Lung Cancer 134 (2019) 127–140

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Immune checkpoint inhibitors, alone or in combination with chemotherapy, as first-line treatment for advanced non-small cell lung cancer. A systematic review and network meta-analysis

Urania Dafni[a,b,c,*], Zoi Tsourti[b], Katerina Vervita[b], Solange Peters[c]

[a] School of Health Sciences, National and Kapodistrian University of Athens (NKUA), Athens, Greece
[b] Frontier Science Foundation-Hellas (FSF-H), Athens, Greece
[c] Department of Oncology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland

ARTICLE INFO

Keywords:
Advanced non-small cell lung cancer
First-line
ICI
Immunotherapy
Network meta-analysis
PD-L1 expression

ABSTRACT

This network meta-analysis (NMA), based on 12 phase-III studies with 9,236 metastatic NSCLC patients, aims to compare the efficacy of treatments including at least one immune-checkpoint inhibitor (ICI) with or without chemotherapy, as frontline therapy for advanced NSCLC patients. The NMA includes direct randomized evidence on treatments of interest along with indirect evidence from randomized studies with chemotherapy as the common comparator. Studies were identified by searching PubMed, and the abstracts of most recent main oncology congresses. The primary endpoint, Hazard-Ratio (HR) of Progression-free Survival (PFS), was estimated by a frequentist-approach NMA. Results are presented in the overall cohort (all-comers or PD-L1-positive) irrespective of histology, and by histology, PD-L1 expression level and sex. According to the primary PFS-NMA in the overall cohort, the combination of chemotherapy, first with pembrolizumab, second with atezolizumab exhibit significantly higher benefit than any other treatment examined. This superior PFS benefit is found for both squamous and non-squamous patients. Similarly for OS, the combination of pembrolizumab/chemotherapy, and atezolizumab/bevacizumab/chemotherapy-(ABC), followed by pembrolizumab-monotherapy and atezolizumab/chemotherapy, are the best treatments in the overall cohort, driven by the non-squamous histology. In the PD-L1-high patients again the combination of chemotherapy with atezolizumab or pembrolizumab, exhibit significant PFS benefit, followed by pembrolizumab-monotherapy. PFS benefit of these ICI/chemotherapy combinations are also found in PD-L1-negative and PD-L1-intermediate patients($1\% \le$ PD-L1 $< 50\%$). Of note, ABC is evaluated only for OS in non-squamous patients while the pembrolizumab-monotherapy PFS benefit and the atezolizumab/chemotherapy OS benefit are probably under-estimated since most of the data stems from non-significant interim analyses of ongoing studies [KN042;IM131/132/150].

In conclusion, the addition of chemotherapy to ICIs enhanced their treatment efficacy as first-line treatment for advanced NSCLC patients. The combination of chemotherapy with either pembrolizumab or atezolizumab show consistently higher efficacy than chemotherapy-alone or any other ICI-combination or monotherapy, particularly in non-squamous patients.

1. Introduction

Lung cancer remains the leading cause of cancer deaths worldwide [1]. Non-small cell lung cancer (NSCLC) represents 80-90% of lung primary malignancies. NSCLC is most often diagnosed at a metastatic stage, where 5-year survival rate ranges between 0 and 5% using traditional chemotherapy-based strategies[2]. The recent introduction of immune checkpoint inhibitors (ICI), has resulted in an increase in overall survival (OS) rates of patients with advanced NSCLC, as well as melanoma, urothelial carcinoma, renal cell carcinoma and head and neck carcinoma.

Activation of checkpoint cascades such as those controlled by PD-1 or CTLA-4, result in inactivation of tumor-specific T-cells and immune evasion. Treatment with ICI using anti-programmed cell death protein 1 (PD-1), anti-programmed death-ligand 1 (PD-L1), and/or anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) agents can reinvigorate T-

* Corresponding Author at: Department of Public Health, Faculty of Nursing, School of Health Sciences, National and Kapodistrian University of Athens, Papadiamantopoulou 123, Athens, GR, 11527, Greece.
E-mail address: udafni@nurs.uoa.gr (U. Dafni).

https://doi.org/10.1016/j.lungcan.2019.05.029
Received 7 April 2019; Received in revised form 23 May 2019; Accepted 26 May 2019
0169-5002/

cells and allows the adaptive immune system to target tumor cells[3–5].

The vast majority of NSCLC cases are attributable to tobacco carcinogens exposure. This aetiological association and the consecutive mutational smoking signature are of particular relevance for cancer immunotherapy[6]. In correlation with tumour immunogenicity, current approaches targeting immune checkpoints exhibit increased activity in tumours with a high number of somatic mutations, such as smoking-induced NSCLC[7]. Conversely, ICI has been significantly less successful in never-smokers, including oncogene-addicted *ALK*-rearranged or *EGFR*-mutated NSCLC as well as other rarer oncogenic drivers [7,8].

Treatment with anti-PD-(L)1 drugs currently represents the mainstay of NSCLC immunotherapy and can result in impressive response rates and durable disease remission, but only in a subset of patients. Anti-PD-1 monoclonal antibodies nivolumab and pembrolizumab, and anti-PD-L1 atezolizumab have all demonstrated an improvement in OS compared with chemotherapy in the second-line and in later therapy lines of advanced NSCLC, offering better survival outcome than docetaxel[9–11].

Tumor cells (TC) PD-L1 expression assessed by immunohistochemistry has been extensively studied as a predictor of response to anti-PD-(L)1 treatment and has been convincingly demonstrated to be a valid biomarker[12–14].

In the frontline setting, pembrolizumab-monotherapy has demonstrated a progression-free survival (PFS) and OS benefit over platinum-based doublet chemotherapy in NSCLC with PD-L1 expression on at least 50% of TC and no epidermal growth factor receptor (*EGFR*) sensitizing mutation or anaplastic lymphoma kinase (*ALK*) gene rearrangement, representing 25-30% of frontline advanced NSCLC(KN024[12,15]). Recently, in a cohort of patients with PD-L1 ≥ 1% (PD-L1-positive), although a pembrolizumab PFS benefit was apparent only for the subgroup of patients with PD-L1 ≥ 50% a significant benefit in OS was found for the full cohort, possibly driven by the PD-L1 ≥ 50%, with higher benefit for higher PD-L1 expression (KN042[16]).

In contrast, PFS was not improved with nivolumab-monotherapy compared with chemotherapy in patients with previously untreated advanced NSCLC and PD-L1 ≥ 5%, nor for the subgroups of PD-L1 ≥ 1% and PD-L1 ≥ 50% (CM026[17]).

Completing the landscape of treatment opportunities in frontline therapy, irrespective of PD-L1 expression, and following the rational interest in the ICI/chemotherapy combination, six trials have assessed (IM130/IM131/IM132;KN189/KN407[18–23]) and reported to date on the combination of platinum-based chemotherapy and anti-PD(L)1 ICI, with one trial adding bevacizumab to that triplet in non-squamous NSCLC (IM150[24]).

All of these trials have demonstrated a variable, but significant, degree of PFS improvement in the intent-to-treat (ITT) cohort, with a magnitude proportionally correlated to the level of PD-L1 expression. Four of these trials have also demonstrated an OS benefit (IM130;KN189/KN407;IM150[18,21–24]).

