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ORIGINAL RESEARCH

Efficacy and safety of first-line checkpoint inhibitors-based treatments for non-oncogene-addicted non-small-cell lung cancer: a systematic review and meta-analysis

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Background: Frontline immune checkpoint inhibitors (ICI)-based regimens in non-oncogene-addicted non-small-cell lung cancer (NSCLC) have been deeply investigated. To rank the available therapeutic options, we carried out a systematic review and Bayesian meta-analysis.
Methods: A comprehensive search for randomized controlled trials (RCTs) of ICI regimens, and a pairwise and a network meta-analysis (NMA) with an all-comers and a stratified strategy were conducted. Endpoints were overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and treatment-related adverse events (TRAEs).
Results: Nineteen RCTs involving 17 treatment regimens were included. For the all-comers population, pembrolizumab/chemotherapy (CT) and cemiplimab were most likely the best treatments. For programmed death-ligand 1 (PD-L1) <1% nivolumab/ipilimumab with/without CT, for PD-L1 >1% and 1%-49% pembrolizumab/CT and for PD-L1 >50% cemiplimab ranked first for OS. In non-squamous (NSQ), pembrolizumab with/without CT ranked first for OS; cemiplimab ranked worse than the unselected population. In squamous (SQ), pooled hazard ratio (HR) showed a better chance in improving efficacy for combination strategy, while monotherapy did not, except for cemiplimab that ranked second. Atezolizumab/CT/bevacizumab ranked first in most subgroups for PFS. Direct comparison showed a non-statistically significant benefit of ICI regimens for the liver metastases cohort in OS, with a good ranking for pembrolizumab/CT and atezolizumab/bevacizumab/CT. Regarding brain metastases, all ICI regimens demonstrated an improvement in OS and PFS compared to CT. Nivolumab/ipilimumab/CT ranked better in this subset.
Conclusions: Our meta-analysis updated on the most recent findings demonstrates that different ICI treatments rank differently in specific NSCLC settings (histology, biomarker and clinical presentation) offering a novel challenging scenario for clinical decision making and research planning.
Key words: non-small-cell lung cancer, checkpoints inhibitors, network meta-analysis, systematic review, frontline therapy

INTRODUCTION

Lung cancer is a worldwide leading cause of death and non-small-cell lung cancer (NSCLC) is the most common histotype.[1] Recently, a wide range of therapeutic options for advanced/metastatic non-oncogene-addicted NSCLC have been approved for their impact on the patient's outcomes in terms of survival and safety profile. Current guidelines support personalized treatment options based on molecular and immunologic features, driving the physician's choice toward tailored oncology. The discovery of immune evasion as a cancer hallmark paved the way to immune checkpoint inhibitors (ICI) in the therapeutic armamentarium against lung cancer, which was based on chemotherapy (CT) doublets only.[2] Nivolumab, pembrolizumab and atezolizumab were initially approved in pretreated patients, significantly improving overall survival (OS) as compared to docetaxel.[3-5] Subsequently, the approval of pembrolizumab for metastatic, treatment-naive, non-oncogene-addicted NSCLC patients with high programmed death-ligand 1 (PD-L1) expression with tumor proportion score (TPS) ≥50%, drove toward the use of ICI in first-line setting with a response

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rate of around 20% and 8% in long-term survivors.[6,7] The identification of patients who are more likely to respond to immunotherapy is therefore of major relevance to maximizing efficacy and minimizing toxicity. Tumor and/or microenvironment PD-L1 expression is the only approved predictive biomarker for programmed cell death protein 1 (PD-1)/PD-L1 blockade in NSCLC and its expression is highly dynamic since it may vary over time and by site among multiple tumor lesions. Despite heterogeneity, PD-L1 expression is currently used for clinical decision making and regulatory approval, with considerable variability across countries.[8] An alternative ongoing approach is to select patients on their tumor mutational burden (TMB) using next-generation sequencing technologies, but this strategy still awaits validation.[9] Moreover, inconsistencies and heterogeneity were observed in trials including patients enrolled under similar criteria, treated with the same ICI and assayed using the same companion diagnostic antibody.[8] Despite this, Liang et al. carried out a meta-analysis also considering TMB confirming its potential predictive role, especially when considering PD-L1 expression.[10]

First-line ICI regimen in non-oncogene-addicted NSCLC has been evaluated in various randomized clinical trials (RCTs). However, the optimal treatment strategy is yet to be established. On this basis, we investigated the efficacy and safety of ICI alone or in combination with CT and/or with another ICI as frontline treatment in NSCLC, directly and indirectly comparing the evidence of the RCTs by pairwise and Bayesian methodologies. This systematic review and meta-analysis aims to provide a ranked scenario for comprehensive evidence to guide trial design and support clinical choice.

METHODS

Systematic literature review

Based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, we systematically carried out a bibliographic search using PubMed, Embase, Cochrane Central Register of Controlled Trials and relevant abstracts and presentations of major meeting databases (American Society of Clinical Oncology, the World Conference on Lung Cancer and the European Society for Medical Oncology). A manual search was also carried out (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100465; Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100465).[11] Timeframe was set from January 2010 to September 2021.

Data extraction and quality assessment

Data were extracted independently by two investigators (MAS and DC) using a predefined protocol/consensus. Hazard ratios (HRs) and 95% confidence interval (CI) were directly extracted for analysis. Both investigators assessed the risk of bias of the included studies by using the Cochrane risk of bias tool.[12] Discrepancies were resolved through discussion with a third reviewer (GC) reaching consensus.

Study selection

Inclusion criteria: (i) phase II or III RCTs; (ii) enrolled patients with either histologically or cytologically confirmed non-oncogene-addicted NSCLC; (iii) compared two or more first-line treatments, including immunotherapy; (iv) reported detailed outcomes including progression-free survival (PFS), OS, objective response rate (ORR) and treatment-related adverse events (TRAEs). Studies failing to meet these criteria were excluded from the network meta-analysis (NMA). We excluded trials evaluating targeted therapy, radiotherapy, immune cells or cytokines, etc. We also excluded analysis of selected population, maintenance strategy or health-related quality of life only. Inclusion/exclusion criteria based on the Population, Intervention, Comparison and Outcomes (PICOS) model are represented in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100465.

Endpoint

Primary endpoints of the meta-analysis were OS (time from randomization to death from any cause) and PFS (time from randomization to the date of objective disease progression or death from any cause in the absence of progression), explored by comparison of HRs estimated with the use of stratified Cox proportional hazards models. Secondary endpoints were ORR and TRAEs [all grades and grade 3 (G3) or higher].

Pairwise and NMA software and analysis

Firstly, we carried out a traditional pairwise meta-analysis for OS, PFS, ORR and TRAEs (all grades and $\geq$G3) for unselected patients and subsequently for primary endpoints in selected study cohorts. This analysis was carried out using the Review Manager 5.4 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Heterogeneity between studies was assessed using Cochrane's Q test and the inconsistency test (I-squared, I^2). Specifically, if I^2 was $>50\%$, corresponding to a high risk of heterogeneity, the meta-analysis was calculated using the random-effects model as established by DerSimonian and Laird; otherwise, the analysis was carried out using the fixed-effects model according to Mantel–Haenszel.[13] Statistical significance was reached for P values ≤ 0.05. HRs for OS and PFS, odds ratio (OR) and relative risk for binary outcomes (ORR and TRAEs), and their 95% CIs were used to measure outcomes and safety. The occurrence of publication bias was investigated by Begg's test and visual inspection of funnel plots. We subsequently carried out a Bayesian NMA[14] using STATA software (StataCorp, version 17 College Station, TX) implemented by a graphical tool and the 'mvmeta' package.[15,16] In NMA, direct and indirect comparisons between different treatments are possible by logical inference, allowing to rank (from best to worst) multiple treatments in a single analysis.[17,18] For each outcome of interest, we carried out a Bayesian NMA using a Markov chain Monte Carlo simulation with up to 30 000 iterations. The network was built through the command 'network plot'. The inconsistency factor (IF) between closed loops (triangular and quadratic loops) was assessed by evaluating the logarithm of the ratio of 2 odds ratios (RoR) by using the 'ifplot' command in STATA. RoR values close to 0 indicate that both direct and indirect evidence agree, whereas IF > 2 indicates a high IF in a closed loop. The outcomes are reported with corresponding 95% credible intervals (CrIs). The NMA was carried out using the commands 'network meta c'. To identify the most credible treatment in the outcome of interest, we ranked the trials using the surface under the cumulative ranking curve (SUCRA), derived by using the command 'sucra': the closer to 1 is the SUCRA of a treatment, the more probable it is to rank the best for the outcome of interest.[19] Finally, to compare the overall effect for outcomes of interest, we created a heat-map graph using GraphPad PRISM 9 (GraphPad Software, Inc., CA).[20]

RESULTS

Systematic literature review and studies included

After duplication removal and title/abstract screening, 580 references were identified through electronic and manual search. Finally, 19 articles involving 13 599 patients and 17 treatment regimens were eligible (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2022.100465).

