Original Article

The best regimens for chemo-naïve incurable non-squamous non-small cell lung cancer with a programmed death-ligand 1, tumor proportion score 1–49%: a network meta-analysis

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Background: Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide. There is a rank order of the efficacy and safety of treatment options, including immune checkpoint inhibitors (ICIs), bevacizumab (Bev), and cytotoxic drugs. When patients have low programmed death-ligand 1 (PD-L1) expression, there are multiple options for treatment. In this study, we focused on ICI regimens in patients with non-squamous NSCLC with low PD-L1 expression and no driver alterations and assessed the efficacy of the regimens using network meta-analysis.

Methods: Randomized trials for incurable chemo-naïve non-squamous NSCLC were collected through electronic searches. The data were independently extracted and cross-checked by two investigators. The primary outcome of this analysis was overall survival (OS). A frequentist weighted least-squares approach random-model network meta-analysis was applied.

Results: Sixty-eight eligible studies and 22,619 patients were identified. Using a platinum + third-generation cytotoxic agent regimen (platinum regimen) as a reference, the platinum regimen + pembrolizumab (Pemb) [hazard ratio (HR) =0.55, 95% confidence interval (CI): 0.34–0.89, P=0.015] showed the best OS, followed by the platinum regimen + nivolumab (Niv) + ipilimumab (Ipi) (HR =0.61, 95% CI: 0.44–0.84, P=0.003) with no heterogeneity (I^2=0%, P=0.348).

Conclusions: The addition of Pemb or Niv/Ipi to platinum-based chemotherapy seems to be a good therapeutic option for non-squamous NSCLC with a PD-L1 tumor proportion score (TPS) of 1–49%.

Keywords: Lung neoplasms; molecular targeted therapy; immune checkpoint inhibitors (ICIs); systematic review; pembrolizumab (Pemb)

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Introduction

Non-small cell lung cancer (NSCLC) is one of the most common cancers and the leading cause of cancer-related death worldwide (1). Platinum doublet and triplet chemotherapies have been the standard of care for patients with inoperable NSCLC without actionable driver mutations or translocations. The development of immune checkpoint inhibitors (ICIs) has offered enhanced therapeutic options for a variety of malignancies (2). ICIs are effective for multiple types of cancers because they treat malignant tumors by blocking checkpoint proteins but not directly attacking tumor cells. For example, programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors prevent tumor cells from inactivating the immune system (3). Currently, the first-line therapeutic option for chemo-naïve patients with stage IV PD-L1-high [tumor proportion score (TPS) 50% or higher] NSCLC without driver alterations is single-agent pembrolizumab (Pemb) (4-7). Several regimens combining ICIs, bevacizumab (Bev), and cytotoxic drugs are recommended even for patients with low or no PD-L1 expression (4-7), since they greatly improve the objective response rate, progression-free survival (PFS), and overall survival (OS) of patients without substantially increasing the risk of adverse events compared to reference platinum regimens without ICIs. Although kinase inhibitors targeting epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), and B-raf proto-oncogene (BRAF) are highly effective for patients with specific actionable mutations or translocations, such kinase inhibitors are not recommended for NSCLC patients without these mutations or translocations (8).

Few randomized clinical trials (RCTs) have directly compared ICI regimens because such a trial requires a large number of participants to reveal small differences in outcomes. However, understanding differences in efficacy and safety among ICI regimens is vital because they are crucial for treatment selection. A network meta-analysis is the best analytical technique for enabling indirect comparison among multiple regimens. Our previous network meta-analysis published in 2017 evaluated only non-ICI, non-kinase inhibitor regimens for chemo-naïve incurable NSCLC (9). The aim of the current study is to update the previous network meta-analysis, focusing on ICI regimens and low PD-L1 expression (TPS 1–49%) in non-squamous NSCLC cases without driver alterations. We present the following article in accordance with PRISMA NMA reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-419) (10).

Methods

Protocol registration and overview

The protocol of this study followed the PRISMA extension statement for network meta-analysis (10), and the study was registered at the University Hospital Medical Information Network Center, Japan (11). There are amendments to information in the protocol (Appendix 1). Patient informed consent and institutional review board approval were not required for a systematic review.

Study search

The MEDLINE, Embase, Web of Science Core Collection, and Cochrane Central Register of Controlled Trials databases were searched to identify eligible articles on October 15, 2020. The formula used for MEDLINE is shown in Appendix 2. Conflicts during the study selection were resolved by discussion between the two reviewers (NF and SK) or inquiry to a third reviewer (NH).

Inclusion criteria: publication type and trial design

Individually randomized controlled trials of incurable NSCLC written in English were collected. Studies focusing on patients with driver mutations or translocations were excluded. A conference abstract was allowed. Trials including random assignment to maintenance therapy, second-line treatment, or later-line treatments were excluded.

Inclusion criteria: treatment

Eligible treatments included first-line chemotherapy, including cytotoxic agents, molecular targeted therapies, and ICIs. Trials adding angiogenesis inhibitor to the platinum regimen were included. ICIs could be used alone or in combination with platinum regimens.

While comparability between cisplatin (CDDP) and carboplatin (CBDCA) in the treatment of NSCLC is controversial (12,13), recent trials have allowed either CDDP or CBDCA based on the physician's choice (14,15). Similarly, one of the important RCTs regarding Pemb, Keynote-047, included a "CBDCA and either paclitaxel

(Ptx) or nanoparticle albumin-bound Ptx (nabPtx)" arm. Therefore, we decided to allow selective administration of CDDP/CBDCA and Ptx/nabPtx for our analysis. Nedaplatin was distinguished from CDDP and CBDCA.

Some recent trials that evaluated adding ICIs to platinum regimens allowed physicians to choose from several platinum regimens; however, a regimen-based network meta-analysis cannot incorporate such trials. Therefore, two models were constructed for analysis. One model, which was termed the "main model", did not distinguish each platinum + third generation cytotoxic agent regimen (platinum regimen). The other model, which was termed the "separate model", recognized each platinum regimen individually.

Kinase inhibitors were beyond the scope of the study because a regimen with these medications was not standard for patients without driver alterations (4-7).

RCTs examining perioperative chemotherapy and combined chemoradiotherapy were excluded from this study.

Inclusion criteria: patients

Patients with advanced, locally advanced, or recurrent non-squamous NSCLC were included. We accepted the disease stage that was mentioned in an article regardless of the historical revisions of the tumor-node-metastasis classification. Patients were not excluded if they had a medical history of radiotherapy or surgery. However, one study focusing on patients with poor performance status and the elderly was excluded. An RCT of large cell neuroendocrine carcinoma was excluded.

Patients whose PD-L1 protein expression as determined by the TPS was 50% or higher were excluded because current guidelines recommend different treatment options for those with a TPS <50% and those with a TPS ≥50%. Patients with a TPS <1% were also excluded because the number of patients with a TPS <1% influenced the results. If a subset of the study population fit our criteria, the subset data were analyzed. For example, when a study separately provided data of three populations with TPS scores of 0%, 1–49%, and ≥50%, we collected the data of the population with a TPS 1–49%.

If a study focused on patients with squamous NSCLC, driver alterations, or a TPS ≥50%, the study was excluded. However, a study without criteria regarding the pathological subclassification of NSCLC, driver gene mutations, and TPS was acceptable; otherwise, most NSCLC studies would have been excluded.

Quality assessment

The Cochrane Risk of Bias tool was used for the quality assessment. This assessment tool included selection, performance, detection, attrition, reporting, and other bias (16).

Outcomes

The primary outcome of this analysis was OS, evaluated using hazard ratio (HRos). The secondary endpoints were the HR for PFS (HRpfs), the odds ratio of adverse events based on the Common Terminology Criteria for Adverse Events grade III or higher (ORae) (17), and the OR of treatment-related death. Disease progression was assessed in compliance with the Response Evaluation Criteria in Solid Tumors guidelines published in 2000 or its 2009 revision (18). Imaging evaluation performed by blinded independent central reviewing was preferred, if available. The first adverse event of grade III or higher was counted even if a patient experienced two or more adverse events.

Data extraction

Characteristics of eligible studies, including the first author name, publication year, sample size, and trial outcome, such as HRos and its 95% confidence interval (CI), were extracted by two reviewers (NF and SK). Consensus was reached by discussion between the two reviewers and arbitration from a third reviewer (NH). Survival updates were included if available. Parmar's method was accepted for the survival data (19). If available, data from intention-to-treat analyses were selected. The treatment arm was named based on the drug combination, regardless of the dose, route, or schedule. We obtained data from a subgroup by subtraction using a fixed-model meta-analysis formula. For example, subtracting data of the "PD-L1 1–49%" subgroup from data of the "PD-L1 <50%" subgroup yielded the data of the "PD-L1 <1%" subgroup. The data on adverse events and treatment-related death could be for patients with any PD-L1 TPS or pathology because these stratified data were rarely described.

