Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods

Study design

Meta-analysis

Search strategy and selection criteria. The meta-analysis was reported in accordance with PRISMA reporting guideline. A systematic literature search of the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases was performed to identify relevant randomized clinical trials (RCTs) published prior to June 2018. The search was performed with the search keywords and MeSH terms pertinent to the intervention of interest, such as "tumor vaccine", "cellular immunotherapy", "immune checkpoint inhibitor", "cytotoxic T-lymphocyte-associated protein 4", "programmed death receptor 1", "programmed death-ligand 1", "ipilimumab", "tremelimumab", "atezolizumab", "durvalumab", "nivolumab", "pembrolizumab", "non-small cell lung carcinoma" and "randomized clinical trial". Furthermore, we also manually searched and checked references of systematic reviews, meta-analyses and conference proceedings of the American Society of Clinical Oncology, the European Society for Medical Oncology, the American Association for Cancer Research, and the World Conference on Lung Cancer. The latest update was in July 2018. The following inclusion criteria were applied: (1) randomized trials comparing immune checkpoint inhibitors, tumor vaccines, or cellular immunotherapy with conventional therapy for patients with advanced or metastatic non-small cell lung carcinoma (NSCLC); (2) trials with reported available data that measured overall survival (OS), progression-free survival (PFS), or objective response rate (ORR); and (3) Trials published in English. The PRISMA flow diagram was shown in eFigure 1 in the supplement.

Study selection, data extraction and quality assessment. Two reviewers (Y.F.Y and S.B.L) independently and in duplicate screened titles and abstracts to identify relevant studies. Studies that appeared to meet the inclusion criteria were further checked by full-text review. Data extraction was also conducted independently by two reviewers (Y.F.Y and S.B.L). Data collected included the first author (or registration number), study design, sample size, treatment group allocated, line of therapy, details about immunotherapy regimens, and patients and tumor characteristics. Hazard ratios (HRs) of OS and PFS with their 95% corresponding confidence intervals (CIs) and the numbers of responders were also extracted. If an inconsistency arose, a consensus was reached by discussion among all investigators. Two reviewers (Y.F.Y and S.B.L) rigorously and independently assessed the risk of bias by using an approach based on the Cochrane Collaboration Handbook[1] with the following seven domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of the participants and personnel; (4) blinding of the outcome assessment; (5) incomplete outcome data; (6) selective outcome reporting; and (7) other biases. Each item was categorized as low, unclear, or high risk of bias by using Review Manager 5.3 software (Cochrane Community). The result of the methodological quality of the randomized trials was shown in eFigure 2 and eFigure 3 in the supplement.

Individual patient-level analysis

Checkpoint inhibitor cohorts. Patients were also eligible if they had durable clinical benefit (DCB; complete response [CR]/partial response [PR] or stable disease [SD] that lasted > 6 months) or no durable benefit (NDB; progressive disease [PD] or SD that lasted < 6 months), which was assessed with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[2]

The Cancer Genome Atlas (TCGA) cohort. Level 3 data (FPKM normalized) for genes from 1,008 lung adenocarcinoma and lung squamous cell carcinoma samples processed on 2017-09-14 were downloaded from the UCSC Xena browser (http://xena.ucsc.edu/) GDC hub. The expression profile (FPKM normalized) was transformed to Transcripts Per Million Kilobases (TPM), converting the FPKM data into values that were more comparable between samples.

Statistical analysis

Meta-analysis

HRs and 95% CIs were pooled to estimate the survival increases in PFS and OS. Dichotomous data, such as ORR data, were analyzed using the risk ratio (RR). The Mantel-Haenszel random-effects model was utilized. Two-sided *P* values less than 0.05 were regarded as statistically significant. I^2 was used to assess the heterogeneity between trials; an I^2 value exceeding 50% indicated the existence of substantial heterogeneity. In addition, the OS and PFS of immunotherapy were compared with those of conventional therapy in key subgroups defined by age, ECOG score, epithelial growth factor receptor (EGFR) status, kirsten rat sarcoma viral oncogene homolog (KRAS) status, histology, programmed death-ligand 1(PD-L1) expression, sex, smoking status and tumor mutation burden (TMB). The differences in treatment impact between subgroups were measured by *P* value for interaction. We evaluated median survival outcomes by assessing the ratio of the median months of survival (Median month ratio = Median month$_{immunotherapy\ group}$ / Median month$_{conventional\ therapy\ group}$). In addition, we conducted network meta-analyses to compare the OS and PFS of different immune checkpoint inhibitor strategies using the random effects Bayesian model.[3] For example, the relative treatment effect of treatment A versus treatment B can be indirectly obtained from the comparisons of treatment A with treatment C and treatment B with treatment C.

The role of trial sequential analysis (TSA) in a meta-analysis is analogous to that of interim analysis in a single trial, with boundaries to decide whether current trials have enough power to draw a reliable conclusion.[4] TSA adjusts the thresholds for the Z values of benefits, harm and futility to reduce type I (false positive) and type II (false negative) errors due to sparse data and repetitive significance testing and could be used to calculate required information size (RIS).[5-7] Sufficient evidence for the anticipated intervention effect is established and no further trials are needed when the cumulative Z-curve crosses the TSA monitoring boundary, while experimental intervention can be considered minimally important to patients if the Z-curve enters the futility boundary. When the Z-curve crosses neither the TSA monitoring boundary for benefit nor the futility boundary for harm, the meta-analysis is inconclusive. A random effects model with an O'Brien-Fleming α-spending function and a two-side boundary was utilized to calculate the TSA monitoring boundary, futility boundary and RIS. A relative risk reduction of 20%, a type I error rate of 5% and a type II error rate of 20% (power = 80%) were set. We adjusted heterogeneity based on model

variance. TSA was performed by using TSA version 0.9 beta software (Copenhagen Trial Unit 2011).

Potential publication bias was visually evaluated using funnel plots and the Copas selection model[8] and was quantified using Begg's and Egger's regression tests.[9,10] A *P* value > 0.05 was considered the criterion for a negligible probability of publication bias. The results of the publication bias analyses were shown in eFigure 4 in the supplement.

The grading of recommendations assessment, development, and evaluation methodology was used to categorize the quality of the evidence as high, moderate, low, or very low. RCTs were initially considered high-quality evidence but could be rated lower because of a risk of bias, imprecision, inconsistency, indirectness, and publication bias.[11,12]

Individual patient-level analysis

Aggregated PFS and OS were computed using the Kaplan-Meier estimates method and compared with the log-rank test. HRs and 95% CIs were calculated by using the Cox regression model. Treatment effect between two groups were also calculated using the difference in restricted mean survival time.[13] Categorical variables were compared with χ^2 or Fisher's exact test, and continuous variables were compared with Wilcoxon rank sum tests for two-group comparisons or the Kruskal-Wallis exact test for multiple comparisons. PD-L1, the TMB and the neoantigen burden (NAB) were categorized into high and low value groups with the optimal cutoff values defined by the R package ggsurvimier. TMB was defined as number of nonsynonymous single nucleotide variants (SNVs) or indels variants. Spearman rank correlation coefficients were used to estimate the correlations. Receiver operating characteristic curves were generated to assess the sensitivity and specificity of continuous variables with the area under the curve. All statistical analyses were performed with R (version 3.4.1, The R Foundation), and a *P* value less than 0.05 was considered statistically significant.

An oncoprint plot was established to compare the differences in the frequencies of altered genes in the DCB and NDB groups using the R package ComplexHeatmap. The Boruta algorithm (a wrapper built around the Random Forest classification algorithm) was used to select DCB-relevant nonsynonymous alterations (SNVs or indels) with 100 iterations.[14] MutSigCV analysis was applied to identify genes that mutated at statistically significant levels,[15] and the frequencies of the identified genes were compared between the DCB group and the NDB group, between the high TMB group and the low TMB group, and between the high PD-L1 expression group and the low PD-L1 expression group using odds ratios and Fisher's exact test.
To quantify the proportions of immune cells in the NSCLC samples, we used the CIBERSORT algorithm[16] and the LM22 gene signature, which allows for highly sensitive and specific discrimination of 22 human immune cell phenotypes including B cells, T cells, natural killer cells, macrophages, dendritic cells, and myeloid subsets. CIBERSORT is a deconvolution algorithm that uses a set of reference gene expression values (a signature with 547 genes) that is considered a minimal representation for each cell type. Based on those values, CIBERSORT infers cell type proportions in data from bulk tumor samples with mixed cell types using support vector regression. gene expression profiles were prepared using standard annotation files, the data were uploaded to

the CIBERSORT web portal (http://cibersort.stanford.edu/), and the algorithm was run using the LM22 signature at 1,000 permutations. Tumors with qualitatively different tumor microenvironment cell infiltration patterns were grouped using a hierarchical agglomerative clustering (based on Euclidean distance and Ward's linkage) method. Unsupervised clustering methods (K-means)[17] were used to analyze the dataset, identify tumor microenvironment patterns and classify patients for further analysis. While applying the consensus clustering algorithm, we varied the cluster number from 2 to 6 to determine the optimal number of clusters, which was associated with the highest stability and the lowest ambiguity. Random forest method was utilized to rank the importance of features (multiple immunologic cells), and features with high score of mean decrease accuracy or mean decrease gini were considered more important than those with low score. This procedure using the ConsensusClusterPlus R package[18] was repeated 1,000 times to ensure the stability of the classification.

eTable 1. Characteristics of the Included Patients and Randomized Clinical Trials

Trial (Year)	Study Design	Tumor Stage	No. of Patients (ECOG PS < 2, %)	Treatment Type	Intervention Drug[a]	Control Drug[a]	Line of Therapy	STEC	Target of Therapy	EGFR or ALK Mutation Status
Butts et al,[19] (2005)	RCT, phase Iib	IIIB-IV	171 (95.3)	TV	Tecemotide + Cyclophosphamide	BSA	First-line MT	RECIST/ WHO	MUC1	NP
Quoix et al,[20] (2011)	RCT, phase Iib	IIIB-IV	148 (99.3)	TV	TG4010 + Platinum-based chemotherapy	Platinum-based chemotherapy	First-line	WHO	MUC1	NP
Alfonso et al,[21] (2014)	RCT	IIIB-IV	176 (96.2)	TV	Racotumomab-alum	Placebo	First-line MT	RECIST	NeuGcGM3 ganglioside	NP
START,[22] (2014)	RCT, phase III	III	1,239 (99.4)	TV	Tecemotide + Cyclophosphamide	Placebo + Saline	First-line MT	RECIST	MUC1	NP
Braun et al,[23] (2015)	RCT, phase II	IV	92 (96.7)	TV	Imprime PGG + Carboplatin/ Paclitaxel/ Bevacizumab	Carboplatin/ Paclitaxel/ Bevacizumab	First-line	RECIST	CR3	NP
Giaccone et al,[24] (2015)	RCT, phase	III-IV	532 (95.3)	TV	Belagenpumatucel-L	Placebo	First-line MT	RECIST	TGF-b2-antisense	NP

	III									
TIME,[25] (2015)	RCT, phase IIb/III	IV	222 (99.5)	TV	TG4010 + Platinum-based chemotherapy	Placebo + Platinum-based chemotherapy	First-line	RECIST	MUC1	Without EGFR mutation
Rodriguez et al,[26] (2016)	RCT, Phase III	IIIB-IV	405 (90.9)	TV	CIMAvax-EGF	BSA	First-line MT	RECIST	EGF	NP
Takayama et al,[27] (2016)	RCT, phase II	IIIB-IV/ recurrent	50 (100)	TV	Personalized peptide vaccination + Docetaxel	Docetaxel + Placebo	Second-line	RECIST/ WHO	EGFR	Without EGFR mutation
Katakami et al,[28] (2017)	RCT, phase I/II	III	172 (100)	TV	Tecemotide + Cyclophosphamide	Placebo + Saline	First-line MT	RECIST	MUC1	EGFR Mutant (n = 16, 9.3%)
Thomas et al,[29] (2017)	RCT, phase II	IIIB-IV	90 (95.5)	TV	BTH1677 + Cetuximab + Platinum-based chemotherapy	Cetuximab + Platinum-based chemotherapy	First-line	RECIST	CR3	NP
Wu et al,[30] (2008)	RCT	IIIA- IV	59 (NP)	CIM	CIK cell + Platinum-based chemotherap	Platinum-based chemother	First-line	RECIST/ WHO	Cytokine	NP

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Li et al,[31] (2012)	RCT, phase II	IIIB-IV	74 (NP)	CIM	CIK cell + Cisplatin + Gemcitabine/ Paclitaxel/Navelbine	Cisplatin + Gemcitabine/ Paclitaxel/ Navelbine	First-line	RECIST	Cytokine	NP
Lynch et al,[32,c] (2012)	RCT, phase II	IIIB-IV	136 (100)	ICI	Ipilimumab+ Platinum-based chemotherapy (Concurrent regimen)	Platinum-based chemotherapy	First-line	WHO/ icRC	CTLA-4	NP
Lynch et al,[32,c] (2012)	RCT, phase II	IIIB-IV	134 (100)	ICI	Ipilimumab + Platinum-based chemotherapy (Phased regimen)	Platinum-based chemotherapy	First-line	WHO/ icRC	CTLA-4	NP
CheckMate-017,[33,34] (2015)	RCT, phase III	IIIB-IV	272 (99.2)	ICI	Nivolumab	Docetaxel	Second-line	RECIST	PD-1	NP

CheckMate-057,[33] (2015)	RCT, phase III	III-IV	582 (NP)	ICI	Nivolumab	Docetaxel	Second-line	RECIST	PD-1	NP
KEYNOTE-010,[35] (2016)	RCT, phase II/III	III-IV	1,034 (99.3)	ICI	Pembrolizumab	Docetaxel	Second-line	RECIST	PD-1	EGFR Mutant (n = 86, 8.3%) ALK Mutant (n = 28, 8%)
KEYNOTE-024,[36] (2016)	RCT, phase III	IV	305 (99.7)	ICI	Pembrolizumab	Platinum-based chemotherapy	First-line	RECIST	PD-1	Without EGFR or ALK mutation
OAK,[37] (2016)	RCT, phase III	IIIB-IV	850 (100)	ICI	Atezolizumab	Docetaxel	Second/ Third-line	RECIST	PD-L1	EGFR Mutant (n = 85, 10%) ALK Mutant (n = 2, 0.2%)
POPLAR,[38] (2016)	RCT, phase II	III-IV	287 (98.9)	ICI	Atezolizumab	Docetaxel	Second/Third-line	RECIST	PD-L1	EGFR Mutant (n = 11, 13%)

										ALK Mutant (n = 3, 5%)
CheckMate-026,[39] (2017)	RCT, phase III	IV	541 (98.9)	ICI	Pembrolizumab	Platinum-based chemotherapy	First-line	RECIST	PD-1	Without EGFR or ALK mutation
Govindan et al,[40] (2017)	RCT, phase III	IV/ recurrent	749 (99.4)	ICI	Ipilimumab + Platinum-based chemotherapy	Platinum-based chemotherapy	First-line	WHO	CTLA-4	NP
PACIFIC,[41] (2017)	RCT, phase III	III	713 (NP)	ICI	Durvalumab	Placebo	First-line MT	RECIST	PD-L1	EGFR Mutant (n = 43, 6%)
CheckMate-078,[42] (2018)	RCT, phase III	IIIB/ IV	272 (87[b])	ICI	Nivolumab	Docetaxel	Second-line	RECIST	PD-1	Without EGFR or ALK mutation
CheckMate-227,[43,d] (2018)	RCT, phase III	IV/ recurrent	139 (100)	ICI	Nivolumab + Ipilimumab	Platinum-based chemotherapy	First-line	RECIST	PD-1 and CTLA-4	Without EGFR or ALK mutation
CheckMate-2	RCT,	IV/	71 (93)	ICI	Nivolumab	Platinum-	First-line	RECIST	PD-1	Without

27,[43,d] (2018)	phase III	recurrent				based chemotherapy				EGFR or ALK mutation
CheckMate-227,[43,d] (2018)	RCT, phase III	IV/ recurrent	101 (93)	ICI	Nivolumab + Ipilimumab	Nivoluma b	First-line	RECIST	PD-1 and CTLA-4	Without EGFR or ALK mutation
Impower131,[44] (2018)	RCT, phase III	IV	683 (NP)	ICI	Atezolizumab + Platinum-based chemotherapy	Platinum-based chemotherapy	First-line	RECIST	PD-L1	NP
Impower150,[45] (2018)	RCT, phase III	IV/ recurrent	800 (99.3)	ICI	Atezolizumab + Bevacizumab + Platinum-based chemotherapy	Bevacizumab + Platinum-based chemotherapy	First-line	RECIST	PD-L1	EGFR Mutant (n = 80, 10%) ALK Mutant (n = 34, 4.3%)
KEYNOTE-021 cohort G,[46] (2018)	RCT, phase II	IIIB-IV	123 (99.5)	ICI	Pembrolizumab + Platinum-based chemotherapy	Platinum-based chemotherapy	First-line	RECIST	PD-1	Without EGFR or ALK mutation

KEYNOTE-042,[47] (2018)	RCT, phase III	III/ IV	1,274 (NP)	ICI	Pembrolizumab	Platinum-based chemotherapy	First-line	RECIST	PD-1	NP
KEYNOTE-407,[48] (2018)	RCT, phase III	III/ IV	559 (NP)	ICI	Pembrolizumab + Platinum-based chemotherapy	Placebo + Platinum-based chemotherapy	First-line	RECIST	PD-1	NP
KEYNOTE-189,[49] (2018)	RCT, phase III	IIIB/ IV	408 (99.5)	ICI	Pembrolizumab + Platinum-based chemotherapy	Placebo + Platinum-based chemotherapy	First-line	RECIST	PD-1	Without EGFR or ALK mutation

Abbreviations: RCT, randomized clinical trial; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NP, not provided; TV, Tumor vaccine; CIM, Cellular immunotherapy; ICI, immune checkpoint inhibitor; CT, chemotherapy; MT, maintenance therapy; STEC, solid tumor evaluation criteria; RECIST, The Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization; icRC, immune-related response criteria; BSA, best supportive care; CR3, complement receptor 3; MUC1, mucin 1; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-cell lymphocyte antigen-4; CIK, cytokine-induced killer; EGF, epithelial growth factor; EGFR, epithelial growth factor receptor; TGF, transforming growth factor; ALK, anaplastic lymphoma kinase.

[a] Platinum-based chemotherapy, which consisted of carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, carboplatin plus paclitaxel or carboplatin plus Nab-paclitaxel.

[b] 87% of the enrolled patients had an ECOG PS score of 1.

[c] This study was divided into two substudies because two different immunotherapy strategy groups were compared with the control group.