Characteristic of included trials

Details of the trials are shown in Table 1. Thus, this meta-analysis included 18 phase III RCTs and only 1 phase II RCT.[14] The experimental arm features 6 ICI-monotherapy regimens [Keynote (KN)-024,[6] KN-042,[7] CheckMate (CM)-026,[21] IMpower (IM)-110,[5] Mystic trial,[22] Empower-Lung 1[23]], 12 ICI/CT-regimens (KN-189,[24] NCT01285609,[25] KN-407,[26] CameL,[27] IM-130,[28] IM-131,[28] IM-132,[29] CM-227 part II,[30] KN-021 cohort G,[14] Rationale 304,[31] Rationale 307,[32] IM-150[33]), 1 ICI/CT/antiangiogenic regimen (IM-150), 2 dual-ICI strategies (CM-227 part I,[34] Mystic trial) and 1 dual-ICI/CT combination (CM-9LA[35]). Among them, four RCTs included only squamous (SQ) histology (NCT01285609, KN-407, IM-131, Rationale-307) and seven RCTs included only non-squamous (NSQ) histology (KN-189, IM-130, IM-132, KN-021 cohort G, CameL, Rationale 304, IM-150), while all others included mixed histology. In the selected studies, there are analytical differences in the determination of PD-L1 expression involving both immunohistochemistry (IHC) companion diagnostic assay and the evaluation only on tumor cells (TPS) or also on immune cells (combined positive score). Therefore, to group the patients according to PD-L1 expression level uniformly, 'TPS $\geq$50%' and 'TC3 or IC3' were analyzed as PD-L1 $\geq$50%; 'TPS $<$1%' and 'TC0 or IC0' as PD-L1 $<$1%; and '1 $\leq$ TPS $\leq$ 49%' and 'TC1,2 or IC1,2' as PD-L1 1%-49%. To minimize heterogeneity, only wild-type populations were considered for IM-130, IM-131, IM-132 and IM-150 trials.

Meta-analysis

To perform this meta-analysis, an all-comers approach was initially used regardless of any other kind of feature. To harmonize available data, information for the entire population was selected if reported. In a wide landscape of evidence, considering the need to identify possible personalized strategies based on specific clinical, immunologic and pathologic characteristics, an enrichment strategy was also used according to specific cohorts of interest. The assessment of bias risk is shown in Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2022.100465.

Pairwise meta-analysis of the unselected cohort

ICI-based therapy was associated with a reduction of death risk (pooled HR = 0.78, 95% CI 0.73-0.83, $P < 0.00001$) and progressive disease (pooled HR = 0.69, 95% CI 0.62-0.77, $P < 0.001$) (Figure 1). A subgroup analysis was carried out confirming the OS benefit for most studies regardless of the type of drug used, although the magnitude was different (Supplementary Figure S3A and B, available at https://doi.org/10.1016/j.esmoop.2022.100465). First-line durvalumab, nivolumab and ipilimumab did not reach statistical significance either for OS or for PFS; tislelizumab and camrelizumab did not demonstrate benefit in OS, but analysis is based on very immature data. In terms of ORR, a benefit was found among the experimental group (pooled OR = 1.69, 95% CI 1.39-2.05, $P < 0.00001$), and the subgroup analysis is described in Supplementary Figure S5A, available at https://doi.org/10.1016/j.esmoop.2022.100465. Regarding safety profile, the pooled risk ratio is 0.94 (95% CI 0.90-0.99, $P < 0.00001$) for any-grade TRAEs and 0.91 (95% CI 0.80-1.02, $P < 0.00001$) for TRAEs $\geq$G3 (Supplementary Figure S5B and C, available at https://doi.org/10.1016/j.esmoop.2022.100465). Predictably, the combination strategies are burdened by more TRAEs than monotherapy. Funnel plots for OS and PFS analyses are shown in Supplementary Figure S6 and Supplementary Figure S7, available at https://doi.org/10.1016/j.esmoop.2022.100465).

NMA of unselected cohort

All regimens were evaluated for differences in OS, PFS, ORR and $\geq$G3 TRAEs (Supplementary Figure S8, available at https://doi.org/10.1016/j.esmoop.2022.100465). Pembrolizumab/CT is most likely to be the best treatment in terms of reducing the death risk (SUCRA = 78%, HR versus CT = 0.43, 95% CrI 0.23-0.82) and disease progression. Interestingly, first-line cemiplimab (SUCRA = 71%) showed significant benefits in OS (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100465; Supplementary Figure S9, available at https://doi.org/10.1016/j.esmoop.2022.100465). Atezolizumab/CT/bevacizumab (HR = 0.28, 95% CrI 0.17-0.48) significantly improved PFS compared to CT (Supplementary Figure S9, available at https://doi.org/10.1016/j.esmoop.2022.100465). Atezolizumab/bevacizumab/CT (HR = 0.09, 95% CrI 0.02-0.84) and pembrolizumab/CT (HR = 0.15, 95% CrI 0.08-0.51) ranked first and second as compared to standard CT for ORR. In general, the ICI-CT schedules ranked better than CT-free combinations.

As expected, combination strategies produced more TRAEs of $\geq$G3, while all ICI monotherapies rank better, as

Table 1. Characteristics of included trials

RCT	Author	Year	Histology	Treatment comparison		Randomization	Sample size	Median follow-up (months)	Main outcomes	Main subgroups	EGFR/ALK mutations	PD-L1 detection assay
				Arm 1	Arm 2							
KN 024	Brahmer[36]	2020	Mixed	Pembro	Platinum-based chemo[a]	1 : 1	154/151	59.9	OS, PFS, ORR, DOR, AEs	ECOG, smoking, race, age histology, brain metastases	No	22C3 pharmDx (Dako)
KN 042	Mok[7]	2019	Mixed	Pembro	Platinum-based chemo[a]	1 : 1	637/637	20	OS, PFS, ORR, AEs, DOR	Race, ECOG, age smoking, histology, brain metastases, PD-L1	No	22C3 pharmDx (Dako)
CM 026	Carbone[21]	2017	Mixed	Nivo	Platinum-based chemo[a]	1 : 1	271/270	13.5	OS, PFS, ORR, AEs	ECOG, smoking, age, histology, brain/liver metastases, PD-L1, TMB	No	28-8 pharmDx
IM 110	Herbst[3]	2020	Mixed	Atezo	Platinum-based c hemo[a]	1 : 1	277/277	13.4	OS, PFS, AEs	ECOG, sex, age, smoking, histology, PD-L1, TMB	No	22C3 pharmDx SP263 (Ventana)
KN 189	Rodríguez-Abreu[24]	2021	NSQ	Pembro + chemo (pemetrexed + platinum)	Placebo + chemo (pemetrexed + platinum)	2 : 1	410/206	31.0	OS, PFS, PFS2, ORR, DOR, AEs	ECOG, smoking, sex, brain metastases, liver metastases, PD-L1	No	22C3 pharmDx (Dako)
KN 407	Paz-Ares[30]	2020	SQ	Pembro + chemo (carboplatin + paclitaxel/nab-paclitaxel)	Placebo + chemo (carboplatin + paclitaxel/nab-paclitaxel)	1 : 1	278/281	14.3	OS, PFS, PFS2, ORR, DOR, AEs	ECOG, smoking, race, histology, brain metastases, PD-L1	No	22C3 pharmDx (Dako)
IM 150	Reck[33]	2020	NSQ	Atezo + beva + chemo Atezo + chemo (carboplatin + paclitaxel)	Beva + chemo (carboplatin + paclitaxel)	1 : 1 : 1	400/402/400	39.3	PFS, OS, AEs, ORR, DOR	ECOG, smoking, race, liver metastases, EGFR, EML4-ALK, PD-L1	Yes	SP142 (Ventana)
IM 130	West[28]	2019	NSQ	Atezo + chemo (carboplatin + nab-paclitaxel)	Chemo (carboplatin + nab-paclitaxel)	2 : 1	483/240	18.5 19.2	OS, PFS, AEs, ORR	ECOG, smoking, sex, race, histology, liver metastases, bone metastases, EGFR/ALK, PD-L1	Yes	SP142 (Ventana)
IM 131	Jotte Robert[37]	2020	SQ	Atezo + chemo (carboplatin + paclitaxel/nab-paclitaxel)	Chemo (carboplatin + nab-paclitaxel)	1 : 1 : 1	343/338/340	26.8 24.8	PFS, OS, ORR, DOR, AEs	ECOG, smoking, sex, race, age, liver metastases, PD-L1	Yes	SP142 (Ventana)
IM 132	Nishio[29]	2020	NSQ	Atezo + chemo (platinum + pemetrexed)	Chemo (platinum + pemetrexed)	1 : 1	292/286	28.4	PFS, OS, ORR, DOR, AEs	ECOG, age, race, smoking, liver metastases, EGFR, KRAS, PD-L1	Yes	SP142 (Ventana)
CM 227	Paz-Ares[30]	2021	Mixed	Nivo + IPI Nivo + chemo	Platinum-based chemo[a]	1 : 1	583/583 377/378	17.1 13.9	OS, PFS, AEs	ECOG, smoking, histology, PD-L1, brain metastases	No	22C3 pharmDx (Dako)
Mystic trial	Rizvi[22]	2020	Mixed	Durva Durva + treme	Platinum-based chemo[a]	1 : 1 : 1	163/163/162	30.2	OS, PFS, AEs, ORR, DOR	ECOG, smoking, histology, TMB, age, sex, brain metastases	No	SP263 (Ventana)
CM 9LA	Paz-Ares[35]	2021	Mixed	Nivo + IPI + chemo	Platinum-based chemo[a]	1 : 1	361/358	30.7	OS, PFS, ORR, AEs	ECOG, age, sex, smoking, histology, brain/liver/bone metastases, PD-L1	No	28.8 pharmDx (Dako)