Statistical analyses

The frequentist weighted least squares approach random-

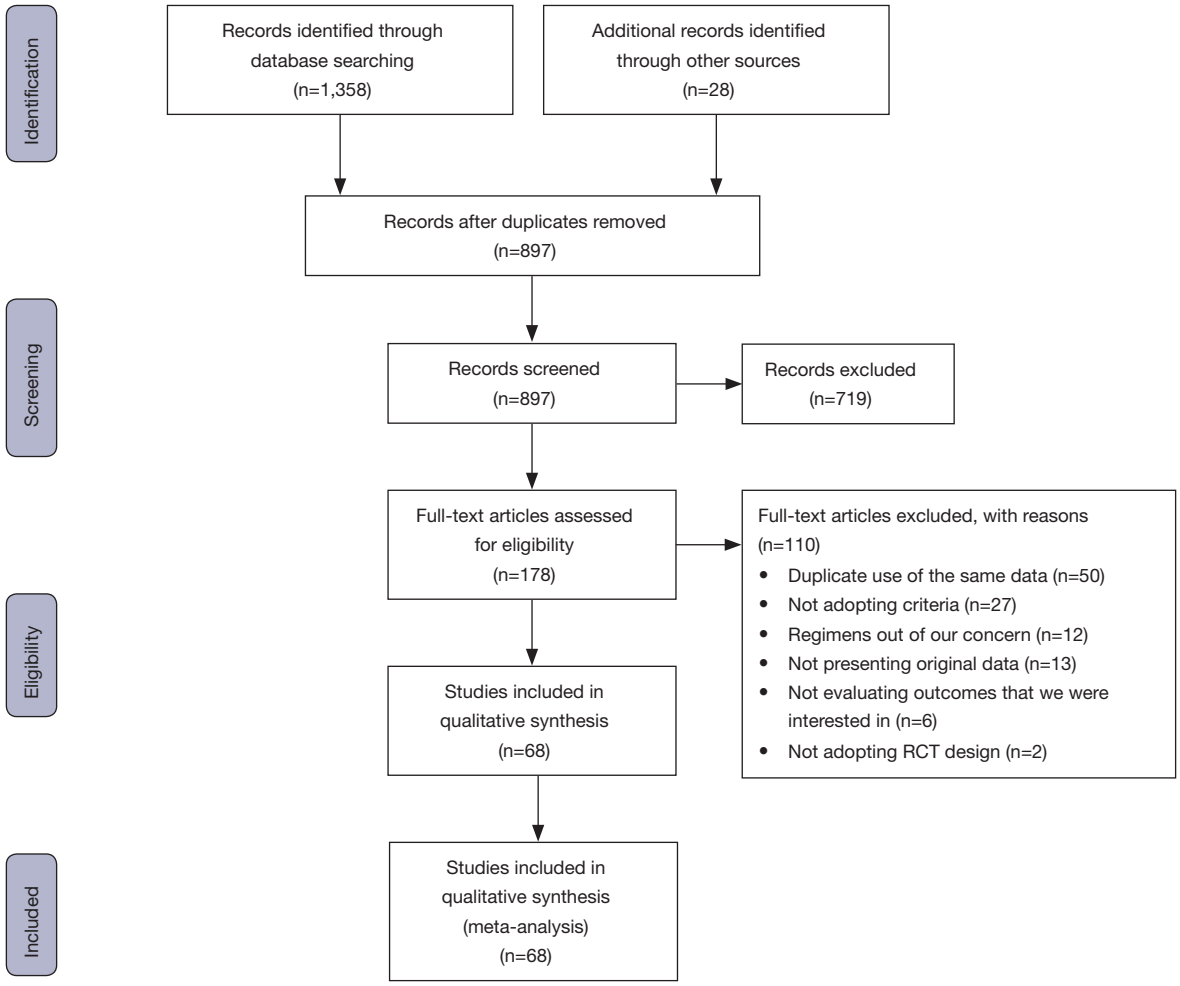

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart for study search. RCT, randomized clinical trials.

model network meta-analysis was applied in our study (20). The OR of a binary outcome was continuously corrected with 0.5, if necessary. The OR and HR were log-converted. In the separate model, platinum + pemetrexed (Pemt) was used as a common reference comparator because this regimen was selected for non-squamous carcinoma in recent trials (14,15). Data were analyzed using R software (Command: netmeta, Package: netmeta) (21). The significance threshold was set at $P<0.05$.

Results

Study search

We identified 1386 articles by electronic and manual searches. Of the 897 articles that met the preliminary criteria, 489, 719, and 110 were excluded through removal of duplicated studies, title/abstract screening, and full article review, respectively. We identified 68 eligible studies (*Figure 1*, Appendix 3).

Characteristics of the included studies

The main model had 26 studies and 53 arms, of which 16 included ICIs. The separate model had 63 studies and 130 arms, of which 9 included ICIs. The median and average age of patients ranged from 51 years to 67 years, with 50 studies having a median/average age in the 60s. The total number of patients was 22,619, and the number of randomized patients in each study ranged from 41 to 1,252, with a median of 248 (*Table 1*, Appendix 4).

According to the Cochrane Risk of Bias evaluation, all but one of the studies had at least one domain with a high risk of bias (Table S1).

Table 1 Characteristics of included studies

Study	Region	Phase	Primary outcome	Pathology	Arm	Stage	PS	Regimens	Pts	Median age
Belani, 2017	India	Not available	OS	NSCLC	2	IIIb, IV	ECOG 0–1	CDDP (100 mg/m^2) + Ptx (175 mg/m^2) + CADI-05 (0.2 mL)	221	58
								CDDP (100 mg/m^2) + Ptx (175 mg/m^2) [M][S]		
Bennouna, 2014	France	II	DCR	NSq	2	IIIb, IV, Rec	KPS ≥80%	CDDP (75 mg/m^2) + Pemt (500 mg/m^2)	153	62
								CDDP (80 mg/m^2) + Vnr [80 mg/m^2 (d 1, 8 po)] [S]		
Carbone, 2017	USA	III	PFS	NSCLC	2	IV, Rec	ECOG 0–1	Niv (3 mg/kg, q2w)	327	64
								1 of 5 platinum doublets [M]		
Chang, 2008	China	Not available	RR	NSCLC	2	IIIb, IV	ECOG 0–2	CDDP (80 mg/m^2) + Gem [1,000 mg/m^2 (d 1, 8, 15)]	83	62
								CDDP (80 mg/m^2) + Vnr [20 mg/m^2 (d 1, 8, 15)] [S]		
Chen, 2007	Taiwan	II	RR	NSCLC	2	IIIb, IV	ECOG 0–2	CDDP (60 mg/m^2) + Vnr [25 mg/m^2 (d 1, 8)]	94	63
								CDDP (60 mg/m^2) + Dtx (60 mg/m^2) [S]		
Che, 2004	Taiwan	II	Not available	NSCLC	2	IIIb, IV	ECOG 0–2	CDDP [60 mg/m^2 (d15)] + Ptx [66 mg/m^2 (d 1, 8, 15)]	140	65
								CDDP [60 mg/m^2 (d15)] + Vnr [23 mg/m^2 (d 1, 8, 15)] [S]		
Comella, 2000	Italy	III	OS	NSCLC	2†	IIIb, IV	ECOG 0–1	CDDP (120 mg/m^2) + Vnr [30 mg/m^2 (weekly)]	120	62
								CDDP (100 mg/m^2) + Gem [1,000 mg/m^2 (d 1, 8, 15)] [S]		
Doebele, 2015	USA	II	PFS	NSq	2	IV	ECOG 0–2	[CDDP (75 mg/m^2) or CDBCA (AUC 6)] + Pemt (500 mg/m^2) + Ram (10 mg/kg)	140	64
								[CDDP (75 mg/m^2) or CDBCA (AUC 6)] + Pemt (500 mg/m^2) [M][S]		
Douillard, 2005	France	II	RR	NSCLC	2	IV	ECOG 0–2	CDDP (100 mg/m^2) + Dtx (75 mg/m^2)	239	57
								CDDP (100 mg/m^2) + Vnr [30 mg/m^2 (d 1, 8)] [S]		

Table 1 (*continued*)

