Supplemental Materials

Supplementary Table S1 Treatment-emergent, all-causality adverse events (all cycles)

	Ivuxolimab + utomilumab						
	Dose escalation						Dose expansion
Adverse event, n (%)	**0.1 mg/kg + 20 mg n=11**	**0.3 mg/kg + 20 mg n=12**	**0.3 mg/kg + 100 mg n=12**	**1 mg/kg + 100 mg n=11**	**3 mg/kg + 100 mg n=11**	**Total N=57**	**Total N=30**
Grade 1	3 (27.3)	1 (8.3)	0	2 (18.2)	0	6 (10.5)	5 (16.7)
Grade 2	2 (18.2)	7 (58.3)	4 (33.3)	2 (18.2)	2 (18.2)	17 (29.8)	9 (30.0)
Grade 3	2 (18.2)	2 (16.7)	5 (41.7)	5 (45.5)	8 (72.7)	22 (38.6)	9 (30.0)
Grade 4	2 (18.2)	1 (8.3)	3 (25.0)	0	0	6 (10.5)	2 (6.7)[a]
Grade 5	2 (18.2)	1 (8.3)	0	2 (18.2)	1 (9.1)	6 (10.5)	5 (16.7)[a]

[a] In the expansion cohorts, treatment-emergent, grade 4 AEs were dyspnea and increased lipase (n=1 each); grade 5 AEs included pulmonary embolism (n=1), myocardial infarction (n=1), disease progression (n=2), and seizure (n=1).
AE, adverse event.

Supplementary Table S2 Pharmacokinetic parameters for ivuxolimab[a]

	Ivuxolimab + utomilumab					
Dose (mg/kg)	**0.1 mg/kg + 20 mg**	**0.3 mg/kg + 20 mg**	**0.3 mg/kg + 100 mg**	**1 mg/kg + 100 mg**	**3 mg/kg + 100 mg**	**30 mg + 20 mg**
Cycle 1						
N, n	10, 9	12, 12	11, 11	10, 10	9, 7	28, 26
C_{max}, µg/mL (%CV)	2.290 (19)	6.965 (23)	7.644 (23)	19.63 (26)	62.45 (31)	10.20 (24)
AUC_{τ}, µg*h/mL (%CV)	270.7 (27)	1022 (29)	1177 (23)	3089 (19)	10100 (19)	1624 (30)
$AUC_{\tau(dn)}$, µg*h/mL/mg/kg (%CV)	2707 (27)	3407 (29)	3924 (23)	3089 (19)	3370 (19)	3848 (35)
Cycle 3						
N, n	9, 3	10, 7	10, 6	8, 5	7, 5	26, 22
C_{max}, µg/mL (%CV)	2.779 (29)	9.049 (21)	9.359 (31)	19.76 (45)	81.49 (51)	10.53 (39)
AUC_{τ}, µg*h/mL (%CV)	340.2 (73)	1739 (26)	2239 (18)	4034 (35)	19190 (48)	2291 (45)
$AUC_{\tau(dn)}$, µg*h/mL/mg/kg (%CV)	3402 (73)	5796 (26)	7463 (18)	4034 (35)	6397 (48)	5376 (47)
R_{ac} (%CV)	1.4 (31)	1.6 (26)	1.8 (12)	1.4 (37)	1.9 (31)	1.4 (31)

[a] Summary statistics are not presented if <3 patients have reportable parameter values.

AUC_{τ}, area under the concentration–time curve from time 0 to time τ, dosing interval; $AUC_{\tau(dn)}$, dose-normalized AUC_{τ}; C_{max}, maximum observed concentration; CV, coefficient of variation; N, number of patients where C_{max} was determined; n, number of patients where AUC_{τ}, $AUC_{\tau(dn)}$, and R_{ac} were determined; R_{ac}, accumulation ratio calculated as AUC_{τ}, cycle 3/AUC_{τ}, cycle 1.

Supplementary Table S3 Pharmacokinetic parameters for utomilumab

	Ivuxolimab + utomilumab					
Dose (mg/kg)	**0.1 mg/kg + 20 mg**	**0.3 mg/kg + 20 mg**	**0.3 mg/kg + 100 mg**	**1 mg/kg + 100 mg**	**3 mg/kg + 100 mg**	**30 mg + 20 mg**
Cycle 1						
N, n	11, 10	12, 11	12, 12	11, 9	10, 7	27, 26
C_{max}, µg/mL (%CV)	4.018 (33)	4.060 (39)	20.33 (43)	17.63 (33)	19.02 (29)	3.232 (22)
AUC_{τ}, µg*h/mL (%CV)	789.4 (23)	596.0 (43)	2465 (33)	2289 (25)	2839 (15)	561.8 (53)
$AUC_{\tau(dn)}$, µg*h/mL/mg/kg (%CV)[b]	39.46 (23)	28.90 (44)[b]	24.79 (34)[b]	22.89 (25)	28.94 (15)[b]	28.10 (53)
Cycle 3						
N, n	9, 2	9, 4	11, 6	9, 5	7, 4	26, 21
C_{max}, µg/mL (%CV)	2.909 (47)	2.554 (79)	20.02 (22)	17.94 (39)	17.84 (54)	2.726 (47)
AUC_{τ}, µg*h/mL (%CV)	NE	343.7 (225)	2765 (77)	673.9 (1191)	2621 (31)	232.1 (1524)
$AUC_{\tau(dn)}$, µg*h/mL/mg/kg (%CV)	NE	17.21 (225)	27.65 (77)	6.739 (1191)	26.21 (31)	11.61 (1524)
R_{ac} (%CV)	NE	0.54 (120)	1.1 (69)	0.27 (1381)	0.90 (26)	0.39 (886)

[a] Summary statistics are not presented if <3 patients have reportable parameter values.