Continued

Table 1. Continued

RCT	Author	Year	Histology	Treatment comparison		Randomization	Sample size	Median follow-up (months)	Main outcomes	Main subgroups	EGFR/ALK mutations	PD-L1 detection assay
				Arm 1	Arm 2							
Empower-Lung 1	Sezer[23]	2021	Mixed	Cemiplimab	Platinum-based chemo[a]	1 : 1	283/280	13.1	OS, PFS, ORR, DOR, AEs	ECOG, age, sex, race, histology, brain metastases, disease stage	No	22C3 pharmDx (Dako)
KN 021 cohort G	Awad[14]	2020	NSQ	Pembro + chemo	Carboplatin + pemetrexed	1 : 1	60/63	49.4	ORR, PFS, DOR, OS, AEs	ECOG, age, sex, smoking, histology, brain metastases, PD-L1	No	22C3 pharmDx (Dako)
NCT01285609	Govindan[25]	2017	SQ	IPI + chemo (carboplatin + paclitaxel)	Placebo + chemo (carboplatin + paclitaxel)	1 : 1	388/361	12.5 11.8	OS, PFS, ORR, DOR, AEs	ECOG, age, sex, race, smoking, disease stage	No	—
CameL	Zhou[27]	2020	NSQ	Camre + chemo (carboplatin + pemetrexed)	Chemo (carboplatin + pemetrexed)	1 : 1	205/207	11.9	PFS, OS, ORR, DOR, DCR, safety, AEs	ECOG, age, smoking, brain metastases, PD-L1	No	22C3 pharmDx (Dako)
Rationale 307	Wang[32]	2021	SQ	Tisle + chemo (carboplatin + paclitaxel/nab-paclitaxel)	Chemo (carboplatin + paclitaxel)	1 : 1 : 1	120/118/117	8.6	PFS, OS ORR, DOR, AEs	Age, sex, smoking, ECOG, disease stage, bone metastases, liver metastases, brain metastases, PD-L1	No	SP263 (Ventana)
Rationale 304	Lu[31]	2021	NSQ	Tisle + chemo	Platinum + pemetrexed	2 : 1	223/111	9.8	PFS, OS, ORR, DOR, AEs	Age, sex, smoking, ECOG, disease stage, histology, PD-L1, bone metastases, liver metastases, brain metastases	No	SP263 (Ventana)

AEs, adverse events; ALK, anaplastic lymphoma kinase; atezo, atezolizumab; beva, bevacizumab; camre, camrelizumab; chemo, chemotherapy; DOR, duration of response; durva, durvalumab; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EML4, echinoderm microtubule-associated protein-like 4; IPI, ipilimumab; KRAS, Kirsten rat sarcoma 2 viral oncogene homolog; nivo, nivolumab; NSQ, non-squamous cell carcinoma; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; PFS, progression-free survival; RCT, randomized clinical trial; SQ, squamous cell carcinoma; tisle, tislelizumab; TMB, tumor mutational burden; treme, tremelimumab.

[a]Investigator's choice.

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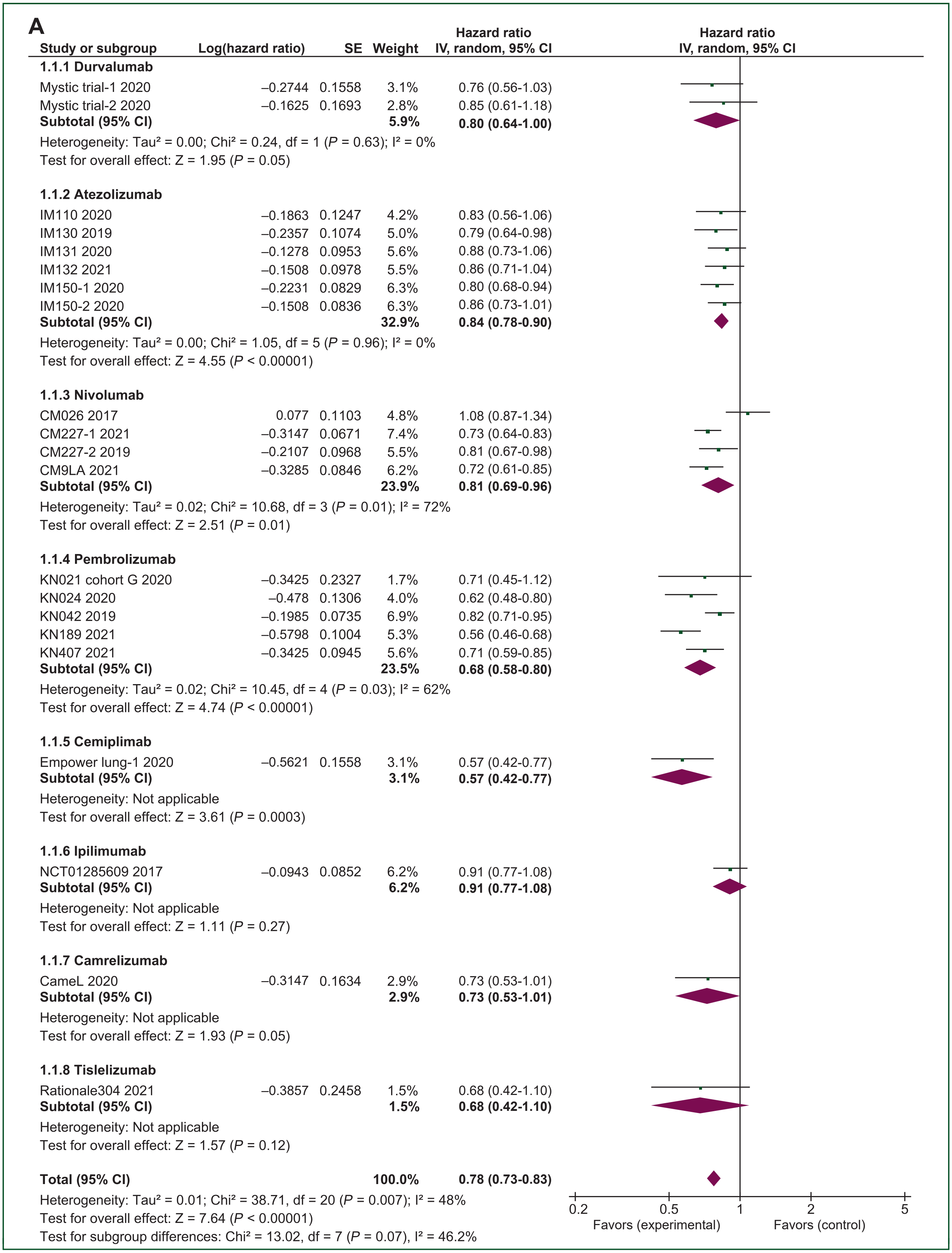


Figure 1. Pooled HR for OS (A) and PFS (B) on head-to-head comparison in unselected cohorts.
Immune checkpoint inhibitor-based regimen represents the experimental group. Subgroups have been created according to the type of drug.
CI, confidence interval; HR, hazard ratio; IV, instrumental variables; OS, overall survival; PFS, progression-free survival; SE, standard error.

