

Appendix 1: Detail search strategies for PubMed, Embase, and the Cochrane Central Register of Controlled Trials databases

PubMed

((“lung cancer” [Title/Abstract]) AND (“NSCLC” [Title/Abstract]) OR (“Non small Cell” [Title/Abstract]) OR (“Non-Small-Cell” [Title/Abstract]) OR (“Non-Small Cell” [Title/Abstract])) OR (“Carcinoma, Non-Small-Cell Lung”[MeSH]))
 AND (“EGFR”[All Fields]) OR (“epidermal growth factor receptor”[All Fields])
 AND (“mutation”[All Fields]) OR (“exon”[All Fields]) OR (“exon 19”[All Fields]) OR (“exon 21”[All Fields]) OR (“19 deletion”[All Fields]) OR (“21 L858R”[All Fields]))
 AND (“pembrolizumab” [Supplementary Concept]) OR (“lambrolizumab” [Title/Abstract]) OR (“Keytruda” [Title/Abstract]) OR (“MK-3475” [Title/Abstract]) OR (“nivolumab” [Supplementary Concept]) OR (“MDX-1106” [Title/Abstract]) OR (“ONO-4538” [Title/Abstract]) OR (“BMS-936558” [Title/Abstract]) OR (“Opdivo” [Title/Abstract]) OR (“atezolizumab” [Supplementary Concept]) OR (“MPDL3280A” [Title/Abstract]) OR (“Tecentriq” [Title/Abstract]) OR (“RG7446” [Title/Abstract]) OR (“RG-7446” [Title/Abstract]) OR (“Durvalumab” [Title/Abstract]) OR (“Imfinzi” [Title/Abstract]) OR (“MEDI4736” [Title/Abstract]) OR (“Camrelizumab” [Title/Abstract]) OR (“SHR-1210” [Title/Abstract]) OR (“Tislelizumab” [Title/Abstract]) OR (“Sintilimab” [Title/Abstract]) OR (“IBI 308” [Title/Abstract]) OR (“anti-PDL1” [Title/Abstract]) OR (“anti-PD1” [Title/Abstract]) OR (“PD-1” [Title/Abstract]) OR (“PD-L1” [Title/Abstract]) OR (“Programmed Death 1” [Title/Abstract]) OR (“Programmed Cell Death 1 Receptor” [Title/Abstract]) OR (“Programmed Death Ligand 1” [Title/Abstract]) OR (“programmed cell death 1 ligand 1 protein” [Title/Abstract]) OR (“immune checkpoint inhibitor” [Title/Abstract]) OR (“immune therapy” [Title/Abstract]) OR (“immunotherapy” [Title/Abstract]))

Embase

(‘lung cancer’:ab,ti OR nsclc:ab,ti OR ‘non small cell’:ab,ti OR ‘non small cell lung cancer’/exp OR ‘non-small cell’:ab,ti)
 AND (‘EGFR’:ab,ti OR ‘epidermal growth factor receptor’:ab,ti)
 AND (‘mutation’ free text OR ‘exon’ free text OR ‘exon 19’ free text OR ‘exon 21’ free text OR ‘19 deletion’ free text OR ‘21 L858R’ free text)
 AND (‘pembrolizumab’/exp OR ‘lambrolizumab’:ab,ti OR ‘Keytruda’:ab,ti OR ‘MK-3475’:ab,ti OR ‘nivolumab’/exp OR ‘MDX-1106’:ab,ti OR ‘ONO-4538’:ab,ti OR ‘BMS-936558’:ab,ti OR ‘Opdivo’:ab,ti OR ‘atezolizumab’/exp OR ‘MPDL3280A’:ab,ti OR ‘Tecentriq’:ab,ti OR ‘RG7446’:ab,ti OR ‘RG-7446’:ab,ti OR ‘Durvalumab’:ab,ti OR ‘Imfinzi’:ab,ti OR ‘MEDI4736’:ab,ti OR ‘Camrelizumab’/exp OR ‘SHR-1210’:ab,ti OR ‘Tislelizumab’/exp OR ‘Sintilimab’/exp OR ‘IBI-308’:ab,ti OR ‘anti-PDL1’:ab,ti OR ‘anti-PD1’:ab,ti OR ‘PD-1’:ab,ti OR ‘PD-L1’:ab,ti OR ‘Programmed Death 1’:ab,ti OR ‘Programmed Cell Death 1 Receptor’:ab,ti OR ‘Programmed Death-Ligand 1’:ab,ti OR ‘programmed cell death 1 ligand 1 protein’:ab,ti OR ‘immune checkpoint inhibitor’:ab,ti OR ‘immune therapy’:ab,ti OR ‘immunotherapy’:ab,ti)