[b] $AUC_{\tau(dn)}$ was determined with 10 patients in the 0.3 mg/kg + 20 mg group, 11 patients in the 0.3 mg/kg + 100 mg group, and 6 patients in the 3 mg/kg + 100 mg group.

AUC_{τ}, area under the concentration–time curve from time 0 to time τ, dosing interval; $AUC_{\tau(dn)}$, dose-normalized AUC_{τ}; C_{max}, maximum observed concentration; CV, coefficient of variation; N, number of patients where C_{max} was determined; n, number of patients where AUC_{τ}, $AUC_{\tau(dn)}$, and R_{ac} were determined; NE, not estimated due to sample size <3; R_{ac}, accumulation ratio calculated as AUC_{τ}, cycle 3/AUC_{τ}, cycle 1.

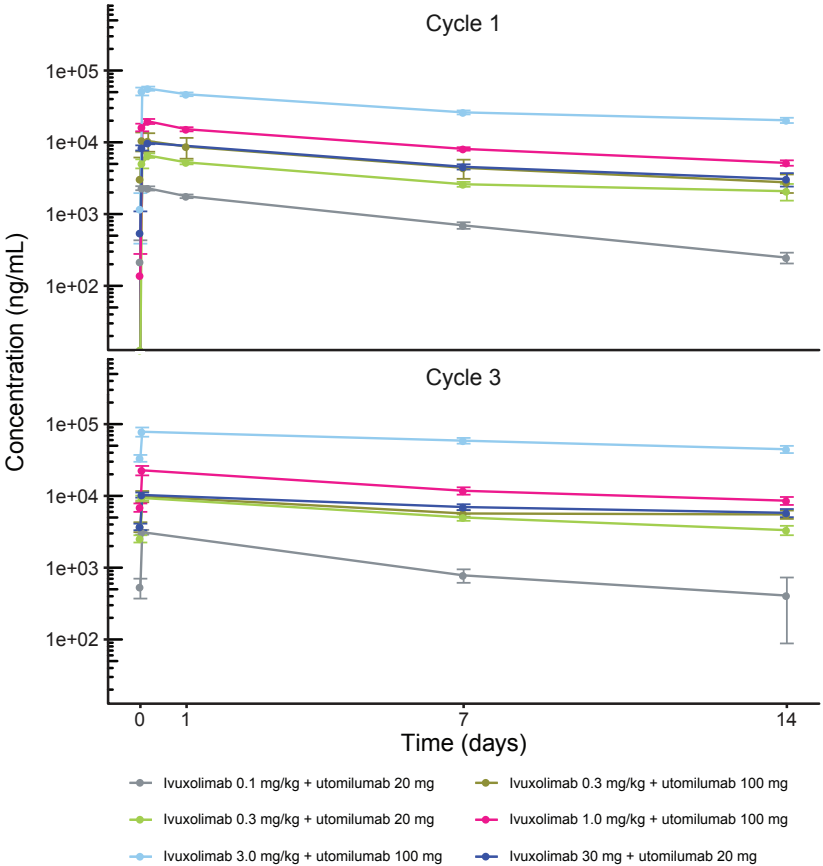
Supplementary Table S4 Best overall response by RECIST and irRECIST in patients with melanoma or NSCLC (dose-expansion portion)

	Ivuxolimab + utomilumab, dose expansion N=30			
	Melanoma n=10		**NSCLC n=20**	
	RECIST	**irRECIST**	**RECIST**	**irRECIST**
CR/irCR, n (%)	0	0	0	0
PR/irPR, n (%)	0	0	1 (5.0)	1 (5.0)
SD/irSD, n (%)	7 (70.0)	7 (70.0)	7 (35.0)	11 (55.0)
PD/irPD, n (%)	3 (30.0)	3 (30.0)	9 (45.0)	4 (20.0)
Indeterminate, n (%)	0	0	0	1 (5.0)
Not evaluable, n (%)	0	0	3 (15.0)	3 (15.0)
ORR (CR+PR/irCR+irPR), n (%), [95% exact CI]	0	0	1 (5.0) [0.1, 24.9]	1 (5.0) [0.1, 24.9]
Disease control rate (CR+PR+SD/irCR+irPR+irSD), n (%)	7 (70.0)	7 (70.0)	8 (40.0)	12 (60.0)
Duration of SD/irSD, median (range), weeks	18.9 (13.9–49.0)	18.9 (13.9–49.0+)[a]	24.1 (14.3–77.9+)[a]	15.3 (7.3–77.9+)[a]

[a] A patient with response or SD/irSD at the last assessment remains on study.