B

Study or subgroup	Log(hazard ratio)	SE	Weight	Hazard ratio IV, random, 95% CI
1.2.1 Camrelizumab				
CameL 2020	−0.5108	0.1468	4.3%	0.60 (0.45-0.80)
Subtotal (95% CI)			**4.3%**	**0.60 (0.45-0.80)**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.48 (*P* = 0.0005)				
1.2.2 Durvalumab				
Mystic trial-1 2020	−0.1393	0.1982	3.5%	0.87 (0.59-1.28)
Mystic trial-2 2020	0.0488	0.1925	3.6%	1.05 (0.72-1.53)
Subtotal (95% CI)			**7.1%**	**0.96 (0.73-1.26)**
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (*P* = 0.50); I² = 0%				
Test for overall effect: Z = 0.31 (*P* = 0.76)				
1.2.3 Atezolizumab				
IM110 2020	−0.2614	0.1024	5.0%	0.77 (0.63-0.94)
IM130 2019	−0.4463	0.0867	5.3%	0.64 (0.54-0.76)
IM131 2020	−0.3425	0.0859	5.3%	0.71 (0.60-0.84)
IM132 2021	−0.5108	0.1033	5.0%	0.60 (0.49-0.73)
IM150-1 2020	−0.3567	0.0959	5.1%	0.70 (0.58-0.84)
Subtotal (95% CI)			**25.8%**	**0.68 (0.63-0.74)**
Heterogeneity: Tau² = 0.00; Chi² = 3.77, df = 4 (*P* = 0.44); I² = 0%				
Test for overall effect: Z = 9.13 (*P* < 0.00001)				
1.2.4 Nivolumab				
CM026 2017	0.174	0.1043	5.0%	1.19 (0.97-1.46)
CM227-1 2021	−0.2357	0.0691	5.5%	0.79 (0.69-0.90)
CM227-2 2019	−0.478	0.0897	5.2%	0.62 (0.52-0.74)
CM9LA 2021	−0.4005	0.0915	5.2%	0.67 (0.56-0.80)
Subtotal (95% CI)			**21.0%**	**0.79 (0.61-1.01)**
Heterogeneity: Tau² = 0.06; Chi² = 25.70, df = 3 (*P* < 0.0001); I² = 88%				
Test for overall effect: Z = 1.87 (*P* = 0.06)				
1.2.5 Pembrolizumab				
KN021 cohort G 2020	−0.6162	0.2212	3.2%	0.54 (0.35-0.83)
KN024 2020	−0.6931	0.1268	4.6%	0.50 (0.39-0.64)
KN042 2019	0.0488	0.0619	5.6%	1.05 (0.93-1.19)
KN189 2021	−0.7133	0.0909	5.2%	0.49 (0.41-0.59)
KN407 2021	−0.5276	0.0948	5.2%	0.59 (0.49-0.71)
Subtotal (95% CI)			**23.8%**	**0.61 (0.42-0.89)**
Heterogeneity: Tau² = 0.16; Chi² = 69.44, df = 4 (*P* < 0.00001); I² = 94%				
Test for overall effect: Z = 2.60 (*P* = 0.009)				
1.2.6 Cemiplimab				
Empower lung-1 2020	−0.6162	0.1162	4.8%	0.54 (0.43-0.68)
Subtotal (95% CI)			**4.8%**	**0.54 (0.43-0.68)**
Heterogeneity: Not applicable				
Test for overall effect: Z = 5.30 (*P* < 0.00001)				
1.2.7 Ipilimumab				
NCT01285609 2017	−0.1393	0.0757	5.4%	0.87 (0.75-1.01)
Subtotal (95% CI)			**5.4%**	**0.87 (0.75-1.01)**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.84 (*P* = 0.07)				
1.2.8 Tislelizumab				
Rationale304 2021	−0.4463	0.1685	3.9%	0.64 (0.46-0.89)
Rationale307 2021	−0.6539	0.1736	3.9%	0.52 (0.37-0.73)
Subtotal (95% CI)			**7.8%**	**0.58 (0.46-0.73)**
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (*P* = 0.39); I² = 0%				
Test for overall effect: Z = 4.52 (*P* < 0.00001)				
Total (95% CI)			**100.0%**	**0.69 (0.62-0.77)**
Heterogeneity: Tau² = 0.05; Chi² = 125.97, df = 20 (*P* < 0.00001); I² = 84%				
Test for overall effect: Z = 6.45 (*P* < 0.00001)				
Test for subgroup differences: Chi² = 23.75, df = 7 (*P* = 0.001), I² = 70.5%				

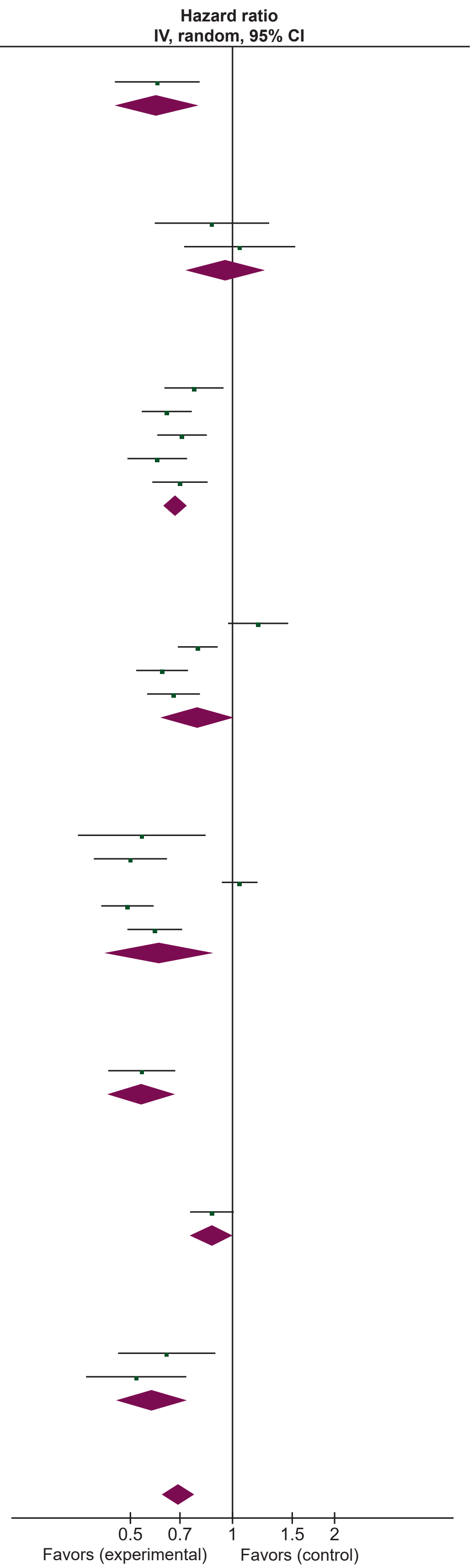


Figure 1. Continued.

Treatment	OS	PFS	SAFETY	ORR	Average	Ranking
Pembro + CT	0.780	0.835	0.415	0.829	0.715	1
Cemi	0.710	0.708	0.705	0.715	0.710	2
Tisle + CT	0.709	0.751	0.319	0.803	0.646	3
Pembro	0.683	0.497	0.871	0.440	0.623	4
Atezo + beva + CT	0.412	0.816	0.238	0.919	0.596	5
Nivo + CT	0.554	0.653	0.230	0.801	0.560	6
Camre + CT	0.645	0.687	0.108	0.789	0.557	7
Nivo + ipi + CT	0.660	0.584	0.292	0.615	0.538	8
Nivo + ipi	0.604	0.390	0.592	0.400	0.497	9
Atezo	0.530	0.444	0.818	0.176	0.492	10
Durva	0.392	0.323	0.926	0.192	0.458	11
Atezo + CT	0.234	0.629	0.381	0.583	0.457	12
Beva + CT	0.162	0.520	0.357	0.560	0.400	13
Nivo	0.277	0.097	0.990	0.069	0.358	14
Durva + treme	0.405	0.078	0.689	0.165	0.334	15
CT	0.311	0.170	0.546	0.241	0.317	16
ipi + CT	0.435	0.322	0.093	0.185	0.259	17

Worst Better

Figure 2. Ranking of treatments based on NMA.
All of the SUCRA values for each regimen with regard to PFS, OS, ORR and G3 or higher AEs. An average SUCRA and the average ranking are provided.
AE, adverse event; atezo, atezolizumab; beva, bevacizumab; camre, camrelizumab; cemi, cemiplimab; CT, chemotherapy; durva, durvalumab; ipi, ipilimumab; nivo, nivolumab; NMA, network meta-analysis; ORR, overall response rate; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; SUCRA, surface under the cumulative ranking curve; tisle, tislelizumab; treme, tremelimumab.

shown in Supplementary Figure S9, available at https://doi.org/10.1016/j.esmoop.2022.100465.

Figure 2 shows the probability of each regimen to be the best first-line treatment based on the efficacy and safety ranking profile. According to average SUCRA values for selected outcomes, pembrolizumab/CT (average SUCRA = 0.715) and cemiplimab (0.710) were associated with the highest probability of ranking first. Moreover, pembrolizumab/CT showed the highest incidence of ≥G3 TRAEs while cemiplimab has an overall good safety and efficacy profile. Specifically, atezolizumab/bevacizumab/CT showed efficacy in PFS and ORR but with a lower improvement on OS and a worse toxicity profile. The addition of CT to nivolumab/ipilimumab enhanced the efficacy but worsened the safety profile. CT alone ranked worse as compared to other regimens.

NMA according to histotype

Considering the substantial differences between SQ and NSQ histotypes in terms of pathology and molecular features as well as for different CT backbones, we firstly carried out a stratification according to histology.