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Study	Region	Phase	Primary outcome	Pathology	Arm	Stage	PS	Regimens	Pts	Median age
Edelman, 2004	USA	II	OS	NSCLC	2	IIIb, IV	ECOG 0–1	CDBCA (AUC 5.5) + Gem [1,000 mg/m^2(d 1, 8)]	204	60
								CDDP (100 mg/m^2) + Vnr [25 mg/m^2 (d 1, 8)] [S]		
Engle-Riedel, 2018	USA	II	RR	NSq	2	IIIb, IV	ECOG 0–1	CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) + BTH1677 (4 mg/kg)	89	59
								CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) [M][S]		
Fossella, 2003	USA	III	OS (non-inf)	NSCLC	3	IIIb, IV, Rec	KPS ≥70%	[CDDP (75 mg/m^2) or CDBCA (AUC 6)] + Dtx (75 mg/m^2)	1,218	60
								CDDP (100 mg/m^2) + Vnr [25 mg/m^2 (weekly)] [S]		
Galetta, 2015	Italy	III	QOL	NSq	2	IIIb, IV	ECOG 0–1	CDDP (75 mg/m^2) + Pemt (500 mg/m^2)	118	62
								CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) [S]		
Gandhi, 2018	USA	III	OS PFS	NSq	2	III, IV, Rec	ECOG 0–1	[CDDP (75 mg/m^2) or CDBCA (AUC 5)] + Pemt (500 mg/m^2) + Pemb (200 mg)	186	64
								[CDDP (75 mg/m^2) or CDBCA (AUC 5)] + Pemt (500 mg/m^2) [M][S]		
Garon, 2016	USA	II	Safety/ torelability	NSq	2	IIIb, IV	ECOG 0–1	CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) + Trmt (60 mg/m^2)	63	62
								CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) [M][S]		
Gebbia, 2010	Italy	II	QOL, symptom, AE	NSCLC	2	IIIb, IV	ECOG 0–1	CDDP (75 mg/m^2) + Dtx (75 mg/m^2)	86	62
								CDDP (80 mg/m^2) + Vnr [30 mg/m^2 (d 1, 8)] [S]		
Gebbia, 2003	Italy	III	TTP & OS	NSCLC	2‡	IIIb, IV	ECOG 0–2	CDDP (100 mg/m^2) + Vnr [25 mg/m^2 (d 1, 8)]	278	62
								CDDP (100 mg/m^2) + Gem [1,400 mg/m^2 (d 1, 8)] [S]		

Table 1 (*continued*)

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Study	Region	Phase	Primary outcome	Pathology	Arm	Stage	PS	Regimens	Pts	Median age
Gronberg, 2009	Norway	III	QOL	NSCLC	2	IIIb, IV	ECOG 0–2	CDBCA (AUC 5) + Pemt (500 mg/m^2)	329	65
								CDBCA (AUC 5) + Gem [1,000 mg/m^2 (d 1, 8)] [S]		
Harada, 2018	Japan	II	PFS	NSq	2	IV, Rec	Not available	CDDP (75 mg/m^2) + Pemt (500 mg/m^2) + Bev (15 mg/kg)	199	Not available
								CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) [S]		
Helbekkmo, 2007	Norwegian	III	OS	NSCLC	2	IIIb, IV	ECOG 0–2	CDBCA (AUC 5) + Vnr [25 mg/m^2 (d 1, 8)]	444	67
								CDBCA (AUC 5) + Gem [1,000 mg/m^2 (d 1, 8)] [S]		
Hellmann, 2019	USA	III	OS	NSCLC	2†	IV, Rec	ECOG 0–1	Niv (240 mg/kg q2w or 360 mg/kg q3w) + Ipi (1 mg/kg q6w)	396	63
								[CDDP (75 mg/m^2) or CDBCA (AUC 5)] + Gem (1,000 mg/m^2)/Pemt (500 mg/m^2) [M][S]		
Herbst, 2020	USA	III	OS	NSCLC	2	IV	ECOG 0–1	Atz (1,200 mg)	572	65
								[CDDP (75 mg/m^2) or CDBCA (AUC 6)] + Pemt 500 mg/m^2 [M]		
Kader, 2013	Egypt	II	Toxicity, PFS	NSq	2	IIIb, IV	ECOG 0–2	CDBCA (AUC 5) + Ptx (60 mg/m^2) + Bev (7.5 mg/kg)	41	52
								CDDP (75 mg/m^2) + Pemt (500 mg/m^2) [S]		
Kaira, 2019	Japan	II	PFS	NSq	2	III, IV, Rec	ECOG 0–1	CDDP (60mg/m^2) + S1 (80 mg/m^2) + Bev (15 mg/kg)	48	65
								CDDP (60 mg/m^2) + Pemt (500 mg/m^2) + Bev (15 mg/kg) [S]		
Kawahara, 2013	Japan	II	PFS	NSCLC	2	IIIb, IV, Rec	ECOG 0–1	CDBCA (AUC 6) + Dtx (60 mg/m^2)	90	67
								CDBCA (AUC 6) + Ptx (200 mg/m^2) [S]		
Khodadad, 2014	Iran	Not available	PFS	NSCLC	2	IIIb, IV	ECOG 0–2	CDDP (75 mg/m^2) + Dtx (75 mg/m^2)	100	51
								CDBCA (AUC 5) + Ptx (200 mg/m^2) [S]		

Table 1 (*continued*)

Table 1 (*continued*)

Study	Region	Phase	Primary outcome	Pathology	Arm	Stage	PS	Regimens	Pts	Median age
Kubota, 2015	Japan	III	OS (non-inf)	NSCLC	2	IIIb, IV, Rec	ECOG 0–1	CDDP [60 mg/m^2 (d 8)] + S1 [80 mg/m^2 (d 1–14 po bid)]	608	62
								CDDP (80 mg/m^2) + Dtx (60 mg/m^2) [S]		
Langer, 2016	USA	II	ORR	NSq	2	IIIb, IV	ECOG 0–1	CDBCA (AUC 5) + Pemt (500 mg/m^2) + Pemb (200 mg)	42	63
								CDBCA (AUC 5) + Pemt (500 mg/m^2) [M][S]		
Lee, 2020	South Korea	III	PFS	NSq	2	IIIb, IV, Rec	Not available	CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) + Niv (360 mg)	550	Not available
								CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) [M][S]		
Martoni, 2005	Italy	III	OR, TTP	NSCLC	2	IIIb, IV, Rec	KPS ≥70%	CDDP (75 mg/m^2) + Vnr [25 mg/m^2 (d 1, 8)]	286	63
								CDDP (75 mg/m^2) + Gem [1,200 mg/m^2 (d 1, 8)] [S]		
Melosky, 2019	Canada	II	RR	NSq	2†	IIIb, IV	ECOG 0–1	Plt [CDDP (75 mg/m^2) or CDBCA (AUC 6)] + Pemt (500 mg/m^2) + selumetinib (75 mg)	62	66
								Plt [CDDP (75 mg/m^2) or CDBCA (AUC 6)] + Pemt (500 mg/m^2) [M][S]		
Minami, 2013	Japan	II	PFS	NSCLC	2	IIIb, IV	ECOG 0–1	CDBCA (AUC 6) + Ptx (200 mg/m^2)	50	64
								CDBCA (AUC 5) + Gem [1,000 mg/m^2 (d 1, 8)] [S]		
Mok, 2019, nsq	HongKong	III	OS	NSq	2	IIIb, IV, Rec	ECOG 0–1	Pemb (200 mg)	404	63
								CDBCA (AUC 5–6) + (Ptx 200 mg/m^2 or Pemt 500 mg/m^2) [M]		
Niho, 2012	Japan	II	PFS	NSq	2	IIIb, IV, Rec	ECOG 0–1	CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg)	180	61
								CDBCA (AUC 6) + Ptx (200 mg/m^2) [S]		

Table 1 (*continued*)

Table 1 (*continued*)