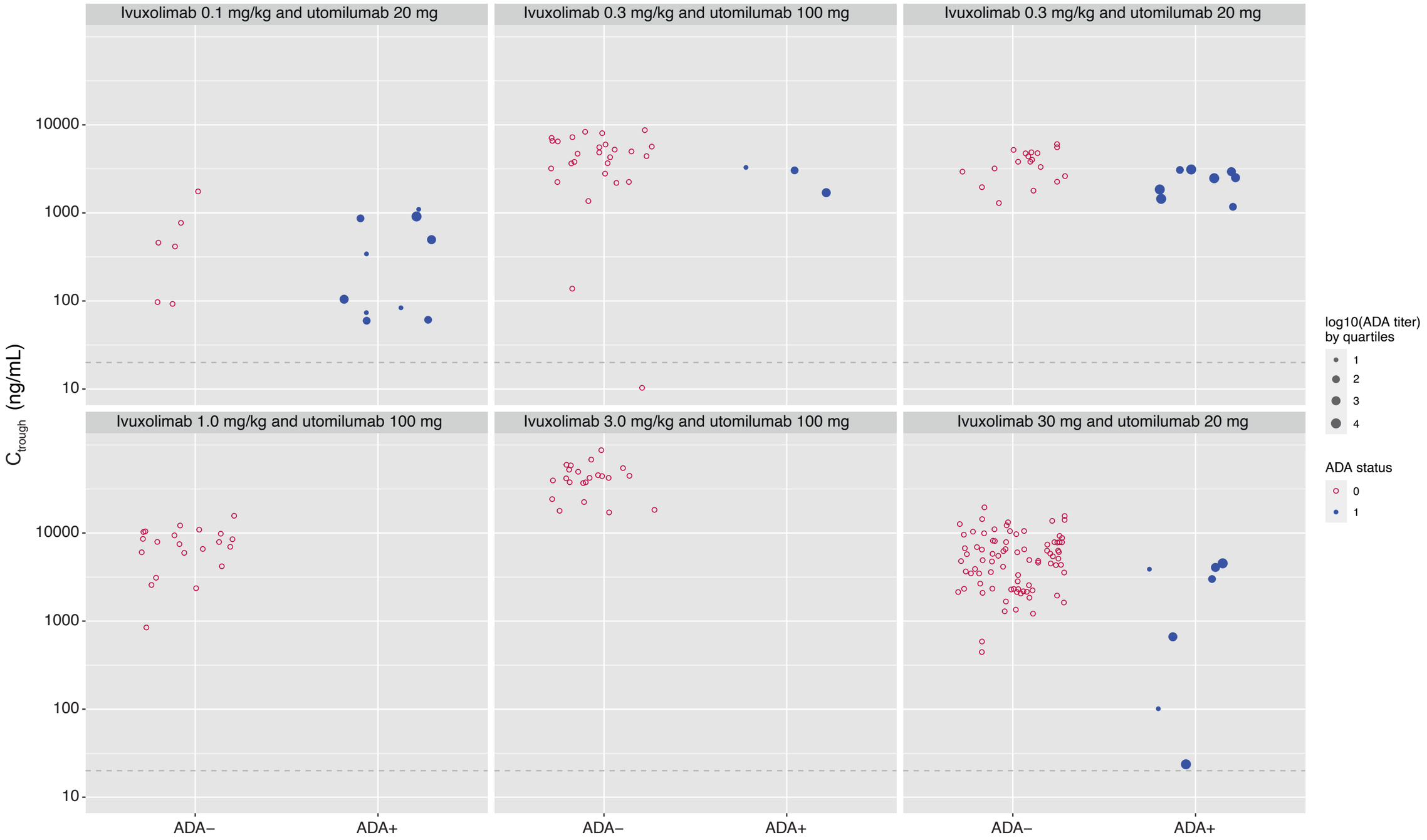
CI, confidence interval; CR, complete response; ir, immune-related; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease.

Supplementary Figure S1. Mean (±SE) serum ivuxolimab concentration–time profiles in ivuxolimab plus utomilumab combination groups.