NSQ cohort

The NSQ-OS meta-analysis included 14 RCTs (7200 patients) while the NSQ-PFS analysis included 14 trials (6583 patients). Direct comparison showed a reduction of death risk (pooled HR = 0.74, 95% CI 0.64-0.85, $P < 0.00001$) and progressive disease (pooled HR = 0.66, 95% CI 0.59-0.74, $P < 0.00001$) (Figure 3). NMA analysis showed that pembrolizumab alone (SUCRA = 75.5%) and pembrolizumab/CT (SUCRA = 71.5%) ranked first in OS (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100465; Supplementary Figure S10, available at https://doi.org/10.1016/j.esmoop.2022.100465). Atezolizumab/bevacizumab/CT ranked first in PFS (SUCRA = 99.9%, HR versus CT = 0.16, 95% CrI 0.11-0.23) followed by pembrolizumab/CT (SUCRA = 90.2%, HR versus CT = 0.19, 95% CrI 0.14-0.27) and pembrolizumab alone (SUCRA 82.8%; HR versus CT 0.57, 95% CrI 0.42-0.78). (Supplementary Figure S10, available at https://doi.org/10.1016/j.esmoop.2022.100465). Of note, contrary to the unselected population, cemiplimab ranked worse in terms of PFS and OS.

SQ cohort

For the SQ histology, 11 studies analyzing for OS and PFS included 3226 and 3413 patients, respectively. Pairwise meta-analysis showed a statistically significant difference in OS and PFS for immunotherapy-based treatment with respect to the control arm with a pooled OS-HR = 0.78 (95% CI 0.71-0.85, $P < 0.00001$) and a pooled PFS-HR = 0.62 (95% CI 0.52-0.73, $P < 0.00001$) (Figure 4). Notably, except for cemiplimab, ICI monotherapies did not reach the OS statistical significance. Nivolumab/ipilimumab showed a good ranking profile in OS and PFS, whereas pembrolizumab ranked first for PFS and cemiplimab second for OS. CT was the worst treatment (Supplementary Figure S11, available at https://doi.org/10.1016/j.esmoop.2022.100465; Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100465).

NMA ACCORDING TO PD-L1 EXPRESSION

PD-L1 negative (<1%)

Data regarding this population are reported in 10 studies for OS ($N = 3161$) and in 12 trials for PFS ($N = 3214$). Pooled HR showed a reduction of death risk with the ICI regimen (HR = 0.79, 95% CI 070-0.88, $P < 0.0001$). However, only nivolumab/ipilimumab ± CT, pembrolizumab/CT in the KN-189 and atezolizumab/CT in the IM-132 have reached statistical significance compared to CT. Immunotherapy approach improved PFS too (pooled HR = 0.74, 95% CI 0.69-0.80, $P < 0.00001$) (Supplementary Figure S12B and C, available at https://doi.org/10.1016/j.esmoop.2022.100465).

Based on NMA analysis (Supplementary Figure S12D and E, available at https://doi.org/10.1016/j.esmoop.2022.100465), for both OS and PFS a benefit was observed. Nivolumab/ipilimumab whether in combination or not with CT ranked first for OS compared to CT (HR versus CT = 0.41, 95% CrI 0.18-0.95, HR versus CT = 0.43, 95% CrI 0.18-1.00). Instead, atezolizumab/bevacizumab/CT was most likely ranked first for PFS (HR versus CT = 0.19, 95% CrI 0.05-0.69) (Supplementary Figure S12A, available at https://doi.org/10.1016/j.esmoop.2022.100465). The corresponding SUCRA of the ranking

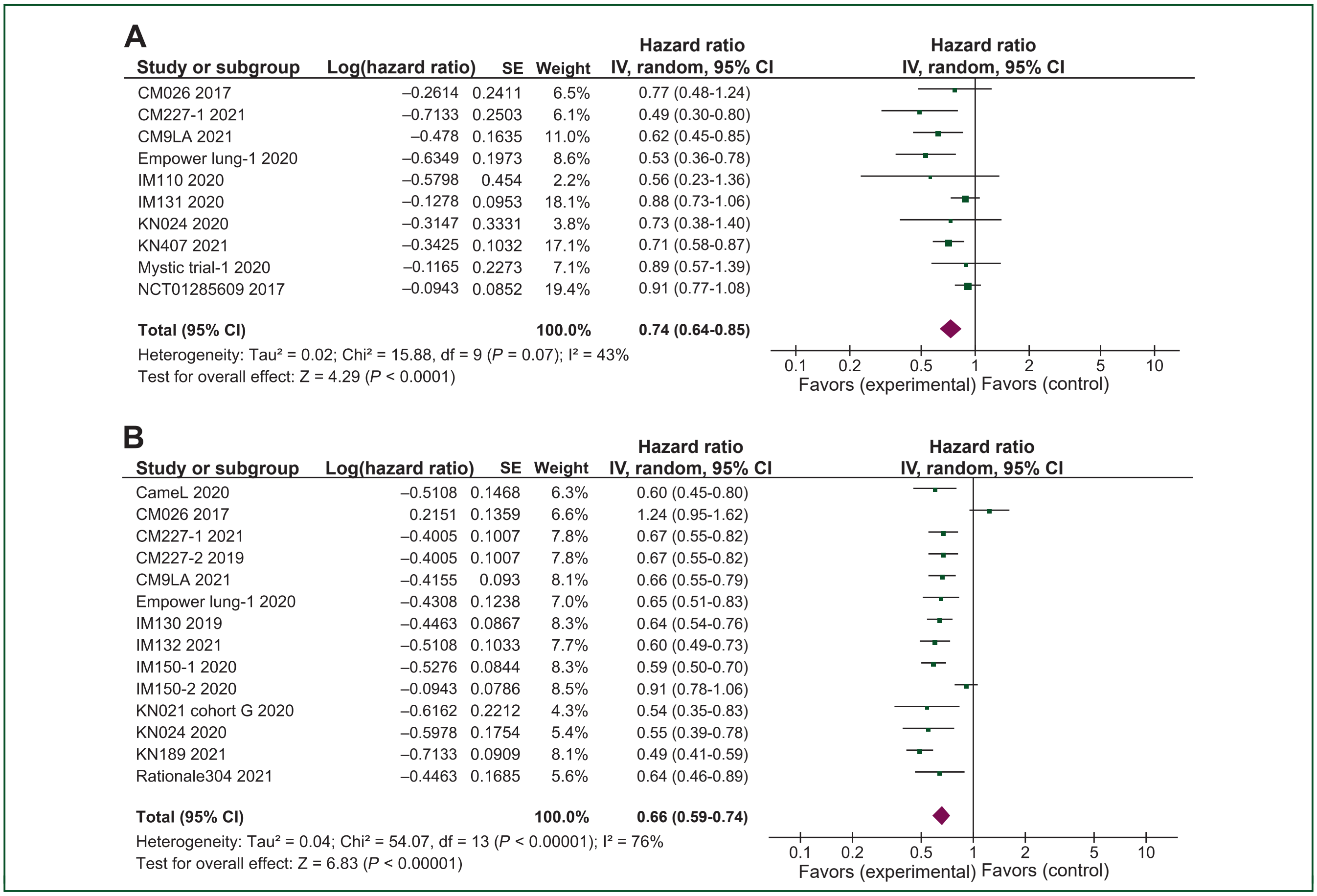


Figure 3. Pooled HR for OS (A) and PFS (B) on head-to-head comparison in NSQ histology cohort.
Network plot of direct (lower) and indirect (upper) comparison of the studies included in the analysis for OS (C) and PFS (D) in the NSQ cohort. Each circular node represents a treatment type. The thickness of the lines is proportional to the number of patients in head-to-head comparisons.
atezo, atezolizumab; beva, bevacizumab; camre, camrelizumab; cemi, cemiplimab; CI, confidence interval; CT, chemotherapy; durva, durvalumab; HR, hazard ratio; ipi, ipilimumab; IV, instrumental variables; nivo, nivolumab; NSQ, non-squamous; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; SE, standard error; tisle, tislelizumab; treme, tremelimumab.

probabilities are shown in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100465.

PD-L1 positive (>1%)

For the PD-L1 >1%, 11 studies reported data for OS ($n = 6845$) and 14 studies for PFS ($n = 6281$). Pooled HR showed a reduction of death risk (HR-OS = 0.83, 95% CI 0.79-0.88, $P < 0.00001$) and progressive disease (HR-PFS = 0.67, 95% CI 0.58-0.78, $P < 0.00001$) in patients receiving ICI compared to the control arm (Supplementary Figure S13A and B, available at https://doi.org/10.1016/j.esmoop.2022.100465). The association of pembrolizumab/CT is 76.7% likely to be the best treatment for OS and 95.3% for PFS. Nivolumab/ipilimumab ± CT ranked better for OS than PFS compared to CT. Conversely, atezolizumab/CT/bevacizumab regimen ranked better for PFS than for OS (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100465; Supplementary Figure S14A, B and E, available at https://doi.org/10.1016/j.esmoop.2022.100465).