Nivolumab/ipilimumab was evaluated in the specific subset of patients with high tumor mutational burden (TMB) (≥10Mut/Mb) and showed a significant increase on the primary-endpoint of PFS compared with chemotherapy irrespective of PD-L1 status (CM227[25,26]), while the secondary endpoint OS did not reach significance to date. In a secondary analysis, PFS was also found significant for all patients irrespective of TMB[25].

In squamous NSCLC, the combination of the anti-CTLA4 ipilimumab with chemotherapy (paclitaxel/carboplatin) did not show statistical benefit neither for the primary endpoint OS nor PFS (GOV17[27]).

The OS and PFS benefit of other ICIs, durvalumab with/without tremelimumab versus platinum-based chemotherapy, was not found significant in the primary cohort of patients with PD-L1 ≥ 25, with a p-value higher than the pre-specified alpha (OS $HR_{durvavschemo}$ = 0.76,97.54%CI[0.56–1.02], p = 0.036; MYSTIC[28]). In exploratory analyses, a benefit in response rate, PFS and OS of the ICI-combination for high bTMB were reported, with improving OS HRs for higher cut-offs (≥20 mut/Mb: HR = 0.49,95%CI[0.32–0.74])[29].

Following these numerous randomized trials, building a high level of evidence landscape, frontline immunotherapy strategy -being monotherapy in high-PD-L1, dual ICI in high-TMB or anti-PD-(L)1 in combination with chemotherapy in all-comers NSCLC- has become a new standard of care in advanced NSCLC in absence of ALK or EGFR addiction. Nevertheless, deciding between therapeutics remains a challenge today.

The various options suffer the lack of direct cross-comparison studies, and inter-trial comparisons are of particular risk for inaccuracy, in the context of differences in study patients' populations and inclusion criteria, in treatments including chemotherapies backbone schedules, in stratification factors and trials maturity. An additional recognized issue is, the non-proportional Hazard-Ratios (HRs) feature describing immunotherapy treatment outcome comparisons, particularly for PFS [30].

The objective of the current study is to summarize and compare in a systematic way, through a Network Meta-Analysis (NMA), all the available to date published information on the efficacy of ICI(s), whether alone, in combination, or with chemotherapy, as first-line treatment for advanced/metastatic NSCLC patients, with wild-type ALK and EGFR. Analogous efforts so far have focused only on pre-treated patients[31–34], or did not include all recent clinical trial evidence [35–38].

2. Methods

Analysis methods and inclusion criteria were specified in advance and the study adheres to the PRISMA guidelines for NMAs[39].

2.1. Data Acquisition

2.1.1. Eligibility criteria

Randomized phase-III studies with at least one treatment with an ICI were eligible for inclusion. The target population was untreated/chemotherapy-naive advanced/metastatic NSCLC patients. Efficacy results expressed as PFS or OS had to be provided. Excluded were trials for pre-treated patients.

2.1.2. Information sources, search strategies and study selection

Studies were identified by searching the PubMed electronic database (search date:3-April-2019; Flow-Chart/MESH-terms:Fig.1), as well as the abstracts in the most recent main oncology congresses (2018: AACR;ASCO;WCLC;ESMO;ESMO-IO; AACR2019), for related phase-III clinical trials identified in the “clinicaltrials.gov” site (Table-S1).

To ascertain the quality of the studies included in the current NMA we used the Cochrane's risk of bias tool for randomized controlled trials [40].

2.2. Statistical analysis

HR estimates (with 95%CIs, p-values) for indirect comparisons are obtained from an NMA[41–45] under a frequentist framework. The current NMA satisfies the technical requirement that each treatment must be represented by at least one study and the network needs to be connected (Network-Structure:Fig.2). Fixed-effect models are used, since in most cases the treatment of interest is evaluated in only one trial.

The primary endpoint of interest in the NMA is PFS in the overall patient cohort, with OS and toxicity also examined. Additional cohorts were based on histology (squamous/non-squamous) and PD-L1 expression [PD-L1-high:PD-L1 ≥ 50%; PD-L1-negative:PD-L1 < 1%); PD-L1-intermediate:(1%≤PD-L1 ≤ 49%)]. Further subgroup analyses by sex, and a direct meta-analysis by liver metastatic status, were

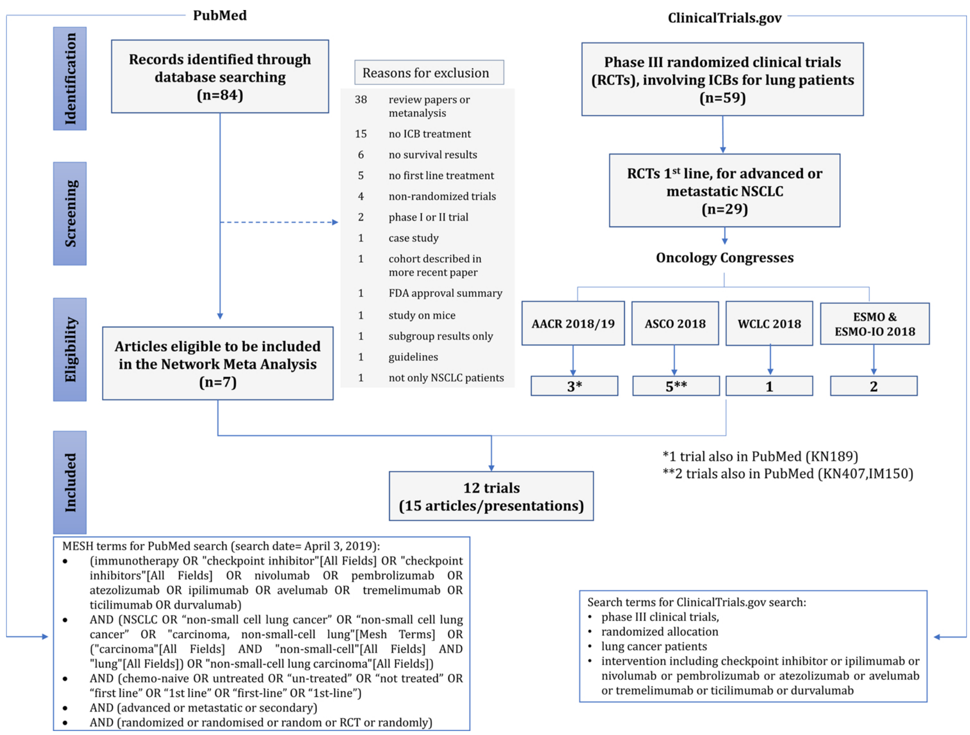


Fig. 1. Flow chart of study selection (up to April 3, 2019)

carried out.

HRs in the logarithmic scale, are analyzed under the normality assumption. Exploration of the surrogacy of PFS for OS is also performed through evaluation of the association of the corresponding HRs, as well as medians and one-year PFS/OS rates. Scatterplots and Spearman's correlation coefficients are shown. Toxicity is also presented as frequency of grade ≥ 3 adverse events (AEs) by randomized arm.

Statistical analysis was carried out in SAS.v4 (SAS Institute,Cary,NC) and R.v3.4.2 (R Foundation for Statistical Computing,Vienna,Austria).