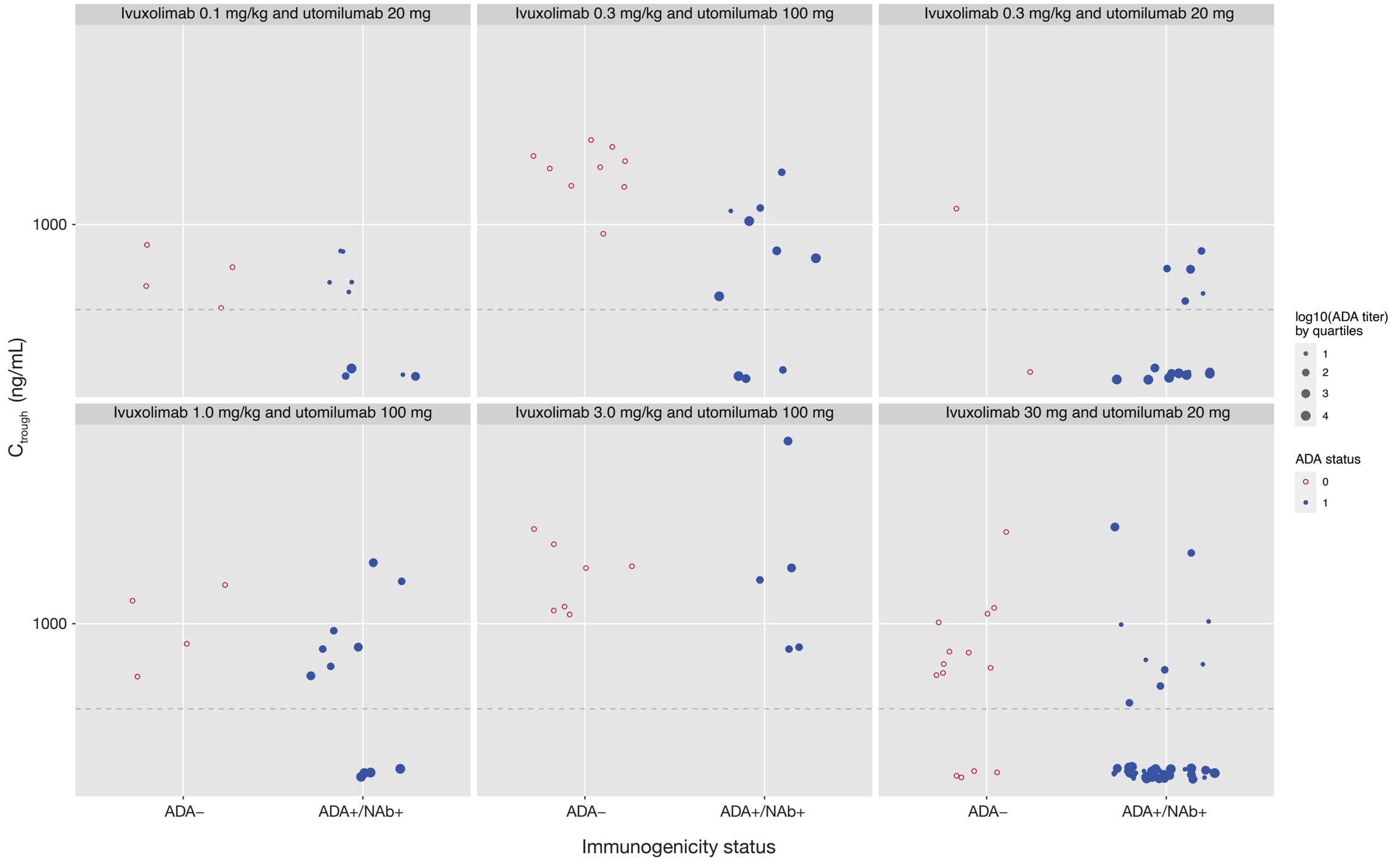
Summary statistics have been calculated by setting concentration values below the LLOQ to 0. The LLOQ is 20.0 ng/mL. The predose sample of cycle 2 day 1 has been used as cycle 1 day 1 336h; the predose sample of cycle 4 day 1 has been used as cycle 3 day 1 336h.
LLOQ, lower limit of quantification.

Supplementary Figure S2. Trough ivuxolimab concentration (C_{trough}) vs. immunogenicity status in ivuxolimab plus utomilumab combination groups.



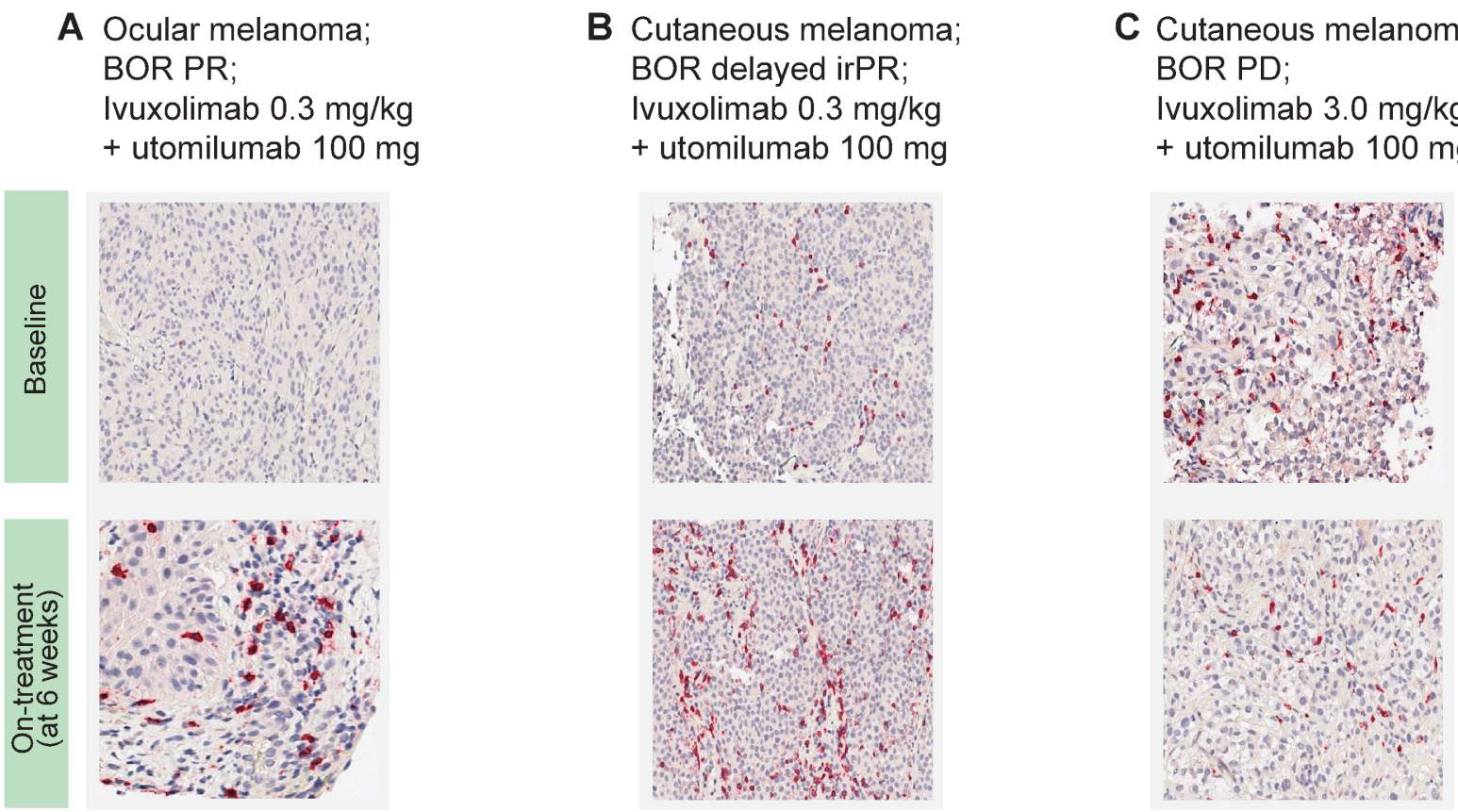
All immunogenicity and the companion C_{trough} data from cycle 3 to cycle 8 from all dose cohorts were included. For ADA+ samples, the size of the symbols corresponds to the log10 of ADA titer by quartiles. The horizontal dashed line represents LLOQ (20.0 ng/mL) for ivuxolimab concentration. All C_{trough} below LLOQ have been assigned the value of 10 ng/mL for purpose of visualization. As there were only 4 ADA+/Nab+ samples, all ADA+ samples regardless of Nab positivity were lumped into one group.
ADA, antidrug antibodies; C_{trough}, trough plasma concentration; LLOQ lower limit of quantification; Nab, neutralizing antibodies.

