Tumor response, disease control, and progression-free survival as surrogate endpoints in trials evaluating immune checkpoint inhibitors in advanced non-small cell lung cancer: study- and patient-level analyses

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Supplementary Materials

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Table S1. Formulas used in database searches.

PubMed, 175 articles
#1 (non-small cell lung cancer [title] OR non-small-cell lung cancer [title] OR non-small-cell lung carcinoma [title] OR NSCLC [title] OR squamous lung [title] OR adenocarcinoma lung [title]) **#2** (randomized[title] OR randomised [title] OR RCT [title] OR phase III [title] OR phase 3 [title] OR randomly OR N Engl J Med) **#3** (ICI [title] OR immune checkpoint inhibitor [title] OR Nivolumab [title] OR Pembrolizumab [title] OR Spartalizumab [title] OR Cemiplimab [title] OR Avelumab [title] OR Atezolizumab [title] OR Durvalumab [title] OR Ipilimumab [title] OR Tremelimumab [title] OR Camrelizumab [title] OR Sintilimab [title] OR Sugemalimab[title]) **#4** (non-small cell lung cancer OR non-small-cell lung cancer OR non-small cell lung carcinoma OR NSCLC OR squamous lung OR adenocarcinoma lung) **#5** (randomized OR randomised OR RCT OR phase III OR phase 3 OR randomly OR N Engl J Med) **#6** (ICI OR immune checkpoint inhibitor OR Nivolumab OR Pembrolizumab OR Spartalizumab OR Cemiplimab OR Avelumab OR Atezolizumab OR Durvalumab OR Ipilimumab OR Tremelimumab OR Camrelizumab OR Sintilimab OR SugemalimabOR Checkmate OR Keynote OR IMpower) **#7** HR OR hazard ratio OR cox hazard **#8** ((#1 AND #2 AND #6) OR (#4 AND #2 AND #3) OR (#1 AND #5 AND #3)) and #7
Web of Science, 230 articles
#1 TI=(non-small cell lung cancer OR non-small-cell lung cancer OR non-small-cell lung carcinoma OR NSCLC OR squamous lung OR adenocarcinoma lung) **#2** TI=(randomized OR randomised OR RCT OR phase III OR phase 3) OR TS=(randomly) **#3** TI=(ICI OR immune checkpoint inhibitor OR Nivolumab OR Pembrolizumab OR Spartalizumab OR Cemiplimab OR Avelumab OR Atezolizumab OR Durvalumab OR Ipilimumab OR Tremelimumab OR Camrelizumab OR Sintilimab OR Sugemalimab) **#4** TS=(non-small cell lung cancer OR non-small-cell lung cancer OR non-small-cell lung carcinoma OR NSCLC OR squamous lung OR adenocarcinoma lung)

#5 TS=(randomized OR randomised OR RCT OR phase III OR phase 3 OR randomly)

#6 TS=(ICI OR immune checkpoint inhibitor OR Nivolumab OR Pembrolizumab OR Spartalizumab OR Cemiplimab OR Avelumab OR Atezolizumab OR Durvalumab OR Ipilimumab OR Tremelimumab OR Camrelizumab OR Sintilimab OR Sugemalimab)

#7 TS=(HR OR hazard ratio OR cox hazard)

#8 ((#1 AND #2 AND #6) OR (#4 AND #2 AND #3) OR (#1 AND #5 AND #3)) and #7

Cochrane CENTRAL, 338 articles

Combine all of the following using AND

Record Title: non-small cell lung cancer OR non-small-cell lung cancer OR non-small-cell lung carcinoma OR NSCLC OR squamous lung OR adenocarcinoma lung

Record Title: ICI OR immune checkpoint inhibitor OR Nivolumab OR Pembrolizumab OR Spartalizumab OR Cemiplimab OR Avelumab OR Atezolizumab OR Durvalumab OR Ipilimumab OR Tremelimumab OR Camrelizumab OR Sintilimab OR Sugemalimab

Abstract: HR OR hazard ratio OR cox hazard

EMBASE, 80 articles

ti(non-small cell lung cancer OR non-small-cell lung cancer OR non-small-cell lung carcinoma OR NSCLC OR squamous lung OR adenocarcinoma lung) AND ti(randomized OR randomised OR phase III OR phase 3)

AND

ti(ICI OR immune checkpoint inhibitor OR Nivolumab OR Pembrolizumab OR Spartalizumab OR Cemiplimab OR Avelumab OR Atezolizumab OR Durvalumab OR Ipilimumab OR Tremelimumab OR Camrelizumab OR Sintilimab OR Sugemalimab OR Checkmate OR Keynote OR IMpower) **AND**

(hazard ratio OR cox hazard)

Table S2. List of studies used for independent-patient-data analysis.