The Cochrane Central Register of Controlled Trials

- #1 MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
- #2 (lung OR pulmo*):ti,ab,kw
- #3 (cancer OR carcinoma OR neoplas*):ti,ab,kw
- #4 #2 AND #3
- #5 #1 OR #4
- #6 (EGFR OR ‘epidermal growth factor receptor’):ti,ab,kw
- #7 (mutation OR exon OR exon 19 OR exon 21 OR 19 deletion OR 21 L858R)
- #8 (‘pembrolizumab’ OR ‘lambrolizumab’ OR ‘Keytruda’ OR ‘MK-3475’ OR ‘nivolumab’ OR ‘MDX-1106’ OR ‘ONO-4538’ OR ‘BMS-936558’ OR ‘Opdivo’ OR ‘atezolizumab’ OR ‘MPDL3280A’ OR ‘Tecentriq’ OR ‘RG7446’ OR ‘RG-7446’ OR ‘Durvalumab’ OR ‘Imfinzi’ OR ‘MEDI4736’ OR ‘Camrelizumab’ OR ‘SHR-1210’ OR ‘Tislelizumab’ OR ‘Sintilimab’ OR ‘IBI 308’ OR ‘anti-PDL1’ OR ‘anti-PD1’ OR ‘PD-1’ OR ‘PD-L1’ OR ‘Programmed Death 1’ OR ‘Programmed Cell Death 1 Receptor’ OR ‘Programmed Death-Ligand 1’ OR ‘programmed cell death 1 ligand 1 protein’ OR ‘immune checkpoint inhibitor’ OR ‘immune therapy’ OR immunotherapy):ti,ab,kw
- #9 #5 AND #6 AND #7 AND #8

A

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
IMpower151	+	+	+	+	+	+
ORIENT31	+	+	+	+	+	+
ATLAS	+	?	+	+	+	?
HARMONi-A	+	+	+	+	+	+

B

	Representativeness of exposure cohort	Selection of non-exposure cohort	Ascertainment of exposure	Demonstration of outcome of interest	Comparability	Assessment of outcome	Follow-up long enough	Adequacy of follow up
J.Mazieres 2019	+	+	+	+	+	+	?	?
K.Hastings 2019	+	+	+	+	?	+	?	?
Takashi Ito 2022	+	+	+	+	+	+	+	?
Tao Jiang 2021	+	+	+	+	+	+	?	+
Tian Tian 2021	+	+	+	+	?	+	?	?
Yaping Long 2022	+	+	+	+	+	+	+	+
Xiaojin Guo 2022	+	+	+	+	+	+	?	?
Chunyang Zhou 2023	+	+	+	+	+	+	?	?
Jinfei Si 2023	+	+	+	+	+	+	?	?
Baohui Han 2024	+	+	+	+	+	+	+	+
Lu Chen 2024	+	+	+	+	?	+	?	+

Figure S1 The methodological quality and risk of bias of individual studies were evaluated using (A) Cochrane Risk of Bias 2 tool to assess the quality of included RCTs and (B) a modified Newcastle-Ottawa scale to assess other studies independently. RCT, randomized control trial.

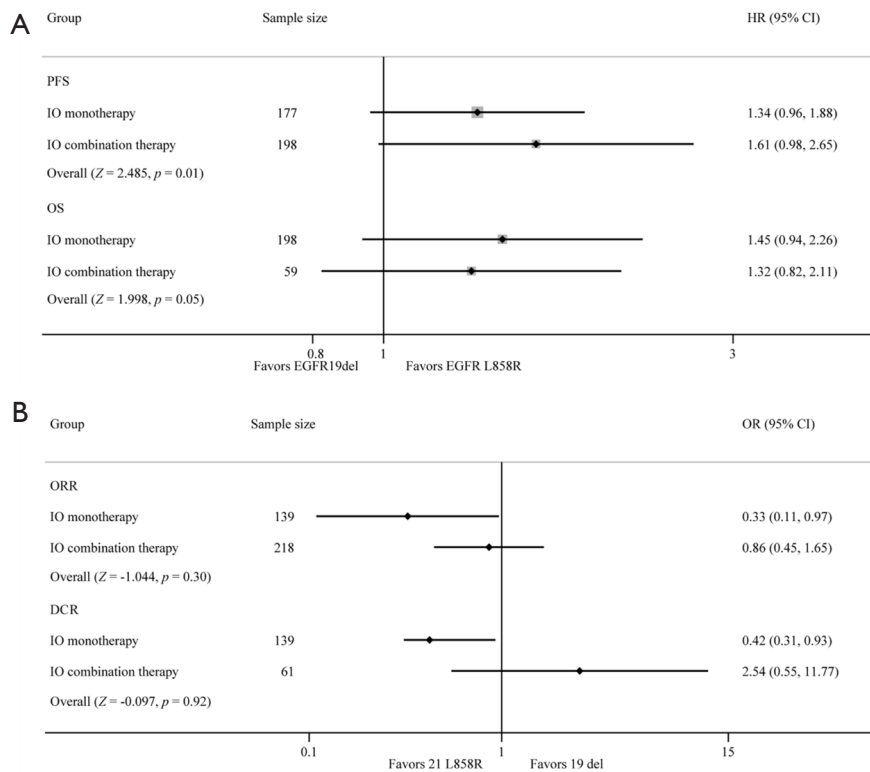


Figure S2 Subgroup analysis of 19 Del vs. 21 L858R in IO monotherapy or IO combination therapy for (A) PFS and OS (B) ORR and DCR. IO: including anti-PD-1/PD-L1 antibody; IO combination: including IO plus chemo or IO plus chemo and antiangiogenic therapy. HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; IO, immunotherapy; OS, overall survival; 19 Del, exon 19 deletion; 21 L858R, exon 21 L858R mutation; OR, odds ratio; ORR, objective response rate; DCR, disease control rate; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; chemo, chemotherapy.