2.2.1. *Sensitivity analysis*

Two different approaches for sensitivity analysis were considered, using both a reduced and an extended analysis cohort. In the reduced scenario, two studies including only PD-L1-positive patients (KN042[16]:pembrolizumab-vs-chemotherapy; CM026[17]:nivolumab-vs-chemotherapy), were removed from the analysis. In the extended scenario, a phase-II trial, was added in the analysis cohort. This multi-cohort trial comparing among others pembrolizumab/chemotherapy versus chemotherapy-alone, satisfied all inclusion criteria except being phase-III (KN021[46,47]).

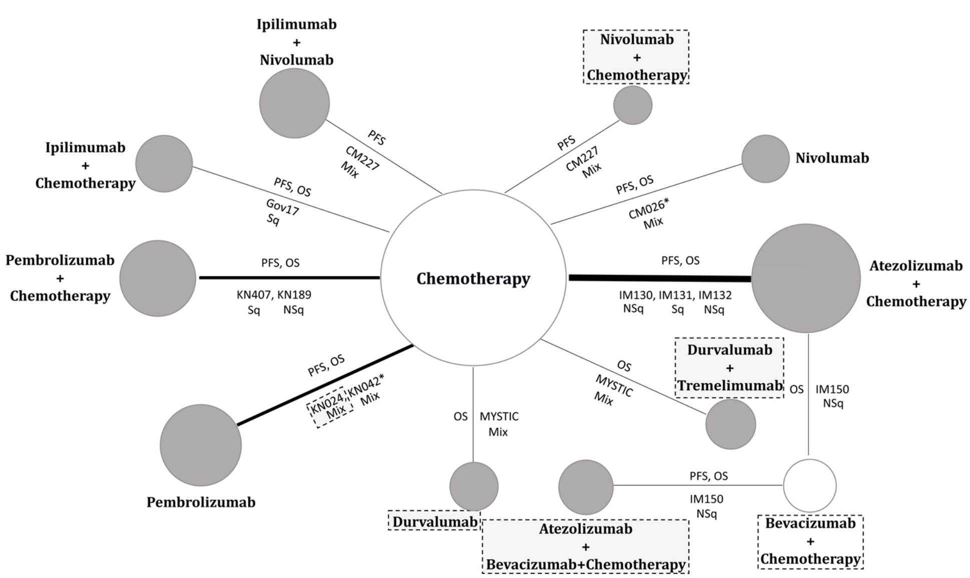


Fig. 2. Network structure; Mix: All histologies, NSq: Non-Squamous patients, Sq: Squamous patients; (*): KN042 and CM026 include patients with PD-L1 ≥ 1%; Notes: White circles correspond to control treatment arms; Trials and treatments in boxes are not evaluated at the primary PFS NMA

In addition, a sensitivity analysis for the OS-NMA excluding the non-significant interim results of three still ongoing atezolizumab/chemotherapy studies (IM150[24,48]/IM131[19]/IM132[20]), was performed.

3. Results

3.1. Studies included in the NMA

A total of 84 abstracts of published articles were screened (PubMed), 7 of which met the inclusion criteria and were eligible to be included in the NMA (selection process:Fig.1).

In parallel, the systematic search of the “clinicaltrials.gov” site, led to the detection of 59 phase-III clinical trials involving ICI for lung cancer patients. Reviewing in detail their characteristics, 29 phase-III trials including untreated advanced/metastatic NSCLC patients with at least one ICI as first-line treatment were identified. Subsequently, the abstracts of most recent main oncology congresses were searched for any of these 29 trials, yielding 11 relevant abstracts (Fig.1).

Removing overlaps, a total of seven distinct published articles and eight presentations were identified as eligible to be included in our analysis. These 15 articles/presentations correspond to 12 clinical trials, further confirmed as eligible (SP).

3.2. Study Characteristics

Study-specific characteristics and NMA cohort information is summarized in Table 1, while study design characteristics in the supplement (Tables-S2&S3).

In 11 studies, the control arm was chemotherapy-alone (3 placebo-controlled[21,22,27]) with only one study adding bevacizumab in both the experimental and control arm (IM150[24,48]). ICI-monotherapy was tested in four studies (pembrolizumab:two, nivolumab:one, durvalumab:one), and in combination with chemotherapy in eight (pembrolizumab:two; nivolumab:one; ipilimumab:one; atezolimumab:four, one with/without bevacizumab). Finally, dual ICI-combination was tested in two trials (nivolumab/ipilimumab; durvalumab/tremelimumab) (Fig.2).

Nine studies use an all-comers design, entering NSCLC patients irrelevant of PD-L1 status. Only three studies use an enrichment design, two by including only PD-L1-positive patients (KN042[16],CM026[17]) and one only PD-L1-high patients (KN024[12]).

Most of the 12 studies, have PFS and OS as co-primary endpoints, with PFS or OS as the only primary endpoint in two studies each (PFS:KN024[12],CM026[17];OS:KN042[16],GOV17[27]). In ten studies, the primary endpoint is evaluated in the overall study cohort (including KN024 for PD-L1-high). In two of them, OS is additionally evaluated as co-primary in subgroups based on PD-L1 cut-offs ($\geq$50% and $\geq$20%; KN042[16]) and on Teff-high-wt population (IM150[24,48]). Finally, there are two studies with primary evaluation only in specific pre-specified subsets based on PD-L1 cut-offs (PFS:PD-L1 $\geq$ 5%,CM026[17]; co-primary PFS/OS:PD-L1 $\geq$ 25%,MYSTIC[28]). Interim analyses were planned in almost all studies.

Only squamous patients were included in three trials while only non-squamous in four. Five included NSCLC patients of both histologies, with histology as stratification factor (Tables 1&S2). For non-squamous histology, ALK/EGFR status was confirmed for all studies except one that simply used the known mutation status (CM026[17]). Patients with confirmed or known ALK/EGFR mutation were excluded from the NMA.

The median follow-up for all studies reporting PFS [range:7.8-20 m] is adequate for this endpoint (Table-S4, Fig.3i). In the control arm, for chemotherapy-alone, the median PFS ranges from 4.8-6.5 m. Interestingly, for the PD-L1-high patients in KN024, the median-control PFS of 6.0 m is within this range. With bevacizumab added to chemotherapy, median-control PFS is somewhat higher, reaching 6.8 m(95%CI[6.0 m-7.1 m];IM150[24]). In most cases with a statistically significant relative benefit in PFS, the median PFS under experimental treatment, improved by at most 2.4 m (except KN189:3.9 m; KN024:4.3 m), while the one-year PFS rate dramatically increased to almost doubling (Table-S4, Fig. 3ii).

This discrepancy was not apparent for OS, observing analogous magnitude in the increase of the absolute benefit in months and in the one-year OS (Table-S4, Fig. 3iii-iv).

Based on Cochrane’s tool for randomized trials, all studies were considered of low risk of bias (Table-S5).

3.3. Cohort description

A total of 9,236 NSCLC patients, randomized to receive as first-line treatment, one or two ICIs (N = 2,220;24%) or in combination with chemotherapy (N = 3,047;33%) or chemotherapy-alone (N = 3,969;43%), were gathered from the 12 randomized studies reported in the last three years (cohort characteristics: Tables 1 and 2& S6).