	Country	Phase	Patho	Stage	PD-L1 status	Driver	PS	Line	Imaging evaluation	Treatment	ROB H/U/L
Fehrenbacher (2016) POPLAR	USA	II	NSCLC	Adv, Met	Any	Any	0-1	2-3	RECIST	Atz (1200 mg) q3w Dtx (75 mg/m2) q3w	2/0/4
Jotte (2020) IMpower131	USA	III	SQ	IV	Any	Any	0-1	1	RECIST	Atz (1200 mg) + Cbdca (AUC 6) + nPtx (100 mg/m2) q3w Cbdca (AUC 6) + nPtx (100 mg/m2) q3w	1/0/5
Peters (2017) BIRCH	Spain	II	NSCLC	IIIb, IV	IC>5% or TC>5%	Any	0-1	1	RECIST ICR	Sigle-arm study Atz (1200 mg) q3w	NA
Rittmeyer (2017) OAK	USA	III	NSCLC	IIIb, IV	IC>1% or TC>1%	Any	0-1	2-3	RECIST	Atz (1200 mg) Dtx	2/0/4
Socinski (2018) IMpower150	Germany	III	NSQ	IV, Rec	Any	EGFR(-), ALK(-)	0-1	1	RECIST ICR	Atz (1200 mg) + Cbdca (AUC 6) + Ptx (200 mg/m2) Atz (1200 mg) + Bev (15 mg/kg) + Cbdca (AUC 6) + Ptx (200 mg/m2) Bev (15 mg/kg) + Cbdca (AUC 6) + Ptx (200 mg/m2)	1/0/5
Spigel (2018) FIR	USA	II	NSCLC	Adv	IC>5% or TC>5%	Any	0-1	Any, no Plat for 6 months	RECIST	Sigle-arm study Atz (1200 mg) q3w	NA
West (2019) IMpower130	Italy	III	NSQ	IV	Any	EGFR(-), ALK(-)	0-1	1	RECIST ICR	Atz (1200 mg) q3w + Cbdca (AUC 6) q3w + nPtx (100 mg/m2) q1w Cbdca (AUC 6) q3w + nPtx (100 mg/m2) q1w	1/0/5

Patho, pathology; NSCLC, non-small cell lung cancer; SQ, squamous cell carcinoma; NSQ, non-squamous cell carcinoma.

Rec, recurrent; Adv, advanced; Met, metastasis; LocAdv, locally advanced;

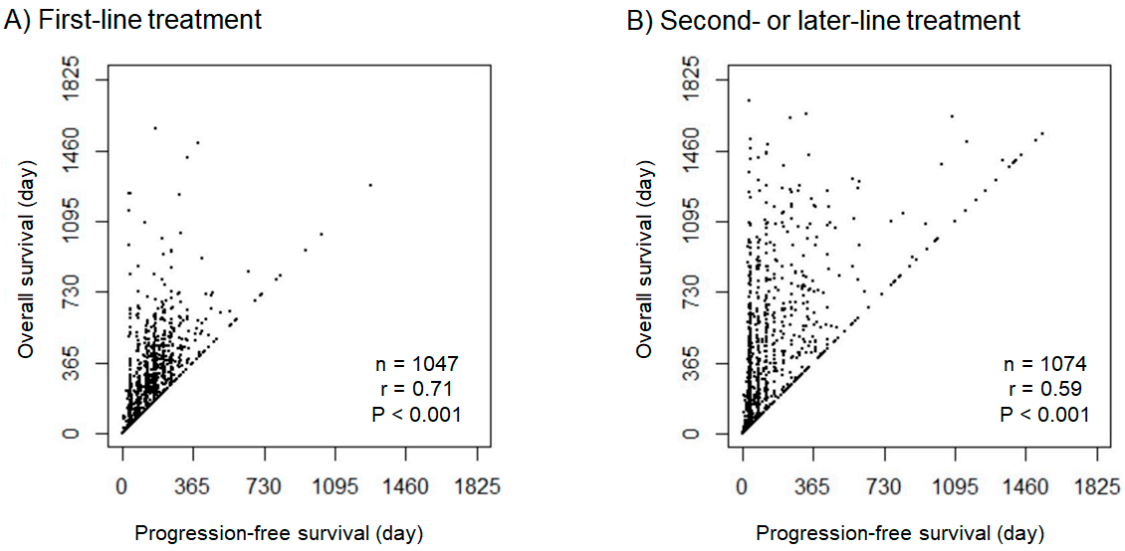
PD-L1, programmed death ligand 1; TC, tumor cells; IC, tumor-infiltrating immune cells; >1%, 1% or higher; >5%, 5% or higher.

