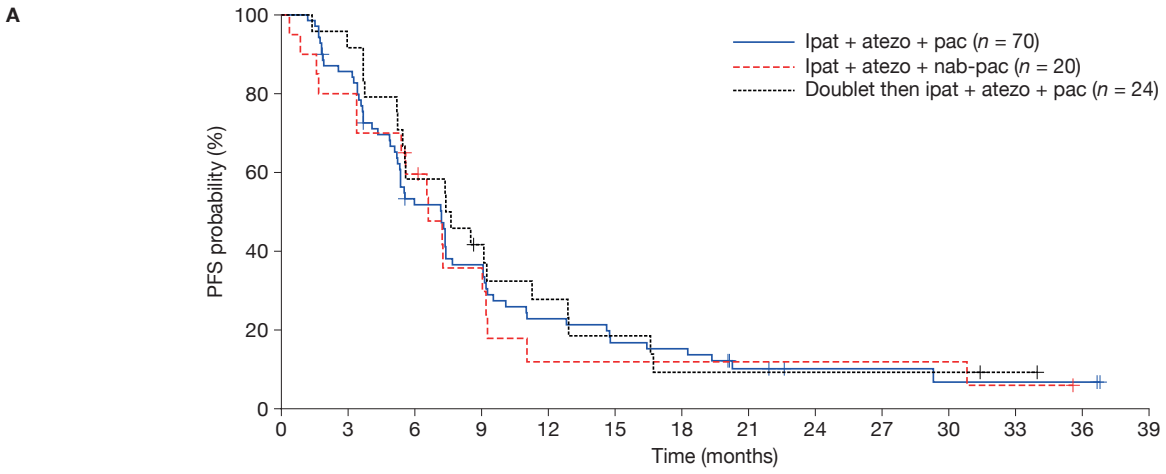


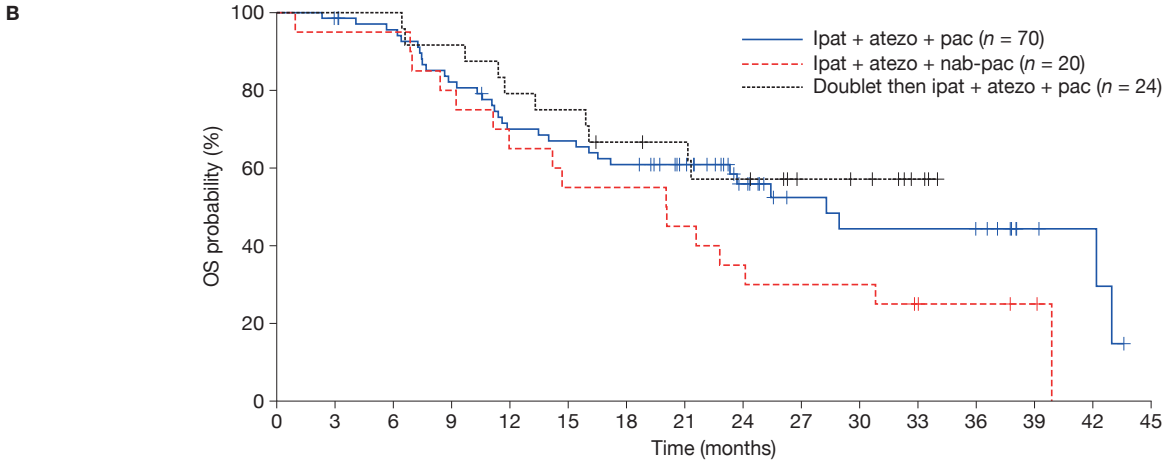
	> median	≤ median
Predicted > median	22	0
Predicted ≤ median	3	25

F



Supplementary Figure S3.
Efficacy by taxane backbone and PD-L1 status in CO40151. **A,** PFS by taxane. **B,** OS by taxane. **C,** PFS by PD-L1 status. **D,** OS by PD-L1 status. atezo, atezolizumab; ipat, ipatasertib; pac, paclitaxel.





