

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

References

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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.

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.

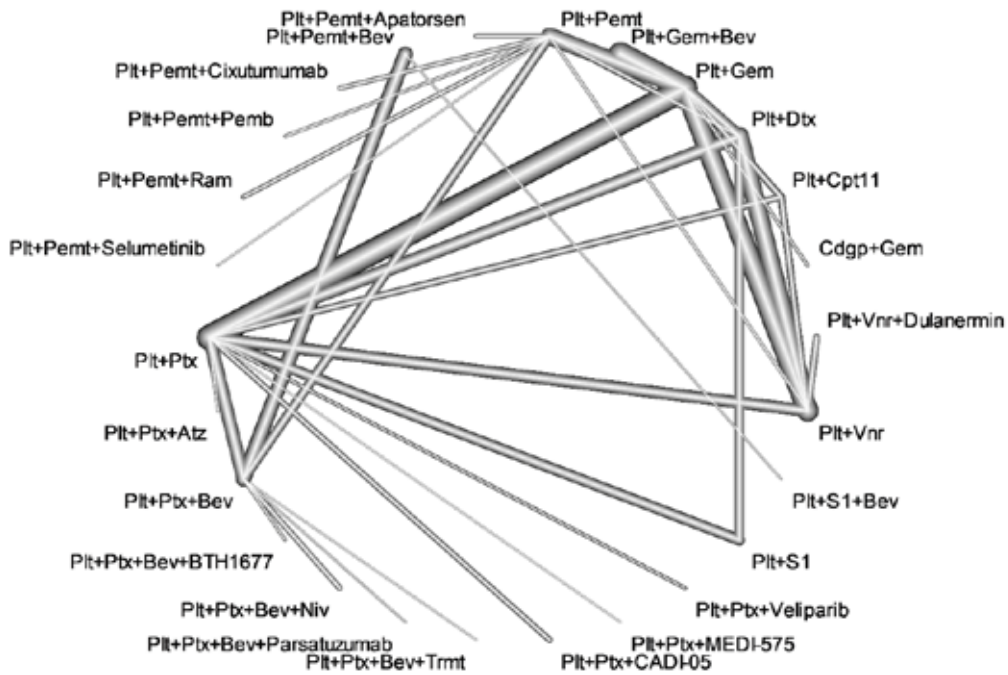


Figure S1 Network diagram for the primary endpoint, HR for OS. Separate model, Whole network level ($I^2=0\%$, $P=0.8940$, total; $P=0.8940$, within designs; $P=0.9491$, between designs; 0.4876). HR, hazard ratio; OS, overall survival; Plt, platinum regimen; Pemt, pemetrexed; Gem, gemcitabine; Dtx, docetaxel;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

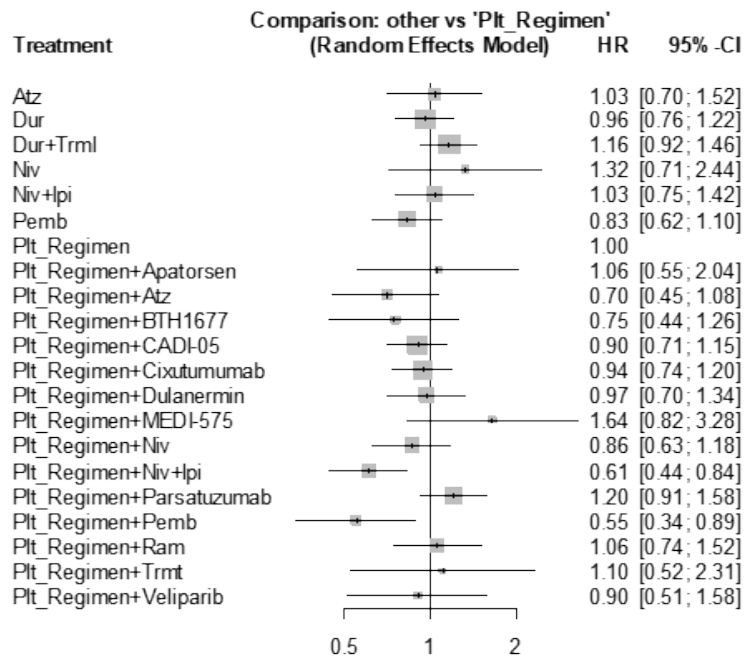
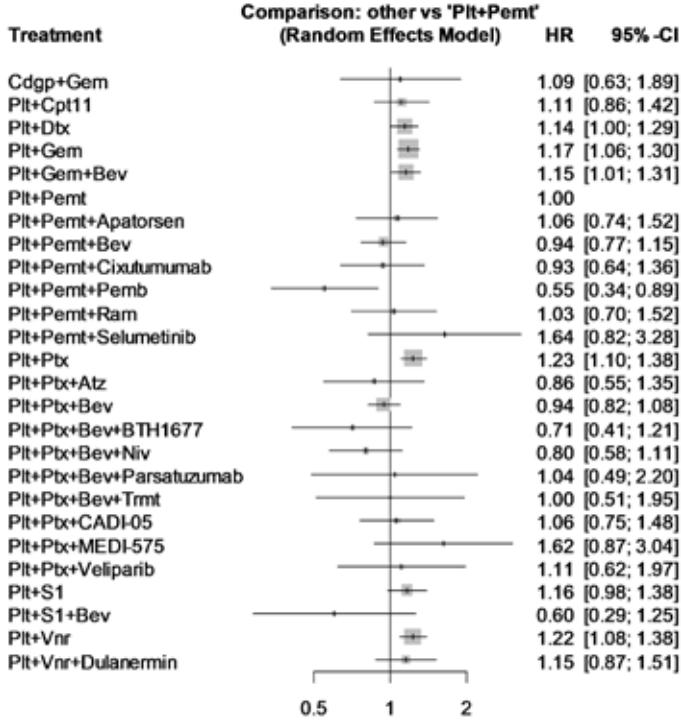
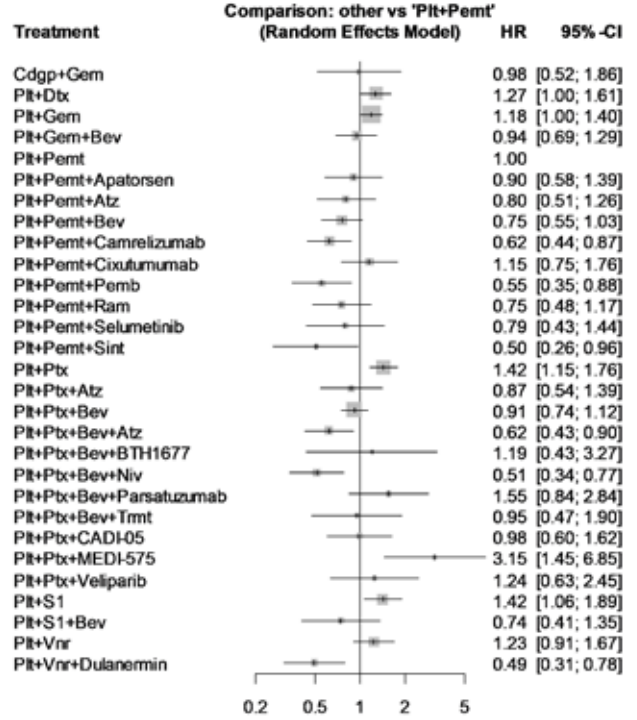