Regarding all-comers, in studies testing atezolizumab and its combinations, PD-L1-high patients correspond only to 13-19% of the cohort, with PD-L1-negative patients around 50%. In the other studies, PD-L1-high patients are more frequently observed (26-33%) and PD-L1-negative patients less (23-35%).

Overall, 36% of the patients included in the NMA are squamous. Among the five studies including all-histology patients, 18-39% are squamous (Tables 1 and 2).

The majority of patients were current/former smokers (77%-93%), males (59%-85%) more frequently so for squamous (81-85%; others: 59-71%), with median age 63-66 years, with PS = 0 in 29-45%. Only a few studies report patients with brain metastasis (8,9,13%; 3 studies) and liver metastasis (13-20%; 6 studies).

3.4. Efficacy Evaluation: Progression-free Survival

PFS information is reported in all 12 studies, with 10 of them on all-comers or a PD-L1 positive cohort (N = 7,890), one only on PD-L1-high patients ([KN024[12]), and one only on patients with PD-L1 $\geq$ 25% (MYSTIC[28]). For PD-L1-high patients, PFS is available in eight studies (N = 1,742), while for PD-L1-negative patients, in six (N = 1,784).

3.5. PFS-NMA for overall study cohort

The primary NMA includes nine of the ten studies with available PFS information either in all-comers or PD-L1-positive patients, evaluating six ICI-including treatments. For the one study not included, PFS is currently available only for a treatment combination not connected in the network (IM150[24,48]) (Fig.2).

In the overall NMA, the active study treatment is directly compared to the corresponding control arm of chemotherapy-alone (Fig.4i). The combination of chemotherapy with pembrolizumab (HR_{pooled} = 0.53,95%CI [0.47-0.61]) or atezolizumab (HR_{pooled} = 0.65[0.59-0.72]) and of nivolumab/ipilimumab (HR = 0.83[0.72-0.96]) show a significant benefit in PFS over chemotherapy-alone. No such significant benefit is found for ipilimumab/chemotherapy or for the ICI-monotherapies examined (pembrolizumab, nivolumab). Of note, negative final results are used for ipilimumab/chemotherapy and nivolumab (GOV17[27],CM026[17]), while interim ones for pembrolizumab-monotherapy ((KN042[16]:study ongoing for PFS).

Based on the NMA estimates, the combination of chemotherapy with either pembrolizumab or atezolizumab exhibit significantly higher benefit than all other treatments evaluated, with the pembrolizumab-combination better than the atezolizumab-combination (HR = 0.82[0.70-0.97]). The combinations of ipilimumab with either nivolumab or chemotherapy are better than the ICI-monotherapies examined.

Table 1
Characteristics of studies included in network meta-analysis, along with information on primary outcome

Study characteristics				NMA cohort characteristics								
Study/ Source	NSCLC Cohort		Primary endpoint	Experimental Arm	Control Arm	Analysis Timing	PFS HR (95%CI)			OS HR (95%CI)		
	Histology	PD-L1 expression					Overall	PD-L1 ≥ 50%	PD-L1 < 1%	Overall	PD-L1 ≥ 50%	PD-L1 < 1%
1.KN024 [12,15]	All	≥50%	PFS (ITT)	Pembro (N = 154)	Chemo (N = 151)	**PFS: Final OS: Final**	-	**0.50 (0.37-0.68)**	-	-	**0.63 (0.47-0.86)**	-
2.CM026 [17]	All	≥1%	PFS (PD-L1 ≥ 5%)	Nivo (N = 271)	Chemo (N = 270)	PFS: Final OS: Final	1.17 (0.95-1.43)	1.07 (0.77-1.49)	-	1.07 (0.88-1.33)	0.90 (0.63-1.29)	-
3.GOV17 [27]	Squamous	All	OS (modified ITT-randomized pts with ≥1 trt cycle)	Ipi + Chemo (N = 388)	Placebo + Chemo (N = 361)	PFS: Final OS: Final	0.87 (0.75-1.01)	-	-	0.91 (0.77-1.07)	-	-
4.KN189 [21]	Non-squamous	All	OS and PFS (ITT)	Pembro +Chemo (N = 410)	Placebo + Chemo (N = 206)	**PFS: Interim OS: Interim**	**0.52 (0.43-0.64)**	**0.36 (0.25-0.52)**	0.75 (0.53-1.05)	**0.49 (0.38-0.64)**	**0.42 (0.26-0.68)**	**0.59 (0.38-0.92)**
5.IM150 [24,48]	Non-squamous (incl. ALK, EGFR mutated)	All	PFS and OS (ITT-wt) OS (Teff-high wt)	Atezo + Chemo (N = 349)	Beva + Chemo (N = 337)	*OS: Ongoing*	-	-	-	0.88* (0.72-1.08)	-	-
				Atezo + Beva + Chemo (N = 359)		**PFS: Final OS: Interim**	**0.59 (0.50-0.70)**	-	-	**0.78 (0.64-0.96)**	-	-
6.KN407 [22]	Squamous	All	OS and PFS (ITT)	Pembro + Chemo (N = 278)	Placebo + Chemo (N = 281)	**PFS: Interim OS: Interim**	**0.56 (0.45-0.70)**	**0.37 (0.24-0.58)**	**0.68 (0.47-0.98)**	**0.64 (0.49-0.85)**	0.64 (0.37-1.10)	**0.61 (0.38-0.98)**
7.CM227 [25,26,49]	All	All	PFS (TMB selected populations) for nivo + ipi vs. chemo OS (PD-L1 selected populations)	Nivo + Ipi (N = 583)	Chemo (N = 583)	**PFS: Final** *OS: Ongoing*	**0.83 (0.72-0.96)**	-	0.79 (0.62-1.01)	-	-	-
				Nivo + Chemo (N = 177; only PD-L1 < 1%)	Chemo (N = 186; only PD-L1 < 1%)		-	-	**0.74 (0.58-0.94)**	-	-	-
8.KN042 [16]	All	≥1%	OS (PD-L1 ≥ 50%, ≥20% and ≥1% pts)	Pembro (N = 637)	Chemo (N = 637)	*PFS: Ongoing* **OS: Interim**	1.07* (0.94-1.21)	**0.81 (0.67-0.99)**	-	**0.81 (0.71-0.93)**	**0.69 (0.56-0.85)**	-
9.IM131 [19]	Squamous	All	PFS and OS (ITT)	Atezo + Chemo (N = 343)	Chemo (N = 340)	**PFS: Final** *OS: Ongoing*	**0.71 (0.60-0.85)**	**0.44 (0.27-0.71)**	0.81 (0.64-1.03)	0.96* (0.78-1.18)	**0.56 (0.32-0.99)**	0.86 (0.65-1.15)
10.IM132 [20]	Non-squamous	All	PFS and OS (ITT)	Atezo + Chemo (N = 292)	Chemo (N = 286)	**PFS: Final** *OS: Ongoing*	**0.60 (0.49-0.72)**	**0.46 (0.22-0.96)**	**0.45 (0.31-0.64)**	0.81* (0.64-1.03)	-	-
11.IM130 [18,23]	Non-squamous (incl. ALK, EGFR mutated)	All	PFS and OS (ITT-wt)	Atezo + Chemo (N = 451)	Chemo (N = 228)	**PFS: Final OS: Final**	**0.64 (0.54-0.77)**	**0.51 (0.34-0.77)**	**0.72 (0.56-0.91)**	**0.79 (0.64-0.98)**	0.84 (0.51-1.39)	0.81 (0.61-1.08)
12.MYSTIC [28]	All	All	PFS and OS (PD-L1 ≥ 25%)	Durva (N = 279)	Chemo (N = 289)	OS: Final	-	-	-	0.88 (0.73-1.07)	0.76 (0.55-1.04)	1.18 (0.86-1.62)
				Durva + Treme (N = 296)			-	-	-	1.01 (0.83-1.21)	0.77 (0.56-1.07)	0.73 (0.51-1.04)
Randomized Phase-II Study												
KN021 [46,47]	Non-squamous	All	ORR (Secondary: PFS and OS)	Pembro + Chemo (N = 60)	Chemo (N = 63)	**Interim (updated)**	**0.53 (0.33-0.86)**	-	-	**0.56 (0.32-0.95)**	-	-