PS, performance status (if not specified, Eastern Cooperative Oncology Group PS).

RECIST, Response Evaluation Criteria in Solid Tumours version 1.1; ICR, independent central review.

Plat, platinum; ATZ, atezolizumab; Cbdca, carboplatin; nPtx, nab-paclitaxel; Ptx, paclitaxel; AUC, area under curve; Bev, bevacizumab. q3w, every 3 weeks. ROB, Cochrane risk of bias; H/U/L, high/unclear/low risk of bias; NA, not applicable because the study was not an RCT.

Figure S1. Scatter plot of overall survival and progression-free survival using independent-patient-data.



N, number of patients.

r, Spearman's rank correlation coefficient.

Figure S2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the trial-level analysis.

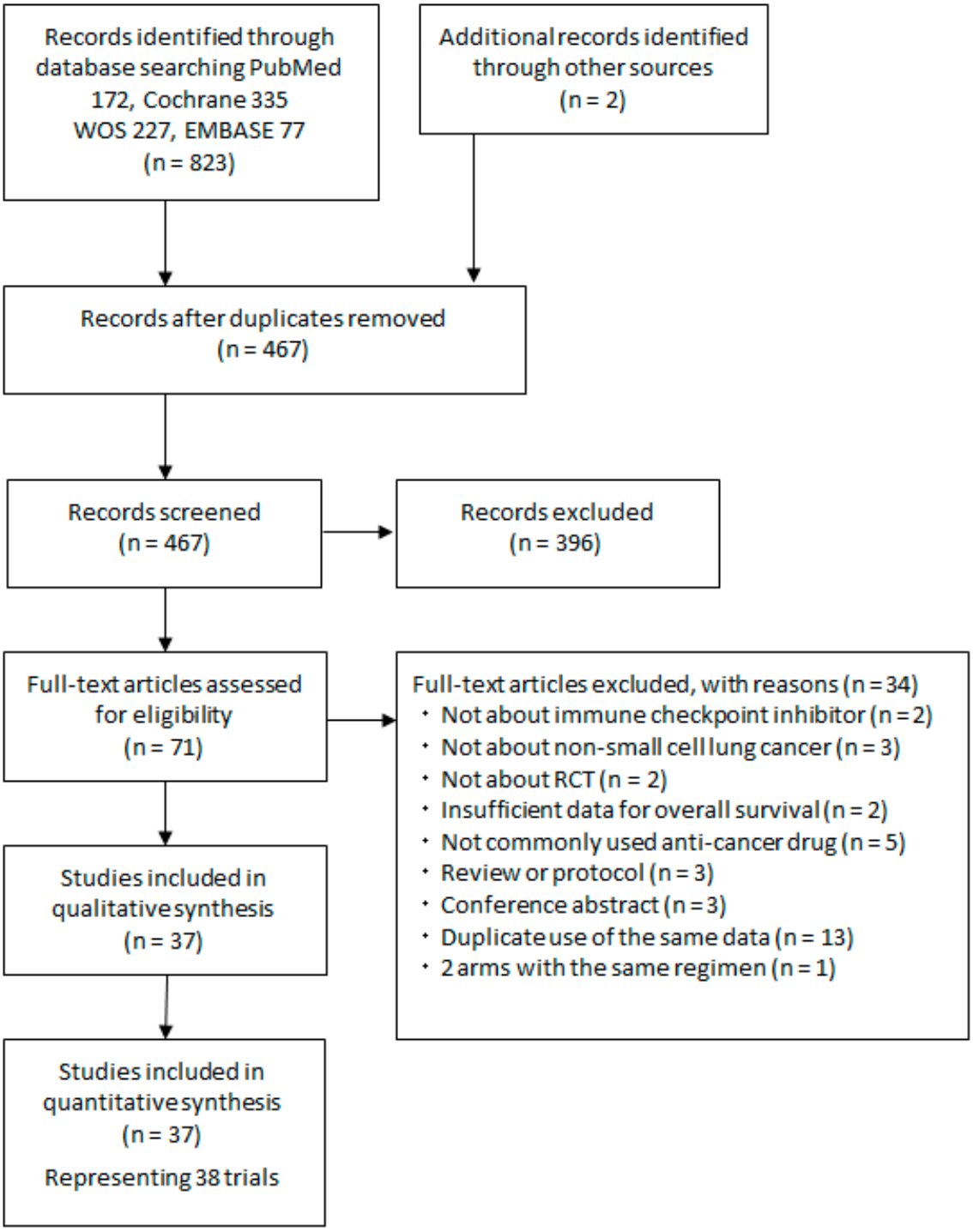
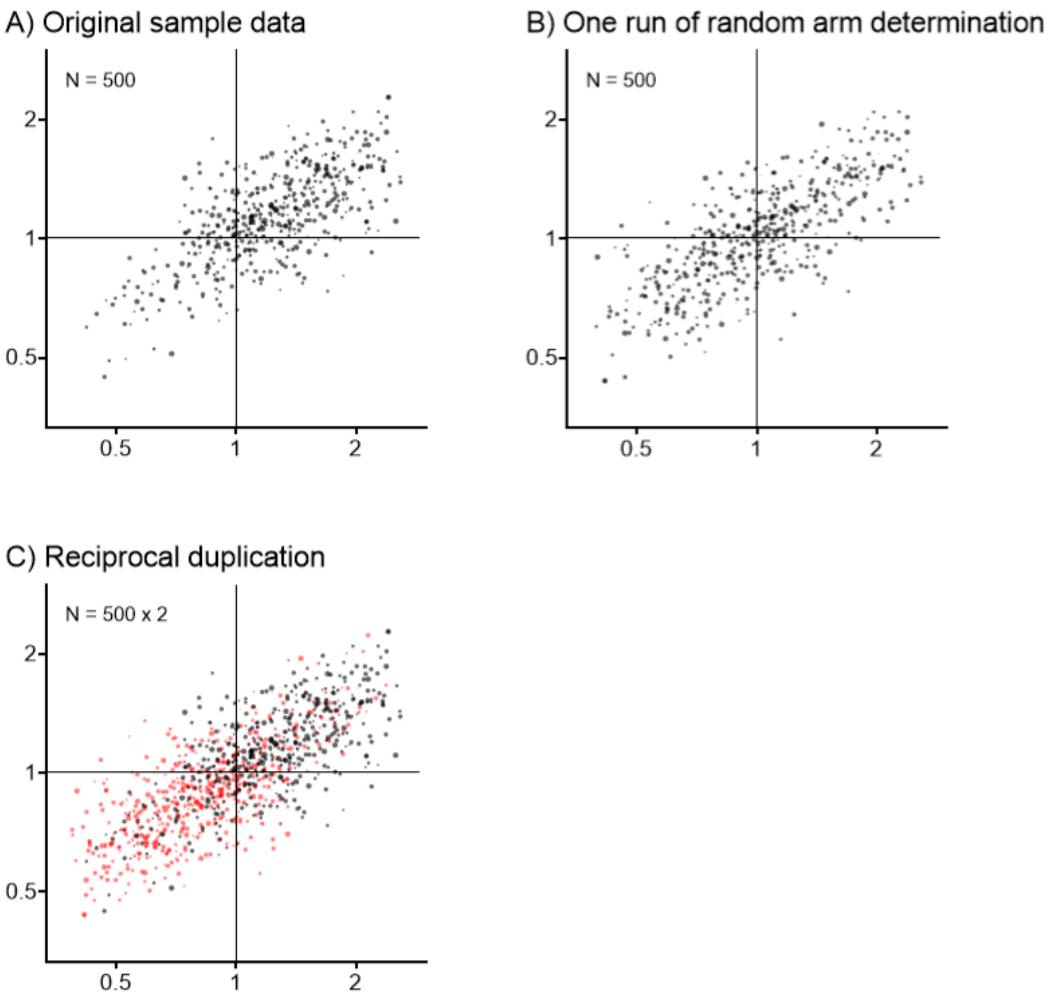


Figure S3. Sample data used for Monte Carlo simulation.



A dot represents a 2-arm trial. Size of a dot indicates weight of a study.