Study	Region	Phase	Primary outcome	Pathology	Arm	Stage	PS	Regimens	Pts	Median age
Novell, 2017	Italy	II	PFS	NSq	2	IV, Rec	ECOG 0–1	CDDP (75 mg/m^2) + Pemt (500 mg/m^2) + cixutumumab (20 mg/kg)	172	59
								CDDP (75 mg/m^2) + Pemt (500 mg/m^2) [M][S]		
Ohe, 2007	Japan	III	OS (non-inf)	NSCLC	4	IIIb, IV	ECOG 0–1	CDDP (80 mg/m^2) + Cpt11 [60 mg/m^2 (d 1, 8, 15)]	602	62
								CDBCA (AUC 6) + Ptx (200 mg/m^2)		
								CDDP (80 mg/m^2) + Gem [1,000 mg/m^2 (d 1, 8)]		
								CDDP (80 mg/m^2) + Vnr [25 mg/m^2 (d 1, 8)] [S]		
Okamoto, 2010	Japan	III	OS (non-inf)	NSCLC	2	IIIb, IV	ECOG 0–1	CDBCA (AUC 5) + S1 [80 mg/m^2 (d 1–14 po bid)]	564	64
								CDBCA (AUC 6) + Ptx (200 mg/m^2) [S]		
Ouyang, 2018	China	III	PFS	NSCLC	2	IIIb, IV, Rec	ECOG 0–2	CDDP (30 mg/m^2 d2,4) + Vnr [25 mg/m^2 (d 1, 8)] + dulanermin (75 μg/kg)	453	57
								CDDP (30 mg/m2 d2,4) + Vnr [25 mg/m^2 (d 1, 8)] [M][S]		
Papadimitrakopoulou, 2018	USA	III	PFS, OS	NSq	2	IV	ECOG 0–1	[CDDP (75 mg/m^2) or CDBCA (AUC 6)] + Pemt (500 mg/m^2) + Atz (1,200 mg)	136	64
								[CDDP (75 mg/m^2) or CDBCA (AUC 6)] + Pemt (500 mg/m^2) [M][S]		
Patel, 2013	USA	III	OS	NSq	2	IIIb, IV	ECOG 0–1	CDBCA (AUC 6) + Pemt (500 mg/m^2) + Bev (15 mg/kg)	939	65
								CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) [S]		
Paz-Ares, 2020	Germany	III	OS	NSCLC	2	IV, Rec	ECOG 0–1	Niv (360 mg q3w) + Ipi (1 mg/kg q6w) + (1 of 4 platinum doublets, 2 cycles)	535.76	65
								1 of 4 platinum doublets, 4 cycles [M]		

Table 1 (*continued*)

Table 1 (*continued*)

Study	Region	Phase	Primary outcome	Pathology	Arm	Stage	PS	Regimens	Pts	Median age
Ramalingam, 2017, NSq	USA	II	PFS	NSq	2	IV	ECOG 0–1	CDBCA (AUC 6) + Ptx (200 mg/m^2) + veliparib (120 mg)	82	63
								CDBCA (AUC 6) + Ptx (200 mg/m^2) [M][S]		
Reck, 2009	Germany	III	PFS	NSq	2[§]	IIIb, IV, Rec	ECOG 0–1	CDDP (80 mg/m^2) + Gem [1,250 mg/m^2 (d 1, 8)] + Bev (7.5 or 15 mg/kg)	1,043	58
								CDDP (80 mg/m^2) + Gem [1,250 mg/m^2 (d 1, 8)] [S]		
Rizvi, 2020	USA	III	OS, PFS	NSCLC	3	IV	ECOG 0–1	Dur (20 mg/kg)	644	65
								Dur 20 mg/kg + Trml (1 mg/kg)		
								1 of 5 platinum doublets [M]		
Rodrigues, 2011	Argentina	III	G3/4PFS	NSq	2	IIIb, IV	ECOG 0–2	CDBCA (AUC 5) + Pemt (500 mg/m^2)	260	60
								CDBCA (AUC 5) + Dtx (75 mg/m^2) [S]		
Sandler, 2006	USA	III	OS	NSq	2	IIIb, IV	ECOG 0–1	CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg)	602	63
								CDBCA (AUC 6) + Ptx (200 mg/m^2) [S]		
Scagliotti, 2008	Italy	III	OS (non-inf)	NSCLC	2	IIIb, IV	ECOG 0–1	CDDP (75 mg/m^2) + Pemt (500 mg/m^2)	1,252	61
								CDDP (75 mg/m^2) + Gem [1,250 mg/m^2 (d 1, 8)] [S]		
Scagliotti, 2002	Italy	III	Not available	NSCLC	3	IIIb, IV, Rec	ECOG 0–2	CDDP (75 mg/m^2) + Gem [1,250 mg/m^2 (d 1, 8)]	612	63
								CDBCA (AUC 6) + Ptx (225 mg/m^2)		
								CDDP (100 mg/m^2) + Vnr [25 mg/m^2 (weekly)] [S]		
Schiller, 2002	USA	Not available	OS	NSCLC	3	IIIb, IV, Rec	ECOG 0–2	(CDDP (75 mg/m^2) or CDBCA (AUC 6)) + Ptx (135 or 225 mg/m^2)	1,207	63
								CDDP (75 mg/m^2) + Gem [1,000 mg/m^2 (d 1, 8, 15)]		
								CDDP (75 mg/m^2) + Dtx (75 mg/m^2) [S]		

Table 1 (*continued*)

Table 1 (*continued*)

Study	Region	Phase	Primary outcome	Pathology	Arm	Stage	PS	Regimens	Pts	Median age
Smit, 2003	Netherlands	III	OS	NSCLC	2†	IIIb, IV	ECOG 0–2	CDDP (80 mg/m^2) + Ptx (175 mg/m^2)	319	57
								CDDP (80 mg/m^2) + Gem [1,250 mg/m^2 (d 1, 8)] [S]		
Socinski, 2018	Germany	III	PFS, OS	NSq	2†	IV, Rec	ECOG 0–1	CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) + Atz (1,200 mg)	652	63
								CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) [M][S]		
Spigel, 2019	USA	II	PFS	NSq	2	IV	ECOG 0–1	CDBCA (AUC 6) + Pemt (500 mg/m^2) + apatorsen (600 mg)	155	66
								CDBCA (AUC 6) + Pemt (500 mg/m^2) [M][S]		
Sun, 2015	Korea	II	RR	NSq	2¶	IIIb, IV, Rec	ECOG 0–1	CDDP (70 mg/m^2) + Pemt (500 mg/m^2)	321	60
								CDDP (70 mg/m^2) + Gem [1,000 mg/m^2 (d 1, 8)] [S]		
Tan, 2009	Singapore	III	TTF	NSCLC	2	IIIb, IV, Rec	KPS ≥80%	CDDP (80 mg/m^2) + Vnr [30 (d 1), 80 (d 8 po) mg/m^2]	390	61
								CDDP (75 mg/m^2) + Dtx (75 mg/m^2) [S]		
Thomas, 2006	France	II	RR	NSCLC	2	IIIb, IV	ECOG 0–2	CDBCA (AUC 6) + Gem [1,250 mg/m^2 (d 1, 8)]	100	58
								CDDP (80 mg/m^2) + Vnr [30 mg/m^2 (weekly)] [S]		
Treat, 2010	USA	III	OS	NSCLC	2†	IIIb, IV, Rec	ECOG 0–2	CDBCA (AUC 5.5) + Gem [1,000 mg/m^2 (d 1, 8)]	758	64
								CDBCA (AUC 6) + Ptx (225 mg/m^2) [S]		
Von Pawel, 2018	Germany	II	PFS	NSq	2	IV, Rec	ECOG 0–1	CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) + parsatuzumab (600 mg)	104	64
								CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg) [M][S]		

Table 1 (*continued*)

Table 1 (*continued*)

Study	Region	Phase	Primary outcome	Pathology	Arm	Stage	PS	Regimens	Pts	Median age
West, 2019	Italy	III	PFS, OS	NSq	2	IV	ECOG 0–1	CDBCA (AUC 6) + nabPtx [100 mg/m^2(d 1, 8, 15)] + Atz (1,200 mg)	368	64
								CDBCA (AUC 6) + nabPtx [100 mg/m^2(d 1, 8, 15)] [M][S]		
Wheatley, 2019	USA	II	PFS	NSCLC	2	IIIb, IV	ECOG 0–1	CDBCA (AUC 6) + Ptx (200 mg/m^2) + MEDI-575 (25 mg/m^2)	81	Not available
								CDBCA (AUC 6) + Ptx (200 mg/m^2) [M][S]		
Wu, 2020	China	III	OS	NSCLC	2	IIIb, IV, Rec	ECOG 0–1	Pemb (200 mg)	116	62
								CDBCA (AUC 5–6) + (Ptx 200 mg/m^2 or Pemt 500 mg/m^2) [M][S]		
Wu, 2014	China	III	OS	NSq	2	IIIb, IV	ECOG 0–1	CDDP (75 mg/m^2) + Pemt (500 mg/m^2)	256	57
								CDDP (75 mg/m^2) + Gem [1,250 mg/m^2 (d 1, 8)] [S]		
Yang, 2012	China	Not available	RR	NSCLC	2	IIIb, IV	ECOG 0–2	Cdgp (80 mg/m^2) + Gem [1,250 mg/m^2 (d 1, 8)]	62	57
								CDBCA (AUC 5) + Gem [1,250 mg/m^2 (d 1, 8)] [S]		
Yang, 2020	China	III	PFS	NSq	2	IIIb, IV	ECOG 0–1	[CDDP (75 mg/m^2) or CDBCA (AUC 5)] + Pemt (500 mg/m^2) + Sint (200 mg)	268	61
								[CDDP (75 mg/m^2) or CDBCA (AUC 5)] + Pemt (500 mg/m^2) [M][S]		
Zhang, 2013	China	II	PFS	NSCLC	2	IIIb, IV, Rec	ECOG 0–1	CDDP (75 mg/m^2) + Pemt (500 mg/m^2)	205	54
								CDDP (75 mg/m^2) + Gem [1,000 mg/m^2 (d 1, 8)] [S]		
Zhou, 2015	China	III	PFS	NSq	2	IV, Rec	ECOG 0–1	CDBCA (AUC 6) + Ptx (175 mg/m^2) + Bev (15 mg/kg)	276	57
								CDBCA (AUC 6) + Ptx (175 mg/m^2) [S]		

