Appendix

Exploration of Modified Progression-free Survival as a Novel Surrogate Endpoint for Overall Survival in Immuno-oncology Trials

Wang ZX et al.

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Wang Z-X, *et al. J Immunother Cancer* 2021; 9:e002114. doi: 10.1136/jitc-2020-002114

Supplemental methods

Literature search strategy

A. PubMed

#1 randomized controlled trial [pt]

#2 controlled clinical trial [pt]

#3 randomized [tiab]

#4 placebo [tiab]

#5 clinical trials as topic [mesh: noexp]

#6 randomly [tiab]

#7 trial [ti]

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 animals [mh] NOT humans [mh]

#10 #8 NOT #9

#11 Nivolumab

#12 Opdivo

#13 BMS-936558

#14 MDX1106

#15 ONO-4538

#16 BMS-936559

#17 MDX1105

#18 Pembrolizumab

#19 Lambrolizumab

#20 Keytruda

#21 MK-3475

#22 Atezolizumab

#23 MPDL3280

#24 MPDL3280A

#25 RG7446

#26 Tecentriq

#27 Avelumab

#28 MSB0010718C

#29 Durvalumab

#30 MEDI4736

#31 cemiplimab

#32 REGN2810

#33 PD-1 inhibitor

#34 Programmed death 1 inhibitor

#35 Anti-PD-1

#36 Anti-Programmed Cell Death 1

#37 PD-L1 inhibitor

#38 Programmed death ligand 1 inhibitor

#39 Anti-PD-L1

#40 Anti-Programmed Cell Death Ligand-1

#41 Checkpoint Inhibitor

#42 Checkpoint blockade

#43 Programmed Cell Death 1 Receptor [mesh]

#44 CTLA4 protein, human

#45 anti CTLA4

#46 anti CTLA-4

#47 cytotoxic T-lymphocyte-associated antigen 4

#48 Cytotoxic T lymphocyte antigen 4

#49 CTLA-4

#50 Cytotoxic T-lymphocyte protein 4

#51 anti-CTLA4 antibodies

#52 Ipilimumab

#53 MDX-010

#54 MDX-101

#55 BMS-734016

#56 Yervoy

#57 Antigens, CD/immunology* [mesh]

#58 CTLA-4 Antigen [mesh]

#59 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or

#55 or #56 or #57 or #58

#60 #10 and #59

B. EMBASE

1 Nivolumab

2 Opdivo

3 BMS-936558

4 MDX1106

5 ONO-4538

6 BMS-936559

7 MDX 1105

8 Pembrolizumab

9 Lambrolizumab

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32 Checkpoint blockade

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40 Cytotoxic T-lymphocyte protein 4

41 anti-CTLA4 antibodies

42 Antigens, CD4

43 MDX-010

44 MDX-101

45 BMS-734016

46 Yervoy

47 CTLA-4 Antigen

48 Ipilimumab

49 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48

50 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'singleblind procedure':de OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti

51 49 and 50

C. Cochrane Central Register of Controlled Trials

#1 Nivolumab

#2 Opdivo

#3 BMS-936558

#4 MDX1106

#5 ONO-4538

#6 BMS-936559

#7 MDX 1105

#8 Pembrolizumab

#9 Lambrolizumab

#10 Keytruda

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#23 PD-1 inhibitor

#24 Programmed death 1 inhibitor

#25 Anti-PD-1

#26 Anti-Programmed Cell Death 1

#27 PD-L1 inhibitor

#28 Programmed death ligand 1 inhibitor

#29 Anti-PD-L1

#30 Anti-Programmed Cell Death Ligand-1

#31 Checkpoint Inhibitor

#32 Checkpoint blockade

#33 MeSH descriptor: [Programmed Cell Death 1 Receptor] explode all trees

#34 CTLA4 protein, human

#35 anti CTLA4

#36 anti CTLA-4

#37 cytotoxic T-lymphocyte-associated antigen 4

#38 Cytotoxic T lymphocyte antigen 4

#39 CTLA-4

#40 Cytotoxic T-lymphocyte protein 4

#41 anti-CTLA4 antibodies

#42 Antigens, CD

#43 MDX-010

#44 MDX-101

#45 BMS-734016

#46 Yervoy

#47 CTLA-4 Antigen

#48 Ipilimumab.mp

#49 MeSH descriptor: [B7-H1 Antigen] explode all trees

#50 MeSH descriptor: [CTLA-4 Antigens] explode all trees

#51 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50

Description of the algorithm for matching the reconstructed, de-identified PFS IPD to OS IPD

The algorithm is based on two rules:

Rule 1. The PFS duration should be no greater than OS duration.