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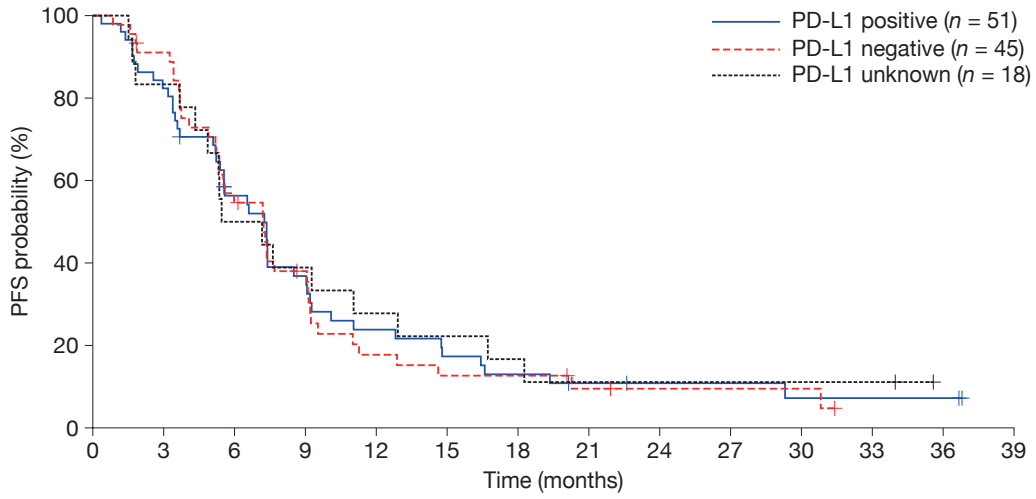
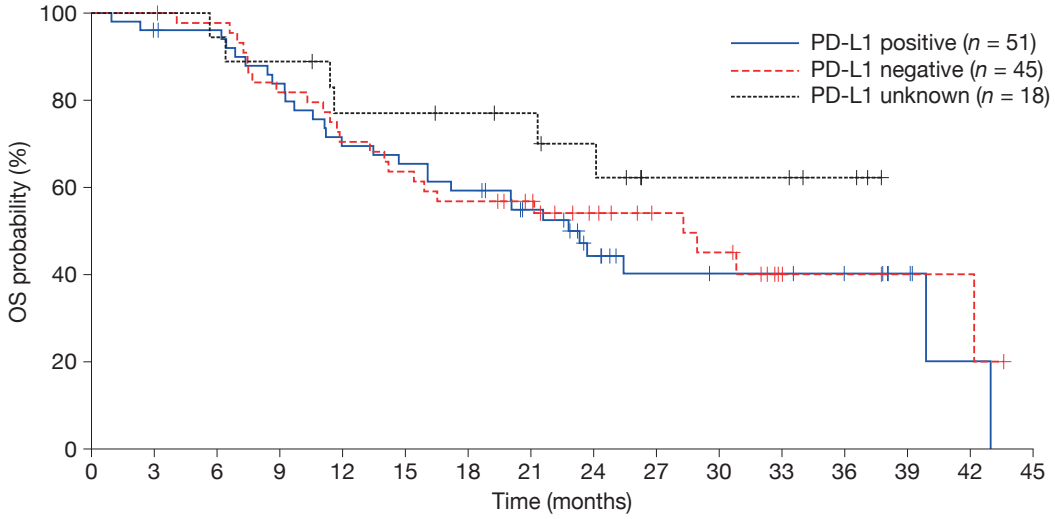