[d] This study was divided into three substudies because three different comparisons were performed by the investigators.

eTable 2. Characteristics and Clinical Outcomes of the Individual Patients in Checkpoint Inhibitor Cohorts

Characteristics/Clinical Outcomes		**Cohort 1 No. (%)**	**Cohort 2 No. (%)**	**OAK trial No. (%)**
No. of patients		349	56	420
Follow up time, median years (IQR)		3.77 (1.83-8.32)	8.29 (3.91-14.59)	12.62 (5.09-20.17)
Age, median years (IQR)		65 (57-72)	61 (56.5-67)	63 (57-70)
Sex	Male	178 (51)	24 (42.9)	257 (61)
	Female	171 (49)	32 (57.1)	163 (39)
Histology	Adenocarcinoma	274 (79)	47 (83.9)	311 (74)
	Squamous	54 (15)	7 (12.5)	109 (26)
	Other	21 (6)	2 (3.6)	0 (0)
Smoking status	Ever	281 (81)	43 (76.8)	336 (80)
	Never	68 (19)	13 (23.2)	84 (20)
Stage	IIIB	9 (3)	NP	NP
	IV	340 (97)	NP	NP
Line of therapy	First-line	51 (15)	NP	0 (0)
	Second-line	127 (36)	NP	316 (75)
	Third or more	62 (18)	NP	104 (25)
Treatment	Monotherapy	240 (69)	56 (100)	420 (100)
	Combination therapy	109 (31)	0 (0)	0 (0)
Best overall response	CR/PR	85 (24)	17 (30.4)	57 (14)
	SD	119 (34)	21 (37.5)	147 (38)
	PD	145 (42)	18 (32.1)	186 (48)
Clinical benefit	DCB	120 (34)	NP	NP
	NDB	213 (61)	NP	NP
	NR	16 (5)	NP	NP
PD-L1 expression	≥ 50%	41 (12)	NP	72 (17)
	1-49%	72 (21)	NP	168 (40)
	< 1%	73 (21)	NP	180 (43)
	NA	163 (47)	NP	0 (0)

Characteristics/Clinical Outcomes		Cohort 1 No. (%)	Cohort 2 No. (%)	OAK trial No. (%)
Tumor mutation burden (cutoff: 175)	High	82 (23)	26 (46.4)	NP
	Low	86 (25)	30 (53.6)	NP
	NA	181 (52)	0 (0)	NP
Candidate neoantigen burden (cutoff: 517)	High	26 (7)	NP	NP
	Low	83 (24)	NP	NP
	NA	240 (69)	NP	NP

Abbreviations: IQR, interquartile range; NP, not provided.

eTable 3. Summary of the Pooled Estimates and Grading of Recommendations, Assessment, Development, and Evaluation Evidence of Progression-Free Survival

Subgroup	Progression-Free Survival					
	No. of Trials	HR	95% CI	*P* Value	I^2, %	GRADE
Immune checkpoint inhibitor						
All trials	22	0.76	0.71 - 0.82	<.0001	82.0	⊕⊕⊕O Moderate[a]
First-line ICI vs CT	5	0.88	0.69 - 1.11	.2812	84.8	⊕⊕OO Low[a,c]
Nivolumab[c]	2	1.09	0.89 - 1.34	.409	0	⊕⊕OO Low[b,c]
Pembrolizumab	2	0.74	0.35 - 1.56	.430	95.1	⊕OOO Very low[a,b,c]
Nivolumab + ipilimumab	1	0.83	0.72 - 0.96	.011	NA	⊕⊕⊕O Moderate[b]
First-line ICI+ICI vs IC (Nivolumab + ipilimumab vs Nivolumab)	1	0.75	0.53 - 1.07	.108	NA	⊕⊕OO Low[b,c]
First-line ICI+CT vs CT	8	0.68	0.58 - 0.80	< .0001	69.7	⊕⊕⊕O Moderate[a]
Ipilimumab	3	0.85	0.74 - 0.96	.014	0	⊕⊕⊕⊕ High
Pembrolizumab	3	0.54	0.47 - 0.62	< .001	0	⊕⊕⊕⊕ High
Atezolizumab	1	0.71	0.60 - 0.85	< .001	NA	⊕⊕⊕O Moderate[b]

Nivolumab	1	0.74	0.58 - 0.94	.015	NA	⊕⊕⊕O Moderate[b]
First-line ICI + anti-VEGFR + CT vs anti-VEGFR + CT (Atezolizumab + bevacizumab)	1	0.61	0.52 - 0.72	< .001	NA	⊕⊕⊕O Moderate[b]
First-line MT ICI vs CT (Durvalumab)	1	0.52	0.42 - 0.65	< .001	NA	⊕⊕⊕O Moderate[b]
Second/third-line ICI vs CT	6	0.85	0.77 - 0.94	.0016	40.1	⊕⊕⊕⊕ High
Atezolizumab	2	0.95	0.83 - 1.08	0.445	0	⊕⊕OO Low[b,c]
Nivolumab	3	0.77	0.64 - 0.93	.006	54.6	⊕⊕⊕O Moderate[a]
Pembrolizumab	1	0.85	0.73 - 0.98	.03	NA	⊕⊕⊕O Moderate[b]
Tumor vaccine						
All trials	11	0.86	0.78 - 0.94	< .0001	0	⊕⊕⊕⊕ High
First-line TV+CT vs CT	3	0.74	0.60 - 0.91	.005	0	⊕⊕⊕⊕ High
First-line MT TV vs no TV	4	0.89	0.81 - 0.99	.023	0	⊕⊕⊕⊕ High
Second-line TV+CT vs CT	1	0.78	0.43 - 1.42	.415	NA	⊕⊕OO Low[b,c]
Cellular immunotherapy						
First-line CIM+CT vs CT	2	0.51	0.24 - 1.10	.083	73.0	⊕OOO Very low[a,b,c]

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; vs, versus; ICI, immune checkpoint inhibitor; TV, tumor vaccine; CIM, cellular immunotherapy; CT, chemotherapy; MT, maintenance therapy; HR, hazard ratio; CI, confidence interval; VEGFR, vascular endothelial growth factor receptor; NA, not available.

[a] Downgraded (-1) for inconsistency: Substantial heterogeneity (I^2 > 50%) was found among the trials.

[b] Downgraded (-1) for imprecision: Fewer than three trials were included in this subgroup.

[c] Downgraded (-1) for imprecision: The 95% CIs were so wide that the result included no effect

and failed to exclude important benefits or serious harmful effects.
GRADE Working Group grades of evidence:
⊕⊕⊕⊕ High quality: Further research is very unlikely to change our confidence in the estimated effect.
⊕⊕⊕O Moderate quality: Further research is likely to have an important impact on our confidence in the estimated effect and might change the estimate.
⊕⊕OO Low quality: Further research is very likely to have an important impact on our confidence in the estimated effect and might change the estimate.
⊕OOO Very low quality: We are very uncertain about the estimate.

eTable 4. Summary of the Pooled Estimates and Grading of Recommendations, Assessment, Development, and Evaluation Evidence of Overall Survival

Subgroup	**Overall Survival**					
	No. of Trials	**HR**	**95% CI**	***P* Value**	**I^2, %**	**GRADE**
Immune checkpoint inhibitor						
All trials	17	0.76	0.70 - 0.83	< .0001	60.0	⊕⊕⊕O Moderate[a]
First-line ICI vs CT	3	0.82	0.65 - 1.03	.094	64.2	⊕⊕OO Low[a,c]
Nivolumab[c]	1	1.02	0.80 - 1.30	.873	NA	⊕⊕OO Low[b,c]
Pembrolizumab	2	0.78	0.69 - 0.89	< .001	51.3	⊕⊕OO Low[a,b]
First-line ICI+CT vs CT	7	0.61	0.58 - 0.93	.0102	76.5	⊕⊕⊕O Moderate[a]
Ipilimumab	3	0.991	0.79 - 1.05	.901	0	⊕⊕⊕O Moderate[c]
Pembrolizumab	3	0.55	0.46 - 0.66	< .001	0	⊕⊕⊕⊕ High
Atezolizumab	1	0.96	0.78 - 1.18	.699	NA	⊕⊕OO Low [b,c]
First-line ICI + anti-VEGFR + CT vs anti-VEGFR + CT (Atezolizumab + bevacizumab)	1	0.78	0.64 - 0.96	.016	NA	⊕⊕⊕O Moderate[b]
Second/third-line ICI vs CT	6	0.70	0.64 - 0.77	< .0001	0	⊕⊕⊕⊕ High

Atezolizumab	2	0.73	0.63 - 0.85	< .0001	0	⊕⊕⊕O Moderate[b]
Nivolumab	3	0.69	0.61 - 0.79	< .0001	0	⊕⊕⊕⊕ High
Pembrolizumab	1	0.67	0.56 - 0.80	< .0001	NA	⊕⊕⊕O Moderate[b]
Tumor vaccine						
All trials	8	0.83	0.76 - 0.91	< .0001	0	⊕⊕⊕⊕ High
First-line TV+CT vs CT	4	0.84	0.68 - 1.03	.100	0	⊕⊕⊕O Moderate[c]
First-line MT TV vs no TV	6	0.83	0.74 - 0.92	.001	7.7	⊕⊕⊕⊕ High
Second-line TV+CT vs CT	1	0.80	0.42 - 1.52	.496	NA	⊕⊕OO Low[b,c]
Cellular immunotherapy						
First-line CIM+CT vs CT	2	0.40	0.17 - 0.96	.038	67.6	⊕⊕OO Low[a,b]

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; vs, versus; ICI, immune checkpoint inhibitor; TV, tumor vaccine; CIM, cellular immunotherapy; CT, chemotherapy; MT, maintenance therapy; HR, hazard ratio; CI, confidence interval; VEGFR, vascular endothelial growth factor receptor; NA, not available.

[a] Downgraded (-1) for inconsistency: Substantial heterogeneity (I^2 > 50%) was found among the trials.

[b] Downgraded (-1) for imprecision: Fewer than three trials were included in this subgroup.

[c] Downgraded (-1) for imprecision: The 95% CIs were so wide that the result included no effect and failed to exclude important benefits or serious harmful effects.

GRADE Working Group grades of evidence:

⊕⊕⊕⊕ High quality: Further research is very unlikely to change our confidence in the estimated effect.

⊕⊕⊕O Moderate quality: Further research is likely to have an important impact on our confidence in the estimated effect and might change the estimate.

⊕⊕OO Low quality: Further research is very likely to have an important impact on our confidence in the estimated effect and might change the estimate.

⊕OOO Very low quality: We are very uncertain about the estimate.

eTable 5. Summary of the Pooled Estimates and Grading of Recommendations, Assessment, Development, and Evaluation Evidence of Objective Response Rate

Subgroup	**Objective Response Rate**					
	No. of	**RR**	**95% CI**	***P* Value**	**I^2, %**	**GRADE**

	Trials					
Immune checkpoint inhibitor						
All trials	16	1.34	1.26 - 1.42	<. 0001	83.6	⊕⊕⊕O Moderate[a]
First-line therapy	10	1.28	1.20 - 1.37	<. 0001	75.4	⊕⊕⊕O Moderate[a]
Second-line therapy	5	2.00	1.66 - 2.41	<. 0001	86.3	⊕⊕⊕O Moderate[a]
Maintenance therapy	1	1.02	0.87 - 1.19	.8119	NA	⊕⊕OO Low[b,c]
Tumor vaccine						
All trials	9	1.04	0.98 - 1.12	.201	58.3	⊕⊕OO Low[a,c]
First-line therapy	4	1.48	1.16 - 1.88	.0014	0	⊕⊕⊕⊕ High
Second-line therapy	1	2.77	0.62 - 12.42	.1835	NA	⊕⊕OO Low[b,c]
Maintenance therapy	4	0.98	0.92 - 1.05	.6197	44.9	⊕⊕⊕O Moderate[c]
Cellular immunotherapy						
First-line therapy	1	1.03	0.58 - 1.84	.908	NA	⊕⊕OO Low[b,c]

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; RR, risk ratio; CI, confidence interval; NA, not available.

[a] Downgraded (-1) for inconsistency: Substantial heterogeneity (I^2 > 50%) was found among the trials.

[b] Downgraded (-1) for imprecision: Fewer than three trials were included in this subgroup.

[c] Downgraded (-1) for imprecision: The 95% CIs were so wide that the result included no effect and failed to exclude important benefits or serious harmful effects.

GRADE Working Group grades of evidence:

⊕⊕⊕⊕ High quality: Further research is very unlikely to change our confidence in the estimated effect.

⊕⊕⊕O Moderate quality: Further research is likely to have an important impact on our confidence in the estimated effect and might change the estimate.

⊕⊕OO Low quality: Further research is very likely to have an important impact on our confidence in the estimated effect and might change the estimate.

⊕OOO Very low quality: We are very uncertain about the estimate.

eTable 6. Summary of the Estimates and Grading of Recommendations, Assessment, Development, and Evaluation Evidence in the Subgroup Analysis of Clinical Outcomes

Quality Assessment								Effect		
No. of trials	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Other Considerations**	**Relative (95% CI)**	**Quality**	**Importance**
Objective response rate among all trials										
26	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	Strongly suspected	None	RR 1.33 (1.18 - 1.51)	⨁⨁OO Low[a,c]	CRITICAL
Objective response rate among the trials investigating immune checkpoint inhibitor therapy										
16	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	Strongly suspected	None	RR 1.47 (1.25 - 1.73)	⨁⨁OO Low[a,c]	CRITICAL
Progression-free survival outcomes among the trials investigating immune checkpoint inhibitor therapy										
Age < 65										
7	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.65 (0.49 - 0.86)	⨁⨁⨁O Moderate[a]	CRITICAL
Age ≥ 65										

7	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.76 (0.61 - 0.94)	⨁⨁⨁O Moderate[a]	CRITICAL
ECOG PS = 0										
6	Randomized trials	No serious risk of bias	Serious	No serious indirectness	Serious	None detected	None	HR 0.76 (0.51 - 1.12)	⨁⨁OO Low[a,d]	CRITICAL
ECOG PS = 1										
6	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.68 (0.56 - 0.82)	⨁⨁⨁O Moderate[a]	CRITICAL
EGFR mutant										
2	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	Serious	None detected	None	HR 0.63 (0.42 - 0.94)	⨁⨁⨁O Moderate[b]	CRITICAL
EGFR wild-type										
8	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.64 (0.53 - 0.77)	⨁⨁⨁O Moderate[a]	CRITICAL

KRAS mutant										
1	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	Serious	None detected	None	HR 0.50 (0.29 - 0.85)	⨁⨁⨁◯ Moderate [b]	CRITICAL
PD-L1 TC0 or IC0										
7	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	No serious imprecision	None detected	None	HR 0.77 (0.67 - 0.89)	⨁⨁⨁⨁ High	CRITICAL
PD-L1 TC1/2/3 or IC1/2/3										
8	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.61 (0.51 - 0.74)	⨁⨁⨁◯ Moderate [a]	CRITICAL
PD-L1 TC2/3 or IC2/3										
5	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.65 (0.45 - 0.94)	⨁⨁⨁◯ Moderate [a]	CRITICAL
PD-L1 TC3 or IC3										
12	Randomized trials	No serious	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.60 (0.47 -	⨁⨁⨁◯ Moderate	CRITICAL

		risk of bias						0.76)	[a]	
Female										
6	Randomized trials	No serious risk of bias	Serious	No serious indirectness	Serious	None detected	None	HR 0.74 (0.49 - 1.10)	⨁⨁OO Low[a,d]	CRITICAL
Male										
6	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.64 (0.50 - 0.83)	⨁⨁⨁O Moderate [a]	CRITICAL
Current or former smoker										
4	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	Serious	None detected	None	HR 0.59 (0.51 - 0.69)	⨁⨁⨁O Moderate [b]	CRITICAL
Never smoked										
3	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	Serious	None detected	None	HR 0.64 (0.43 - 0.97)	⨁⨁⨁O Moderate [b]	CRITICAL
Squamous-type tumor										

8	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	No serious imprecision	None detected	None	HR 0.73 (0.64 - 0.84)	⊕⊕⊕⊕ High	CRITICAL
Nonsquamous-type tumor										
8	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.70 (0.55 - 0.88)	⊕⊕⊕O Moderate[a]	CRITICAL
High tumor mutation burden										
2	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	Serious	None detected	None	HR 0.58 (0.46 - 0.74)	⊕⊕⊕O Moderate[b]	CRITICAL
Low tumor mutation burden										
2	Randomized trials	No serious risk of	Serious	No serious indirectness	Serious	None detected	None	HR 1.20 (0.81 - 1.79)	⊕OOO Very Low[a,b,d]	CRITICAL
Overall survival outcomes among the trials investigating immune checkpoint inhibitor therapy										
Age < 65										
8	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.73 (0.62 - 0.87)	⊕⊕⊕O Moderate[a]	CRITICAL

Age ≥ 65										
8	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	No serious imprecision	None detected	None	HR 0.80 (0.70 - 0.90)	⨁⨁⨁⨁ High	CRITICAL
ECOG PS = 0										
8	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	No serious imprecision	None detected	None	HR 0.75 (0.63 - 0.9)	⨁⨁⨁⨁ High	CRITICAL
ECOG PS = 1										
8	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.75 (0.66 - 0.85)	⨁⨁⨁◯ Moderate [a]	CRITICAL
ALK wild-type										
1	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	Serious	None detected	None	HR 0.49 (0.38 - 0.64)	⨁⨁⨁◯ Moderate [b]	CRITICAL
EGFR mutant										
3	Randomized trials	No serious	No serious inconsistencie	No serious indirectness	Serious	None detected	None	HR 1.12 (0.80 -	⨁⨁⨁◯ Moderate	CRITICAL

		risk of bias	s					1.56)	[d]	
EGFR wild−type										
8	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.68 (0.58 - 0.79)	⊕⊕⊕O Moderate [a]	CRITICAL
KRAS mutant										
3	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	No serious imprecision	None detected	None	HR 0.65 (0.44 - 0.96)	⊕⊕⊕⊕ High	CRITICAL
KRAS wild-type										
4	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	No serious imprecision	None detected	None	HR 0.81 (0.69 - 0.95)	⊕⊕⊕⊕ High	CRITICAL
PD-L1 TC0 or IC0										
7	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	No serious imprecision	None detected	None	HR 0.72 (0.61 - 0.86)	⊕⊕⊕⊕ High	CRITICAL
PD-L1 TC1/2/3 or IC1/2/3										

8	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.60 (0.46 - 0.79)	⊕⊕⊕O Moderate [a]	CRITICAL
PD-L1 TC2/3 or IC2/3										
7	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.64 (0.51 - 0.81)	⊕⊕⊕O Moderate [a]	CRITICAL
PD-L1 TC3 or IC3										
11	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	No serious imprecision	None detected	None	HR 0.55 (0.47 - 0.65)	⊕⊕⊕⊕ High	CRITICAL
Female										
8	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.71 (0.54 - 0.95)	⊕⊕⊕O Moderate [a]	CRITICAL
Male										
8	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	No serious imprecision	None detected	None	HR 0.78 (0.72 - 0.85)	⊕⊕⊕⊕ High	CRITICAL

Current or former smoker										
7	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.79 (0.69 - 0.90)	⨁⨁⨁◯ Moderate[a]	CRITICAL
Never smoked										
6	Randomized trials	No serious risk of bias	Serious	No serious indirectness	Serious	None detected	None	HR 0.75 (0.53 - 1.06)	⨁⨁◯◯ Low[a,d]	CRITICAL
Squamous-type tumor										
7	Randomized trials	No serious risk of bias	No serious inconsistencies	No serious indirectness	No serious imprecision	None detected	None	HR 0.77 (0.69 - 0.86)	⨁⨁⨁⨁ High	CRITICAL
Nonsquamous-type tumor										
8	Randomized trials	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None detected	None	HR 0.77 (0.67 - 0.88)	⨁⨁⨁◯ Moderate[a]	CRITICAL

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; RR, risk ratio; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; KRAS, kirsten rat sarcoma viral oncogene homolog; PD-L1, programmed death-ligand 1; TC, tumor cells; IC, tumor-infiltrating immune cells.