Figure S2 Forest plots for primary outcomes (HR for OS) in main model that excepted conference abstracts. HR, hazard ratio; OS, overall survival; Plt, platinum regimen; Pemb, pembrolizumab; Niv, nivolumab; Ipi, ipilimumab; Dur, durvalumab; Trml, tremelimumab; Atz, atezolizumab; Trmt, tromethamine; Ram,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

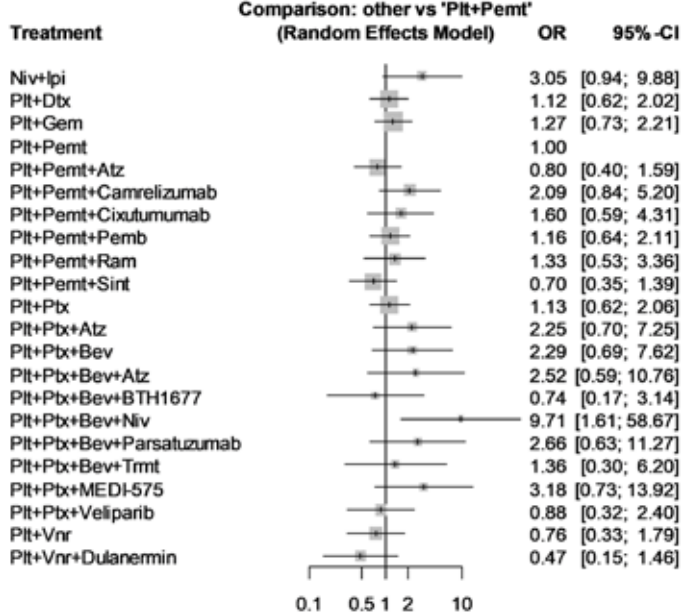
A



B



C



D

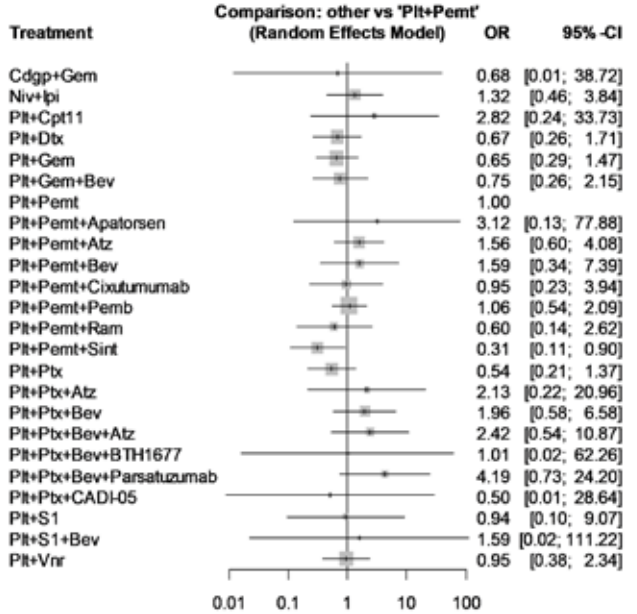


Figure S3 Forest plots for primary and secondary outcomes in separate model. (A) HR for OS. (B) HR for PFS. (C) OR for adverse events (\geq grade 3). (D) OR for chemo related death. HR, hazard ratio; OS, overall survival; PFS, progression-free survival; OR, odds ratio; Cdgp, nedaplatin; Gem, gemcitabine; 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.