Rule 2. The patients with events in the OS IPD dataset should be a subgroup of the patients with events in the PFS IPD dataset.

The algorithm needs to be applied separately to the subgroup in the experimental treatment arm and the subgroup in the control arm for each trial. The algorithm comprises the following steps:

Step 1. According to Rule 2, for the patients with events in the OS IPD dataset, the PFS IPD that are matched to the OS IPD are generated by randomly sampling the PFS IPD from patients with events in the PFS IPD dataset, on the premises of Rule 1.

Step 2. For the patients without events in the OS IPD dataset, the PFS IPD that are matched to the OS IPD are generated by randomly sampling the PFS IPD from the patients in the PFS IPD dataset that are left out in Step 1, on the premises of Rule 1.

Supplementary Figures

Fig. S1 Pipeline of generating reconstructed individual patient-level data (IPD) where the progression-free survival (PFS) data were matched to the overall survival (OS) data by patient. First, on the basis of survival curves and number at risk data from a given trial, we reconstructed IPD for PFS and OS, which were de-identified. Next, by applying a simulation-based algorithm to the reconstructed, de-identified PFS and OS IPD, we generated qualified datasets of matched PFS-OS IPD that fulfilled the following requirements: (1) For a given patient, the PFS duration should be no greater than the OS duration; and (2) the patients with events in the OS IPD dataset should be a subgroup of the patients with events in the PFS IPD dataset. PD denotes disease progression.

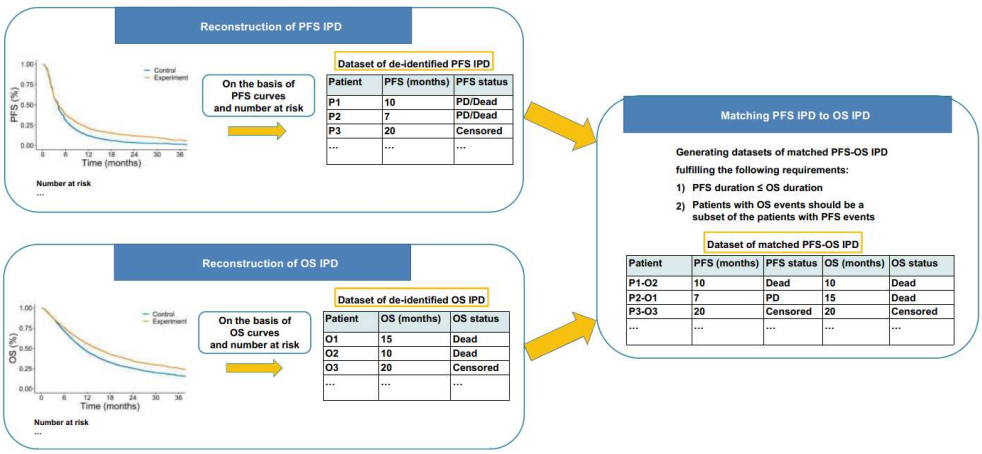


Fig. S2. The agreement of progression-free survival (PFS; A) and overall survival (OS; B) hazard ratios (HRs) between the reconstructed and original individual patient-level data. The data points generally lie within ±5% of deviation.