[a] Downgraded (-1) for inconsistency: Substantial heterogeneity (I^2 > 50%) was found among the trials.

[b] Downgraded (-1) for imprecision: Fewer than three trials were included in this subgroup.

[c] Downgraded (-1) for publication bias: The *P* values of the Egger's and Begg's regression tests were < 0.05 in this subgroup.

[d] Downgraded (-1) for imprecision: The 95% CIs were so wide that the result included no effect and failed to exclude important benefits or serious harmful effects.

PD-L1 scoring criteria:

TC3 or IC3: TC3 ≥50% or IC3 ≥10%.

TC2 or IC2: TC2 ≥5% and <50% or IC2 ≥5% and <10%.

TC1 or IC1: TC1 ≥1% and <5% or IC1 ≥1% and <5%.

TC0 or IC0: TC0 <1% or IC0 <1%.

GRADE Working Group grades of evidence:

⊕⊕⊕⊕ High quality: Further research is very unlikely to change our confidence in the estimate of effect.

⊕⊕⊕O Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

⊕⊕OO Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

⊕OOO Very low quality: We are very uncertain about the estimate.

eTable 7. Summary of the Estimates Stratified by Programmed Cell Death Ligand 1 Expression and Treatment Strategy

	Overall Survival						**Progression-free Survival**					
Subgroup	**No. of Trials**	**HR**	**95% CI**	***I²* (%)**	***P* Value**	***P* for Interaction** [a]	**No. of Trials**	**HR**	**95% CI**	***I²* (%)**	***P* Value**	***P* for Interaction** [a]
TC3 or IC3						.6381						.0002
ICI vs CT	8	0.57	0.46 - 0.71	55.9	< .0001		8	0.73	0.58 - 0.94	73.8	.0123	
ICI+CT vs CT	3	0.52	0.38 - 0.71	0	< .0001		3	0.38	0.30 - 0.49	0	< .0001	
TC2/3 or IC2/3						.5361						.1726
ICI vs CT	6	0.65	0.51 - 0.84	74.5	.0011		4	0.79	0.56 - 1.09	82.6	.1551	

ICI+CT vs CT	1	0.55	0.34 - 0.90	NA	.016		1	0.55	0.37 - 0.81	NA	< .0001	
TC1/2/3 or IC1/2/3						.0296						.002
ICI vs CT	6	0.70	0.61 - 0.79	30.6	< .0001		4	0.85	0.69 - 1.05	75.7	.1204	
ICI+CT vs CT	2	0.50	0.38 - 0.66	0	< .001		3	0.53	0.43 - 0.66	41.9	< .0001	
TC0 or IC0						.9536						.5751
ICI vs CT	4	0.72	0.56 - 0.94	48.2	.0166		2	0.90	0.51 - 1.61	79.8	.719	
ICI+CT vs CT	3	0.72	0.55 - 0.93	26.2	.0115		4	0.76	0.66 - 0.87	0	< .0001	

Abbreviations: HR, hazard ratio; CI, confidence interval; PD-L1, programmed death-ligand 1; TC, tumor cells; IC, tumor-infiltrating immune cells; ICI, immune checkpoint inhibitor; CT, chemotherapy.

[a] The *P* value for interaction reflects the difference between ICI alone and ICI + CT, as calculated by the χ^2 test comparing the HRs of the subgroups; NA, not available.

PD-L1 scoring criteria:

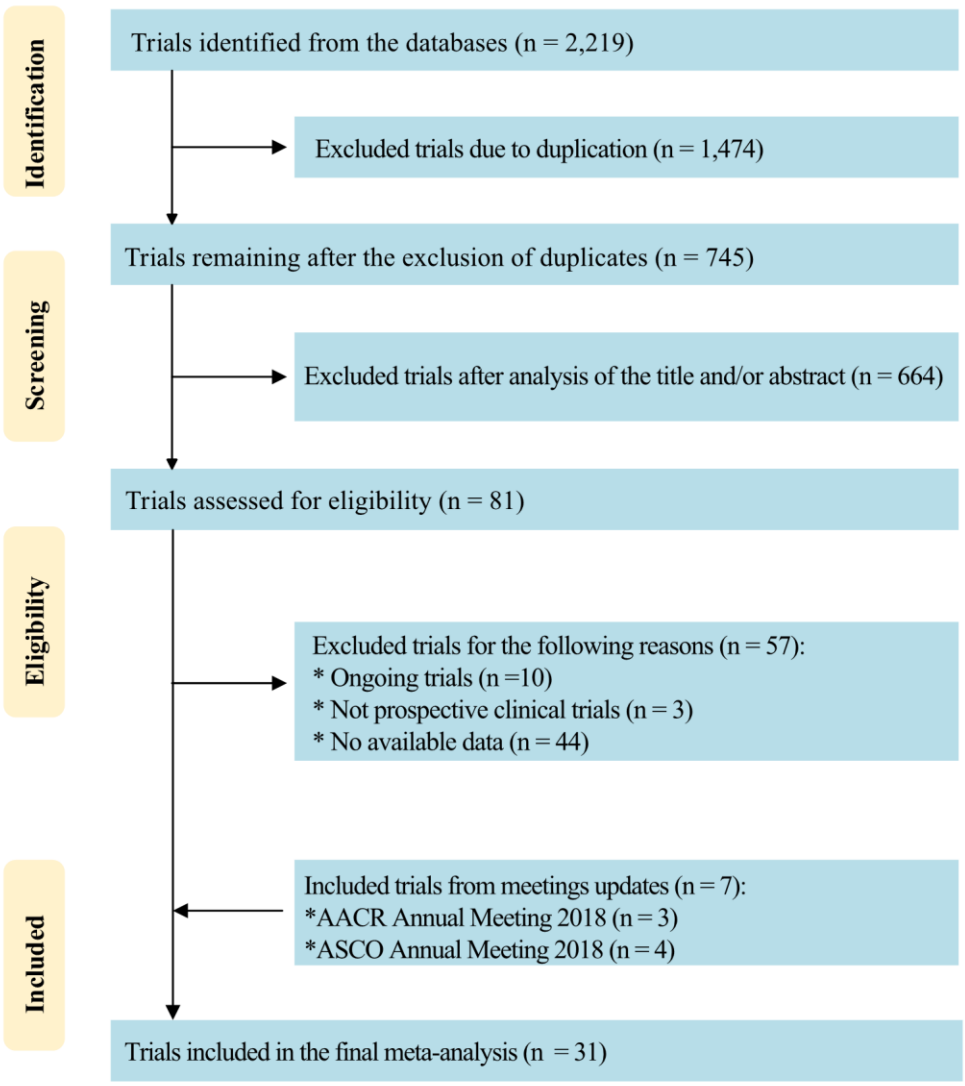
TC3 or IC3: TC3 ≥50% or IC3 ≥10%.

TC2 or IC2: TC2 ≥5% and <50% or IC2 ≥5% and <10%.

TC1 or IC1: TC1 ≥1% and <5% or IC1 ≥1% and <5%.

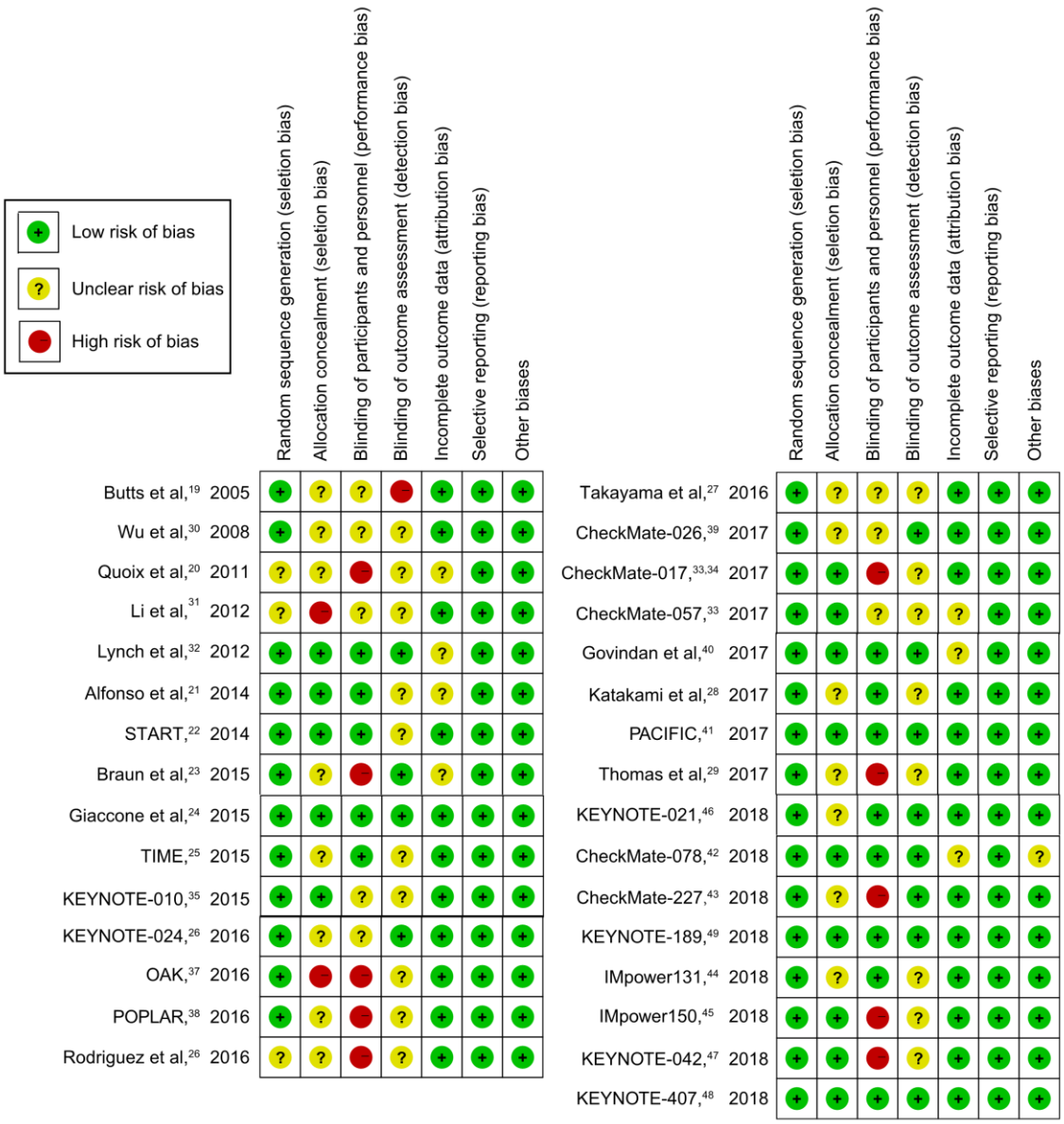
TC0 or IC0: TC0 <1% or IC0 <1%.

eFigure 1. PRISMA Flow Diagram for the Meta-analysis



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ASCO, the American Society of Clinical Oncology; AACR, the American Association for Cancer Research.

eFigure 2. Risk of Bias Summary of the Randomized Trials Included in the Meta-analysis



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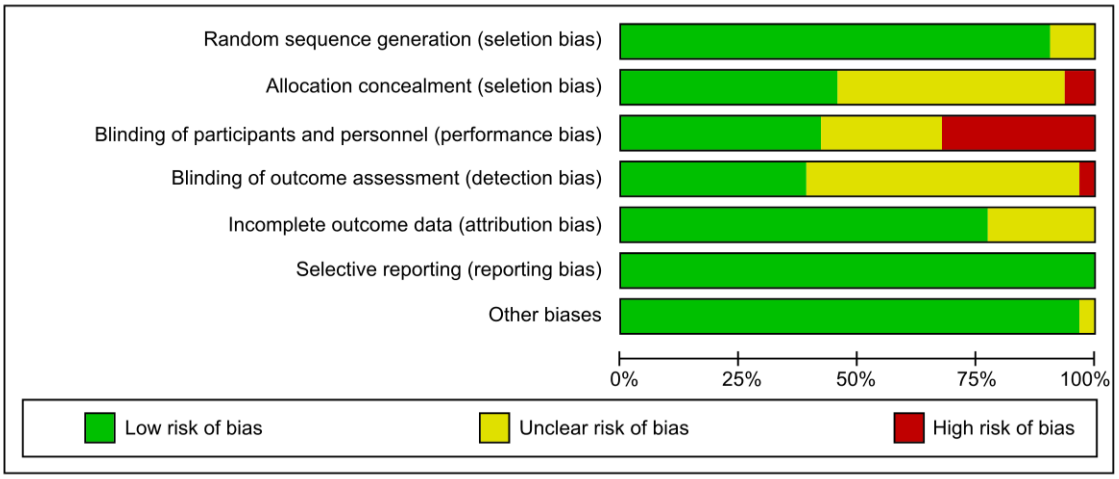
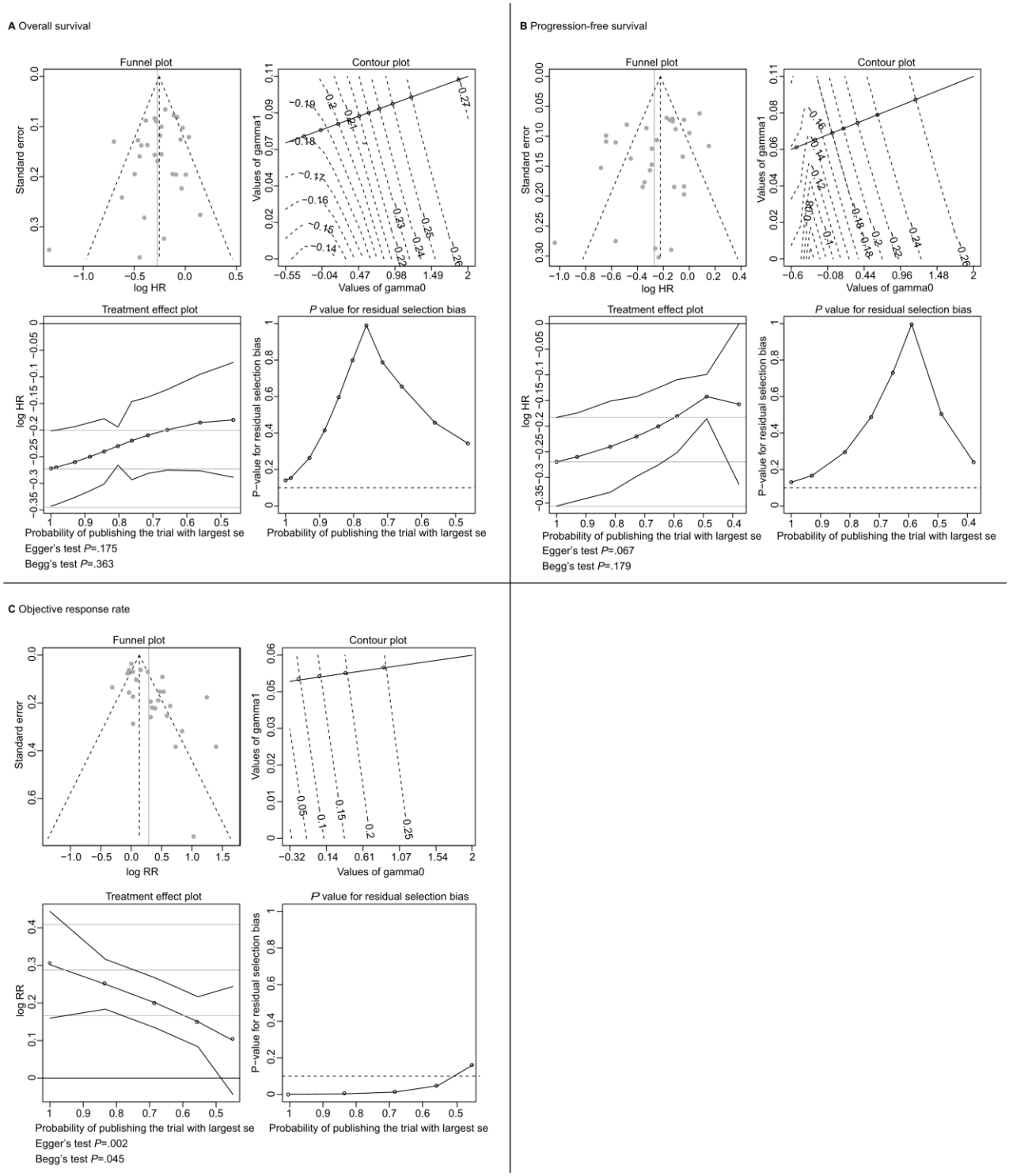
eFigure 3. Risk of bias graph for the Randomized Trials Included in the Meta-analysis