Table 1 (*continued*)

Table 1 (*continued*)

Study	Region	Phase	Primary outcome	Pathology	Arm	Stage	PS	Regimens	Pts	Median age
Zhou, 2020	China	III	PFS	NSq	2	IIIb, IV	ECOG 0–1	CDBCA (AUC 5) + Pemt (500 mg/m^2) + camrelizumab (200 mg)	323	60
								CDBCA (AUC 5) + Pemt (500 mg/m^2) [M][S]		
Zhu, 2018	China	Not available	Not available	NSCLC	2	III, IV	ECOG 0–2	CDDP (75 mg/m^2) + Pemt (500 mg/m^2)	240	53
								CDDP (75 mg/m^2) + Gem (1,000 mg/m^2) [S]		
Zinner, 2015	USA	III	G4PFS	NSq	2	IV	ECOG 0–1	CDBCA (AUC 6) + Ptx (200 mg/m^2) + Bev (15 mg/kg)	361	66
								CDBCA (AUC 6) + Pemt (500 mg/m^2) [S]		

Study: first author, publication year, specific study name if available are presented; updated: updated data that were published later were available; patients: numbers of patients randomized for evaluated arms; median age: when median age (years) is not available, average age (years) is presented instead. †, 3>2 (excluded); ‡, 4>2 (excluded); §, two arms were regarded as one arm; ¶, stratified by TS, then randomized: the original study evaluated regimen(s) out of our concern. [M]: study incorporated in main model; [S]: study incorporated in separate model. NS, not specified; OS, overall survival; PFS, progression-free survival; QOL, quality of life; RR, response rate; DCR, disease control rate; TTP, time to progression; AE, adverse event; G3/4PFS, PFS without grade 3/4 AE; G4PFS, PFS without grade 4 AE; non-inf, primary outcome was evaluated by non-inferiority analysis; NS, not specified; NSCLC, non-small cell lung cancer; NSq, non-squamous carcinoma; Rec, recurrent; ECOG, Eastern Cooperative Oncology Group performance status; KPS, Karnofsky performance status; CDDP, cisplatin; CBDCA, carboplatin; Cdgp, nedaplatin; Dtx, docetaxel; Ptx, paclitaxel; Vnr, vinorelbine; Gem, gemcitabine; Cpt11, irinotecan; Pemt, pemetrexed; S1, Tegafur gimeracil oteracil; d, day; po, oral administration; bid, twice daily.

Efficacy analysis

Data for HRos were obtained in 26 studies with 7,142 patients (*Table 1*). In the main model, the HRos of 23 pairwise comparisons ranged from 0.55 to 1.64, with a median of 0.94. Q statistics and a test for heterogeneity did not reveal inconsistency at any level (whole network level I^2=0%, total; P=0.348, within designs; P=0.348) (*Figure 2*, Figure S1). Eligible treatments were clustered into the same node. The platinum regimen + Pemb (HRos =0.55, 95% CI: 0.34–0.89, P=0.015) showed the best OS, followed by the platinum regimen + nivolumab (Niv) + ipilimumab (Ipi) (HR = 0.61, 95% CI: 0.44–0.84, P=0.003) (*Figure 3A*). The HRos of these regimens were significant against the platinum regimen. The HRos of the other regimens were not significantly different from that of the platinum regimen. The platinum regimen + atezolizumab (Atz) (HR =0.70, 95% CI: 0.45–1.08, P=0.110) did not show superiority to the platinum regimen in terms of OS. We conducted a subgroup analysis excepting conference abstracts, which did not conflict with the main analysis with the conference abstract (Figure S2). In the separate model, the platinum regimen + Pemt + Pemb (HR =0.55, 95% CI: 0.34–0.89, P=0.014) showed the best OS. This regimen was significantly different in the separate model (Figure S3).

The HRpfs of the platinum regimen + Pemb were significantly decreased compared to the platinum regimen alone (HRpfs =0.55, 95% CI: 0.37–0.81, P=0.003) (*Figure 3B*). The lowest HRpfs was observed in the platinum regimen + dulanermin (HRpfs =0.40, 95% CI: 0.32–0.50, P<0.001), followed by the platinum regimen + sintilimab (Sint), the platinum regimen + Pemb, the platinum regimen + Niv, the platinum regimen + camrelizumab, and the platinum regimen + Atz.

Safety analysis

The lowest risk of grade III adverse events was observed in the Pemb arm (OR =0.20, 95% CI: 0.11–0.37, P<0.001) against the platinum regimen, followed by Niv, durvalumab,

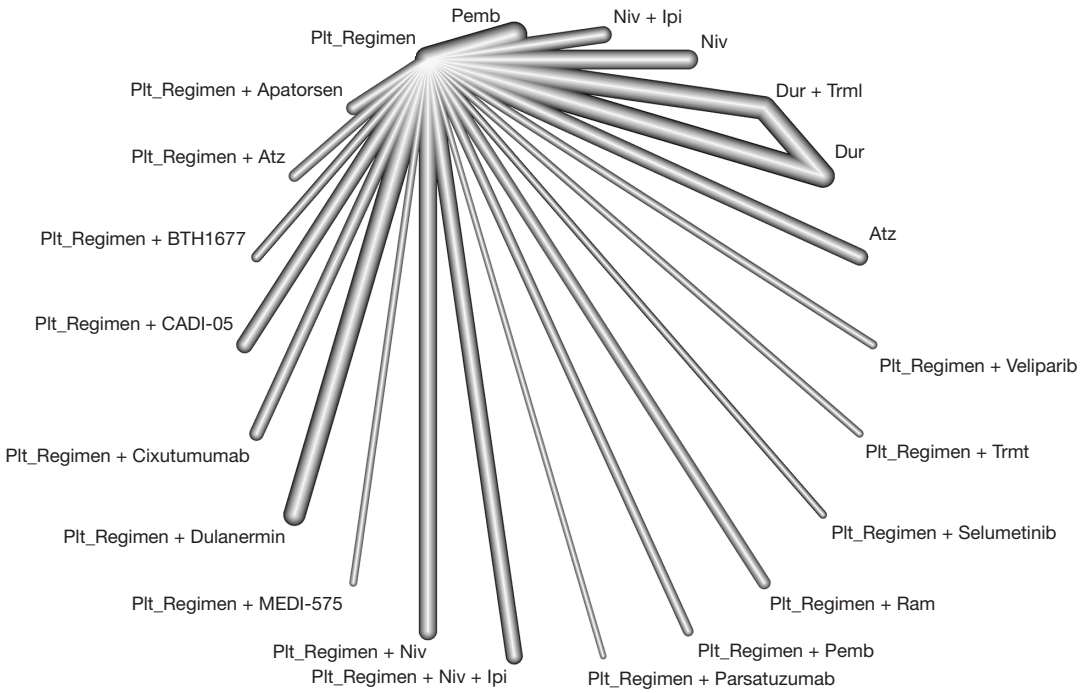

Figure 2 Network diagram for the primary endpoint, HR for OS. Addiction model, whole network level (I^2=0%, P=0.3483). HR, hazard ratio; OS, overall survival; Plt, platinum regimen; Pemb, pembrolizumab; Niv, nivolumab; Ipi, ipilimumab; Dur, durvalumab; Trml, tremelimumab; Atz, atezolizumab; Trmt, tromethamine; Ram, ramucirumab

and Atz (*Figure 3C,3D*). Regarding chemotherapy-related death, there was no significant difference in regimens except the platinum regimen + Sint (OR =0.31, 95% CI: 0.11–0.90, P=0.029).