(*): Interim non-significant, study ongoing
Note: HR (95%CI) and Analysis Timing in bold indicate significant differences

Table 2
Patient characteristics of the included studies (overall cohort).

Study	Experimental arm(s)	Total N	% PD-L1 ≥ 50%	% PD-L1 < 1%	% squamous	% Current /Former smokers	% Males	Median age* (range)	% PS 0/ 1/2	% brain metastasis	% liver metastasis
1.KN024	Pembro	305	100.0	0.0	18.4	92.1	61.3	64.5/66 (33-90)	35.1/ 64.6/ 0.3	9.2	-
2.CM026	Nivo	541	39.6	0.0	24.0	87.8	61.4	64 (29-89)	32.9/ 66.0/ 0.9	12.8	16.6
3.GOV17	Ipi/Chemo	749	-	-	100.0	-	84.8	64 (28-85)	34.6/ 64.8/ 0.7	-	-
4.KN189	Pembro/ Chemo	616	32.8	30.8	0.0	88.1	58.9	63.5/65 (34-84)	43.2/ 56.2/ 0.2	-	18.7
5.IM150	ABC or Atezo/ Chemo	1202	18.0	48.6	0.0	80.4	59.9	63 (31-90)	43.1/ 56.9/ 0.0	-	13.5
6.KN407	Pembro/ Chemo	559	26.1	34.7	100.0	92.7	81.4	65 (29-88)	29.2/ 70.8/ 0.0	7.9	-
7.CM227	Nivo/Ipi	1166	-	32.0	28.0	85.5	66.6	64 (–)	34.0/ 65.0/ < 1.0	-	-
8.KN042	Pembro	1274	47.1	0.0	38.7	78.0	71.0	63 (25-90)	30.4/ 69.6/ 0.0		-
9.IM131	Atezo/Chemo	683	14.8	48.5	100.0	77.2	81.6	65 (23-86)	33.0/ 67.0/ 0.0	-	20.4
10.IM132	Atezo/Chemo	578	13.1^	47.4^	0.0	88.4	66.4	- (31-85)	41.5/ 58.5/ 0.0	-	12.6
11.IM130	Atezo/Chemo	679	19.1	52.4	0.0	90.4	58.9	-	41.2/ 58.5/ 0.1	-	14.7
12.MYSTIC	Durva or Durva/ Treme	1188	29.8	22.7	32.2	85.7	69.0	64.5 (32-87)	39.4/ 60.0/ 0.0	-	-

(*): In cases that median age is not available for overall cohort, values by arm are presented
(^): Percentages based on patients with available information about PD-L1 status (IM132: N = 344; 176 patients in atezo + chemo arm and 168 in chemo arm)
Notes:
KN024: Includes only patients with PD-L1 ≥ 50%
IM150: Baseline characteristics are presented for the ITT population (N = 402 for atezo + chemo arm, 400 for atezo + beva + chemo arm and 400 for beva + chemo arm; data cut-off: January 22, 2018)
MYSTIC: Baseline characteristics are presented for patients with PD-L1 ≥ 25% (N = 163 for durva arm, 163 for durva + treme arm and 162 for chemo arm); Percentages for PD-L1 expression based on all randomized patients

The findings remain essentially the same in the sensitivity analyses performed (Fig.S1i-ii).

3.6. PFS-NMA by histological subtype

PFS results were reported separately for 2,120 squamous patients and 2,285 non-squamous from seven trials (Squamous: GOV17,KN407,IM131; Non-squamous: KN189,IM130/132; Mixed: CM026). For both subtypes, the combinations of either pembrolizumab or atezolizumab with chemotherapy are significantly better than chemotherapy-alone and not significantly different between them (Fig. 4ii.a-b). The combination ipilimumab/chemotherapy, evaluated only in squamous patients, is no better than chemotherapy or nivolumab-monotherapy. Nivolumab shows an effect not significantly different than chemotherapy for the squamous patients, while significantly worse than chemotherapy for the non-squamous patients ($p_{interaction}$ = 0.074).

3.7. PFS-NMA by PD-L1 category

3.7.1. PD-L1 ≥ 50% Cohort

The PFS-NMA for PD-L1-high patients is based on eight trials evaluating four experimental treatments (N = 1,742) (Fig. 4iii). The ICI/chemotherapy combinations of atezolizumab or pembrolizumab, are significantly better than chemotherapy-alone as well as the ICI-monotherapies examined, and no different between them. Pembrolizumab is also significantly better than chemotherapy and nivolumab.

3.7.2. PD-L1 < 1% Cohort

The PFS-NMA for PD-L1-negative patients (Fig. 4iv) is based on six trials evaluating four experimental treatments, all combinations of ICIs (with chemotherapy:3; dual-ICIs:1) (N = 1,784), with no ICI-alone used for PD-L1-negative patients. The combination of nivolumab/chemotherapy is evaluated only for this cohort (CM227[25,49]). Any tested combination of ICI/chemotherapy is significantly better than chemotherapy-alone (HRs:0.69-0.74), with no treatment combination significantly better than another (HRs:0.88-1.04). The dual-ICI combination (nivolumab/ipilimumab) is marginally non-significantly better than chemotherapy (p = 0.058).

3.7.3. Intermediate PD-L1 (1 ≤ PD-L1 ≤ 49%) Cohort

For the subgroup of PD-L1-intermediate patients, results are more limited (five studies, 972 patients). The only treatments evaluated are the combination of chemotherapy with either pembrolizumab or atezolizumab versus chemotherapy-alone. Both of the combinations are significantly better than chemotherapy-alone (HR_{pooled} = 0.55[0.44-0.70]; HR_{pooled} = 0.68[0.57-0.81]) while not different between them (Fig.S2).