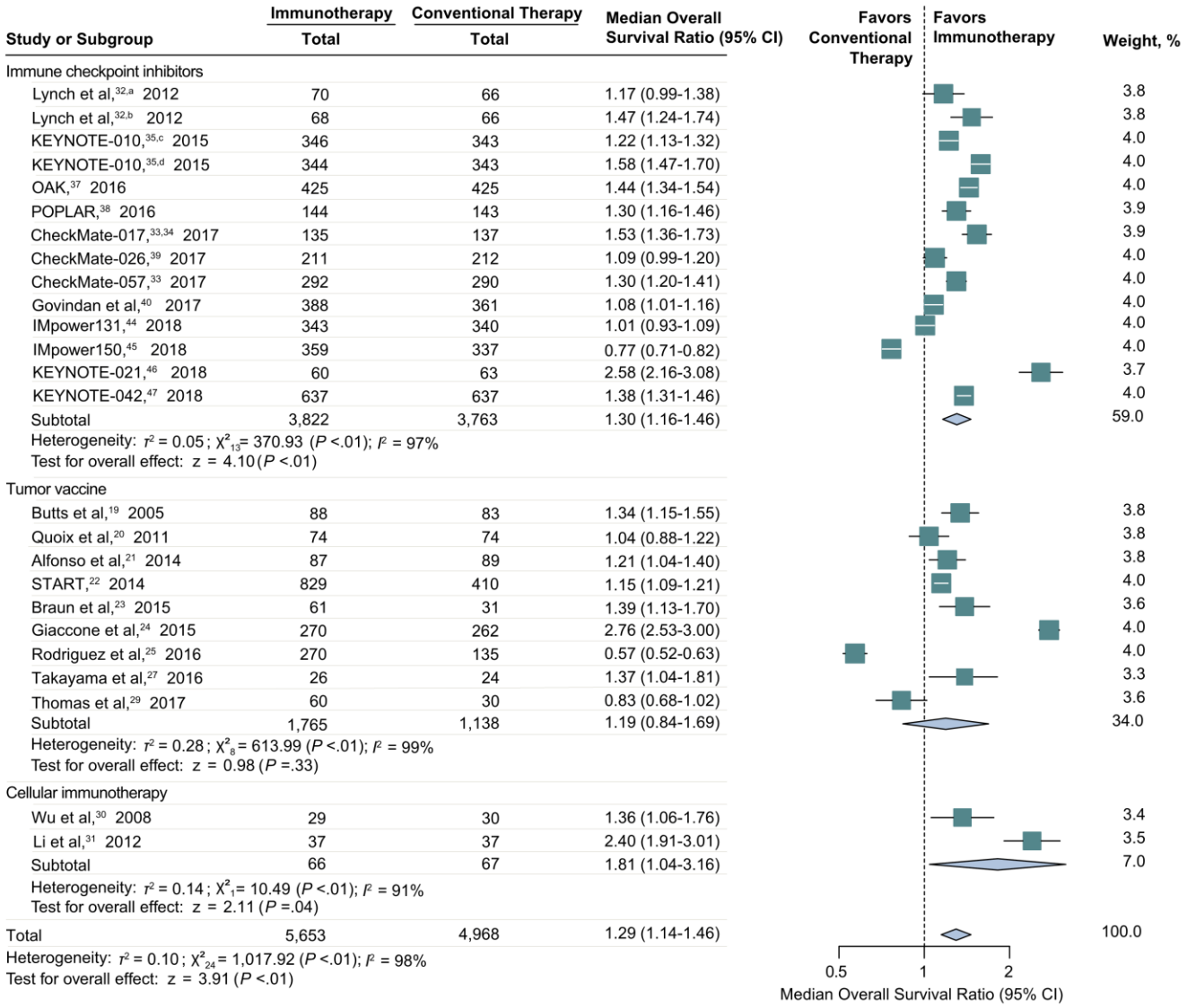


eFigure 4. Analysis of Publication Bias in the Meta-analyses of Immunotherapy vs Conventional Therapy



The outcomes assessed were overall survival (A), progression-free survival (B) and the objective response rate (C). HR, hazard ratio; RR, risk ratio.

eFigure 5. Pooled Analysis of the Ratio of the Median Overall Survival With Immunotherapy vs Conventional Therapy



Size of boxes is proportional to the weight of each trial, and the diamonds indicate the point estimate and confidence interval of the combined result.

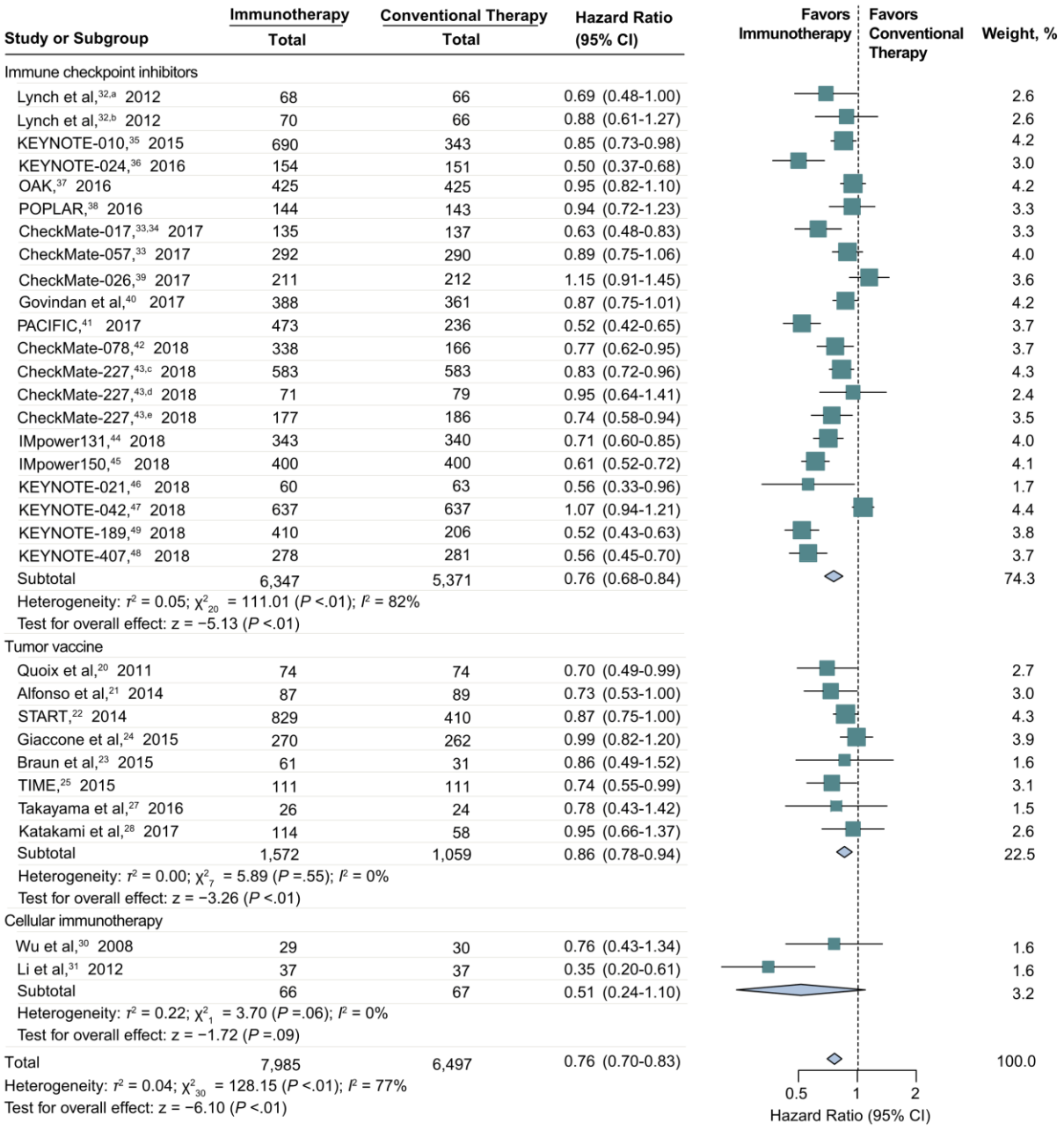
[a] Patients were treated by concurrent regimen.

[b] Patients were treated by phased regimen.

[c] Drugs were administered at a dose of 2 mg/kg.

[d] Drugs were administered at a dose of 10 mg/kg.

eFigure 6. Pooled Hazard Ratios for Progression-Free Survival With Immunotherapy vs Conventional Therapy



Size of boxes is proportional to the weight of each trial, and the diamonds indicate the point estimate and confidence interval of the combined result.

[a] Patients were treated by phased regimen.

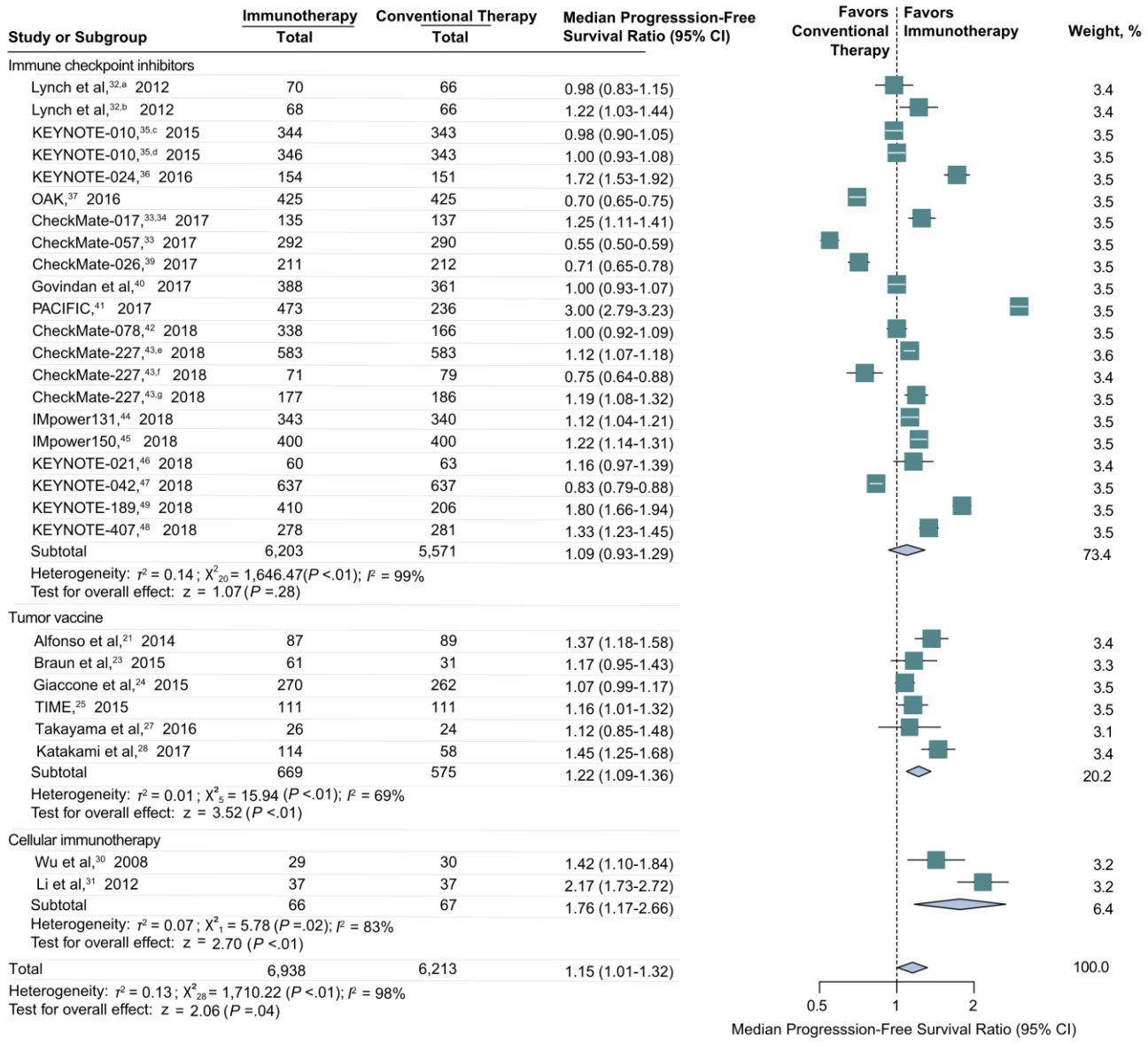
[b] Patients were treated by concurrent regimen.

[c] Comparison between nivolumab + ipilimumab and chemotherapy.

[d] Comparison between nivolumab and chemotherapy.

[e] Comparison between nivolumab + ipilimumab and nivolumab.

eFigure 7. Pooled Analysis of the Ratio of the Median Progression-Free Survival With Immunotherapy vs Conventional Therapy



Size of boxes is proportional to the weight of each trial, and the diamonds indicate the point estimate and confidence interval of the combined result.

[a] Patients were treated by concurrent regimen.

[b] Patients were treated by phased regimen.

[c] Drugs were administered at a dose of 2 mg/kg.

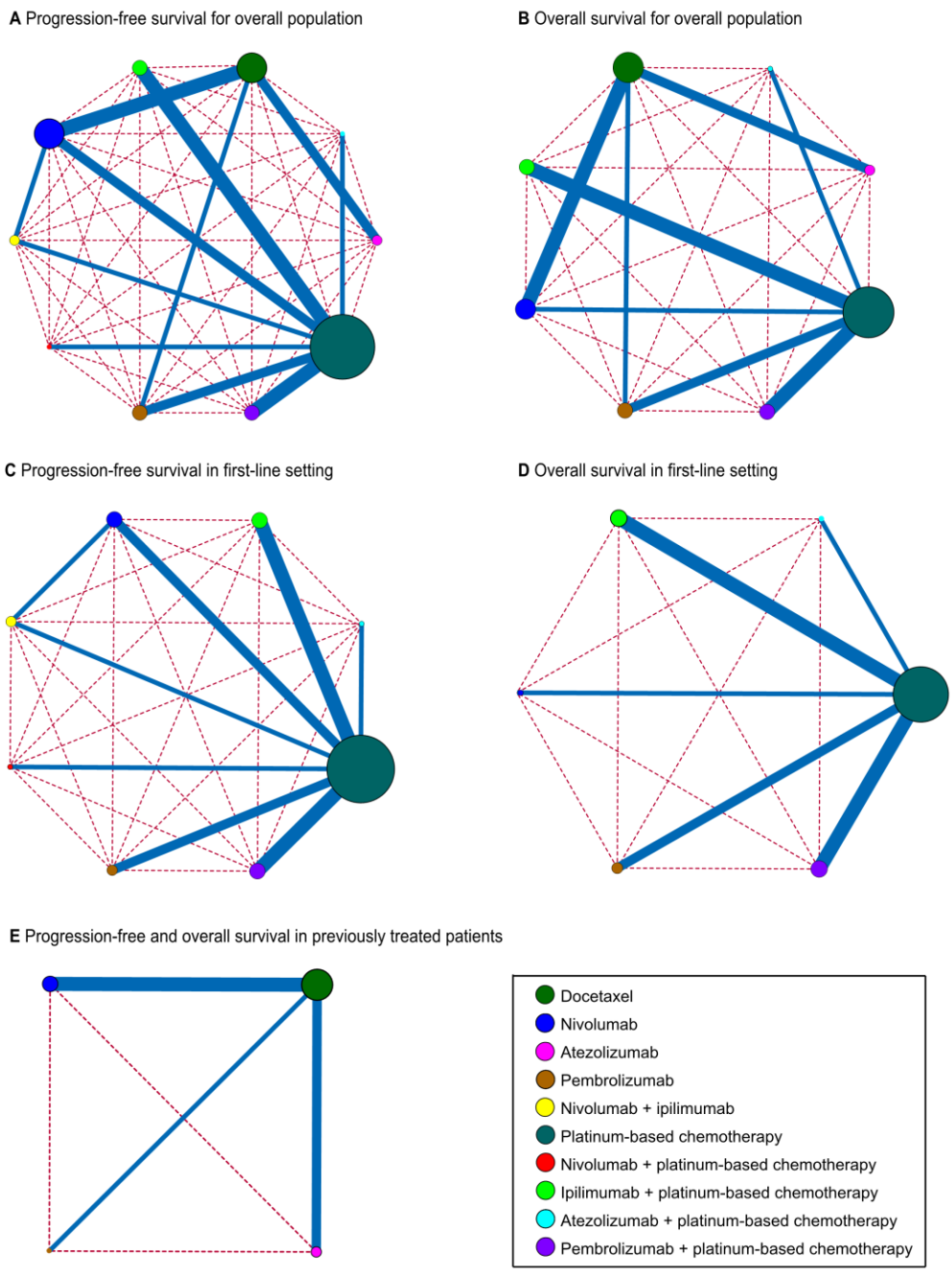
[d] Drugs were administered at a dose of 10 mg/kg.

[e] Comparison between nivolumab + ipilimumab and chemotherapy.

[f] Comparison between nivolumab and chemotherapy.