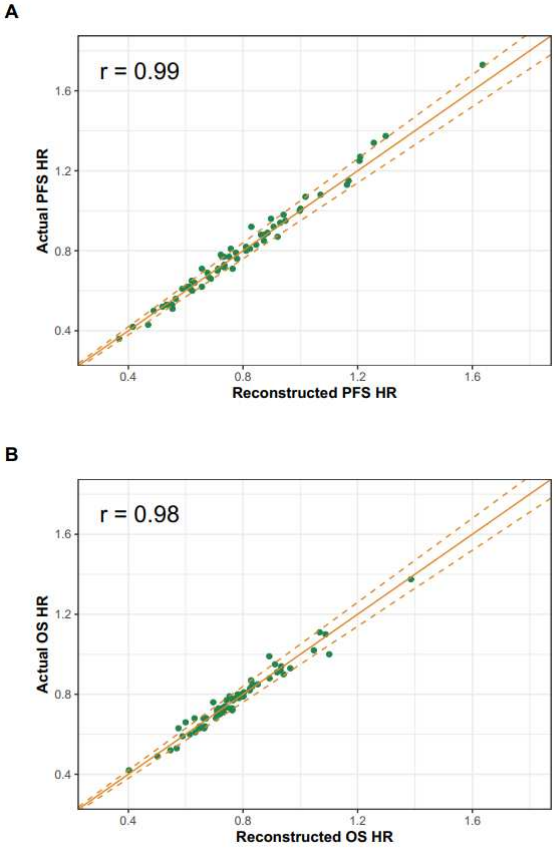


Fig. S3 The distribution of Pearson correlation coefficient between modified progression-free survival (mPFS) and overall survival (OS) (A) and Spearman's rank correlation coefficient between mPFS (or PFS) and OS (B) according to the cumulative number of simulated, matched PFS-OS datasets for each trial. To be noted, the Pearson correlation coefficient between PFS hazard ratios and OS hazard ratios was constant among the 1,000 simulations

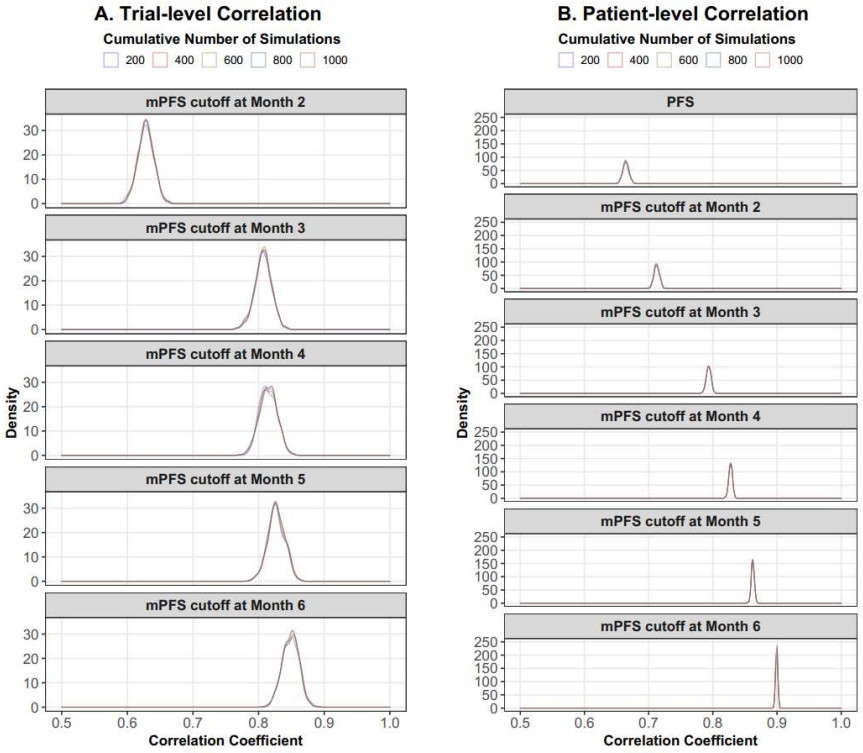


Fig. S4 Flowchart of trial selection. *One trial (JAVELIN Lung 200) aberrantly reported a fewer number of progression-free survival (PFS) events than that of overall survival (OS) events and therefore was excluded from analysis.