Supplementary Figure S3. Trough utomilumab concentration (C_{trough}) vs. immunogenicity status in ivuxolimab plus utomilumab combination groups.

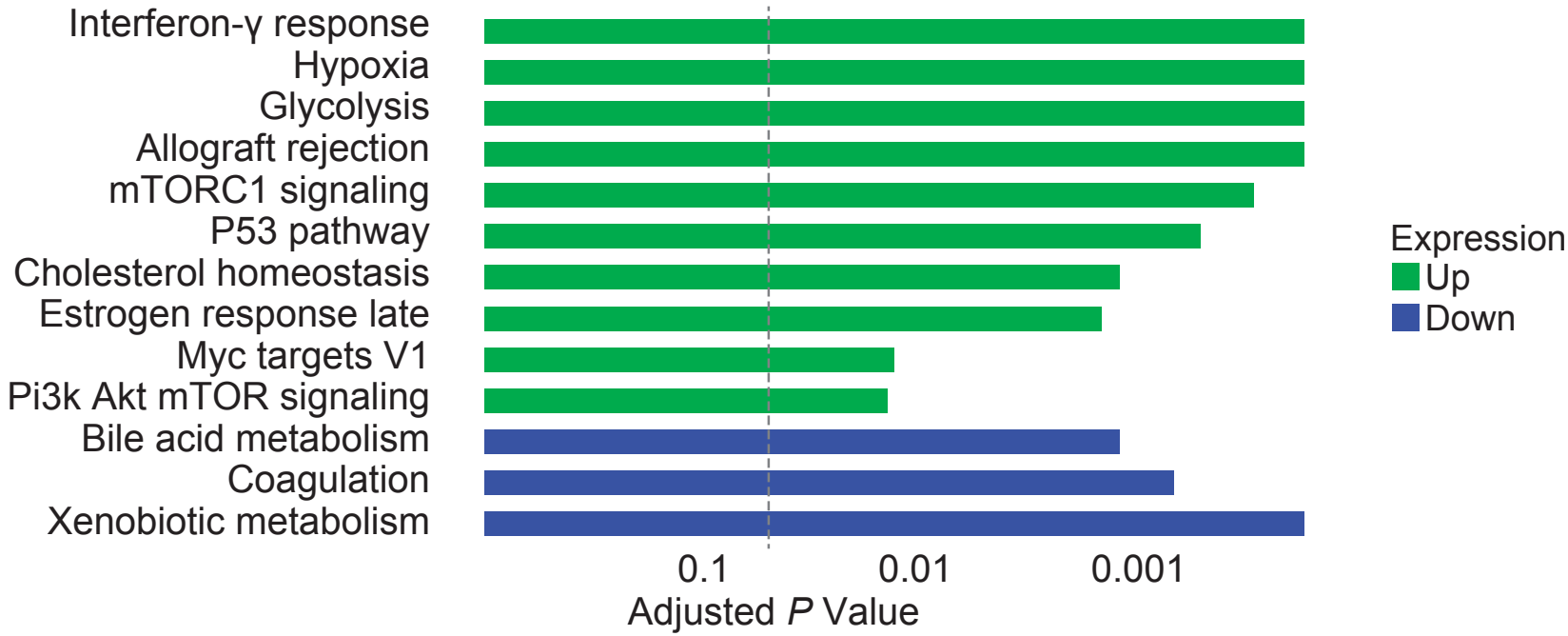


All immunogenicity and the companion C_{trough} data from cycle 3 to cycle 8 from all dose cohorts were included. For ADA+ samples, the size of the symbols corresponds to the log10 of ADA titer by quartiles. The horizontal dashed line represents LLOQ (400 ng/mL) for utomilumab concentration. All C_{trough} below LLOQ have been assigned the value of 200 ng/mL for purpose of visualization.
ADA, antidrug antibodies; C_{trough}, trough plasma concentration; LLOQ, lower limit of quantification; NAb, neutralizing antibody.