[g] Comparison between nivolumab + ipilimumab and nivolumab.

eFigure 8. Network Diagram of Studies Comparing Clinical Outcomes of Different Immune Checkpoint Inhibitors Strategies for Advanced Non–Small Cell Lung Cancer



Network diagrams were plotted for (A) progression-free survival for overall population; (B) overall survival for overall population; (C) progression-free survival for first-line therapy; (D) overall survival for first-line therapy; (E) progression-free and overall survival in previously treated patients. The size of connected nodes is proportional to the number of patients receiving the treatment, and the line width is proportional to the number of trials included in the comparison of two treatment groups.

eFigure 9. Network Meta-analysis of Immune Checkpoint Inhibitors in Terms of Progression-Free Survival

Atezolizumab	1.20 (0.77-1.80)	1.30 (0.82-2.20)	1.40(0.83-2.50)	0.95 (0.68-1.30)	1.60 (0.83-3.10)	1.40 (0.80-2.40)	1.50 (0.79-3.00)	**2.10 (1.20-3.70)**	1.10 (0.71-1.80)
0.86 (0.57-1.30)	Nivolumab	1.10 (0.81-1.60)	1.20(0.84-1.80)	0.82 (0.64-1.00)	1.40 (0.80-2.30)	1.20 (0.79-1.80)	1.30 (0.76-2.30)	**1.80 (1.20-2.70)**	0.98 (0.73-1.30)
0.78 (0.46-1.20)	0.90 (0.62-1.20)	Pembrolizumab	1.10 (0.69-1.70)	**0.73 (0.50-1.00)**	1.20 (0.70-2.10)	1.10 (0.69-1.60)	1.20 (0.66-2.00)	**1.60 (1.00-2.40)**	0.88 (0.64-1.20)
0.70 (0.40-1.20)	0.81 (0.55-1.20)	0.90 (0.59-1.40)	Nivolumab + ipilimumab	0.66 (0.43-1.00)	1.10 (0.63-2.00)	0.97 (0.61-1.50)	1.10 (0.59-1.90)	1.50 (0.90-2.30)	0.80 (0.55-1.10)
1.10 (0.76-1.50)	1.20 (0.96-1.60)	**1.40 (1.00-2.00)**	1.50 (0.98-2.40)	Docetaxel	1.70 (0.96-3.00)	1.50 (0.94-2.30)	1.60 (0.91-2.90)	**2.20 (1.40-3.50)**	1.20 (0.86-1.70)
0.62 (0.32-1.20)	0.72 (0.43-1.20)	0.80 (0.48-1.40)	0.89 (0.51-1.60)	0.59 (0.34-1.00)	Atezolizumab + platinum-based chemotherapy	0.86 (0.51-1.50)	0.96 (0.50-1.90)	1.30 (0.76-2.20)	0.71 (0.45-1.10)
0.72 (0.41-1.20)	0.84 (0.55-1.30)	0.93 (0.63-1.40)	1.00 (0.65-1.60)	0.68 (0.44-1.10)	1.20 (0.67-2.00)	Ipilimumab + platinum-based chemotherapy	1.10(0.63-1.90)	1.50 (0.99-2.30)	0.82 (0.61-1.10)
0.65 (0.33-1.30)	0.75 (0.43-1.30)	0.84 (0.49-1.50)	0.93 (0.51-1.70)	0.61 (0.34-1.10)	1.00 (0.54-2.00)	0.90 (0.52-1.60)	Nivolumab + platinum-based chemotherapy	1.40 (0.77-2.40)	0.74 (0.46-1.20)
0.48 (0.27-0.84)	**0.55 (0.37-0.84)**	**0.62 (0.42-0.97)**	0.68 (0.43-1.10)	**0.45 (0.29-0.71)**	0.76 (0.45-1.30)	0.66 (0.44-1.00)	0.73 (0.42-1.30)	Pembrolizumab + platinum-based chemotherapy	**0.54 (0.41-0.73)**
0.88 (0.55-1.40)	1.00 (0.77-1.40)	1.1 (0.87-1.60)	1.30 (0.89-1.80)	0.83 (0.59-1.20)	1.40 (0.89- 2.20)	1.20 (0.91-1.60)	1.40 (0.84-2.20)	**1.80 (1.40-2.50)**	Platinum-based chemotherapy

Comparisons should be read clockwise. Hazard ratios were compared between column-defining and row-defining treatments. Numbers in bold font on a darker cell background are statistically significant.

eFigure 10. Network Meta-analysis of Immune Checkpoint Inhibitors in Terms of Overall Survival

Atezolizumab	1.00 (0.80-1.30)	1.20 (0.88-1.60)	**0.73 (0.60-0.89)**	0.98 (0.65-1.50)	1.00 (0.72-1.50)	**1.70 (1.20-2.50)**	0.94 (0.69-1.30)
0.98 (0.76-1.30)	Nivolumab	1.10 (0.92-1.50)	**0.71 (0.61-0.83)**	0.96 (0.67-1.40)	1.00 (0.74-1.30)	**1.70 (1.20-2.30)**	0.91 (0.73-1.10)
0.86 (0.63-1.10)	0.88 (0.69-1.10)	Pembrolizumab	**0.63 (0.50-0.76)**	0.84 (0.60-1.10)	0.88 (0.67-1.10)	**1.40 (1.10-1.90)**	**0.80 (0.66-0.95)**
1.40 (1.10-1.70)	**1.40 (1.20-1.60)**	**1.60 (1.30-2.00)**	Docetaxel	1.30 (0.94-1.90)	**1.40 (1.00-1.90)**	**2.30 (1.70-3.20)**	**1.30 (1.00-1.60)**
1.00 (0.68-1.50)	1.00 (0.73-1.50)	1.20 (0.87-1.70)	0.75 (0.52-1.10)	Atezolizumab + platinum-based chemotherapy	1.00 (0.75-1.50)	**1.70 (1.20-2.40)**	0.96 (0.73-1.30)
0.98 (0.68-1.40)	1.00 (0.75-1.30)	1.10 (0.90-1.50)	**0.71 (0.53-0.96)**	0.96 (0.69-1.30)	Ipilimumab + platinum-based chemotherapy	**1.70 (1.30-2.20)**	0.92 (0.76-1.10)
0.59 (0.41- 0.85)	**0.61 (0.44-0.82)**	**0.69 (0.53-0.91)**	**0.43 (0.31-0.58)**	**0.58 (0.41-0.81)**	**0.60 (0.46-0.79)**	Pembrolizumab + platinum-based chemotherapy	**0.55 (0.45-0.68)**
1.10 (0.79-1.40)	1.10 (0.87-1.40)	**1.20 (1.10-1.50)**	**0.78 (0.62-0.98)**	1.00 (0.79-1.40)	1.10 (0.91-1.30)	**1.80 (1.50-2.20)**	Platinum-based chemotherapy

Comparisons should be read clockwise. Hazard ratios were compared between column-defining and row-defining treatments. Numbers in bold font on a darker cell background are statistically significant.

eFigure 11. Network Meta-analysis of Immune Checkpoint Inhibitors as a First-line Therapy in Terms of Progression-Free Survival

Nivolumab	1.40 (0.79-2.50)	1.30 (0.81-2.10)	1.50 (0.74-3.00)	1.30 (0.77-2.20)	1.40 (0.71-2.90)	**2.00 (1.10-3.30)**	1.10 (0.72-1.60)
0.74 (0.40-1.30)	Pembrolizumab	0.96 (0.50-1.70)	1.10 (0.52-2.20)	0.96 (0.54-1.60)	1.10 (0.50-2.10)	1.50 (0.80-2.40)	0.79 (0.50-1.20)
0.76 (0.48-1.20)	1.00 (0.58-2.00)	Nivolumab + ipilimumab	1.20 (0.55-2.40)	1.00 (0.56-1.80)	1.10 (0.52-2.30)	1.50 (0.84-2.70)	0.82 (0.52-1.30)
0.66 (0.33-1.30)	0.90 (0.46-1.90)	0.86 (0.42-1.80)	Atezolizumab + platinum-based chemotherapy	0.86 (0.44-1.70)	0.96 (0.42-2.20)	1.30 (0.66-2.60)	0.71 (0.40-1.30)
0.76 (0.45-1.30)	1.00 (0.62-1.90)	1.00 (0.56-1.80)	1.20 (0.58-2.30)	Ipilimumab + platinum-based chemotherapy	1.10 (0.55-2.20)	1.50 (0.90-2.50)	0.82 (0.57-1.20)
0.69 (0.34-1.40)	0.94 (0.47-2.00)	0.90 (0.43-1.90)	1.00 (0.46-2.40)	0.90 (0.46-1.80)	Nivolumab + platinum-based chemotherapy	1.40 (0.68-2.70)	0.74 (0.41-1.40)
0.51 (0.30-0.87)	0.69 (0.41-1.30)	0.66 (0.37-1.20)	0.76 (0.39-1.50)	0.66 (0.40-1.10)	0.73 (0.37-1.50)	Pembrolizumab + platinum-based chemotherapy	**0.54 (0.38-0.78)**
0.93 (0.64-1.40)	1.30 (0.87-2.00)	1.20 (0.77-1.90)	1.40 (0.79-2.50)	1.20 (0.86-1.80)	1.30 (0.74-2.40)	**1.80 (1.30-2.60)**	Platinum-based chemotherapy

Comparisons should be read clockwise. Hazard ratios were compared between column-defining and row-defining treatments. Numbers in bold font on a darker cell background are statistically significant.

eFigure 12 Network Meta-analysis of Immune Checkpoint Inhibitors as a First-line Therapy in Terms of Overall Survival

Nivolumab	1.30 (0.84-2.30)	1.10 (0.59-1.90)	1.10 (0.68-1.80)	**1.80 (1.10-3.00)**	1.00 (0.67-1.50)
0.74 (0.43-1.20)	Pembrolizumab	0.79 (0.46-1.20)	0.83 (0.53-1.20)	1.40 (0.88-2.00)	**0.76 (0.54-0.98)**
0.94 (0.53-1.70)	1.30 (0.81-2.20)	Atezolizumab + platinum-based chemotherapy	1.00 (0.66-1.70)	**1.70 (1.10-2.80)**	0.96 (0.65-1.40)
0.90 (0.56-1.50)	1.20 (0.85-1.90)	0.95 (0.60-1.50)	Ipilimumab + platinum-based chemotherapy	**1.70 (1.20-2.40)**	0.92 (0.72-1.20)
0.54 (0.33-0.89)	0.73 (0.51-1.10)	**0.57 (0.36-0.92)**	**0.60 (0.42-0.87)**	Pembrolizumab + platinum-based chemotherapy	**0.55 (0.42-0.72)**
0.98 (0.65-1.50)	**1.30 (1.00-1.90)**	1.00 (0.70-1.50)	1.10 (0.84-1.40)	**1.80 (1.40-2.40)**	Platinum-based chemotherapy

Comparisons should be read clockwise. Hazard ratios were compared between column-defining and row-defining treatments. Numbers in bold font on a darker cell background are statistically significant.

eFigure 13. Network Meta-analysis of Immune Checkpoint Inhibitors in Terms of Progression-Free Survival in Previously Treated Patients

Atezolizumab	1.20 (0.84-1.90)	1.10 (0.66-1.90)	0.95 (0.70-1.30)
0.82 (0.54-1.20)	Nivolumab	0.91 (0.55-1.50)	**0.78 (0.59-0.98)**
0.90 (0.53-1.50)	1.10 (0.68-1.80)	Pembrolizumab	0.85 (0.56-1.30)
1.10 (0.77-1.40)	**1.30 (1.00-1.70)**	1.20 (0.77-1.80)	Docetaxel

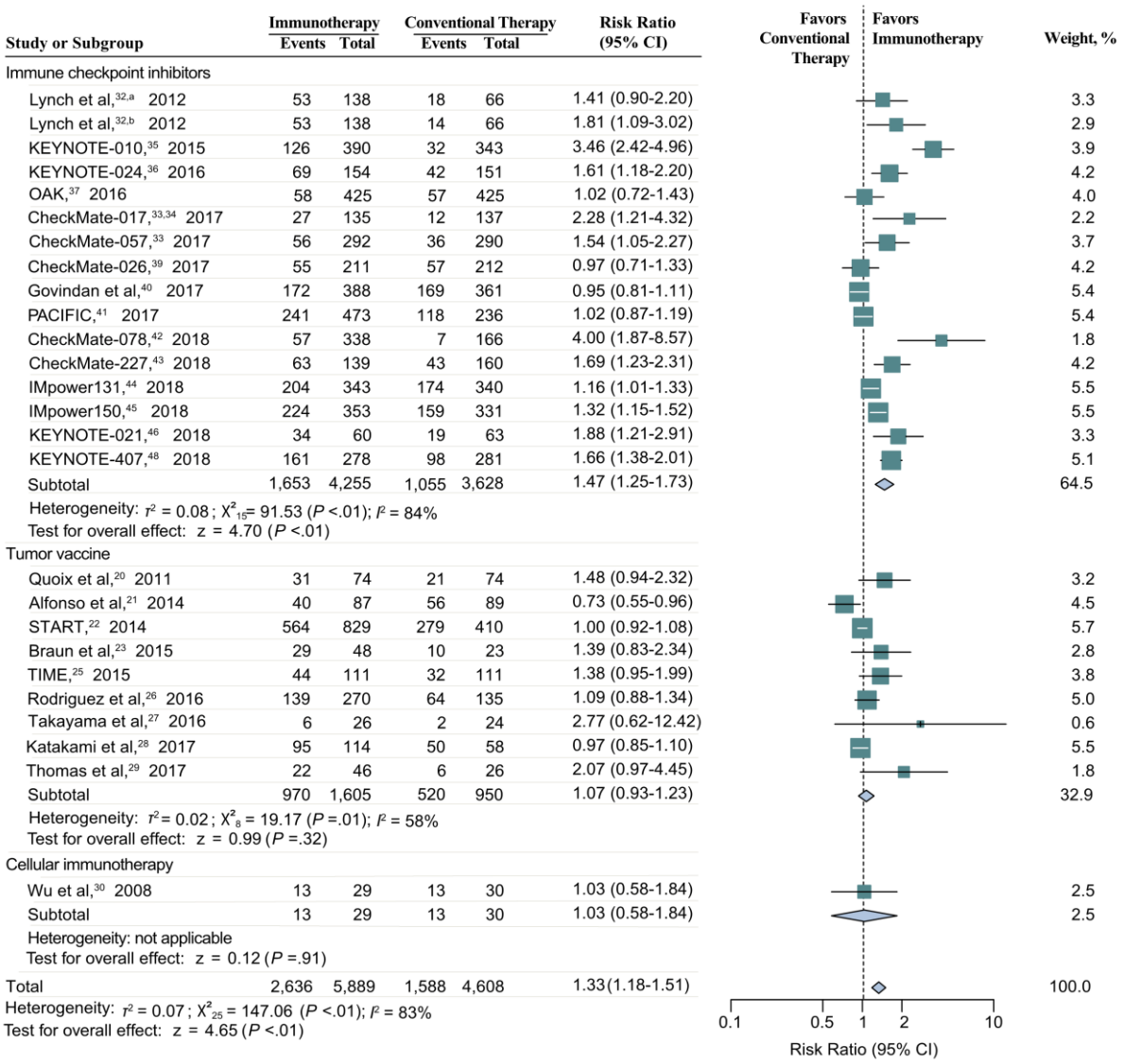
Comparisons should be read clockwise. Hazard ratios were compared between column-defining and row-defining treatments. Numbers in bold font on a darker cell background are statistically significant.

eFigure 14. Network Meta-analysis of Immune Checkpoint Inhibitors in Terms of Overall Survival in Previously Treated Patients

Atezolizumab	1.10 (0.75-1.50)	1.10 (0.69-1.70)	**0.73 (0.56-0.96)**
0.94 (0.66-1.30)	Nivolumab	1.00 (0.67-1.50)	**0.69 (0.55-0.85)**
0.92 (0.59-1.40)	0.97 (0.65, 1.50)	Pembrolizumab	**0.67 (0.47-0.96)**
1.40 (1.00-1.80)	**1.50 (1.20, 1.80)**	**1.50 (1.00-2.10)**	Docetaxel

Comparisons should be read clockwise. Hazard ratios were compared between column-defining and row-defining treatments. Numbers in bold font on a darker cell background are statistically significant.

eFigure 15. Pooled Analysis of the Objective Response Rate With Immunotherapy vs Conventional Therapy

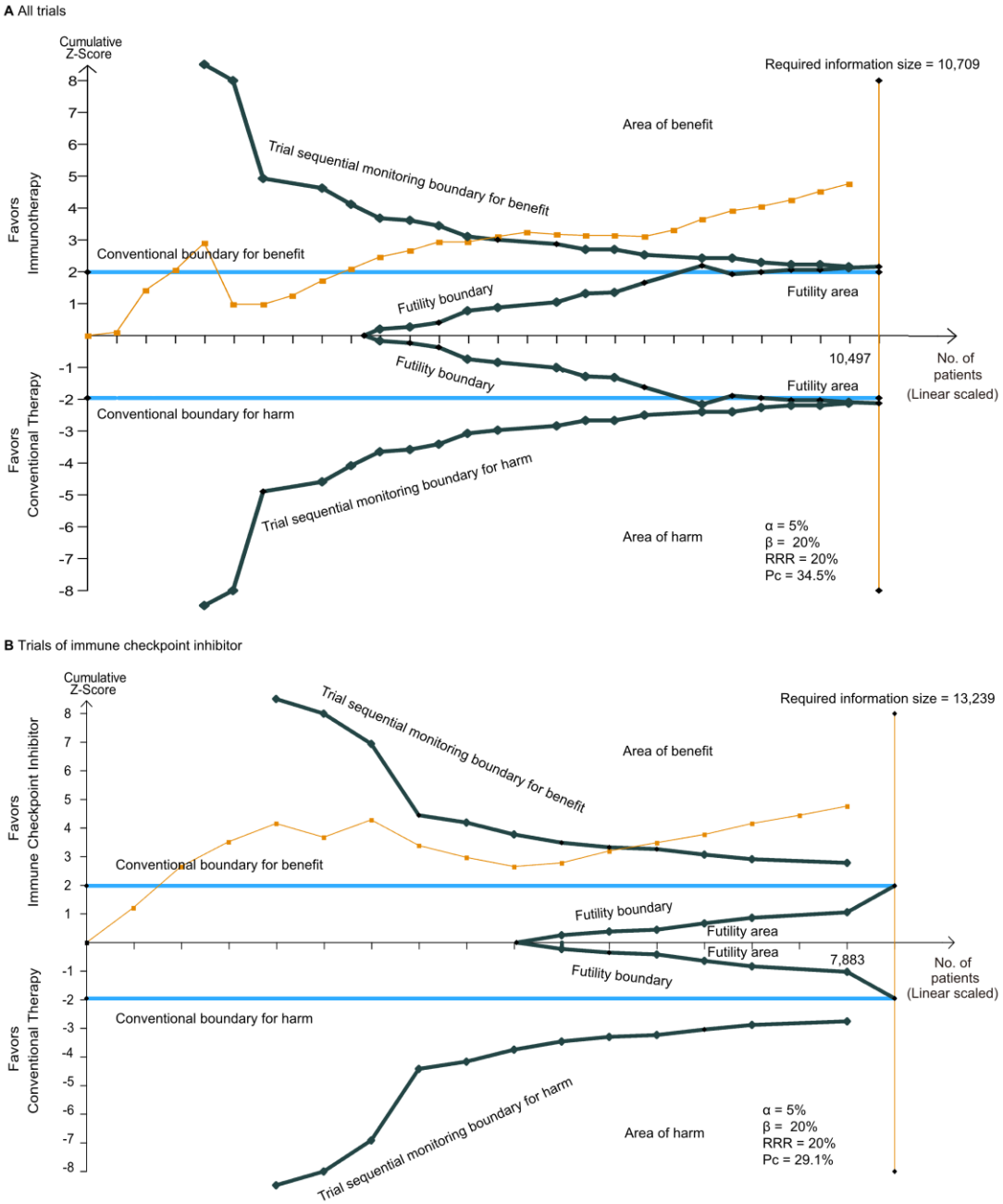


Size of boxes is proportional to the weight of each trial, and the diamonds indicate the point estimate and confidence interval of the combined result.

[a] Response was assessed by using immune-related response.