A) Many dots are plotted in right upper quadrant, where suggests x- and y-axes values >1, meaning that more events were observed in the experimental than in the reference arm.

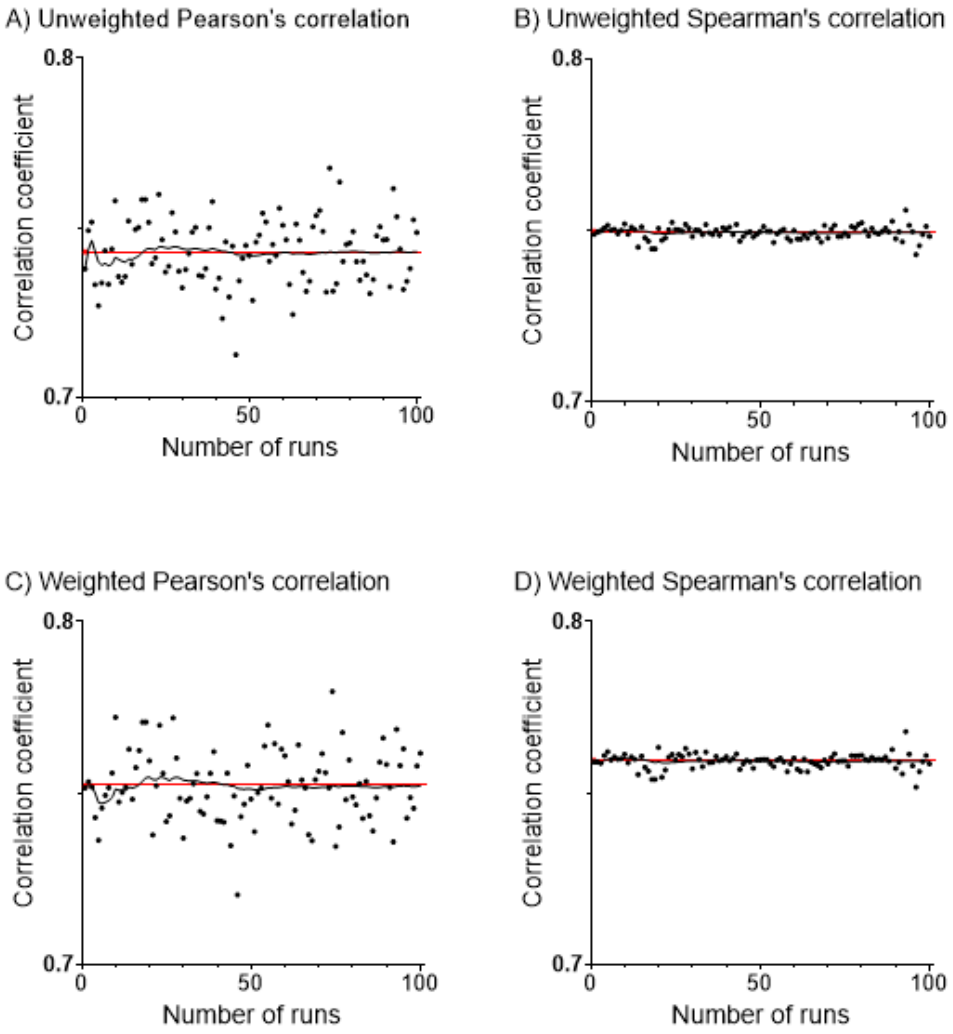
B) This figure illustrates one run of random arm determination with 500 trials. The experimental and standard arms were randomly selected. Similar numbers of dots were equally plotted in the right upper and left lower quadrants, indicating that the overall event frequencies were similar in both arms. Another run of random arm determination with 500 trials is expected to produce a similar result because the sample size is sufficiently

large.

C) Reciprocal duplication. For each of the 500 2-arm trials, original position is plotted in black and the position of point symmetry is plotted in red.

We hypothesized that the correlation coefficient based on random arm determination (B) was an approximation of the correlation coefficient following reciprocal duplication (C).

Figure S4. Monte-Carlo simulation for reciprocal duplication.



Dot: Each dot represents one run of random arm determination for 500 2-arm trials.

Black line: Average correlation coefficient of present and previous runs.

Red line: Correlation coefficient based on reciprocal duplication (N = 500 × 2).

As the number of runs increased, the black line approached to the red line.

Reference S1. Review articles used in hand search

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