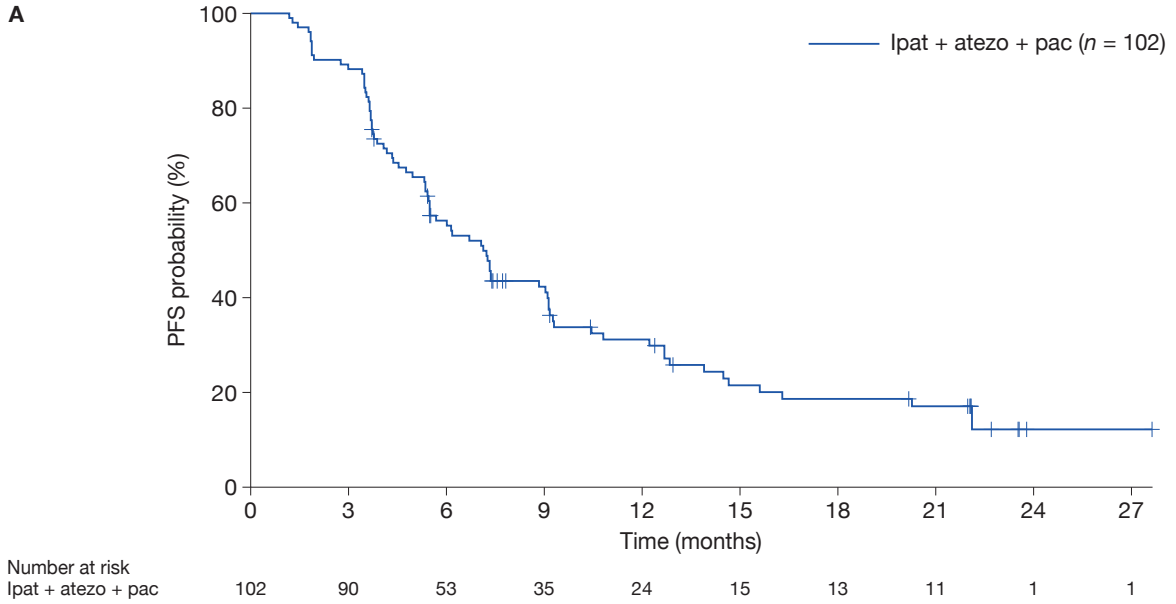
Number at risk														
PD-L1 positive	51	42	26	17	11	8	6	4	3	3	2	2	2	0
PD-L1 negative	45	40	24	15	7	5	5	3	2	2	2	0	0	0
PD-L1 unknown	18	15	9	7	5	4	3	2	2	2	2	2	0	0

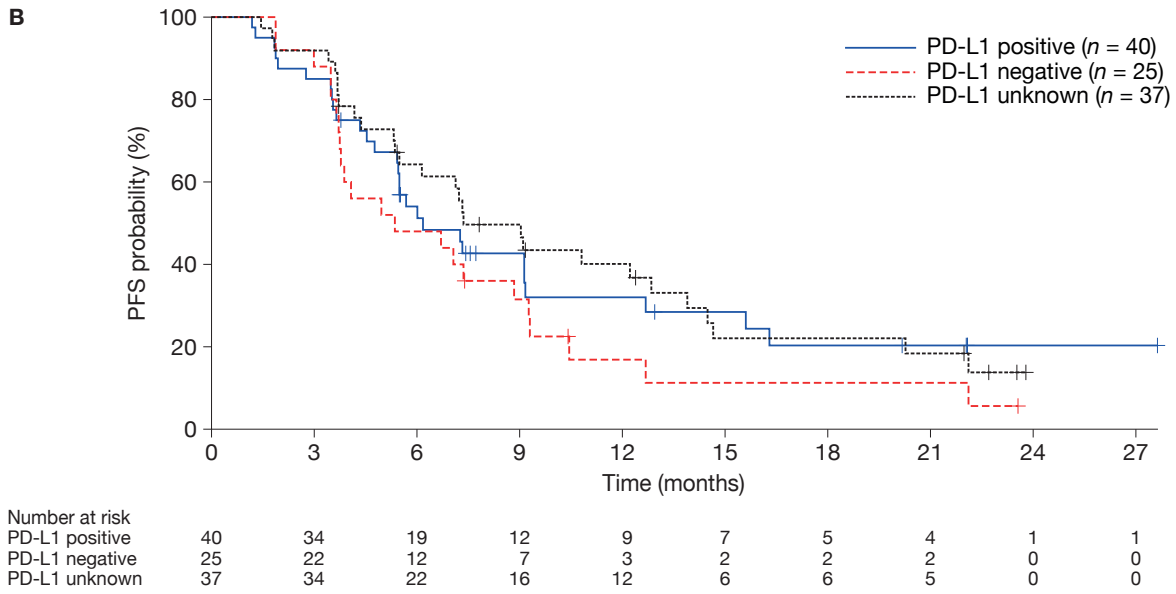
D



Number at risk															
PD-L1 positive	51	48	47	41	34	32	29	23	15	10	9	9	7	4	1	0
PD-L1 negative	45	45	43	36	31	28	25	22	16	12	10	4	3	2	2	0
PD-L1 unknown	18	18	17	16	13	13	12	11	9	5	5	5	3	0	0	0

Supplementary Figure S4.
Efficacy in IPATunity130 Cohort C (*PIK3CA/AKT1/PTEN* non-altered). **A,** PFS in all patients. **B,** PFS by PD-L1 status. **C,** OS in all patients. atezo, atezolizumab; ipat, ipatasertib; pac, paclitaxel.