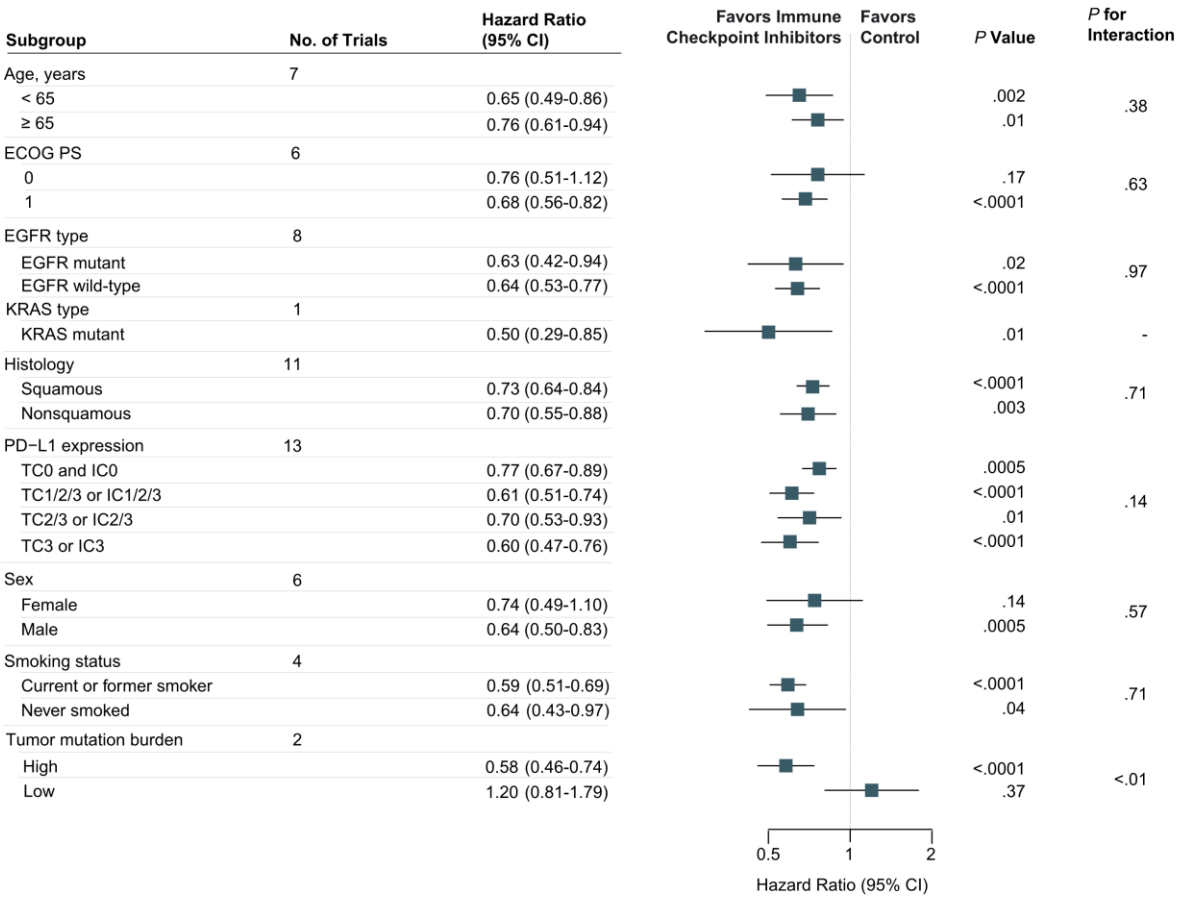
[b] Response was assessed by using modified WHO criteria.

eFigure 16. Trial Sequential Analyses of Trials Comparing Immunotherapy With Conventional Therapy



Panel A shows the results of the trial sequential analysis (TSA) for all trials, and panel B shows the results of the TSA for the trials of immune checkpoint inhibitor. α, type I error rate; β, type II error rate; RRR, relative risk reduction; Pc, event proportion of the control group.

eFigure 17. Subgroup Analyses of Progression-Free Survival in Patients Receiving Immune Checkpoint Inhibitor Therapy



ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epithelial growth factor receptor; KRAS, kirsten rat sarcoma viral oncogene homolog; PD-L1, programmed death-ligand 1; TC, tumor cells; IC, tumor-infiltrating immune cells. The *P* value for interaction reflects the difference between subgroups.

PD-L1 scoring criteria:

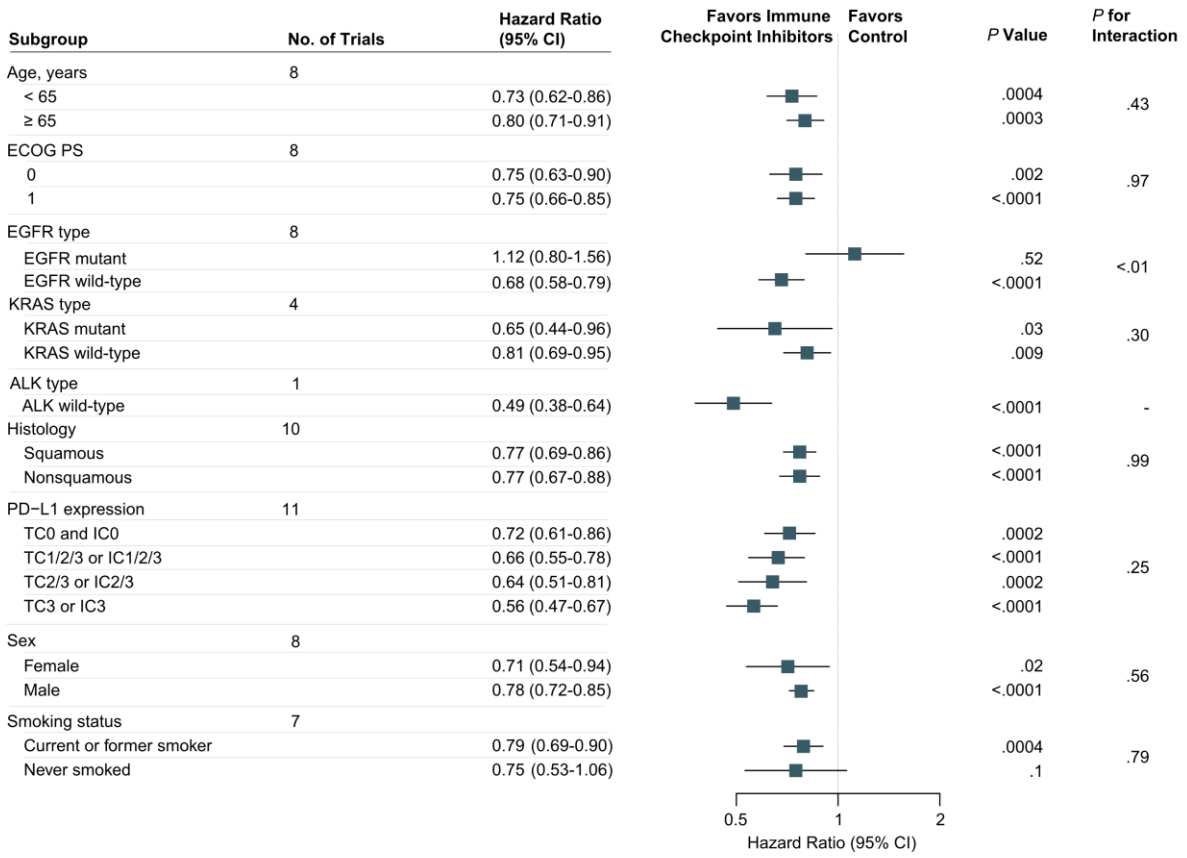
TC3 or IC3: TC3 ≥50% or IC3 ≥10%.

TC2 or IC2: TC2 ≥5% and <50% or IC2 ≥5% and <10%.

TC1 or IC1: TC1 ≥1% and <5% or IC1 ≥1% and <5%.

TC0 or IC0: TC0 <1% or IC0 <1%.

eFigure 18. Subgroup Analyses of Overall Survival in Patients Receiving Immune Checkpoint Inhibitor Therapy



ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epithelial growth factor receptor; KRAS, kirsten rat sarcoma viral oncogene homolog; ALK, anaplastic lymphoma kinase; PD-L1, programmed death-ligand 1; TC, tumor cells; IC, tumor-infiltrating immune cells. The *P* value for interaction reflects the difference between subgroups.

PD-L1 scoring criteria:

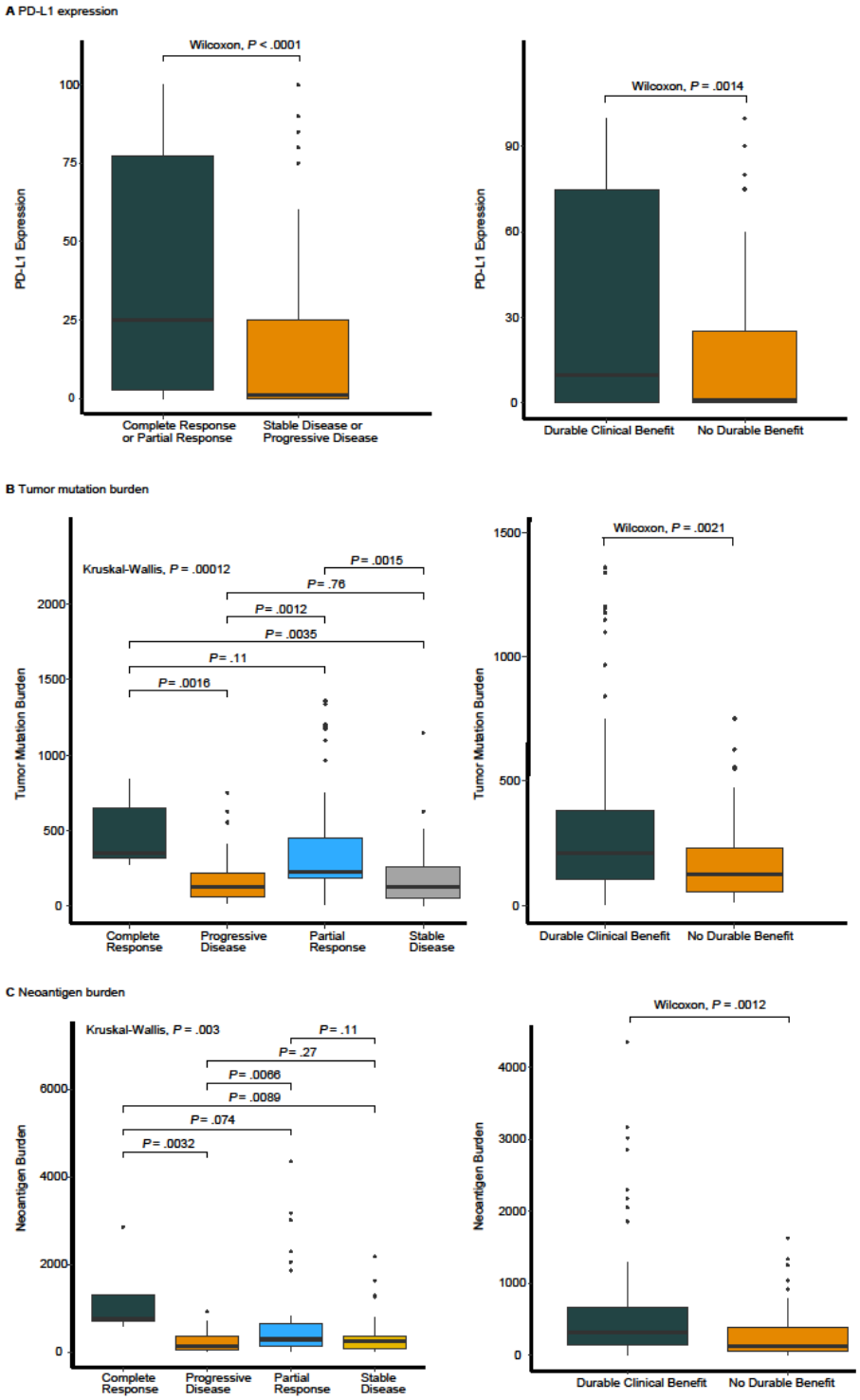
TC3 or IC3: TC3 ≥50% or IC3 ≥10%.

TC2 or IC2: TC2 ≥5% and <50% or IC2 ≥5% and <10%.

TC1 or IC1: TC1 ≥1% and <5% or IC1 ≥1% and <5%.

TC0 or IC0: TC0 <1% or IC0 <1%.

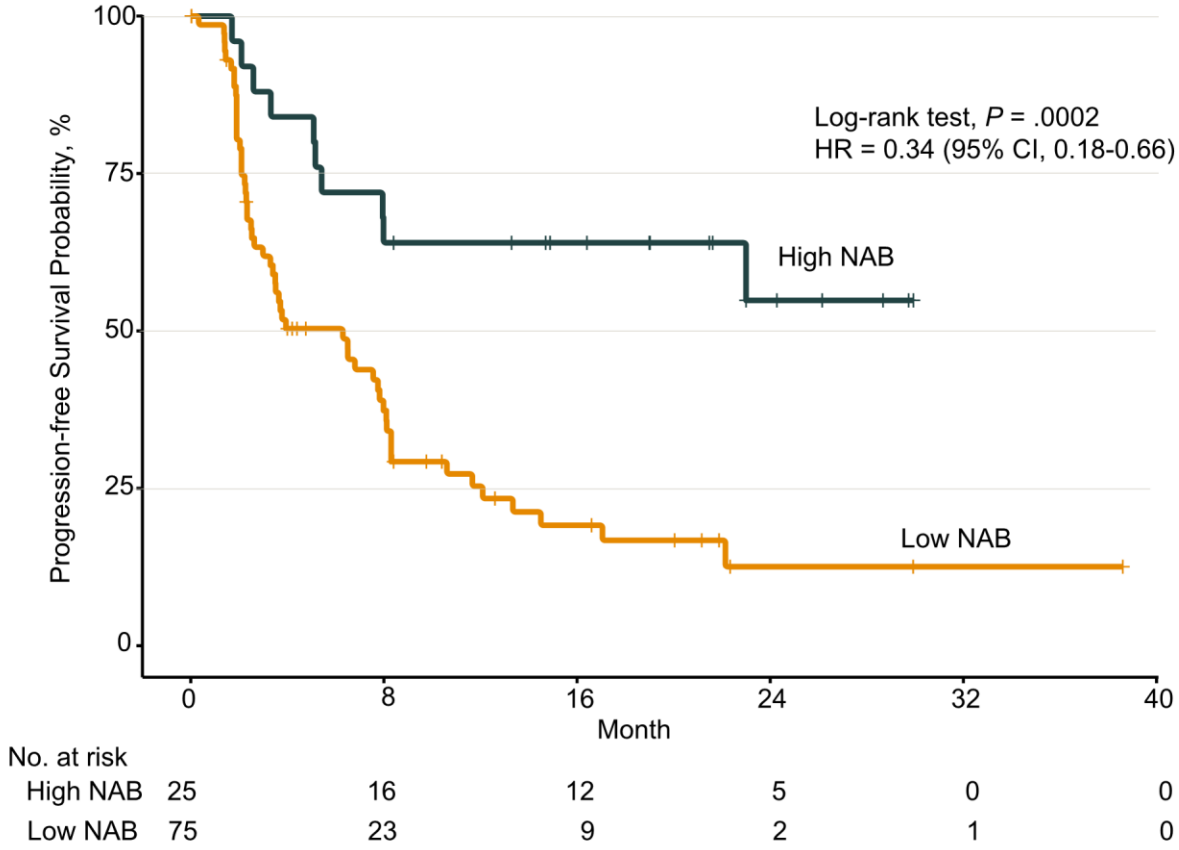
eFigure 19. Response and Clinical Benefit to Checkpoint Inhibitor Relative to Molecular Features in Cohort 1



The PD-L1 expression, tumor mutation burden (TMB) and neoantigen burden (NAB) in patients with a complete response, a partial response, stable disease or progressive disease are shown in the left graphs in the Panels A, B and C, respectively. The PD-L1 expression,

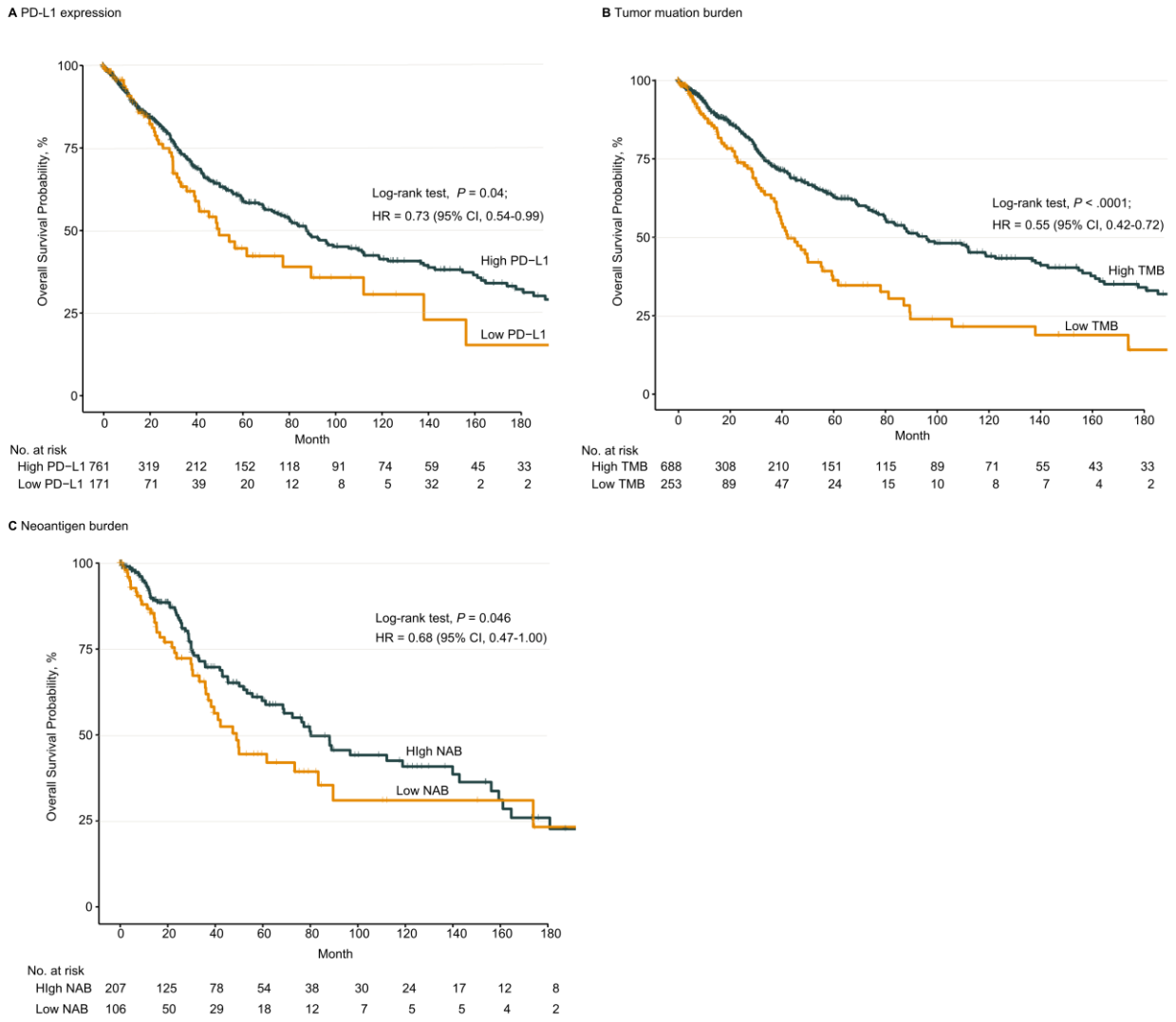
TMB and NAB in patients with durable clinical benefit versus those with no durable clinical benefit are shown in the right graphs in the Panels A, B and C, respectively.