Discussion

We carried out the first network meta-analysis to compare regimens including cytotoxic agents, molecular targeted therapies, and ICIs for chemo-naïve incurable NSCLC with low PD-L1 expression. The network method was able to concurrently compare a variety of chemotherapy regimens. Moreover, the sufficient statistical power supported by the substantial studies ensured the validity of the results.

The immune response activated by PD-L1 inhibition is enhanced by cytotoxic chemotherapy, which reduces regulatory T-cell activity (22). Combination therapy is expected to improve the anticancer activity. Among the 22 regimens, the HRos of the platinum regimen + Pemb and the platinum regimen + Niv + Ipi were 0.55 (95% CI: 0.34–0.89) and 0.61 (95% CI: 0.44–0.84), respectively, with the platinum regimen alone as the reference. These regimens in this order showed the best performance in terms of OS (*Figure 3A*). The platinum regimen + Pemb also showed a high rank in terms of improving PFS (*Figure 3B*). Combination therapy is said to provide an early disease control relative to ICI monotherapy (15), preventing early disease progression. Moreover, less than half of patients with advanced NSCLC receive second-line therapy (23). Patients treated with monotherapy may miss the opportunity to receive other regimens.

The adverse events of the platinum regimen + Pemb (ORae =1.30, 95% CI: 0.68–2.49) and the platinum regimen + Niv + Ipi (ORae =1.24, 95% CI: 0.52–2.95) were not significantly greater than those of the platinum regimen alone (*Figure 3C*). We recommend the platinum regimen + Pemb or the platinum regimen + Niv + Ipi when the PD-L1 TPS is 1–49%. By contrast, there was no significant difference between the HRos of ICI monotherapy and the platinum regimen; therefore, ICI monotherapy is not recommended. However, ICI monotherapy tends to have a low risk of adverse events. The ORae with Pemb

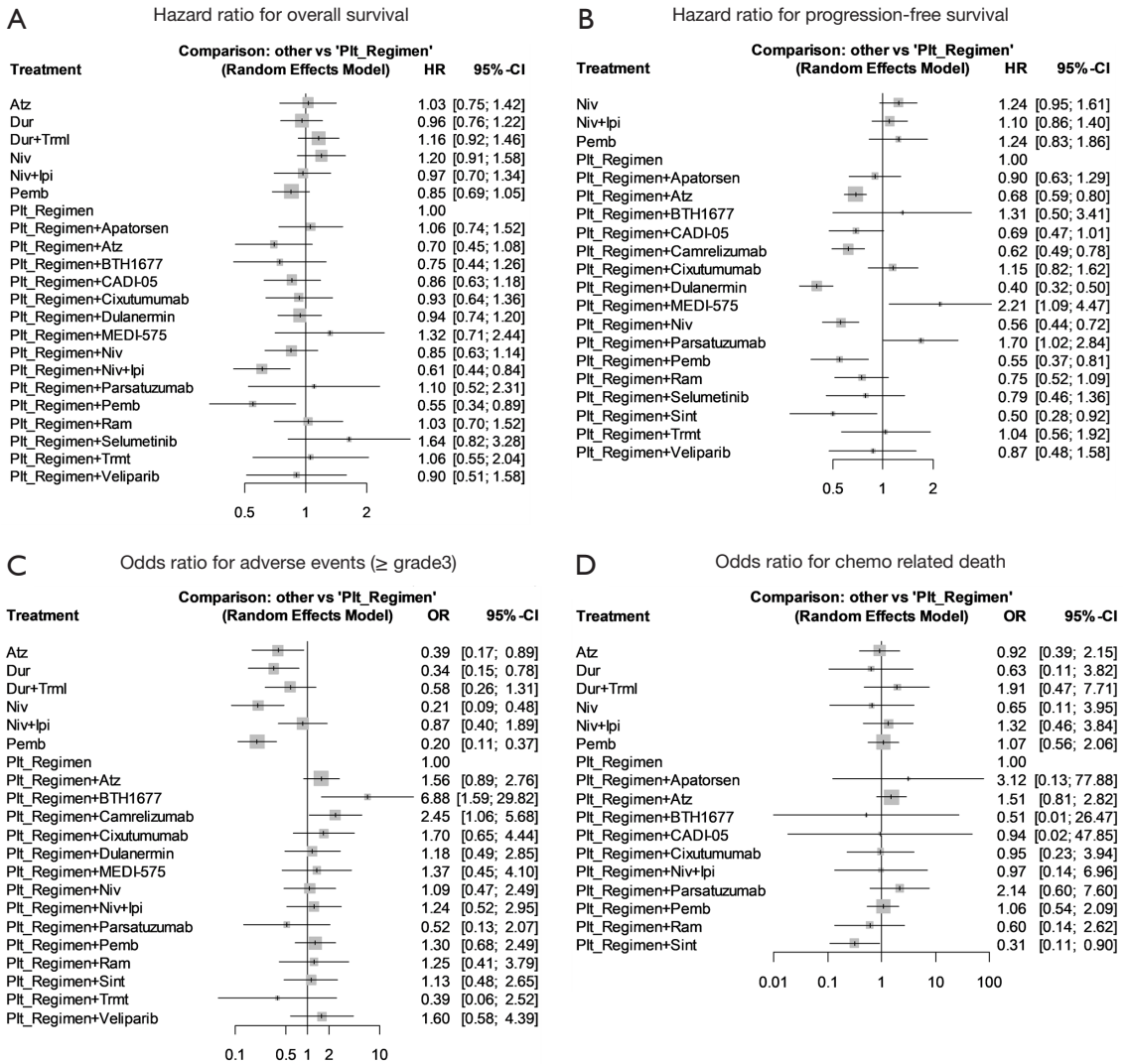

Figure 3 Forest plots for primary and secondary outcomes in main model. (A) HR for OS. (B) HR for PFS. (C) OR for adverse events (≥ grade 3). (D) OR for chemo related death. HR, hazard ratio; OS, overall survival; PFS, progression-free survival; OR, odds ratio; Plt, platinum regimen; Pemb, pembrolizumab; Niv, nivolumab; Ipi, ipilimumab; Dur, durvalumab; Trml, tremelimumab; Atz, atezolizumab; Trmt, tromethamine; Ram, ramucirumab; Sint, sintilimab; HR, hazard ratio; OR, odds ratios; CI, confidence interval.

monotherapy was the lowest in this study (ORae =0.20, 95% CI: 0.11–0.37) (*Figure 3C*). These regimens can be considered if the patients are elderly and have a low PS.

The platinum regimen + dulanermin did not have a significant effect on OS compared to the platinum regimen, but this regimen had the lowest HRpfs. Dulanermin is recombinant TRAIL/Apo2L, a novel molecular target, which can induce apoptosis in tumor cells. However, dulanermin is administered intravenously on days 1 to 14 in a cycle until disease progression.

When a patient fulfills the criteria of this study, the Japanese Lung Cancer Society Guideline (4) recommends adding Atz to the platinum regimen in accordance with the guidelines of the American Society of Clinical Oncology, National Comprehensive Cancer Network, and European Society for Medical Oncology. Our study did not show a significant effect of the Atz regimen on OS (HR =0.70, 95% CI: 0.45–1.08) (*Figure 3A*). Impower 150 (24), which compared platinum + Ptx + Bev + Atz and platinum + Ptx + Bev, indicated that adding Atz was effective in terms of PFS

(HRpfs =0.68, 95% CI: 0.56–0.82, P<0.001), but the HRos in patients with low PD-L1 expression (1–49%) was not shown.

There were some limitations to our study. First, most of the evaluated original trials had a high risk of bias, as judged by the Cochrane tool. Unfortunately, in practical terms, it is difficult to conduct a double-blinded trial without sponsorship, and we believe that these factors do not largely reduce the credibility. Second, because the main model regarded each platinum regimen as identical, the results may not be accurate. However, we believe that the two models have similar consequences. Thirdly, different PD-L1 assays were usually selected for pathological specimen based on the ICI drug selection. Furthermore, there is no universally accepted judgement for PD-L1 positivity. As a result, even though we tried to find out original studies with cutoff value of PD-L1 1% and 50%, such cutoff values might be slightly different among studies (25). In conclusion, we conducted a systematic review and network meta-analysis examining ICIs in patients with non-squamous NSCLC with low PD-L1 expression. Based on 20,257 NSCLC patients constituting 59 RCTs, the platinum regimen + Pemb and the platinum regimen + Niv + Ipi seem to be reasonable first-line regimens for non-squamous NSCLC with a PD-L1 TPS 1–49%.