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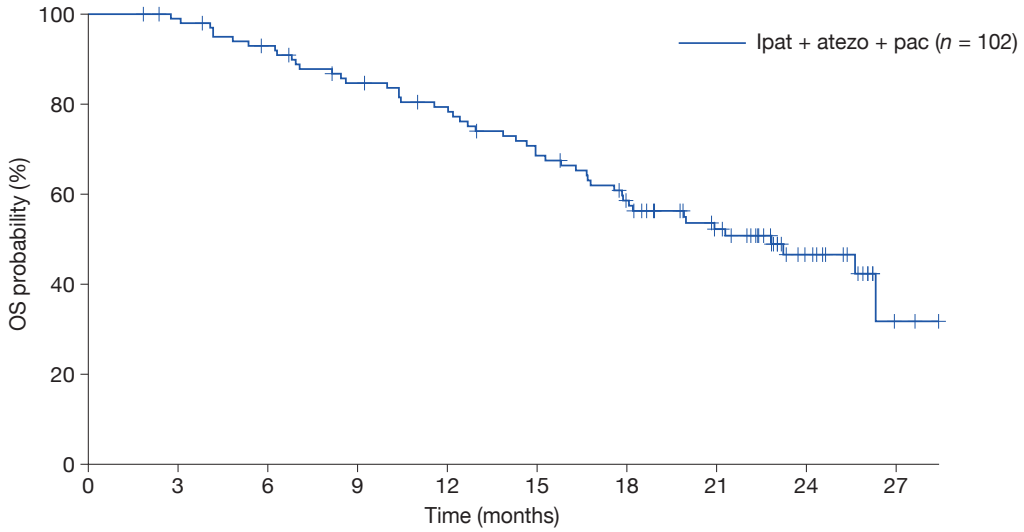
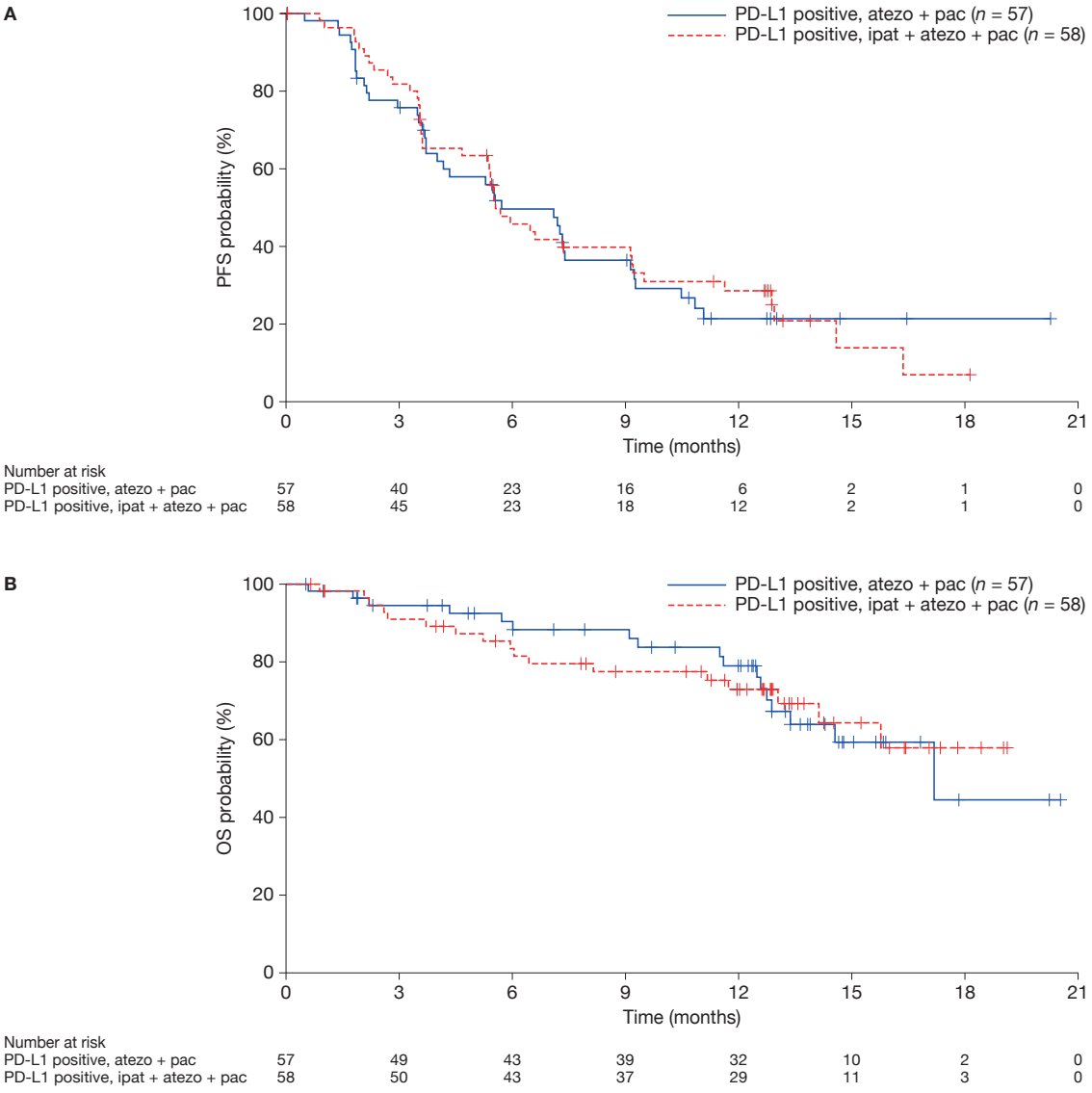