PDL1 1%-49% cohort

The OS analysis for the 1%-49% PD-L1 cohort is based on 10 RCTs (2824 patients) and the PFS analysis is based on 12 RCTs (2774 patients). Direct comparison demonstrated a statistically significant difference favoring an ICI-based regimen (pooled OS-HR = 0.85, 95% CI 0.78-0.93, $P = 0.0005$; pooled PFS-HR = 0.69, 95% CI 0.57-0.84, $P < 0.00001$) (Supplementary Figure S13C and D, available at https://doi.org/10.1016/j.esmoop.2022.100465). Comprehensively, NMA confirmed a better OS for the immunotherapy strategies toward standard CT (Supplementary Figure S14C, D and F, available at https://doi.org/10.1016/j.esmoop.2022.100465). Pembrolizumab/CT (HR versus CT = 0.38, 95% CrI 0.20-0.73, SUCRA = 89.3%) and nivolumab/ipilimumab/CT (HR versus CT = 0.37, 95% CrI 0.15-0.95, SUCRA = 87.7%) reduce the overall death risk as compared to CT alone (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100465). Instead, atezolizumab/bevacizumab/CT is 78.6% likely to be the best treatment for PFS, whereas pembrolizumab/CT ranked second (SUCRA = 76%, HR versus CT = 0.30, 95% CrI 0.12-0.72) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100465; Supplementary Figure S14F, available at https://doi.org/10.1016/j.esmoop.2022.100465).

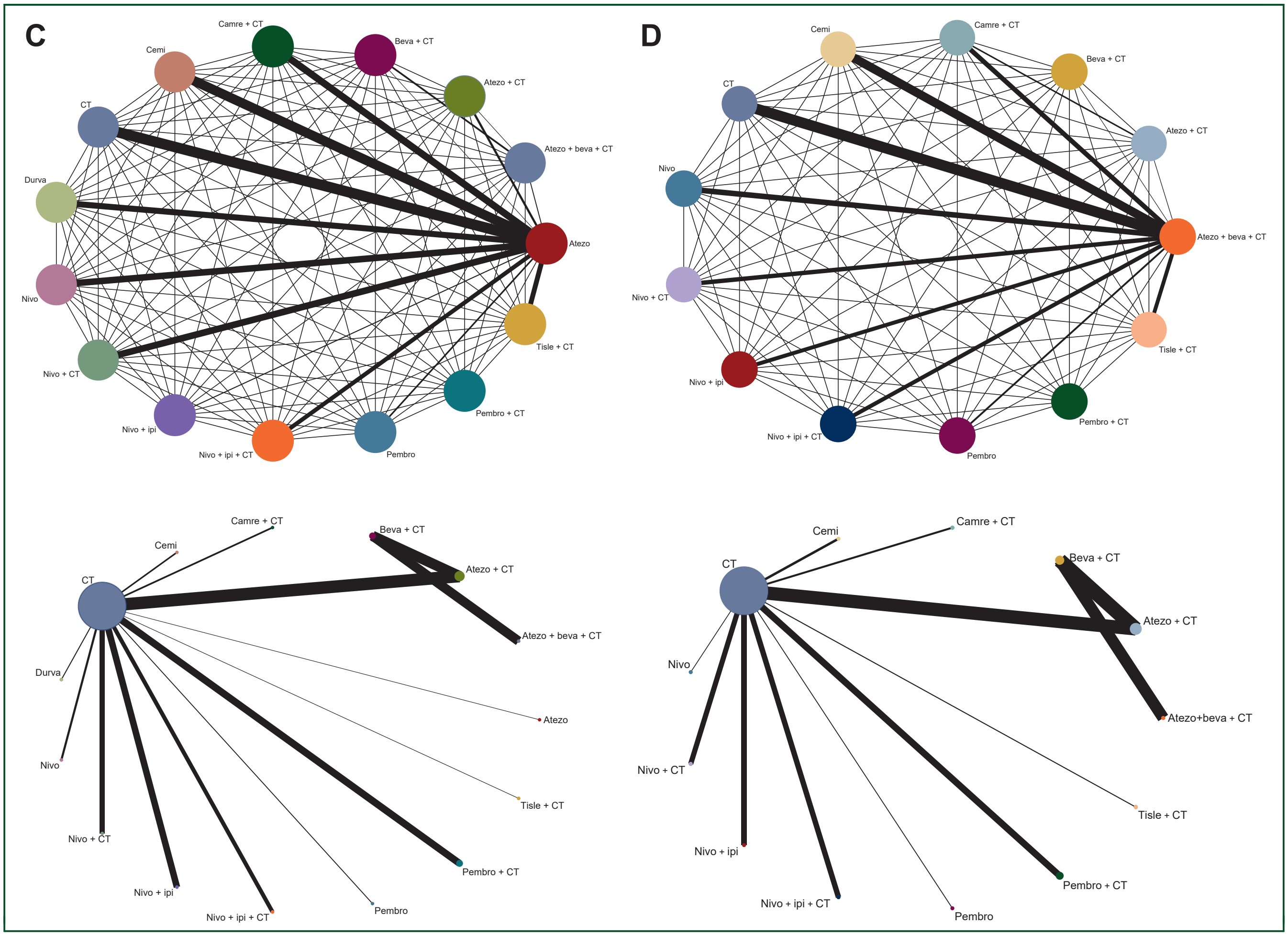


Figure 3. Continued.

PD-L1 >50% cohort

The PD-L1 >50% analysis is based on 14 trials (3536 patients) for OS and on 16 trials (3339 patients) for PFS. Pooled OS-HR = 0.68 (95% CI 0.62-0.74, $P < 0.00001$), while pooled PFS-HR = 0.58 (95% CI 0.53-0.63, $P < 0.00001$) (Supplementary Figure S15, available at https://doi.org/10.1016/j.esmoop.2022.100465). Regarding OS-NMA, cemiplimab ranked first with a 76.6% likeliness to be the most effective treatment (HR versus CT = 0.33, 95% CrI 0.14-0.75) based on Empower-Lung 1 data, followed by atezolizumab (IM-110). Instead, atezolizumab/bevacizumab/CT is 95.9% likely to be the best regimen in reduction of the risk of disease progression (HR versus CT = 0.06, 95% CrI 0.01-0.23) (Figure 5; Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100465; Supplementary Figure S12F and G, available at https://doi.org/10.1016/j.esmoop.2022.100465).

LIVER METASTASES

Data on patients with liver metastases (LM) were reported in nine studies (2024 patients for OS and 1371 patients for PFS). Direct comparison showed a pooled OS-HR for ICI-based strategy favoring patients without LM (HR = 0.76, 95% CI 0.71-0.81) versus with LM (HR = 0.86, 95% CI 0.74-1.00). Notably, only KN-189 and IM-150 part I impact on OS with statistical significance. Instead, the pooled PFS-HR = 0.65 (95% CI 0.55-0.77, $P < 0.00001$) in patients who had LM and 0.61 (95% CI 0.57-0.65, $P < 0.00001$) for patients without distant lesions (Supplementary Figure S16, available at https://doi.org/10.1016/j.esmoop.2022.100465). Both in the presence and absence of LM, atezolizumab/CT, pembrolizumab/CT and nivolumab/ipilimumab/CT ranked first for OS and tislelizumab/CT, pembrolizumab/CT and atezolizumab/CT ranked first for PFS (Supplementary Figure S17A, B and E, available at https://doi.org/10.1016/j.esmoop.2022.100465).

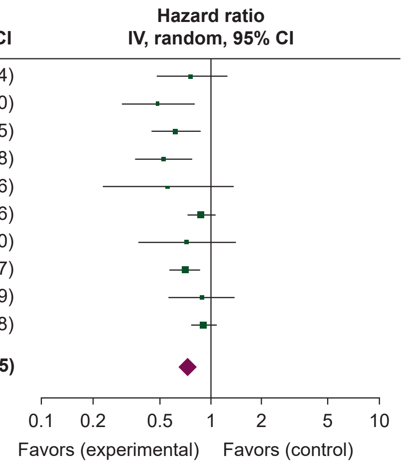
BRAIN METASTASES

Meta-analysis of the brain metastases (BM) cohort is based on five trials for OS (683 patients) and six trials for PFS (698 patients). In terms of reducing the death risk, ICI-based regimen demonstrated a better pooled HR with respect to patients without BM (HR = 0.47, 95% CI 0.36-0.60, $P < 0.00001$) (Supplementary Figure S18, available at https://doi.org/10.1016/j.esmoop.2022.100465). Also pooled HR-PFS in patients with BM is lower compared to patients who do not have BM (HR = 0.51, 95% CI 0.41-0.64, $P < 0.00001$). Both in the presence and absence of BM, cemiplimab,

A

Study or subgroup	Log(hazard ratio)	SE	Weight	Hazard ratio IV, random, 95% CI
CM026 2017	–0.2614	0.2411	6.5%	0.77 (0.48-1.24)
CM227-1 2021	–0.7133	0.2503	6.1%	0.49 (0.30-0.80)
CM9LA 2021	–0.478	0.1635	11.0%	0.62 (0.45-0.85)
Empower lumg-1 2020	–0.6349	0.1973	8.6%	0.53 (0.36-0.78)
IM110 2020	–0.5798	0.454	2.2%	0.56 (0.23-1.36)
IM131 2020	–0.1278	0.0953	18.1%	0.88 (0.73-1.06)
KN024 2020	–0.3147	0.3331	3.8%	0.73 (0.78-1.40)
KN407 2021	–0.3425	0.1032	17.1%	0.71 (0.58-0.87)
Mystic trial-1 2020	–0.1165	0.2273	7.1%	0.89 (0.57-1.39)
NCT01285609 2017	–0.0943	0.0852	19.4%	0.91 (0.77-1.08)
Total (95% CI)			**100.0%**	**0.74 (0.64-0.85)**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 15.88$, df = 9 ($P = 0.07$); $I^2 = 43\%$
Test for overall effect: Z = 4.29 ($P < 0.0001$)