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Footnote

Reporting Checklist: The authors have completed the PRISMA NMA reporting checklist. Available at https://dx.doi.org/10.21037/tlcr-21-419

Peer Review File: Available at https://dx.doi.org/10.21037/tlcr-21-419

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tlcr-21-419). Dr. NH has received personal fee from Taiho Pharmaceutical and research grant from Taiho Pharmaceutical outside of the work. Dr. KW has received personal fee from AstraZeneca, Ono Pharmaceutical and Boehringer Ingelheim outside of the work. Dr. YH has received personal fee from AstraZeneca and Boehringer Ingelheim outside of the work. Dr. NK has received personal fee from Chugai Pharmaceutical, AstraZeneca, Boehringer Ingelheim, Sanofi, Ono Pharmaceutical, MSD, Bristol Myers Squibb, Eli Lilly, Kyowa Kirin and research grant from Chugai Pharmaceutical, Boehringer Ingelheim, MSD, Eli Lilly, Kyowa Kirin, Daiichi Sankyo, Pfizer outside of the work. Dr. TK has received personal fee from Chugai Pharmaceutical, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Taiho Pharmaceutical, Chugai Pharmaceutical, Daiichi Sankyo, Sanofi, Pfizer and research grant from MSD, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, Chugai Pharmaceutical, Daiichi Sankyo, Pfizer, Shionogi outside of the work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Appendix 1

The amendments to information in the protocol

- OR of objective response rate was not evaluated;
- The populations with TPS 0% were excluded.

Appendix 2

Search formulas

MEDLINE

(non-small OR squamous OR adenocarcinoma OR non-squamous OR NSCLC) AND (lung cancer OR lung carcinoma OR lung malignancy OR lung tumor OR NSCLC) AND (advanced OR metastasis OR recurrent OR recurrence OR inoperable OR relapsed OR incurable OR stage 3 OR stage 3a OR stage 3b OR stage III OR stage IIIa OR stage IIIb OR stage 4 OR stage 4a OR stage 4b OR stage IV OR stage IVa OR stage IVb) AND (naïve OR untreated OR chemo naïve OR chemo-naïve OR non-treated OR nontreated OR first-line OR front-line OR initial treatment OR "previously not treated") AND (randomised[title] OR randomized[title] OR randomly OR phase 3[title] OR phase III[title] OR RCT[title] OR (nejm AND (randomized OR randomly OR phase 3 OR phase III OR RCT))).

Appendix 3

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https://dx.doi.org/10.21037/tlcr-21-419

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Appendix 4

Characteristics of the included studies

The included studies were reported in a variety of countries worldwide. The United States of America had the most included studies (20 studies). The articles were published between 2000 and 2020. Among 68 reports, 37 were phase III studies, 26 evaluated OS as the primary endpoint, 43 included ECOG 0–1 cases. We regarded 3 studies as three-arm studies, 1 study as a four-arm study, and the other 64 as two-arm studies.

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Table S1 The Cochrane Risk of Bias evaluation sheet

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Belani, 2017	Low	High	Low	Low	Low	Low
Bennouna, 2014	Unclear	High	Low	Low	Low	High
Carbone, 2017	Low	High	Low	Low	Low	High
Chang, 2008	Unclear	High	Low	Low	Low	Low
Chen, 2007	Unclear	High	Low	Low	High	Low
Chen, 2004	Unclear	High	Low	Low	Low	Low
Comella, 2000	Low	High	Low	Low	Low	Low
Doebele, 2015	Low	High	Low	Low	Low	High
Douillard, 2005	Unclear	High	Low	Low	Low	High
Edelman, 2004	Low	High	Low	Low	Low	Low
Engle-Riedel, 2018	Low	High	Low	Low	Low	Low
Fossella, 2003	Low	High	Low	Low	Low	High
Galetta, 2015	Unclear	High	Low	Low	Low	Low
Gandhi, 2018	Low	Low	Low	Low	Low	High
Garon, 2016	Low	High	Low	Low	Low	High
Gebbia, 2010	Low	High	Low	Low	Low	Low
Gebbia, 2003	Unclear	High	Unclear	Low	Low	Low
Gronberg, 2009	Low	High	Unclear	Low	Low	High
Harada, 2018	Unclear	High	Low	Low	Low	Unclear
Helbekkmo, 2007	Low	High	Low	Low	Low	Low
Hellmann, 2019	Low	High	Low	Low	Low	High
Herbst, 2020	Low	High	Low	Low	Low	High
Kader, 2013	High envelope	High	Low	Low	Low	Low
Kaira, 2019	Low	High	Low	Low	Low	High
Kawahara, 2013	Low	High	Low	Low	Low	Low
Khodadad, 2014	Unclear	High	Low	Low	Low	High
Kubota, 2015	Low	High	Low	Low	Low	High
Langer, 2016	Low	High	Unclear	Low	Low	High
Lee, 2020	Unclear	Low	Low	Unclear	Low	High
Martoni, 2005	Unclear	High	Unclear	Low	Low	Low
Melosky, 2019	Low	High	Low	Low	Low	High
Minami, 2013	Unclear	High	Low	Low	Low	Low
Mok, 2019, NSq	Low	High	Low	Low	Low	High
Niho, 2012	Low	High	Low	Low	Low	High
Novell, 2017	Low	High	Low	Low	Low	High
Ohe, 2007	Low	High	Low	Low	Low	High
Okamoto, 2010	Low	High	Low	Low	Low	High
Papadimitrakopoulou, 2018	Unclear	High	Unclear	Unclear	Low	High
Ouyang, 2018	Low	Low	Low	Low	Low	High
Patel, 2013	Unclear	High	Low	Low	Low	High
Paz-Ares, 2020	Low	Low	Low	Low	Low	High
Ramalingam, 2017, NSq	Low	Low	Low	Low	Low	High
Reck, 2009	Unclear	High	Low	Low	Low	High
Rizvi, 2020	Low	High	Low	Low	Low	High
Rodrigues, 2011	Low	High	Low	Low	Low	High
Sandler, 2006	Unclear	High	Low	Low	Low	Low
Scagliotti, 2008	Low	High	Low	Low	High	High
Scagliotti, 2002	Unclear	High	Low	Low	Low	High
Schiller, 2002	Unclear	High	Low	Low	Low	Low
Smit, 2003	Low	High	Low	Low	Low	High
Socinski, 2018	Low	High	Unclear	Low	Low	High
Spigel, 2019	Low	Low	Low	Low	Low	High
Sun, 2015	Unclear	High	Low	Low	Low	High
Tan, 2009	Low	High	Low	Low	Low	Low
Thomas, 2006	Unclear	High	Low	Low	Low	High
Treat, 2010	Unclear	High	Low	Low	Low	High
Von Pawel, 2018	Low	Low	Low	Low	Low	High
West, 2019	Low	High	Low	Low	Low	High
Wheatley, 2019	Low	High	Low	Low	Low	High
Wu, 2020	Unclear	High	Low	Low	Low	High
Wu, 2014	Low	High	Low	Low	Low	High
Yang, 2012	Unclear	High	Low	High	Low	Low
Yang, 2020	Low	Low	Unclear	Low	Low	High
Zhang, 2013	Low	High	Low	Low	Low	High
Zhou, 2015	Low	Low	Low	Low	Low	Low
Zhou, 2020	Low	High	Unclear	Low	Low	High
Zhu, 2018	Low	High	Unclear	Low	High	Low
Zinner, 2015	Unclear	High	Low	Low	Low	High

One study had a high risk of selection bias due to randomization using an envelope method, 59 studies had a high risk of performance bias due to a non-blinded study design, 1 study had a high risk of attrition bias because 21% of the randomized patients did not receive the assigned regimen, and 3 studies had a high risk of reporting bias because the primary endpoint was not specified. Forty-six studies were marked as having a high risk of other bias for potential conflicts of interest because the studies were directly funded or advised by pharmaceutical companies.