3.7.4. PFS-NMA by sex

PFS results were reported separately for 782 females and 1,635 males from four studies (CM026;KN189;IM131;IM132). For the aggregate comparison of ICI(s) with/without chemotherapy versus chemotherapy-alone the interaction of sex with the treatment is not significant (mixed effects model: HR_{women} = 0.65[0.38-1.12], HR_{men} = 0.74[0.61-0.91], $p_{interaction}$ = 0.59), (Fig.S3a-b). However, treatment-specific sex differences are observed. In particular, women seem to derive higher benefit, from the combination of pembrolizumab/chemotherapy versus either chemotherapy or nivolumab-monotherapy ($p_{interaction}$ = 0.018 and 0.0058, respectively).

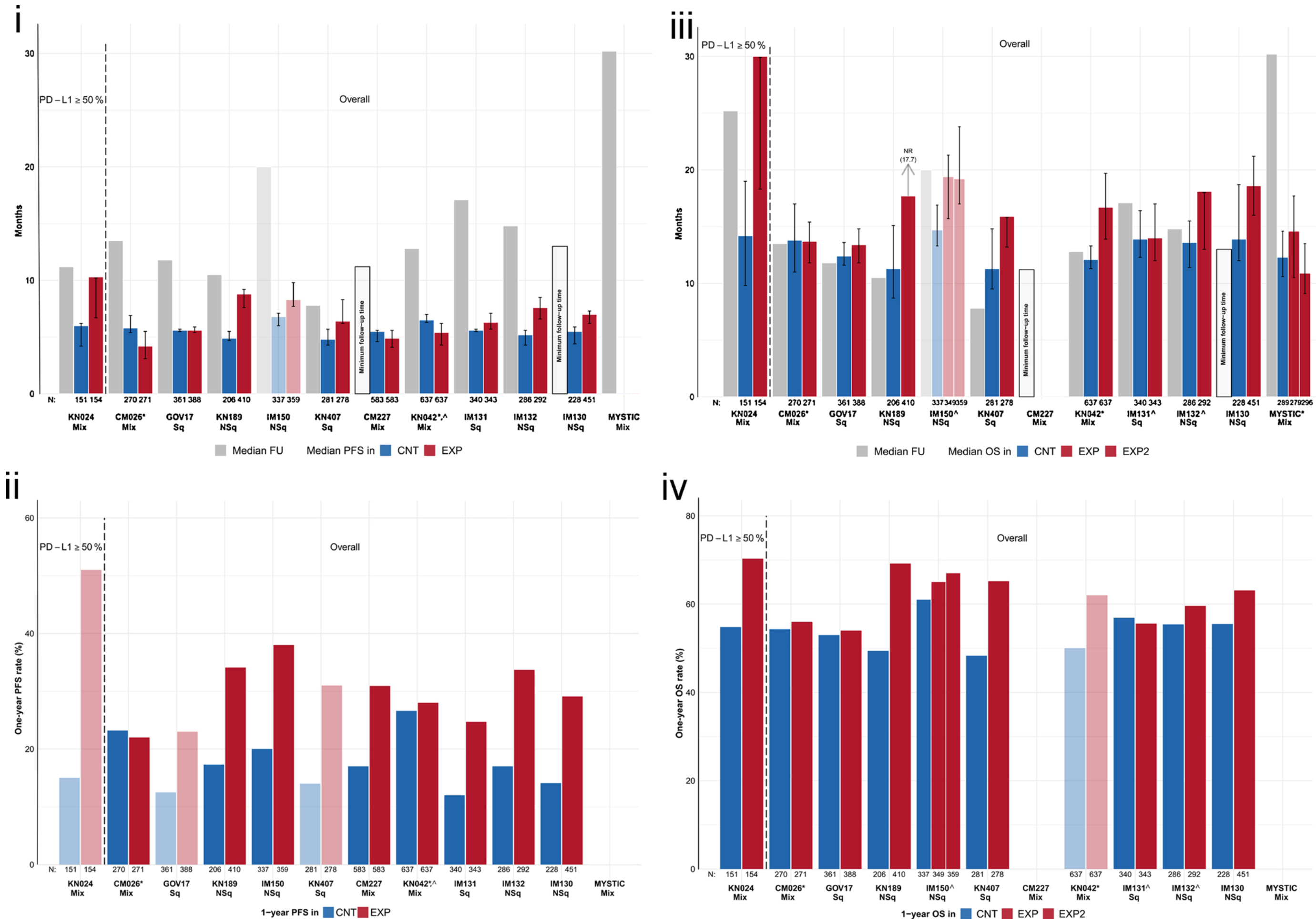


Fig 3. i Median PFS and follow-up times by study; CNT: Control arm, EXP, Experimental arm, FU: Follow-up, Mix: All histologies, NSq: Non-Squamous patients, Sq: Squamous patients, |——|: 95% CI of the median PFS; (*): Median PFS for patients with PD-L1 ≥ 1% (CM026 and KN042); (^): Trial still ongoing for PFS (KN042); Notes: KN024: In the EXP arm the upper limit of the 95% CI is not evaluable; data cut-off: May 9, 2016; IM150: CNT = beva + chemo, EXP = atezo + beva + chemo (lighter colour since control different); CM227 and IM130: The minimum follow-up time is provided; MYSTIC: The reported median follow-up time is for patients with PD-L1 ≥ 25%; No PFS information available; ii: One-year PFS by study; CNT: Control arm, EXP: Experimental arm, Mix: All histologies, NSq: Non-Squamous patients, Sq: Squamous patients; (*): One-year PFS for patients with PD-L1 ≥ 1% (CM026 and KN042); (^): Trial still ongoing for PFS (KN042); Notes: For KN024, GOV17 and KN407, 1-year PFS estimates have been derived based on visual inspection of the reported Kaplan-Meier plot (lighter colour) (KN024; data cut-off: May 9, 2016); IM150: CNT = beva + chemo, EXP = atezo + beva + chemo; MYSTIC: No PFS information available; iii: Median OS and follow-up times by study; CNT: Control arm, EXP: Experimental arm, FU: Follow-up, Mix: All histologies, NR: Not Reached, NSq: Non-Squamous patients, Sq: Squamous patients, |——|: 95% CI of the median OS; (*): Median OS for patients with PD-L1 ≥ 1% (CM026, KN042 and MYSTIC); (^): Trial still ongoing for OS (IM150(ongoing only for atezo + chemo vs beva + chemo), IM131 and IM132); Notes: KN024, KN407 and IM132: In the EXP arm the upper limit of the 95% CI is not evaluable (KN024; data cut-off: July 10, 2017); KN189: The median OS for the EXP arm is reported as NR. The estimate *is (1/HR)*(Median in the CNT group)*; IM150: CNT = beva + chemo, 1 st EXP = atezo + chemo, 2nd EXP = atezo + beva + chemo (lighter colour since control different); CM227 and IM130: The minimum follow-up time is provided (CM227; no OS information available); MYSTIC: The reported median follow-up time is for patients with PD-L1 ≥ 25%; 1 st EXP = durva, 2nd EXP = durva + treme; iv: One-year OS by study; CNT: Control arm, EXP: Experimental arm, Mix: All histologies, NSq: Non-Squamous patients, Sq: Squamous patients; (*): One-year OS for patients with PD-L1 ≥ 1% (CM026 and KN042); (^): Trial still ongoing for OS (IM150(ongoing only for atezo + chemo vs beva + chemo), IM131 and IM132); Notes: KN024; data cut-off: July 10, 2017; IM150: CNT = beva + chemo, 1 st EXP = atezo + chemo, 2nd EXP = atezo + beva + chemo; CM227 and MYSTIC: No OS information available; KN042: 1-year OS estimates have been derived based on visual inspection of the reported Kaplan-Meier plot (lighter colour)

3.7.5. PFS Meta-analysis by liver metastasis

Differential effect of ICI treatment by liver metastatic status could be addressed in the context of the four studies evaluating atezolizumab, where the PFS is reported by liver metastatic status (IM130/IM131/IM132[18–20]; IM150[24]). Recently, results from KN189 on pembrolizumab/chemotherapy by liver metastatic status have also been presented [50].