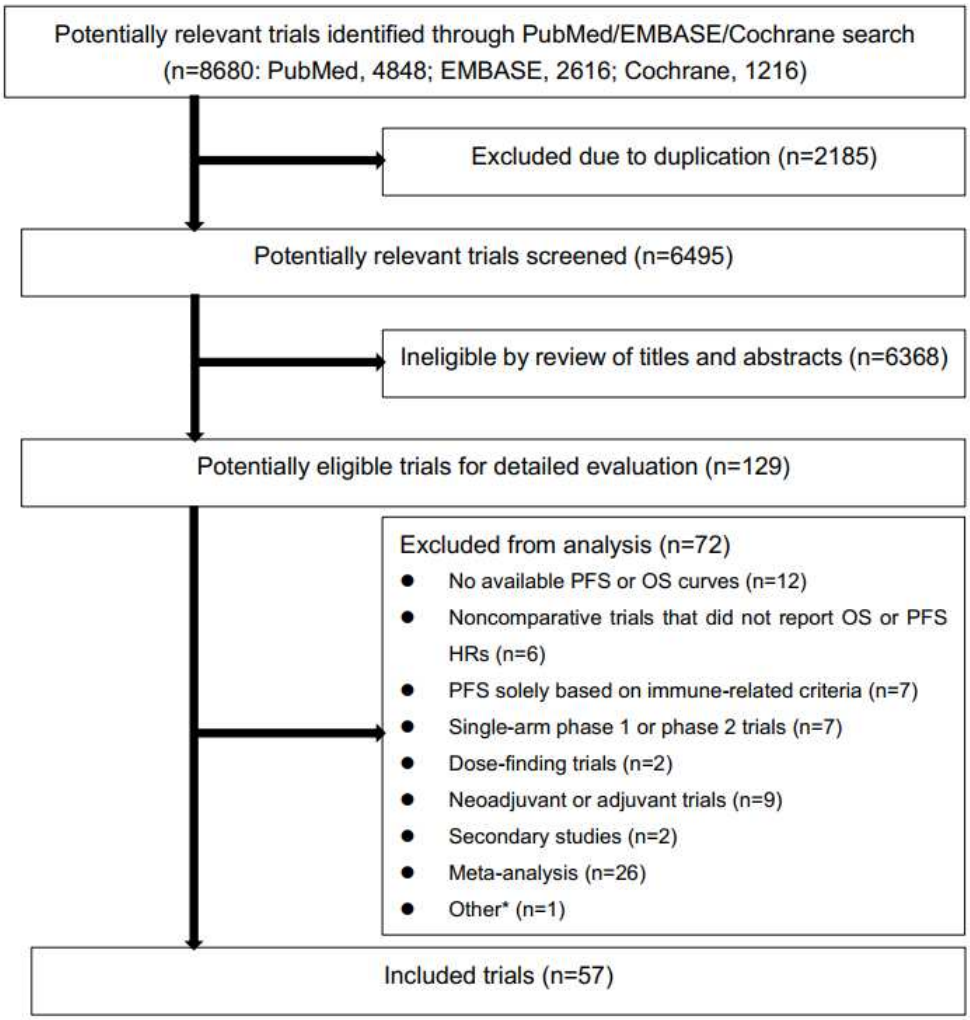


Fig. S5 Trial-level correlation between hazard ratios (HRs) for modified progression-free survival (mPFS) and overall survival (OS) by cutoff timepoint for defining mPFS among different subgroups.

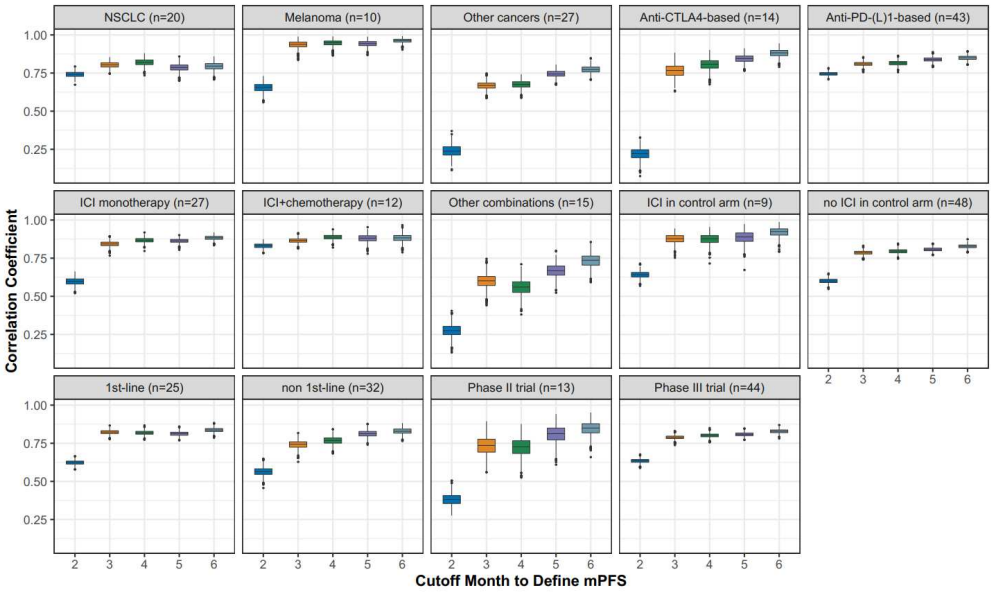


Fig. S6 Relative reduction in the number of events when using modified progression-free survival (mPFS). The relative reduction in the number of events is defined as the difference in mPFS and PFS event numbers divided by PFS event number. Red diamonds indicate the relative reduction in the number of events for overall survival (OS) versus progression-free survival (PFS). The number of mPFS (cutoff at Month 3) events was consistently greater than that of OS events for all trials (one-sided Wilcoxon signed-rank test P<0.001 for all).