Number at risk										
Ipat + atezo + pac	102	99	91	81	74	63	51	37	17	2

Supplementary Figure S5.
Efficacy by cohort (PD-L1 status) and treatment arm in IPATunity170. **A,** PFS in Cohort 2 (PD-L1-positive). **B,** OS in Cohort 2 (PD-L1-positive). **C,** PFS in Cohort 1 (PD-L1-negative/unknown). **D,** OS in Cohort 1 (PD-L1-negative/unknown). atezo, atezolizumab; ipat, ipatasertib; pac, paclitaxel.



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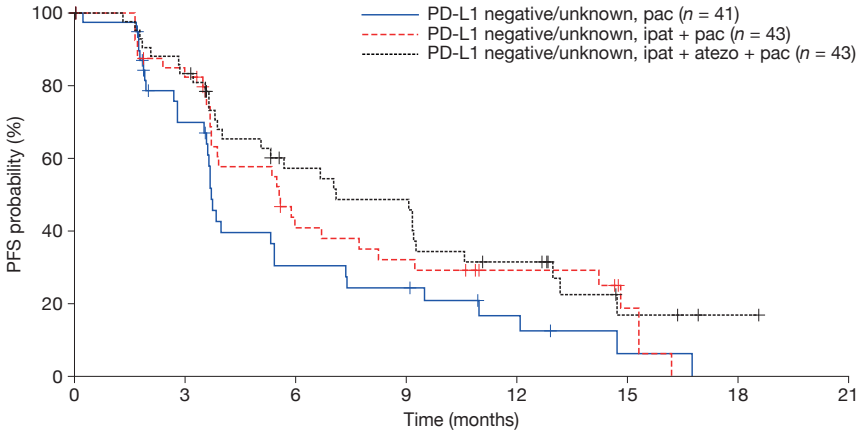
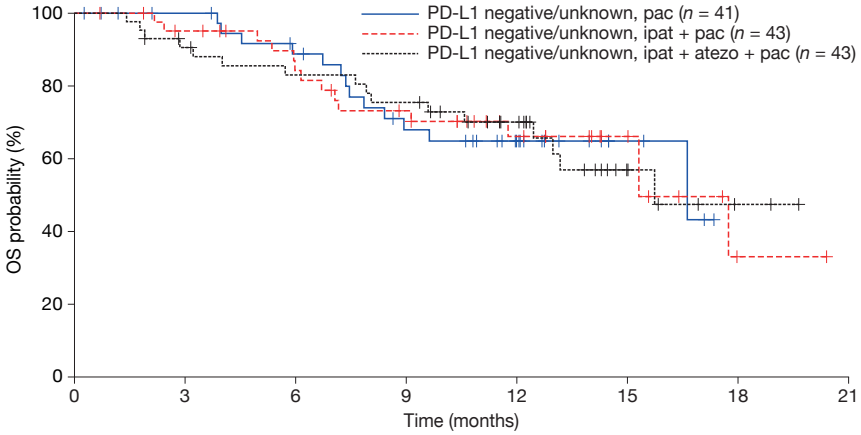