B

Study or subgroup	Log(hazard ratio)	SE	Weight	Hazard ratio IV, random, 95% CI
CM026 2017	–0.1393	0.2529	6.9%	0.87 (0.53-1.43)
CM227-1 2021	–0.6733	0.1637	10.7%	0.51 (0.37-0.70)
CM9LA 2021	–0.5621	0.1558	11.2%	0.57 (0.42-0.77)
Empower lung-1 2020	–0.6349	0.1436	11.8%	0.53 (0.40-0.70)
IM131 2020	–0.3425	0.0859	15.1%	0.71 (0.60-0.84)
KN024 2020	–1.0498	0.3684	4.1%	0.35 (0.17-0.72)
KN407 2021	–0.5621	0.0984	14.4%	0.57 (0.47-0.69)
NCT01285609 2017	–0.1393	0.0757	15.6%	0.87 (0.75-1.01)
Rationale307 2021	–0.6439	0.1736	10.2%	0.52 (0.37-0.73)
Total (95% CI)			**100.0%**	**0.62 (0.52-0.73)**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 27.88$, df = 8 ($P = 0.0005$); $I^2 = 71\%$
Test for overall effect: Z = 5.67 ($P < 0.00001$)

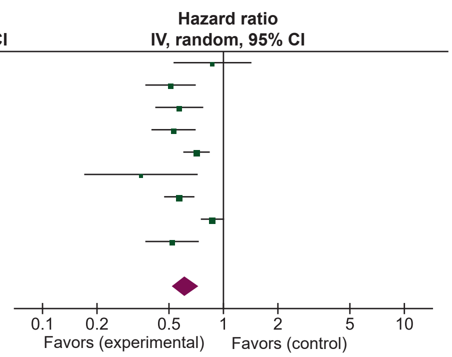


Figure 4. Pooled HR for OS (A) and PFS (B) on head-to-head comparison in SQ histology cohort.
CI, confidence interval; HR, hazard ratio; IV, instrumental variables; OS, overall survival; PFS, progression-free survival; SE, standard error; SQ, squamous.

nivolumab/ipilimumab/CT and pembrolizumab/CT ranked first for OS and nivolumab/ipilimumab/CT and pembrolizumab/CT ranked first for PFS (Supplementary Figure S17C, D and F, available at https://doi.org/10.1016/j.esmoop.2022.100465). Notably, pembrolizumab monotherapy (KN-024) ranked fifth for OS and PFS in the presence of BM while in their absence ranked third for OS and first for PFS. Also, camrelizumab/CT ranked first for PFS in patients with BM while it ranked poorly in the absence of brain involvement. Finally, the addition of CT to nivolumab/ipilimumab improved ranking for OS and PFS

PFS

Rank 13° (Nivo) — Rank 1° (Atezo+beva+CT)

Nivo	0.87 (0.35-2.15)	0.46 (0.11-1.84)	0.36 (0.12-1.10)	0.35 (0.10-1.25)	0.33 (0.09-1.21)	0.30 (0.08-1.10)	0.25 (0.07-0.91)	0.18 (0.06-0.52)	0.13 (0.04-0.49)	0.13 (0.04-0.41)	0.11 (0.04-0.34)	0.05 (0.01-0.26)
	CT	0.53 (0.18-1.51)	0.42 (0.22-0.79)	0.40 (0.16-0.99)	0.39 (0.16-0.95)	0.35 (0.14-0.87)	0.29 (0.12-0.72)	0.21 (0.12-0.36)	0.15 (0.06-0.39)	0.16 (0.08-0.30)	0.13 (0.07-0.25)	0.06 (0.01-0.23)
		Beva+CT	0.79 (0.23-2.70)	0.76 (0.19-3.03)	0.73 (0.18-2.93)	0.66 (0.16-2.66)	0.55 (0.14-2.22)	0.40 (0.16-0.99)	0.29 (0.07-1.19)	0.29 (0.09-1.01)	0.25 (0.07-0.84)	0.11 (0.04-0.27)
			Pembro	0.96 (0.32-2.91)	0.93 (0.31-2.81)	0.84 (0.28-2.56)	0.70 (0.23-2.13)	0.51 (0.22-1.16)	0.37 (0.12-1.15)	0.37 (0.15-0.93)	0.31 (0.13-0.77)	0.14 (0.03-0.64)
				Atezo	0.97 (0.27-3.48)	0.88 (0.24-3.17)	0.73 (0.20-2.64)	0.53 (0.18-1.51)	0.38 (0.10-1.42)	0.39 (0.13-1.19)	0.33 (0.11-0.99)	0.14 (0.03-0.76)
					Nivo+ipi	0.91 (0.25-3.28)	0.76 (0.21-2.73)	0.55 (0.19-1.56)	0.40 (0.11-1.47)	0.40 (0.13-1.23)	0.34 (0.11-1.02)	0.15 (0.03-0.79)
						Nivo+ipi+CT	0.84 (0.23-3.02)	0.60 (0.21-1.73)	0.44 (0.12-1.63)	0.44 (0.15-1.36)	0.37 (0.12-1.13)	0.16 (0.03-0.87)
							Cemi	0.72 (0.25-2.06)	0.52 (0.14-1.94)	0.53 (0.17-1.62)	0.44 (0.15-1.35)	0.20 (0.04-1.04)
								Atezo+CT	0.72 (0.24-2.15)	0.74 (0.32-1.70)	0.62 (0.27-1.42)	0.27 (0.08-0.99)
									Camre+CT	1.02 (0.32-3.21)	0.85 (0.27-2.68)	0.38 (0.07-2.04)
										Tisle+CT	0.84 (0.34-2.08)	0.37 (0.08-1.72)
											Pembro+CT	0.44 (0.10-2.06)
												Atezo+beva+CT

OS

Rank 1° (Cemi) — Rank 13° (Nivo)

Cemi												
0.93 (0.29-3.01)	**Atezo**											
0.86 (0.31-2.38)	0.92 (0.33-2.55)	**Pembro+CT**										
0.90 (0.20-4.09)	0.96 (0.21-4.39)	1.04 (0.26-4.23)	**Atezo+beva+CT**									
0.75 (0.27-2.06)	0.80 (0.29-2.21)	0.87 (0.38-1.99)	0.83 (0.21-3.37)	**Pembro**								
0.74 (0.28-1.93)	0.79 (0.30-2.07)	0.86 (0.40-1.84)	0.82 (0.25-2.65)	0.99 (0.46-2.11)	**Atezo+CT**							
0.72 (0.22-2.35)	0.78 (0.24-2.52)	0.84 (0.30-2.33)	0.81 (0.18-3.68)	0.97 (0.35-2.68)	0.98 (0.37-2.58)	**Nivo+ipi+CT**						
0.66 (0.21-2.13)	0.71 (0.22-2.29)	0.77 (0.28-2.12)	0.74 (0.16-3.35)	0.88 (0.32-2.44)	0.90 (0.34-2.34)	0.91 (0.28-2.95)	**Nivo+ipi**					
0.56 (0.17-1.81)	0.60 (0.19-1.94)	0.65 (0.24-1.80)	0.62 (0.14-2.85)	0.75 (0.27-2.07)	0.76 (0.29-1.99)	0.78 (0.24-2.51)	0.85 (0.26-2.74)	**Durva**				
0.55 (0.17-1.76)	0.58 (0.18-1.89)	0.63 (0.23-1.75)	0.61 (0.13-2.77)	0.73 (0.26-2.01)	0.74 (0.28-1.94)	0.75 (0.23-2.44)	0.83 (0.26-2.66)	0.97 (0.30-3.14)	**Durva+treme**			
0.40 (0.11-1.44)	0.43 (0.12-1.54)	0.47 (0.15-1.45)	0.45 (0.20-1.03)	0.54 (0.18-1.67)	0.55 (0.24-1.26)	0.56 (0.16-1.99)	0.61 (0.17-2.17)	0.72 (0.20-2.56)	0.74 (0.21-2.63)	**Beva+CT**		
0.33 (0.14-0.75)	0.35 (0.15-0.80)	0.38 (0.21-0.68)	0.36 (0.10-1.29)	0.44 (0.24-0.78)	0.44 (0.27-0.72)	0.45 (0.20-1.04)	0.49 (0.22-1.13)	0.58 (0.25-1.33)	0.60 (0.26-1.37)	0.81 (0.31-2.11)	**CT**	
0.04 (0.01-0.13)	0.04 (0.01-0.14)	0.05 (0.02-0.13)	0.04 (0.01-0.20)	0.05 (0.02-0.15)	0.05 (0.02-0.14)	0.05 (0.02-0.18)	0.06 (0.02-0.19)	0.07 (0.02-0.23)	0.07 (0.02-0.24)	0.10 (0.03-0.35)	0.12 (0.05-0.28)	**Nivo**

Figure 5. Hazard ratios and 95% CrI for OS and PFS of the NMA in the PD-L1 >50% cohort.
The results are presented as column-defined treatment versus row-defined treatment.
atezo, atezolizumab; beva, bevacizumab; camre, camrelizumab; cemi, cemiplimab; CI, confidence interval; CrI, credible interval; CT, chemotherapy; durva, durvalumab; HR, hazard ratio; ipi, ipilimumab; nivo, nivolumab; NMA, network meta-analysis; NSQ, non-squamous; OS, overall survival; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; PFS, progression-free survival; tisle, tislelizumab; treme, tremelimumab.

in patients with BM (Supplementary Figure S17C, D and F, available at https://doi.org/10.1016/j.esmoop.2022.100465).