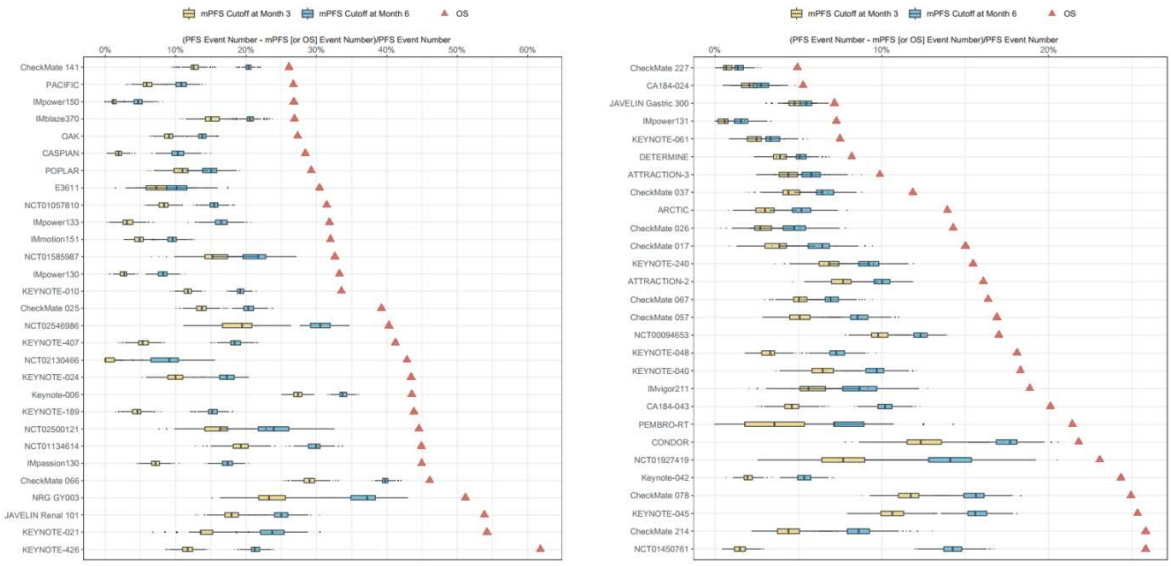


Fig. S7 Log-rank test Z statistic of overall survival (OS), progression-free survival (PFS) and modified PFS (mPFS) among 32 trials where the experimental treatment significantly improved OS.

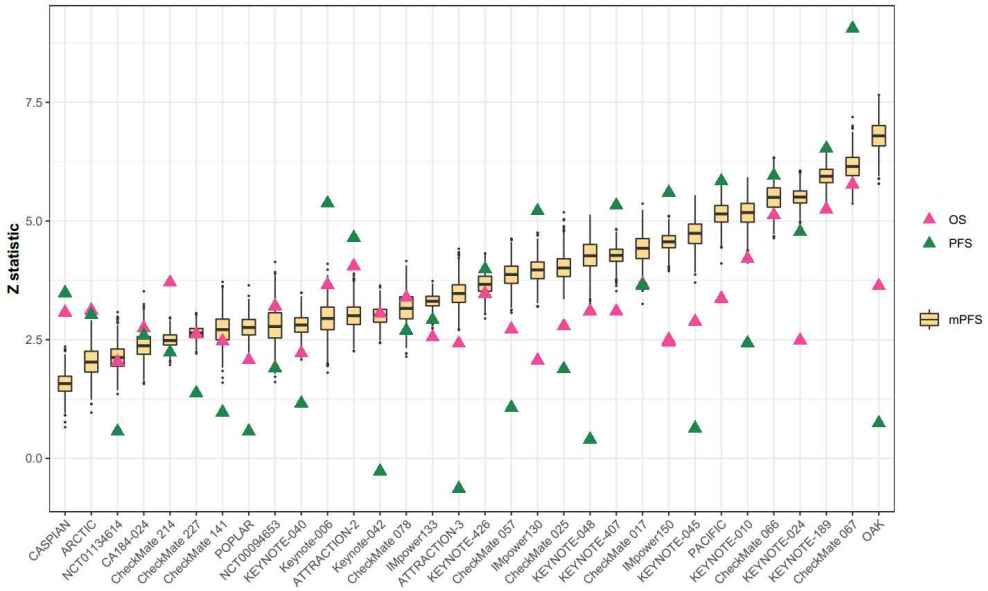


Fig. S8 Trial-level correlation between hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS) in an exemplar simulation where the correlation coefficient equals its median.