A direct meta-analysis of the efficacy of the combination atezolizumab/chemotherapy versus chemotherapy-alone (Fig.5), indicates a differential effect of atezolizumab by liver metastatic status ($p_{interaction}$ = 0.035). For patients with liver metastasis the PFS benefit of adding atezolizumab to chemotherapy is non-significant (HR = 0.81[0.64-1.04]), while significant for patients without liver metastasis (HR = 0.61[0.55-0.68]). However, this difference in effect is not present when incorporating the treatment arms including bevacizumab (IM150[24]), with both groups deriving a significant benefit from the atezolizumab combination ($p_{interaction}$ = 0.32; HR = 0.71[0.57-0.88]; HR = 0.61[0.56-0.68]; for with and without liver metastasis, respectively).

Similarly, in the case of pembrolizumab/chemotherapy, no differential effect by liver metastatic status is found, and patients either with or without liver metastasis display higher benefit under the pembrolizumab/chemotherapy treatment (HR = 0.52[0.34-0.81] and HR = 0.48[0.39-0.59], respectively; $p_{interaction}$ = 0.74).

When evaluating jointly IMP131/132/130 and KN189, treatment with ICI/chemotherapy combination is found to provide benefit in both

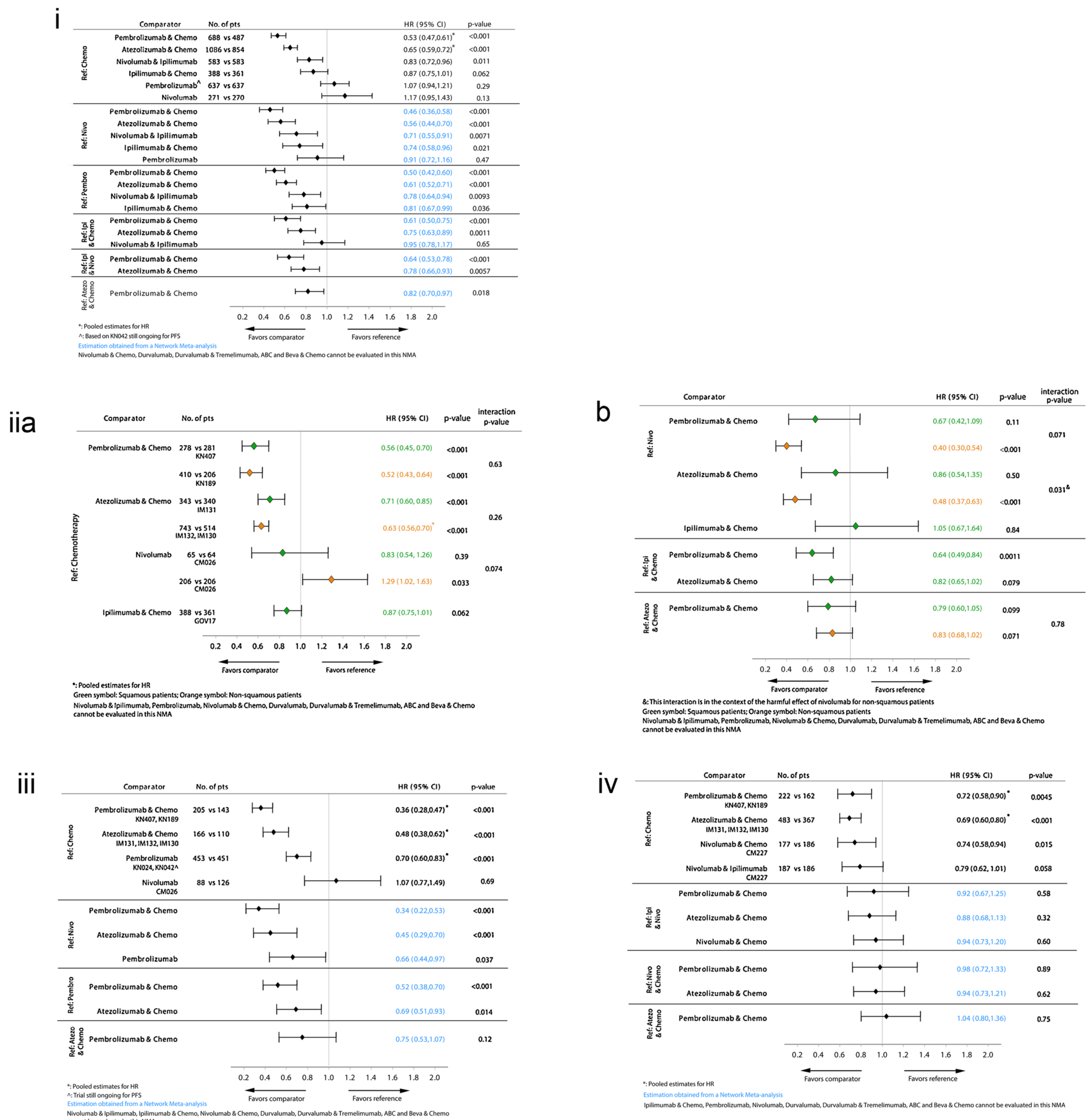


Fig. 4. Forest plot for PFS HRs for direct and indirect comparisons **i:** overall cohorts; **ii.a,b:** By histology; **iii:** PD-L1-high; **iv:** PD-L1-negative