DISCUSSION

In the current complex scenario in metastatic treatment-naive wild-type NSCLC, the selection of optimal treatment is challenging. This systematic review and meta-analysis has been carried out to summarize and rank the efficacy and safety profile of different available treatments taking into account specific disease settings.

Using an all-comers approach, ICI-based therapy alone or in combination was associated with better clinical benefits (OS, PFS, ORR). For efficacy and safety outcomes, pembrolizumab/CT and cemiplimab monotherapy were associated with the highest probability of first ranking. Specifically, pembrolizumab/CT showed highest TRAEs G3-G4 compared to cemiplimab. Indeed, cemiplimab monotherapy improved PFS and OS in patients with PD-L1 $>50\%$ compared to standard CT based on Empower-Lung1[23]. Data at longer follow-up are needed to confirm this benefit. However, the high crossover rate (74%) and 32% of patients receiving extended treatment beyond progression with the addition of CT should be considered. Therefore, in this setting, immunotherapy alone seems to be the best strategy. Despite the lower response rate in PD-L1-negative patients, the ORRs were significantly higher in those PD-L1-positive mainly in melanoma, lung and head and neck cancers suggesting that PD-L1 could be a predictive biomarker in selected tumors, but it neither guaranteed nor precluded response to PD-1/PD-L1 therapy.[38,39]

Combination strategy (ICI/CT, ICI/ICI, ICI/antiangiogenetic drug) may improve response with several mechanisms[40] but causing more TRAEs.

Atezolizumab/bevacizumab/CT demonstrated a good ranking in PFS and ORR based on IM-150 which, however, investigated only NSQ.[33] Bevacizumab, other than the known antiangiogenetic effect, has a powerful immune-modulator role reverting immune-suppressive tumor microenvironment.[41] The analysis of efficacy of ICI-based regimens according to histological features is necessary also considering the different CT backbones. Hence, it is not unreasonable to assume that different CT schedules might exert dissimilar synergistic/additive effects when combined with ICI. In the NSQ cohort, data confirm what has been pointed out in the all-comers population; however, cemiplimab improved less both OS and PFS. For SQ, nivolumab/ipilimumab $\pm$ CT, unlike the all-comers population, showed a better ranking profile in OS and PFS, revealing a possible role for this dual-ICI regimen. Remarkably in the SQ cohort, cemiplimab showed better ranking profiles in OS and PFS compared to NSQ histology and other ICI-monotherapy regimens. However, the identification of the best treatment strategy in SQ histology requires further investigation given their limited representation in clinical trials and its specific clinicopathological features. Indeed, smoking influence, comorbidities, age and molecular profile make SQ histotype a much more challenging disease.[42]

Regarding the analysis according to PD-L1 expression levels, in the PD-L1 $<1\%$ cohort, nivolumab/ipilimumab $\pm$ CT ranked first in OS. It remains critical to understand if PD-1/PD-L1 axis was active even more considering limitations and heterogeneity on the assay.[39] Combination strategies have emerged useful in turning 'cold' in 'hot' tumors, involving dual-ICI regimen, combination with CT, antiangiogenic, bispecific antibody involving tumor microenvironment targets, chimeric antigen receptor T cell, etc.[43] Nivolumab/ipilimumab have a potentially synergistic effect leading to functional convergence through enhancement of T-cell activity, also through upregulation of additional immune checkpoint molecules. Despite this, the Mystic trial showed no significant improvement in OS and PFS compared with CT when combining durvalumab (anti-PD-L1) and tremelimumab in the primary study population with PD-L1 $\geq 25\%$.[22] In patients with PD-L1-positive and intermediate, pembrolizumab/CT ranked first for OS. Nivolumab/ipilimumab $\pm$ CT ranked second and third for OS.

With respect to LM, the direct comparisons showed a lower OS benefit for ICI-based regimens. IM-150 showed a significant reduction in both OS and PFS, whereas other atezolizumab clinical trials did not, suggesting a specific role of bevacizumab in this setting of patients. The use of bevacizumab/atezolizumab was recently approved in first-line hepatocellular carcinoma taking advantage of their synergistic effect.[44]

BMs are a frequent metastatic site in NSCLC, correlating with poor outcome and significant morbidity, but limited data are available in patients with non-oncogene-addicted disease. These patients are underrepresented in clinical trials and only patients with stable BM were allowed. Moreover, it is often necessary to use steroids for symptomatic edema with a negative impact on the ICI activity. Furthermore, most of the available data are derived from retrospective post-hoc analysis. The integrity of the blood—brain barrier was compromised in BM, allowing T-cell infiltration and antibody crossing; furthermore, high mutational load and increased frequency of neoantigens were observed in BM.[45,46] Checkpoint blockade has shown some preliminary but encouraging results, changing the traditional paradigm of central nervous system immune privilege. Nivolumab/ipilimumab/CT ranked better in patients with BM, emphasizing a possible role in these subgroups, confirming the already known efficacy finding in the melanoma setting.[45] Finally, cemiplimab seems to have the best effect in OS.

Unlike previous meta-analyses investigating in this field, our work compared more extensively the available treatment strategies, given the number of included RCTs and most recent updates.[10,47-49] Among the most recent meta-analysis, Liu et al. considered only combination strategies, excluding mono-ICI regimens.[47] Wang et al. also carried out an analysis based on treatment line setting but Empower-Lung 1, Rationale-304, Rationale-307, CameL, IM-150 and CM-9LA were not included.[48] Moreover, Xu et al.[49] in a recent paper carried out an NMA for frontline treatment of non-oncogene-addicted NCSLC. Our manuscript reports a larger analysis by including published data from several trials updated in 2021 and also included an NMA of patients with BM and LM that have a relevant role in clinical practice and prognosis. We consider this point crucial taking into account the new combinations made available for clinical practice and which need to be considered in these unfavorable disease settings.

Several limitations in this meta-analysis should be acknowledged.

Firstly, data were extrapolated from published RCTs rather than from individual patients. Heterogeneity was evident when pooling data across different ICI or CT backbone, trial design, histotype and PD-L1 expression cohorts and in the different test platforms used to detect PD-L1. Furthermore, the potential impact of second- or later-line therapies on the efficacy outcomes has not been investigated owing to limited available data. RCTs often allowed the patients to cross over when disease progression occurs, which could underestimate treatment benefits in our meta-analysis. For the same reason, an analysis on immune-related adverse events could not be carried out. Further studies are needed to investigate comprehensively the safety profile. Additionally, several data evaluated in this study are based on *post-hoc* analyses and ongoing trials do not report survival outcomes with potential risk of bias. It is common view that immunotherapy requires a longer follow-up to define with certainty its impact on OS. Finally, tislelizumab and camrelizumab were investigated only in the Chinese population, which carry out a potential risk of bias.

Conclusions

The main findings of this NMA are as follows: (i) direct comparisons show that ICI-based regimens rank better in terms of efficacy in the unselected and stratified population compared to CT except for OS in patients with LM. This confirms a key role of ICI in frontline NSCLC treatment; (ii) considering together the efficacy and safety ranking profile, pembrolizumab/CT and cemiplimab rank first in the overall population with a better safety profile when compared with combinatory approaches burdened by more TRAEs; (iii) different ICI treatments rank differently in specific NSCLC cohorts of interest, emphasizing the lack of the optimal one-treatment-fits-all strategy. Atezolizumab/bevacizumab/CT ranks better in PFS in most cases but with a worse safety profile. In particular, nivolumab/ipilimumab $\pm$ CT ranks better for OS in the PD-L1-negative, SQ and BM population, while cemiplimab ranks better in PD-L1 $>$50%. In SQ, a combination strategy is better than ICI alone except for cemiplimab which shows a better ranking profile compared to NSQ.

In the absence of head-to-head RCTs, these findings define the current scenario and therefore could be of help to provide recommendations for clinical practice in selecting the optimal first-line strategy in different conditions and offer valuable information for the design of future research.

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DISCLOSURE

The authors have declared no conflicts of interest.

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