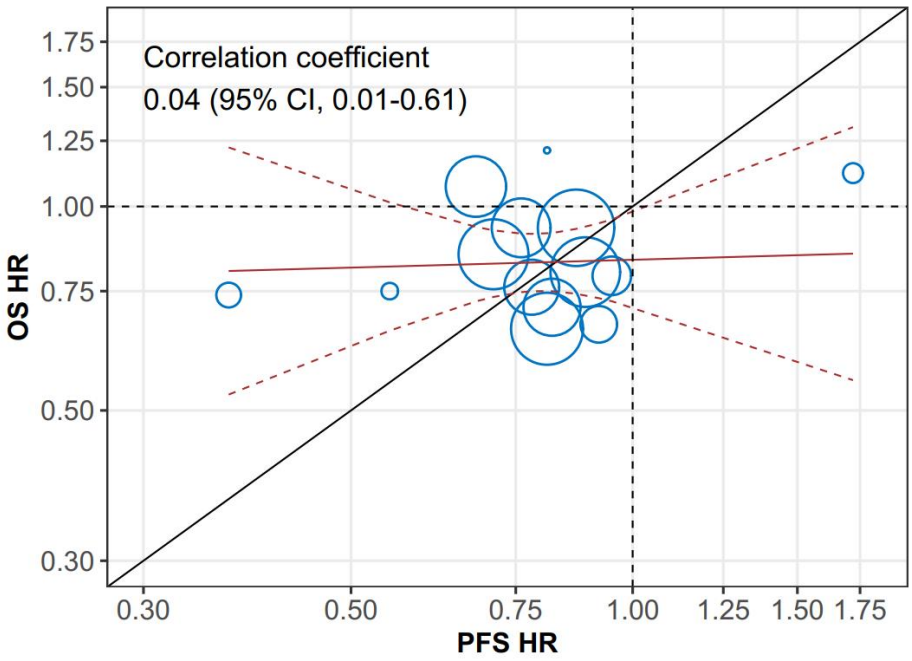
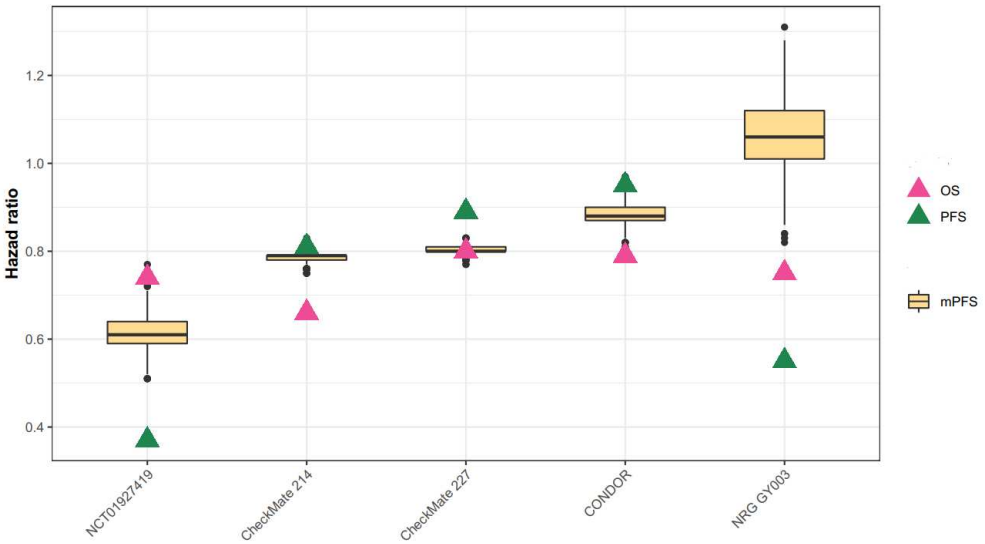


Fig. S9 Hazard ratios for overall survival (OS), progression-free survival (PFS) and modified PFS (mPFS) among five trials involved anti-CTLA4 and anti-PD-(L)1 combination therapy.