eFigure 20. Progression-Free Survival Analysis Stratified by Neoantigen Burden in Cohort 1



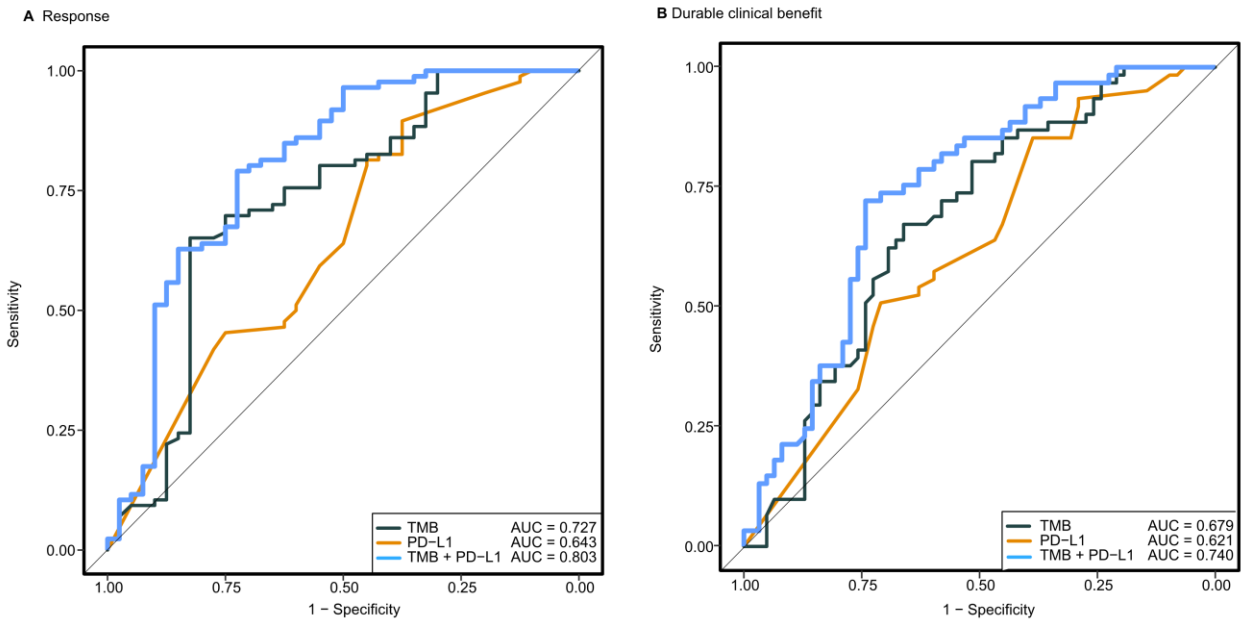
HR, hazard ratio; NAB, neoantigen burden.

eFigure 21. Overall Survival Analysis Stratified by Molecular Features in the TCGA Cohort



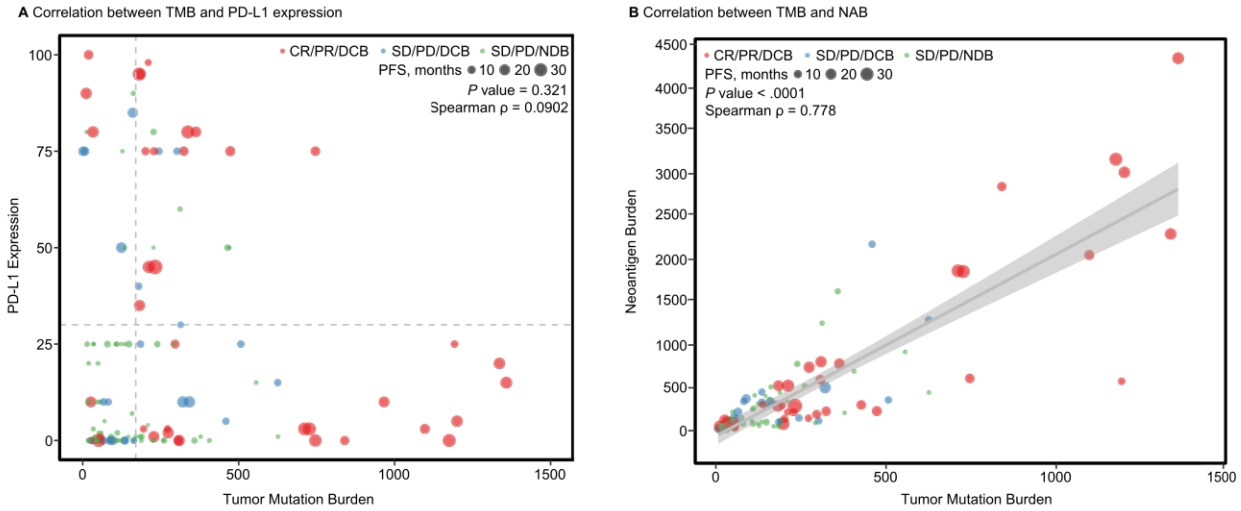
Overall survival curves of high PD-L1 expression versus low PD-L1 expression, high tumor mutation burden versus low tumor mutation burden and high neoantigen burden versus low neoantigen burden are shown in Panels A, B and C, respectively. TCGA, Cancer Genome Atlas; HR, hazard ratio; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden; NAB, neoantigen burden.

eFigure 22. Receiver Operating Characteristic Curves Correlating Molecular Features With Clinical Outcomes in Cohort 1



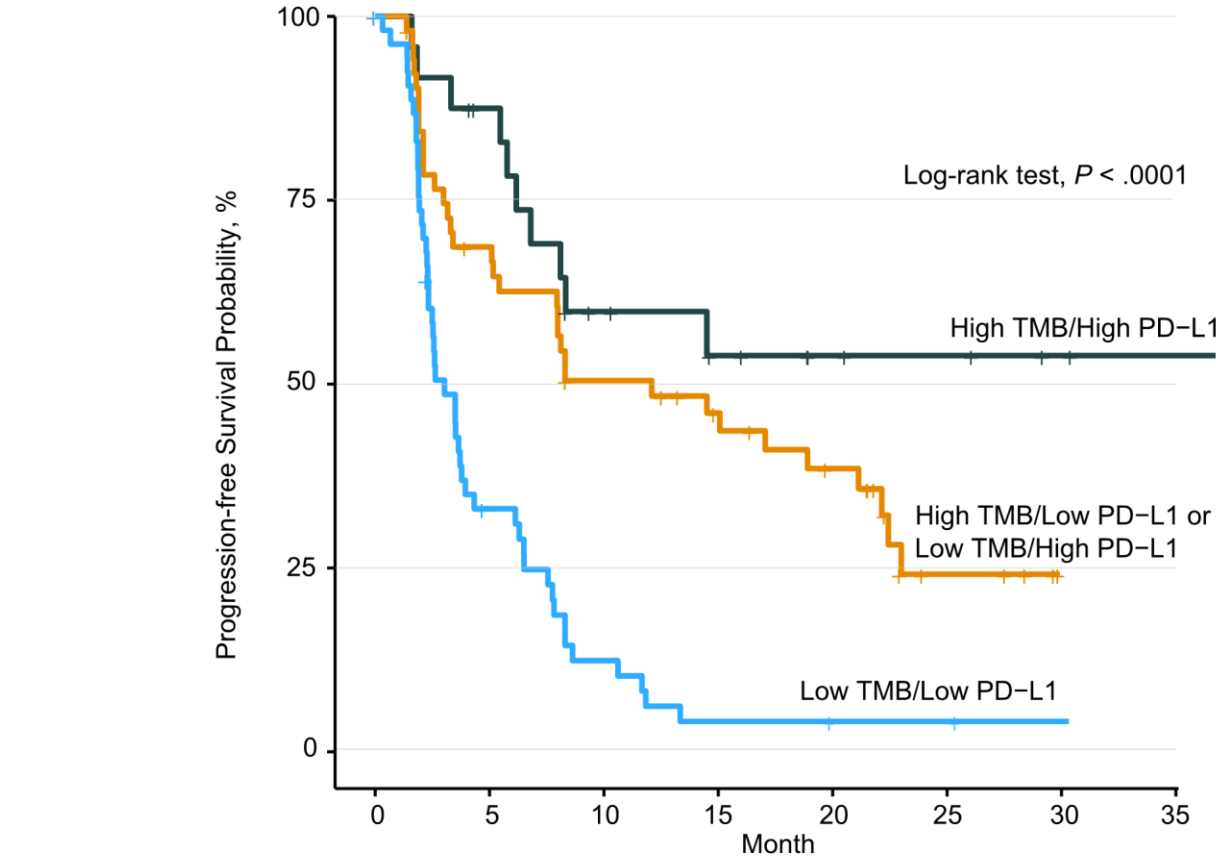
Panel A shows the receiver operating characteristic (ROC) curves for the correlation of tumor mutation burden/PD-L1 expression with complete response/partial response; Panel B shows the ROC curves for the correlation of tumor mutation burden/PD-L1 expression with durable clinical benefit. AUC, the area under the curve; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden.

eFigure 23. Scatterplots of Molecular Features in Cohort 1



Panel A shows the correlation between the tumor mutation burden and expression of PD-L1; Panel B shows the correlation between tumor mutation burden and neoantigen burden. PD-L1, programmed death-ligand 1; TMB, tumor mutation burden; NAB, neoantigen burden; PFS, progression-free survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCB, durable clinical benefit; NDB, no durable benefit.

eFigure 24. Progression-Free Survival Analysis Stratified by Programmed Cell Death Ligand 1 Expression and Tumor Mutation Burden in Cohort 1

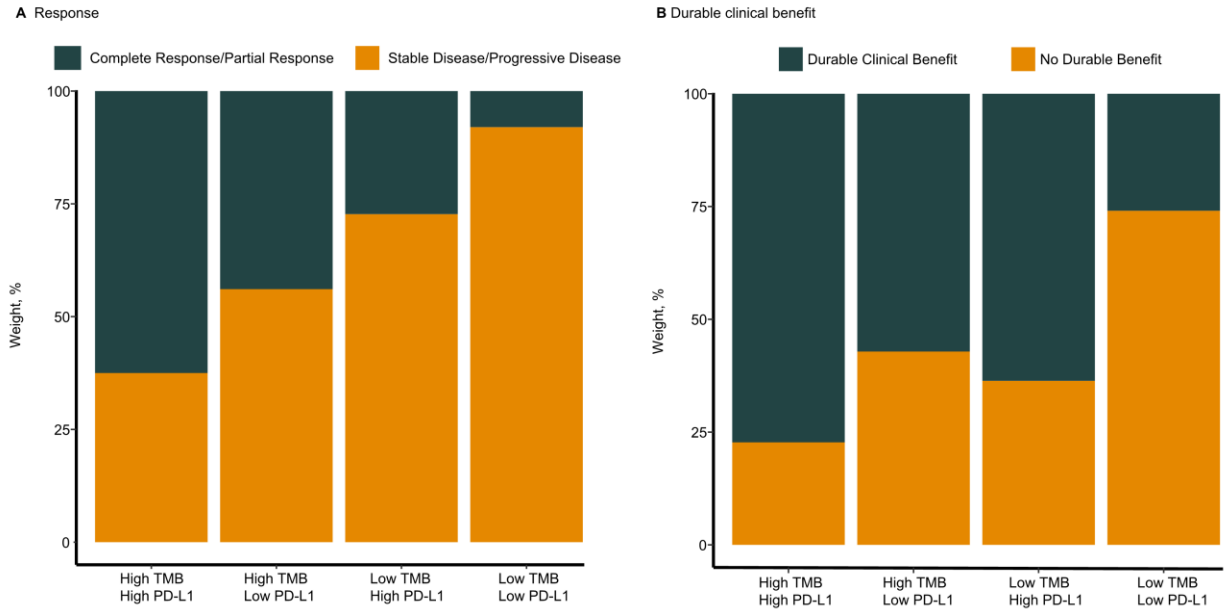


No. at risk

High TMB/High PD−L1	24	19	11	8	5	4	3	1
High TMB/Low PD−L1 or Low TMB/High PD−L1	54	34	24	19	14	4	0	0
Low TMB/Low PD−L1	54	16	6	2	2	1	1	0

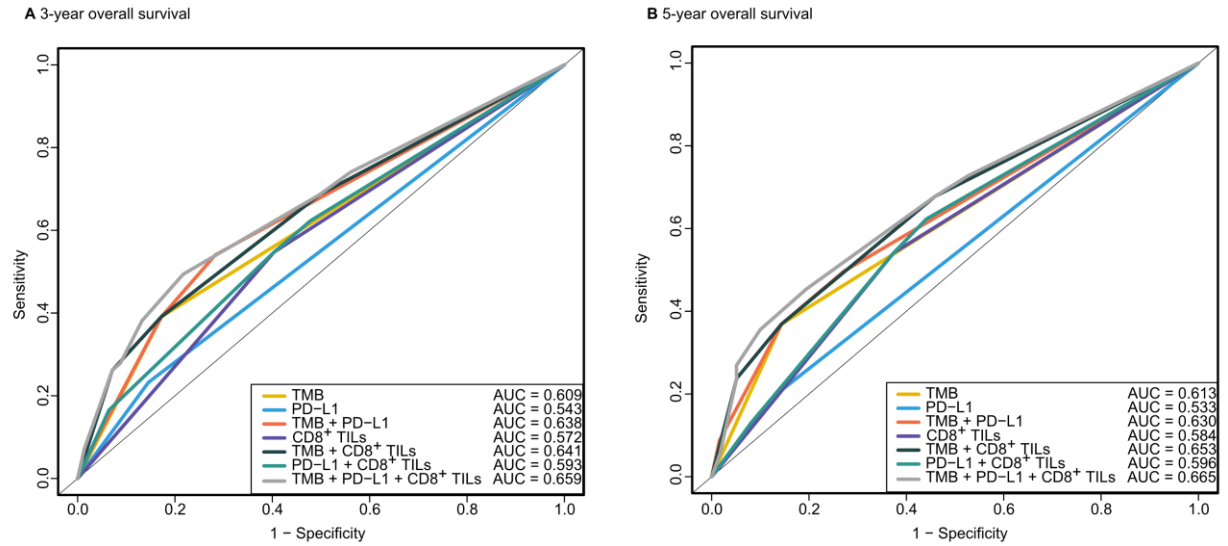
PD-L1, programmed death-ligand 1; TMB, tumor mutation burden.

eFigure 25. Response and Clinical Benefit to Checkpoint Inhibitor Stratified by Programmed Cell Death Ligand 1 and Tumor Mutation Burden



Panel A shows the complete response/partial response and stable disease/progressive disease rates in patients with different combinations of the tumor mutation burden and expression of PD-L1; Panel B shows the durable clinical benefit/no durable benefit rates in patients with different combinations of the tumor mutation burden and expression of PD-L1; TMB, tumor mutation burden; PD-L1, programmed death-ligand 1.

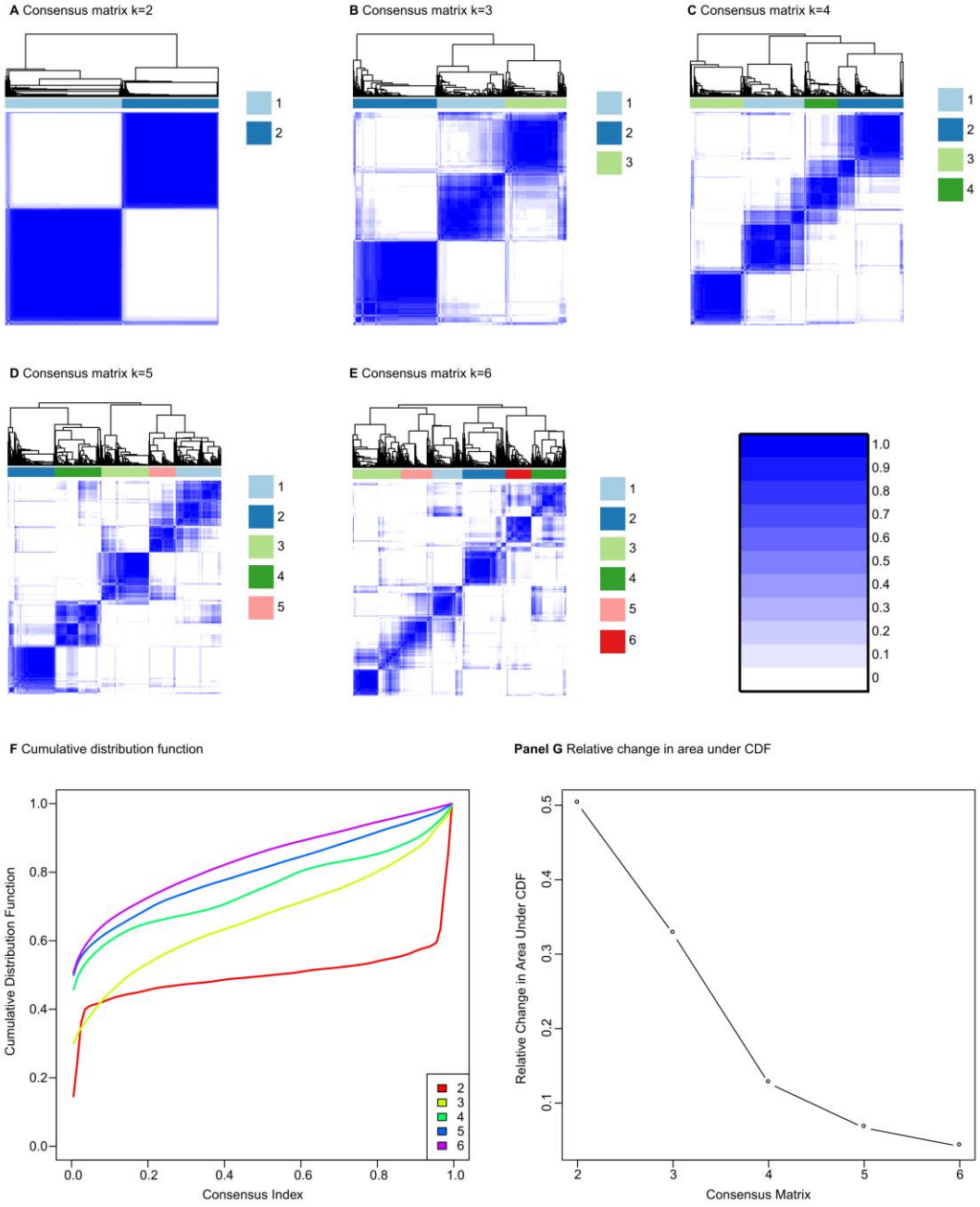
eFigure 26. Receiver Operating Characteristic Curves Correlating Molecular Features With Survival in the Cancer Genome Atlas Cohort



A, Receiver operating characteristic curves correlating multiple molecular features with 3-year overall survival. B, Same as A but were plotted for 5-year overall survival. Abbreviations: PD-L1,

programmed death-ligand 1; TMB, tumor mutation burden; TILs, tumor-infiltrating lymphocytes; TCGA, The Cancer Genome Atlas.