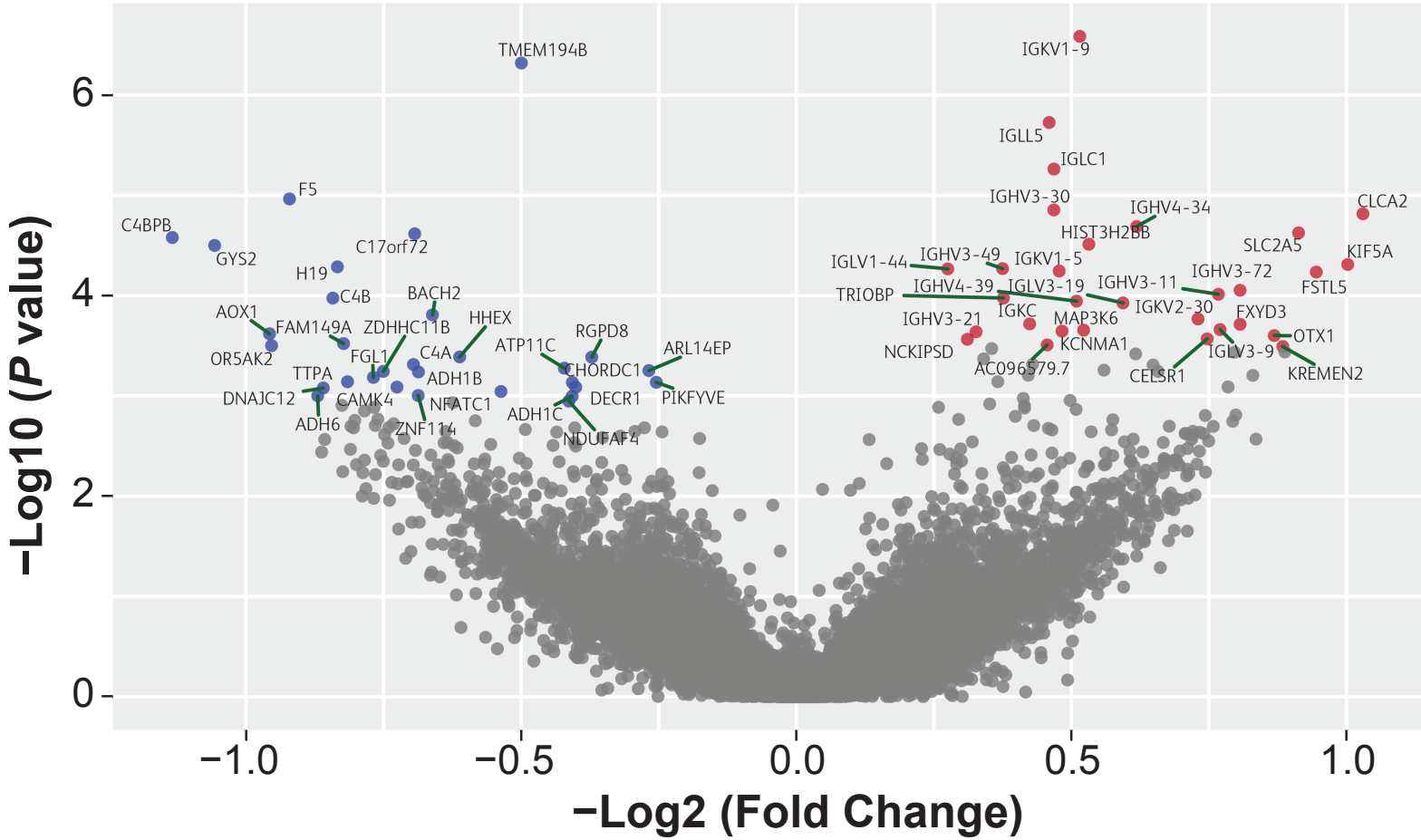
at baseline (pre-treatment) and 6 weeks (on-treatment).



20x magnification; 4µm slides were stained with anti-CD8 antibody from Dako (clone M7130).
BOR, best overall response; ir, immune-related; PD, progressive disease; PR, partial response.