Supplementary Tables

Table S1. Characteristics of eligible trials

Trial	Author	Year of publication	Trial phase	Treatment setting	Cancer type	Experimental arm	Control arm	Sample size (experimental/control)	Primary endpoint
POPLAR[1]	Fehrenbacher	2016	2	≥2nd	NSCLC	Atezolizumab	Docetaxel	144/143	OS
OAK[2]	Rittmeyer	2016	3	≥2nd	NSCLC	Atezolizumab	Docetaxel	425/425	OS
KEYNOTE-021[3]	Langer	2016	2	1st	NSCLC	Pembrolizumab+carboplatin+pemetrexed	Carboplatin+pemetrexed	60/63	ORR
NCT01927419[4]	Hodi	2016	2	1st	Melanoma	Nivolumab+ipilimumab	Ipilimumab	95/47	ORR
CheckMate 026[5]	Carbone	2017	3	1st	NSCLC	Nivolumab	Physician's choice chemotherapy	211/212	PFS
NCT00094653[6]	Hodi	2010	3	≥2nd	Melanoma	Ipilimumab+gp100	gp100	403/136	OS
CA184-024, NCT00324155[7]	Robert	2011	3	1st	Melanoma	Ipilimumab+dacarbazine	Placebo+dacarbazine	250/252	OS
NCT01134614[8]	Hodi	2014	2	≥2nd	Melanoma	Ipilimumab+sargramostim	Ipilimumab	123/122	OS
CA184-043[9]	Kwon	2014	3	2nd	Prostate cancer	Ipilimumab+radiotherapy	Placebo+radiotherapy	399/400	OS
CheckMate 141[10]	Ferris	2016	3	≥2nd	HNSCC	Nivolumab	Physician's choice chemotherapy	240/121	OS
CheckMate 066[11]	Robert	2014	3	1st	Melanoma	Nivolumab	Dacarbazine	210/208	OS
CheckMate 057[12]	Borghaei	2015	3	≥2nd	NSCLC	Nivolumab	Docetaxel	292/290	OS

CheckMate 017[13]	Brahmer	2015	3	≥2nd	NSCLC	Nivolumab	Docetaxel	135/137	OS
CheckMate 025[14]	Motzer	2015	3	2nd/3rd	Renal-cell carcinoma	Nivolumab	Everolimus	410/411	OS
CheckMate 037[15]	Larkin	2017	3	≥2nd	Melanoma	Nivolumab	Physician's choice chemotherapy	272/133	OS
KEYNOTE-045[16]	Bellmunt	2017	3	2nd	Urothelial cancer	Pembrolizumab	Physician's choice chemotherapy	270/272	OS
KEYNOTE-024[17]	Reck	2016	3	1st	NSCLC	Pembrolizumab	Physician's choice chemotherapy	154/151	PFS
KEYNOTE-010[18]	Herbst	2016	2+3	≥2nd	NSCLC	Pembrolizumab 2 or 10 mg/kg	Docetaxel	690/343	OS
Keynote-006[19]	Schachter	2015	3	1st/2nd	Melanoma	Pembrolizumab every 2 or 3 weeks	Ipilimumab	556/278	OS
NCT01450761[20]	Reck	2016	3	1st	SCLC	Ipilimumab+etoposide+platinum	Etoposide+platinum	478/476	OS
ATTRACTION-2[21]	Kang	2017	3	≥3rd	Gastric cancer	Nivolumab	Placebo	330/163	OS
NCT01057810[22]	Beer	2016	3	1st	Prostate cancer	Ipilimumab	Placebo	400/202	OS
IMvigor211[23]	Powels	2017	3	1st or later	Urothelial cancer	Atezolizumab	Physician's choice chemotherapy	116/118	OS
JAVELIN Gastric 300[24]	Bang	2018	3	3rd	Gastric cancer	Avelumab	Physician's choice chemotherapy	185/186	OS
KEYNOTE-061[25]	Shitara	2018	3	2nd	Gastric cancer	Pembrolizumab	Paclitaxel	196/199	OS,PFS
CheckMate 214[26]	Motzer	2018	3	1st	Renal-cell carcinoma	Nivolumab+ipilimumab	Sunitinib	425/426	OS,PFS,ORR
KEYNOTE-040[27]	Cohen	2018	3	≥2nd	HNSCC	Pembrolizumab	Physician's choice systemic therapy	247/248	OS
DETERMINE[28]	Maio	2018	2b	2nd/3rd	Mesothelioma	Tremelimumab	Placebo	382/189	OS
KEYNOTE-189[29]	Gandhi	2018	3	1st	NSCLC	Pembrolizumab+pemetrex+platinum	Placebo+pemetrex+platinum	410/206	OS,PFS