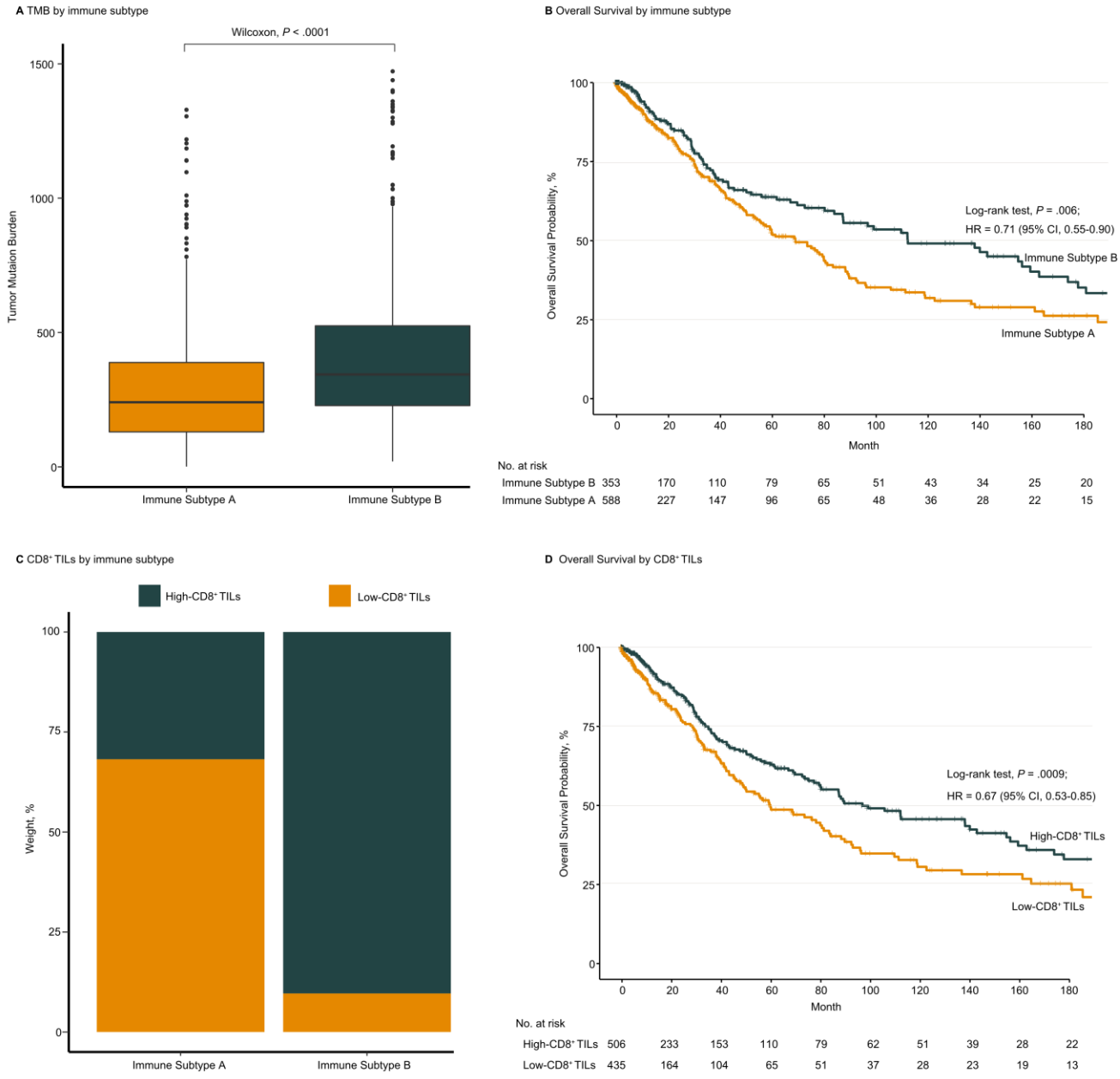
eFigure 27. Unsupervised Consensus Clustering of Immune Subtypes in the Cancer Genome Atlas Cohort



Panels A to E show the consensus matrices represented as heatmaps for the chosen cluster numbers (k = 2 to 6); Panel F shows the cumulative distribution function curve for the chosen cluster

numbers (k = 2 to 6); Panel G shows the corresponding relative change in the area under the cumulative distribution function curve when the cluster number changes from 2 to 6. CDF, cumulative distribution function curve; TCGA, The Cancer Genome Atlas.

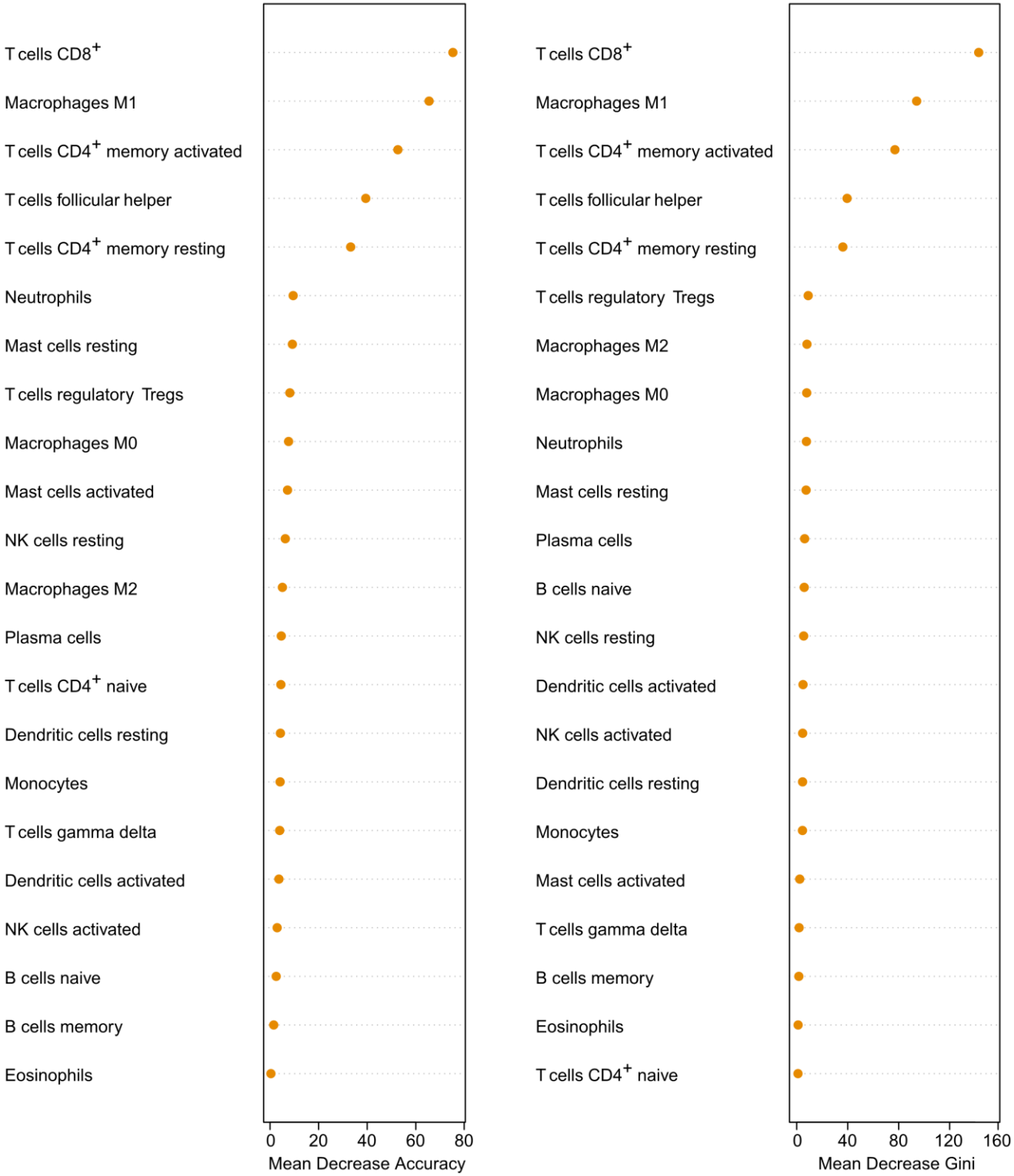
eFigure 28. Molecular Features and Survival Stratified by Immune Subtype in the Cancer Genome Atlas Cohort



Panel A shows the tumor mutation burden in the patients with the immune subtype A tumors versus those with immune subtype B tumors. Panel B shows the overall survival curve of the

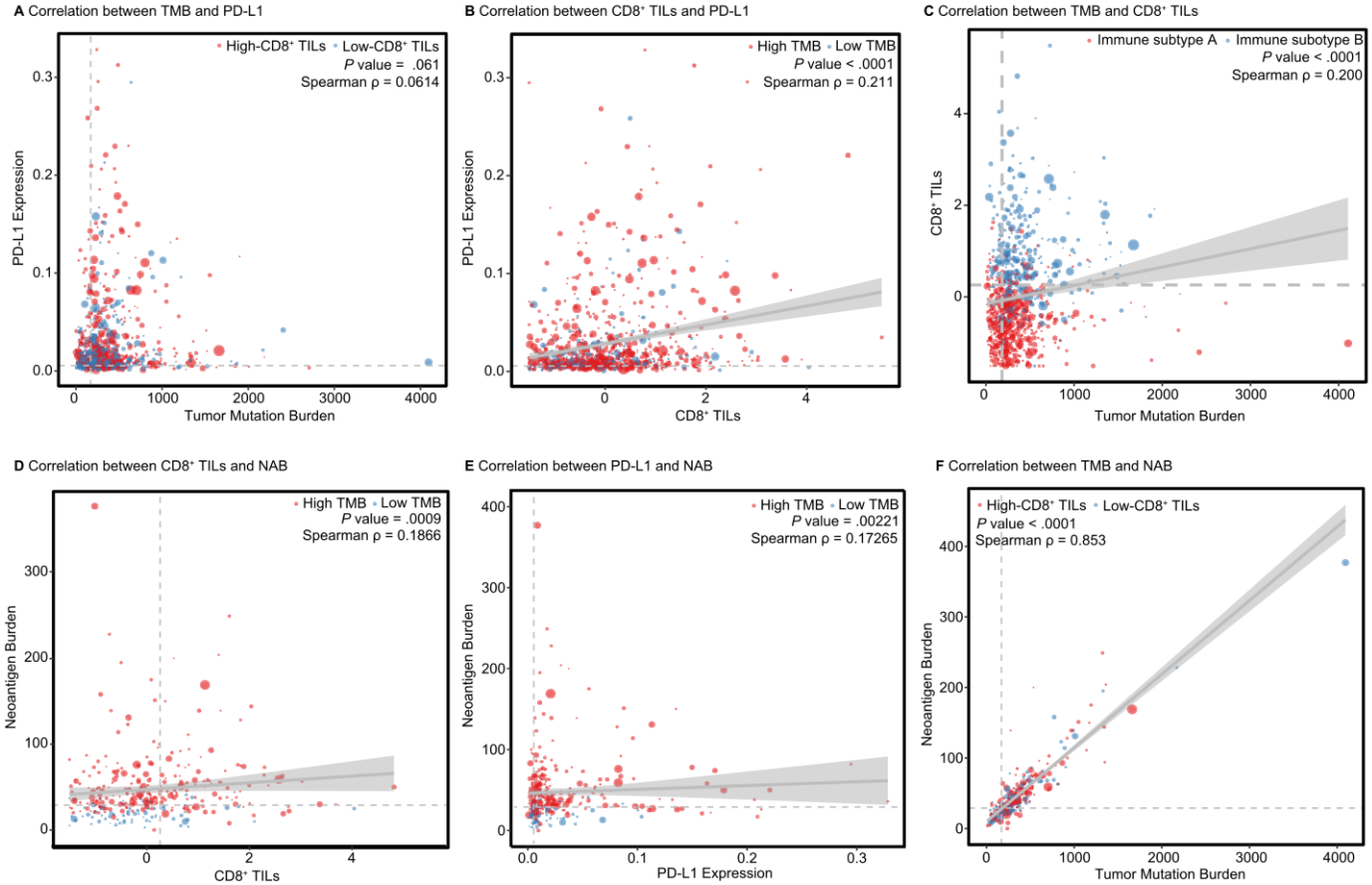
immune subtype A group versus that of the immune subtype B group. Panel C shows the proportions of high- and low- $CD8^+$ tumor-infiltrating lymphocytes (TILs) in patients with immune subtype A versus those with immune subtype B. Panel D shows the overall survival curve of the high-$CD8^+$ TILs group versus that of the low-$CD8^+$ TILs group. TMB, tumor mutation burden; HR, hazard ratio; TCGA, The Cancer Genome Atlas; TILs, tumor-infiltrating lymphocytes.

eFigure 29. Identification of the Most Important Immune Feature Using Random Forest Method



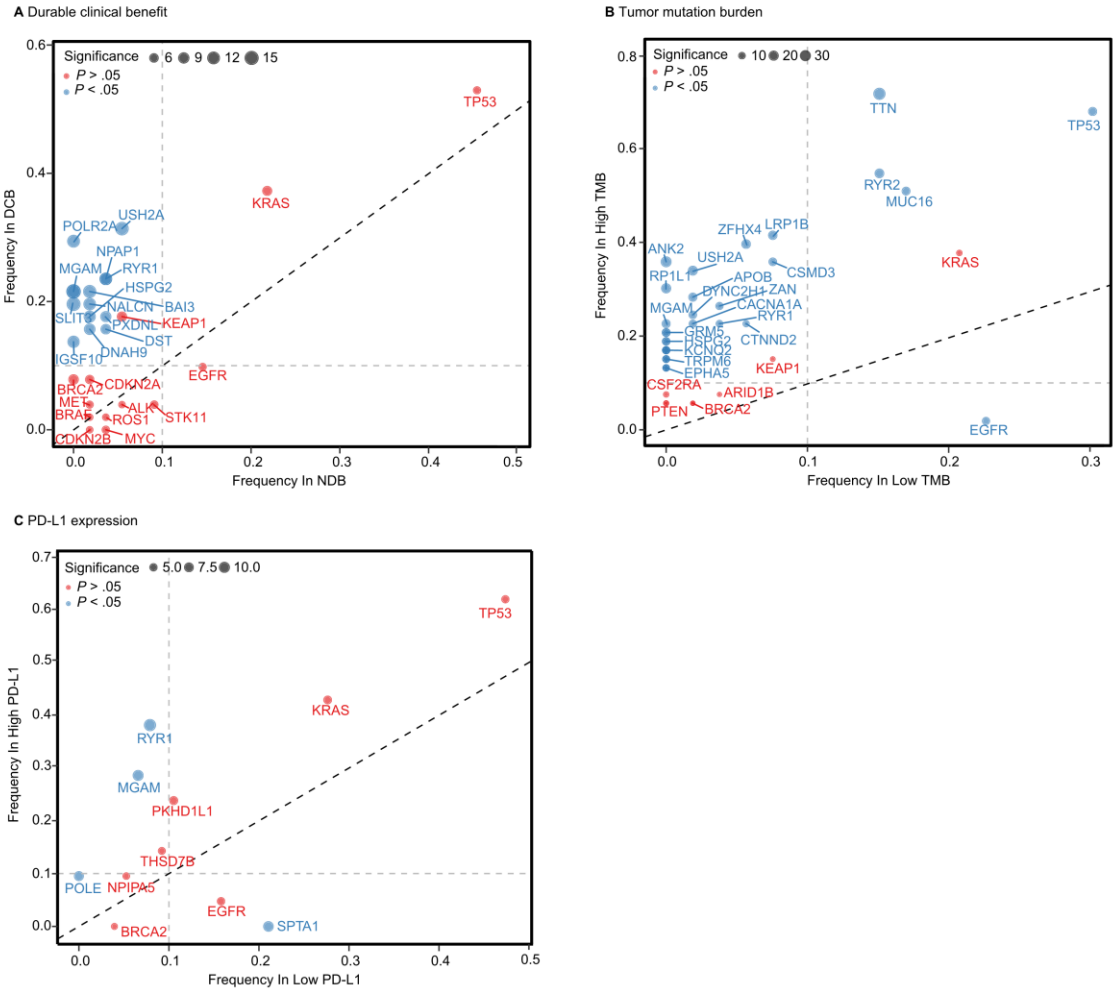
Abbreviations: NK, natural killer.

eFigure 30. Scatterplots of Molecular Features in the Cancer Genome Atlas Cohort



Panel A shows the correlation between the tumor mutation burden (TMB) and expression of PD-L1; Panel B shows the correlation between $CD8^+$ tumor-infiltrating lymphocytes (TILs) and PD-L1 expression; Panel C shows the correlation between the TMB and $CD8^+$ TILs. Panel D shows the correlation between $CD8^+$ TILs and the neoantigen burden (NAB); Panel E shows the correlation between the NAB and expression of PD-L1; and Panel F shows the correlation between the TMB and NAB. PD-L1, programmed death-ligand 1; TMB, tumor mutation burden; NAB, neoantigen burden; TILs, tumor-infiltrating lymphocytes; TCGA, The Cancer Genome Atlas

eFigure 31. Individual Gene Alterations Associated With Checkpoint Blockade Efficacy and Molecular Features



A, The frequencies of the altered genes in patients with durable clinical benefit versus those with no durable benefit. B, Same as B but comparing the high tumor mutation burden group versus the low tumor mutation burden group. C, Same as B but comparing the high PD-L1 group versus the low PD-L1 group. Abbreviations: DCB, durable clinical benefit; NDB, no durable benefit; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden.

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1. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org. (accessed April 14, 2017).
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