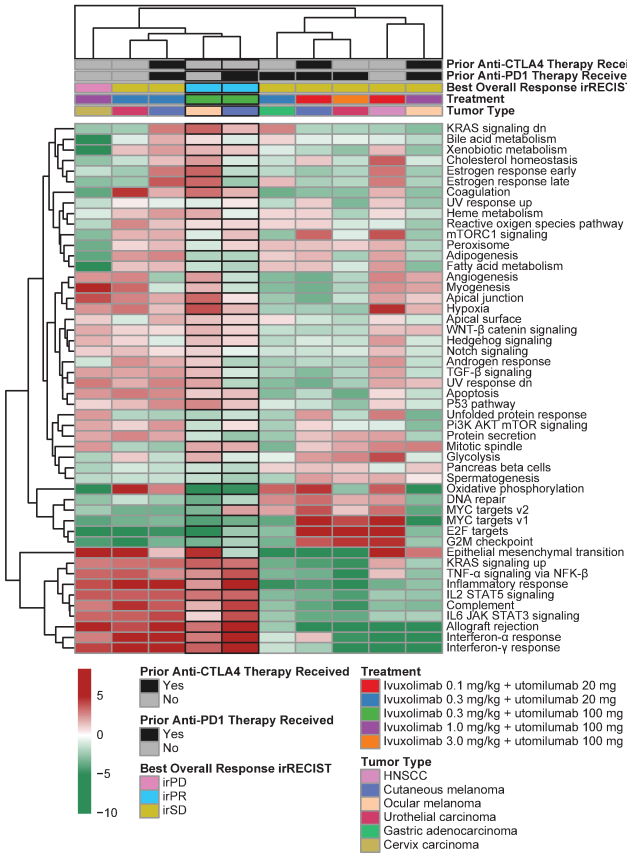


Hallmark gene sets that exhibited increased expression (green bars) and decreased expression (blue bars) are listed in order of most significant increase to most significant decrease. Gray vertical line indicates adjusted *P* value = 0.05. For gene set enrichment analysis, genes were first ranked by differential statistic calculated by DESeq26 in the order of most significant increase to most significant decrease. Then, FGSEA was used to detect significantly enriched hallmark gene sets. FGSEA, gene ranking-based gene set enrichment analysis; Pi3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin.



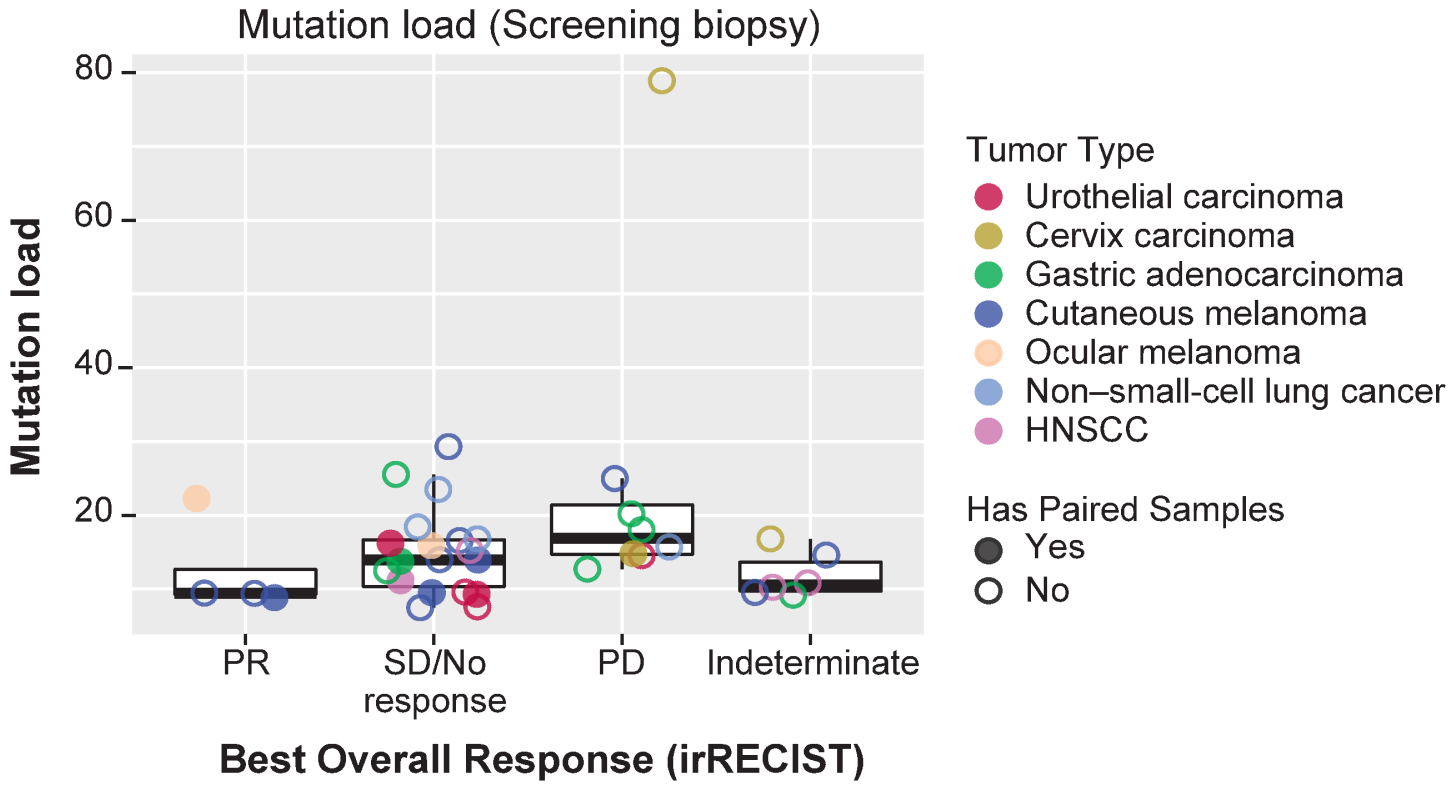
Top 30 upregulated genes (red dots) and downregulated genes (blue dots) in biopsies at 6 weeks relative to screen biopsies. RNAseq data set includes combined analysis of 10 paired FFPE tumor tissue samples. Tumor types: HNSCC (n=1), melanoma (n=5), urothelial carcinoma (n=2), gastric adenocarcinoma (n=1), cervix carcinoma (n=1). ESTIMATE was used to estimate tumor purity from RNAseq data, and then DEseq2 was used for differential analysis with tumor purity as a covariate. ESTIMATE, Estimation of STromal and Immune cells in MAlignant Tumor tissues using Expression data; FFPE, formalin fixed, paraffin embedded; HNSCC, head and neck squamous cell carcinoma; RNAseq, RNA sequencing.