KEYNOTE-407[30]	Paz-Ares	2018	3	1st	NSCLC	Pembrolizumab+carboplatin+paclitaxel or nab-paclitaxel	Placebo+carboplatin+paclitaxel or nab-paclitaxel	278/281	OS,PFS
IMpower133[31]	Horn	2018	3	1st	SCLC	Atezolizumab+carboplatin+etoposide	Placebo+carboplatin+etoposide	201/202	OS,PFS
IMpower150[32]	Socinski	2018	3	1st	NSCLC	Atezolizumab+bevacizumab+carboplatin+paclitaxel	Bevacizumab+carboplatin+paclitaxel	400/400	OS,PFS
NCT01585987[33]	Bang	2017	2	Maintenance	Gastric	Ipilimumab	Placebo	57/57	PFS
IMpassion130[34]	Schmid	2018	3	1st	Breast cancer	Atezolizumab+nab-paclitaxel	placebo+nab-paclitaxel	451/451	OS,PFS
CheckMate 067[35]	Larkin	2019	3	1st	Melanoma	Nivolumab+ipilimumab, or nivolumab	Ipilimumab	630/315	OS,PFS
IMblaze370[36]	Eng	2019	3	≥3rd	Colorectal cancer	Atezolizumab+cobimetinib	Regorafenib	183/90	OS
Keynote-042[37]	Mok	2019	3	1st	NSCLC	Pembrolizumab	Physician's choice chemotherapy	637/637	OS
JAVELIN Renal 101[38]	Choueiri	2020	3	1st	Renal-cell carcinoma	Avelumab+axitinib	Sunitinib	442/444	OS,PFS
KEYNOTE-426[39]	Rini	2019	3	1st	Renal-cell carcinoma	Pembrolizumab+axitinib	Sunitinib	432/429	OS,PFS
IMmotion151[40]	Rini	2019	3	1st	NSCLC	Atezolizumab+Bevacizumab	Sunitinib	454/461	OS,PFS
IMpower130[41]	West	2019	3	1st	NSCLC	Atezolizumab+carboplatin+nab-paclitaxel	Carboplatin+nab-paclitaxel	451/228	OS,PFS
NCT02130466[42]	Ascierto	2019	2	1st	Melanoma	Pembrolizumab+dabrafenib+trametinib	Dabrafenib+trametinib	60/60	PFS
CheckMate 227[43]	Hellmann	2019	3	1st	NSCLC	Nivolumab+ipilimumab	Physician's choice chemotherapy	396/397	OS

Keynote-048[44]	Burtness	2019	3	1st	HNSCC	Pembrolizumab+chemotherapy, or pembrolizumab	Cetuximab+chemotherapy	301/300;281/278	OS,PFS
PACIFIC[45]	Antonia	2018	3	Maintenance	NSCLC	Durvalumab	Placebo	476/237	OS,PFS
ATTRACTION-3[46]	Kato	2019	3	2nd	ESCC	Nivolumab	Physician's choice chemotherapy	210/209	OS
NCT02546986[47]	Levy	2018	2	2nd	NSCLC	Pembrolizumab+CC-486	Pembrolizumab+placebo	51/49	PFS
CASPIAN[48]	Paz-Ares	2019	3	1st	SCLC	Durvalumab+platinum-etoposide	Platinum-etoposide	268/269	OS
CONDOR[49]	Siu	2018	2	2nd	HNSCC	Durvalumab + tremelimumab	Durvalumab or tremelimumab	133/134	ORR
E3611[50]	Tarhini	2018	2	1st/2nd	Melanoma	Ipilimumab+HDI	Ipilimumab	37/44	PFS
PEMBRO-RT[51]	Theelen	2019	2	>=2nd	NSCLC	Pembrolizumab following SBRT	Pembrolizumab	36/40	ORR
CheckMate 078[52]	Wu	2019	3	>=2nd	NSCLC	Nivolumab	Docetaxel	338/166	OS
KEYNOTE-240[53]	Finn	2019	3	2nd	HCC	Pembrolizumab	Placebo	278/135	OS,PFS
IMpower131[54]	Jotte	2020	3	1st	NSCLC	Atezolizumab+carboplatin+nab-paclitaxel	Carboplatin+nab-paclitaxel	343/340	OS,PFS
NCT02500121[55]	Galsky	2020	2	Maintenance	Urothelial cancer	Pembrolizumab	Placebo	55/52	PFS
ARCTIC[56]	Planchard	2020	3	3rd	NSCLC	Durvalumab + tremelimumab, or durvalumab	Physician's choice chemotherapy	236/182	OS,PFS
NRG GY003[57]	Zamarin	2020	2	>=2nd	Ovarian cancer	Nivolumab+ipilimumab	Nivolumab	51/49	ORR

Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; HNSCC, head and neck squamous cell carcinoma; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; ORR, objective response rate.

Reference:

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