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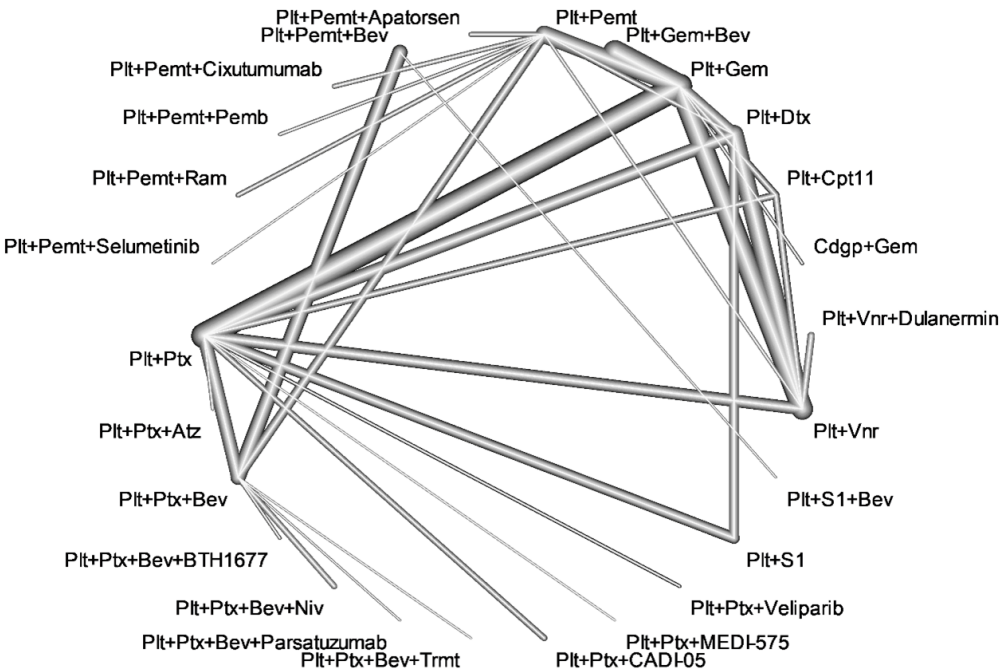

Figure S1 Network diagram for the primary endpoint, HR for OS. Separate model, Whole network level (I^2=0%, P=0.8940, total; P=0.8940, within designs; P=0.9491, between designs; 0.4876). HR, hazard ratio; OS, overall survival; Plt, platinum regimen; Pemt, pemetrexed; Gem, gemcitabine; Dtx, docetaxel; Cpt11, irinotecan; Cdgp, nedaplatin; Vnr, vinorelbine; S1, tegafur gimeracil oteracil; Bev, bevacizumab; Ptx, paclitaxel; Trmt, tromethamine; Niv, nivolumab; Atz, atezolizumab; Ram, ramucirumab; Pemb, pembrolizumab.

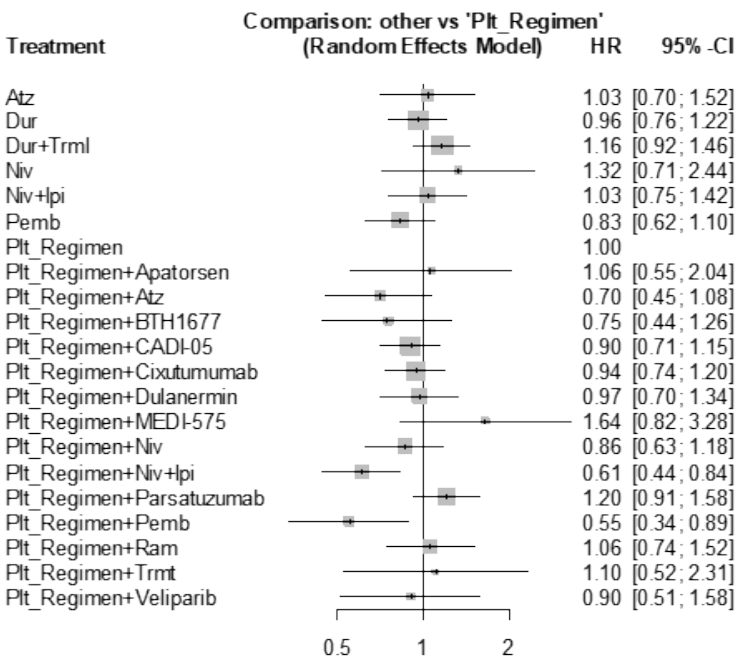

Figure S2 Forest plots for primary outcomes (HR for OS) in main model that excepted conference abstracts. HR, hazard ratio; OS, overall survival; Plt, platinum regimen; Pemb, pembrolizumab; Niv, nivolumab; Ipi, ipilimumab; Dur, durvalumab; Trml, tremelimumab; Atz, atezolizumab; Trmt, tromethamine; Ram, ramucirumab; CI, confidence interval.

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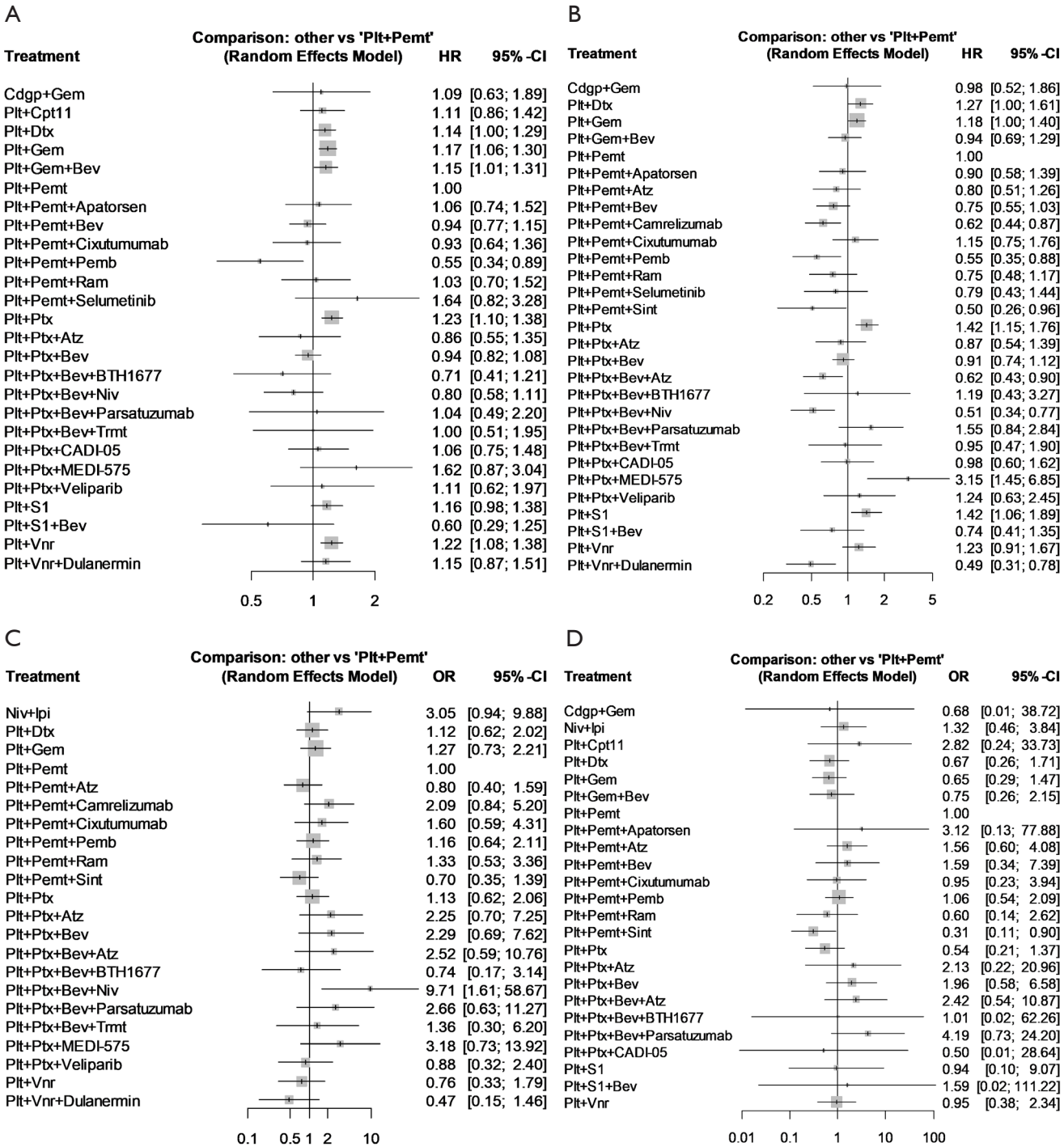

Figure S3 Forest plots for primary and secondary outcomes in separate model. (A) HR for OS. (B) HR for PFS. (C) OR for adverse events (≥ grade 3). (D) OR for chemo related death. HR, hazard ratio; OS, overall survival; PFS, progression-free survival; OR, odds ratio; Cdgp, nedaplatin; Gem, gemcitabine; Plt, platinum regimen; Cpt11, irinotecan; Dtx, docetaxel; Bev, bevacizumab; Pemt, pemetrexed; Pemb, pembrolizumab; Ram, ramucirumab; Ptx, paclitaxel; Atz, atezolizumab; Niv, nivolumab; Trmt, tromethamine; S1, tegafur gimeracil oteracil; Vnr, vinorelbine; Sint, sintilimab; CI, confidence interval.

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