Supplementary Figure S7. Heat map of normalized enrichment score of hallmark gene sets in on treatment tumor tissues.



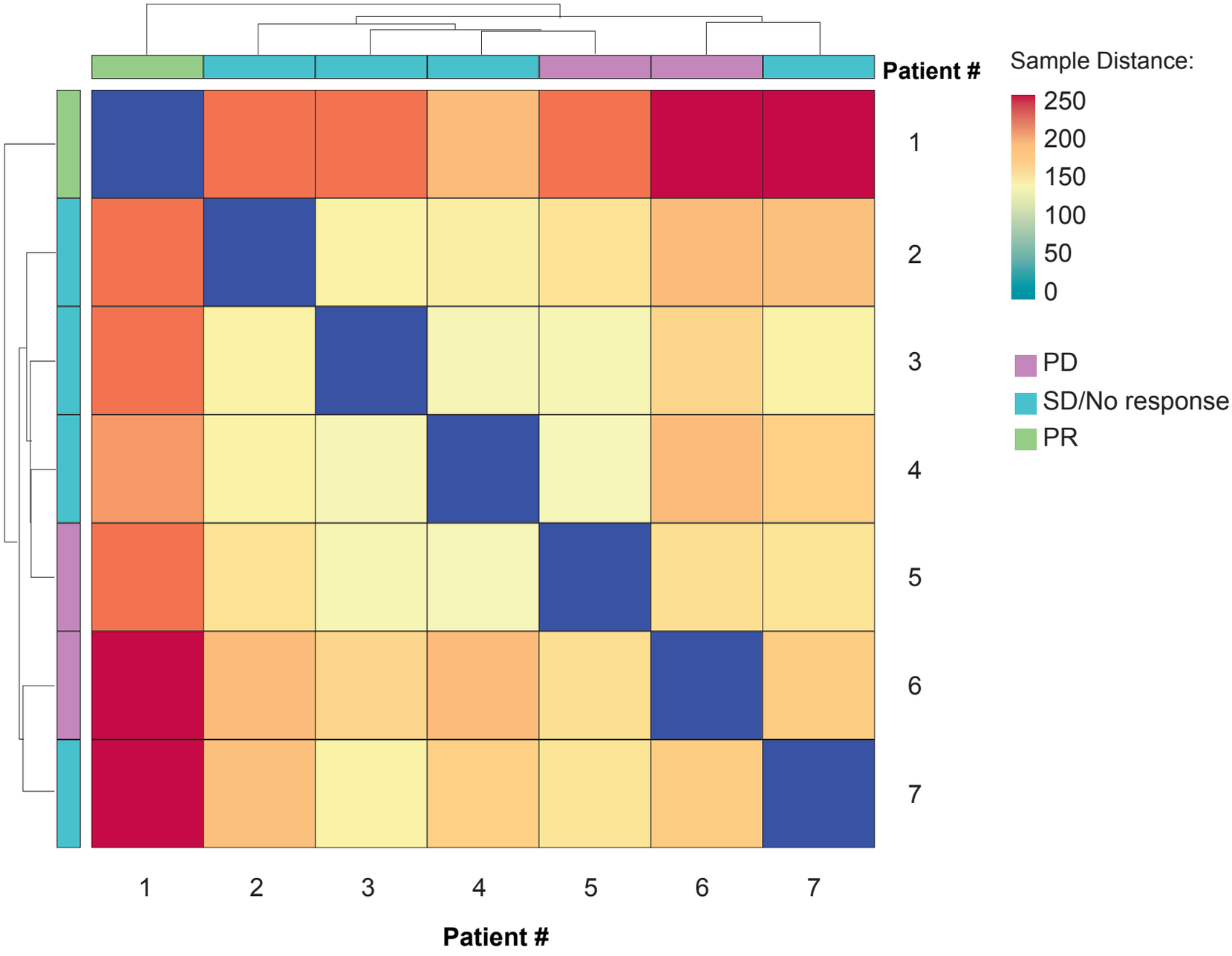
For each patient, genes were ranked by expression changes between screening and 6-week biopsies in the order of highest increase to highest decrease. Next, FGSEA was used to estimate the enrichment of hallmark gene sets. Cells highlighted in black are for ocular and cutaneous melanoma patients who achieved PR and delayed irPR, respectively.
CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; FGSEA, Fast Gene Set Enrichment Analysis; HNSCC, head and neck squamous cell carcinoma; ir, immune-related; PD-1, programmed cell death protein 1; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

≥10 reads (mutation load, y-axis) derived from RNAseq data are depicted for 37 available baseline FFPE tumor samples by response.



Tumor types are indicated by colored circles.
FFPE, formalin fixed, paraffin embedded; HNSCC, head and neck squamous cell carcinoma; ir, immune-related; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; RNAseq, RNA sequencing; SD, stable disease.

Supplementary Figure S9. Clustering of patients with NSCLC.



The figure depicts the pair-wise correlation or distance between any patient pair. The one patient with PR (green) has the largest distance to any other patient, indicating that this patient is very different from the other 6 patients. NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.