Number at risk								
PD-L1 negative/unknown, pac	41	24	10	8	4	1	0	0
PD-L1 negative/unknown, ipat + pac	43	32	14	11	7	3	0	0
PD-L1 negative/unknown, ipat + atezo + pac	43	35	20	17	10	3	1	0

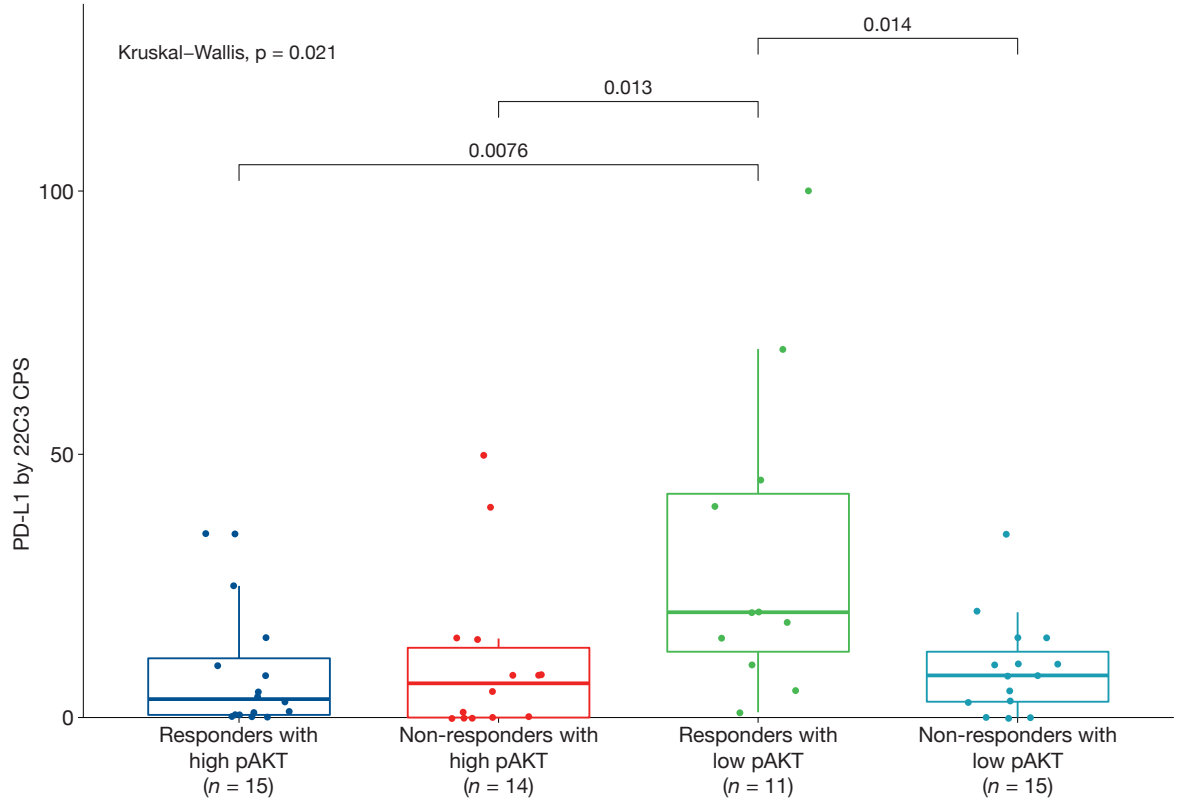
D



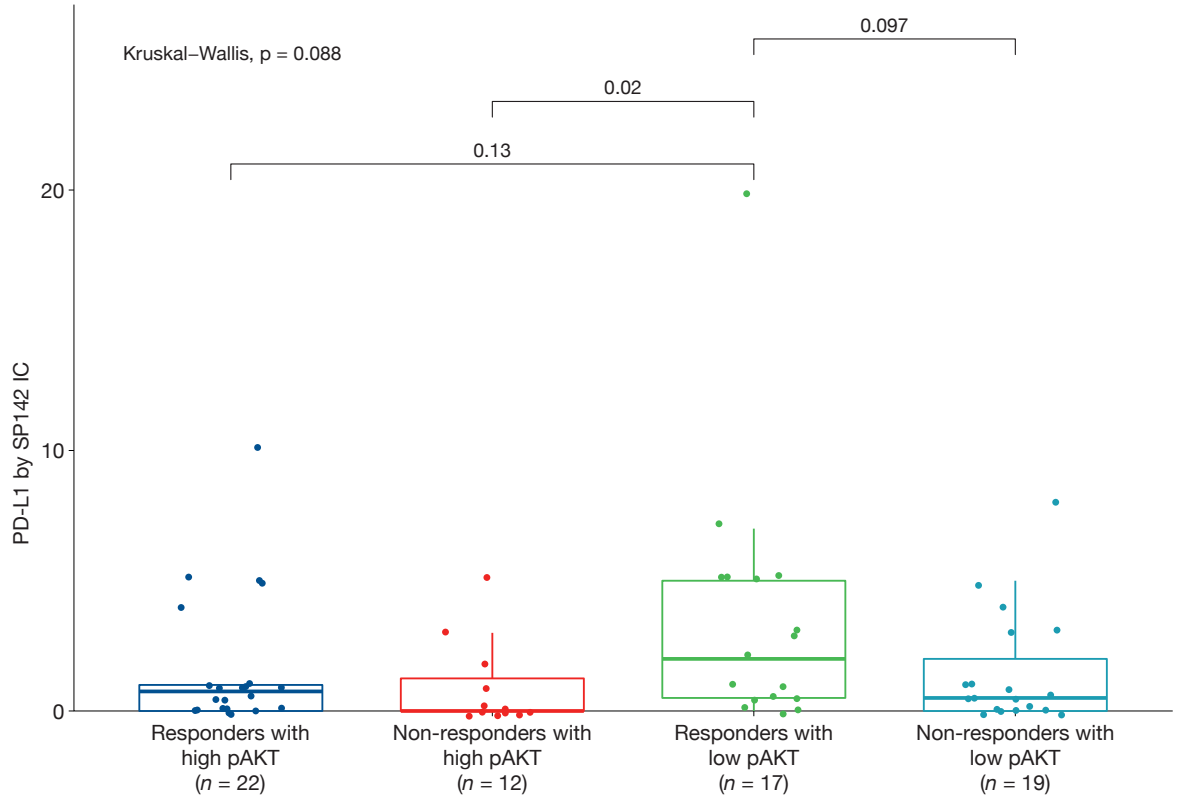
Number at risk								
PD-L1 negative/unknown, pac	41	37	31	22	14	4	0	0
PD-L1 negative/unknown, ipat + pac	43	38	31	25	16	9	1	0
PD-L1 negative/unknown, ipat + atezo + pac	43	37	33	30	21	7	2	0

Supplementary Figure S6.
PD-L1 level according to predicted pAKT level and response status, with PD-L1 status assessed by: **A,** 22C3; **B,** SP142. The lower and upper bounds of the rectangles represent the first and third quartiles, the horizontal line represents the median, the whiskers extend to the highest and lowest values within 1.5 × the interquartile range, and data beyond the end of the whiskers are outliers and are plotted as points. CPS, combined positive score.

A



B


Kruskal–Wallis, p = 0.088
0.097
0.02
0.13
20
10
0
PD-L1 by SP142 IC
Responders with high pAKT (n = 22)
Non-responders with high pAKT (n = 12)
Responders with low pAKT (n = 17)
Non-responders with low pAKT (n = 19)