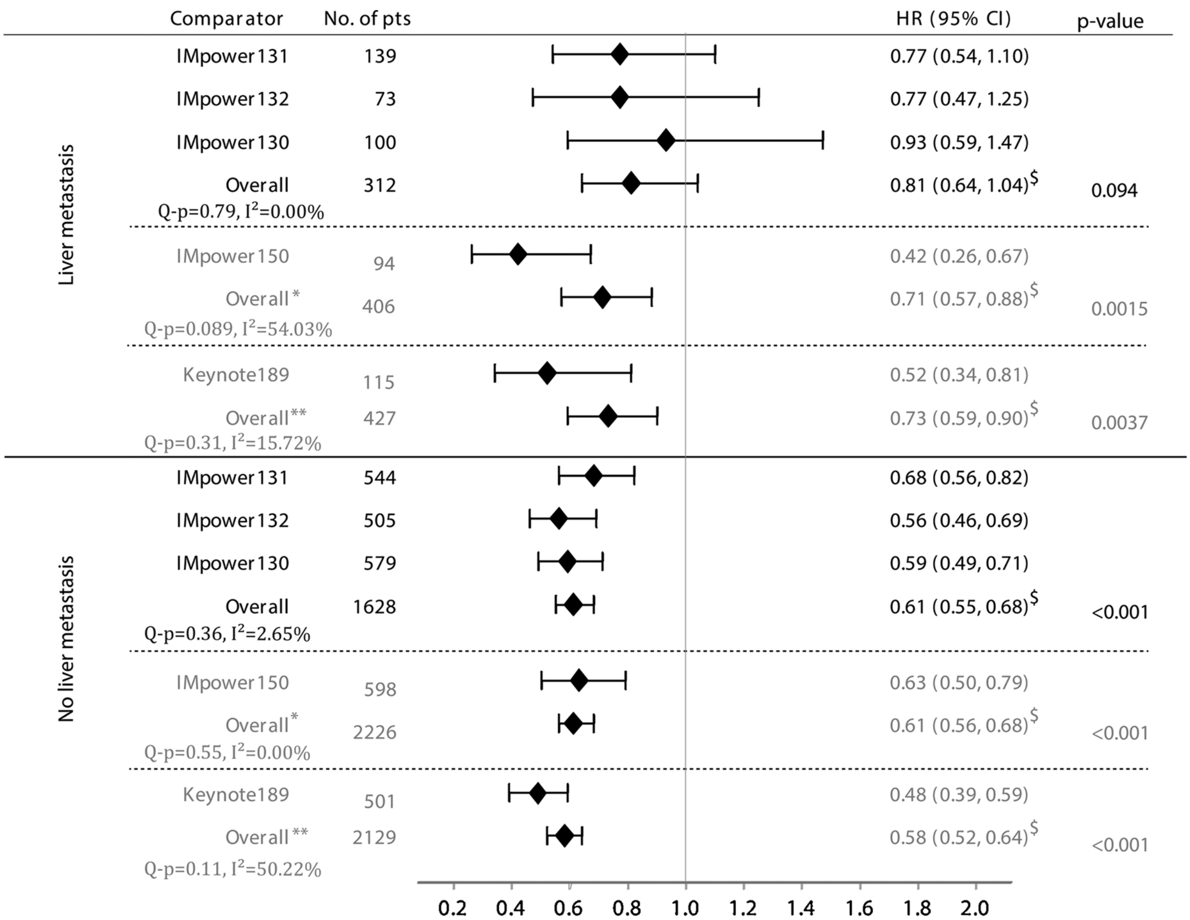
subgroups, with an apparent higher benefit in the subgroup without liver metastasis (HR = 0.73[0.59-0.90] and HR = 0.58[0.52-0.64] for with and without liver metastasis, respectively; $p_{interaction}$ = 0.087).

3.8. Efficacy Evaluation: Overall Survival

Information on OS is provided in 11 studies with 10 of them on all-comers or a PD-L1 positive cohort (Fig.2) (N = 7,588). The OS-NMA includes two more ICIs than the PFS-NMA, (durvalumab with/without tremelimumab) (MYSTIC[28]), as well as chemotherapy combined with bevacizumab and/or atezolizumab (IM150[24,48]). OS is reported for the triple combination of atezolizumab/bevacizumab/chemotherapy (ABC) only for the full cohort (IM150[24,48]). For three of the studies evaluating atezolizumab/chemotherapy, available immature OS information is used, based on non-significant results from interim analysis (IM150[24,48], IM131[19], IM132[20]). Eight of the studies provide information for the subgroup of PD-L1-high patients, while only five for PD-L1-negative and PD-L1 intermediate.

3.8.1. OS-NMA for full study cohort

In the overall NMA model for OS, with data from 10 studies, initially nine experimental treatments are compared to the chemotherapy-alone control arm, including an indirect comparison of the bevacizumab combinations (Fig.6i.a-b). The combinations of chemotherapy with



*: Overall estimation based on IM131/132/130 and IM150, **: Overall estimation based on IM131/132/130 and KN189
$: Estimates of HR (95% CI) based on fixed effect model
Notes:
Experimental = atezo+chemo (except for IM150: atezo+beva+chemo and KN189: pembro+chemo); Control = chemo (except for IM150: beva+chemo)
Number of patients not available by treatment arm
Recent results from KN189 were also included in this analysis
Q-p: p-value from Cohran's Q test
For IM131/132/130 p-interaction=0.035, with addition of IM150 p-interaction=0.32; For KN189 p-interaction=0.74; For IM131/132/130 with addition of KN189 p-interaction=0.087

Fig. 5. Forest plot for PFS HRs according to liver metastasis status

pembrolizumab (HR_{pooled} = 0.54[0.46-0.64]) or atezolizumab (with/without bevacizumab) (NMA estimate: HR = 0.75[0.59-0.94]; HR_{pooled} = 0.85[0.75-0.95], respectively) as well as the pembrolizumab-monotherapy (HR = 0.81[0.71-0.93]) show a significant OS benefit over chemotherapy-alone.

Based on the NMA estimates, the combination of pembrolizumab/chemotherapy is estimated to be consistently better than all other treatments evaluated (HRs:0.51-0.72), while other promising treatments are ABC and pembrolizumab-monotherapy, followed by atezolizumab/chemotherapy, all no different between them. Pembrolizumab-monotherapy and ABC are also better than the durvalumab/tremelimumab combination, with ABC also better than bevacizumab/chemotherapy. Excluding the non-significant interim analysis results on atezolizumab/chemotherapy combination (IM150[24,48], IM131[19], IM132[20]), similar evidence for the OS benefit is provided (results not shown).

3.8.2. OS-NMA by histological subtype

OS results by histology were similar to the overall cohort regarding the combination of pembrolizumab/chemotherapy being the better treatment choice for both histological types, with also ABC and atezolizumab/chemotherapy in non-squamous (Fig. 6ii.a-b). ABC is evaluated only in non-squamous, ipilimumab/chemotherapy only in squamous, while pembrolizumab-monotherapy (among others) could not be evaluated here.

3.8.3. OS-NMA by PD-L1 category

3.8.3.1. PD-L1 ≥ 50% Cohort. : The OS-NMA for PD-L1-high patients is based on eight trials evaluating six experimental treatments with 1,113 patients, and 917 patients in the control arm of chemotherapy-alone.

Pembrolizumab-alone and its combination with chemotherapy are significantly better treatments than chemotherapy-alone (HR = 0.67[0.56-0.80] and HR = 0.49[0.35-0.67], respectively). These treatments do not display a significantly different OS between them or compared to the combination of atezolizumab and chemotherapy, the third preferred treatment according to the overall OS NMA (Fig. 6iii).

3.8.3.2. PD-L1 < 1% Cohort. : The NMA OS analysis for PD-L1-negative patients is based on five trials evaluating four experimental treatments (N = 1325). Available immature OS information, from the non-significant interim analysis of IM131 is used for atezolizumab/chemotherapy along with the final OS data from IM130. Both combinations of pembrolizumab and atezolizumab with chemotherapy display a significant benefit over chemotherapy-alone (HR_{pooled} = 0.60[0.45-0.80] and HR_{pooled} = 0.83[0.69-1.00], respectively). Based on NMA estimates, durvalumab-monotherapy is worse than all combination treatments (pembrolizumab/chemotherapy, atezolizumab/chemotherapy, durvalumab/

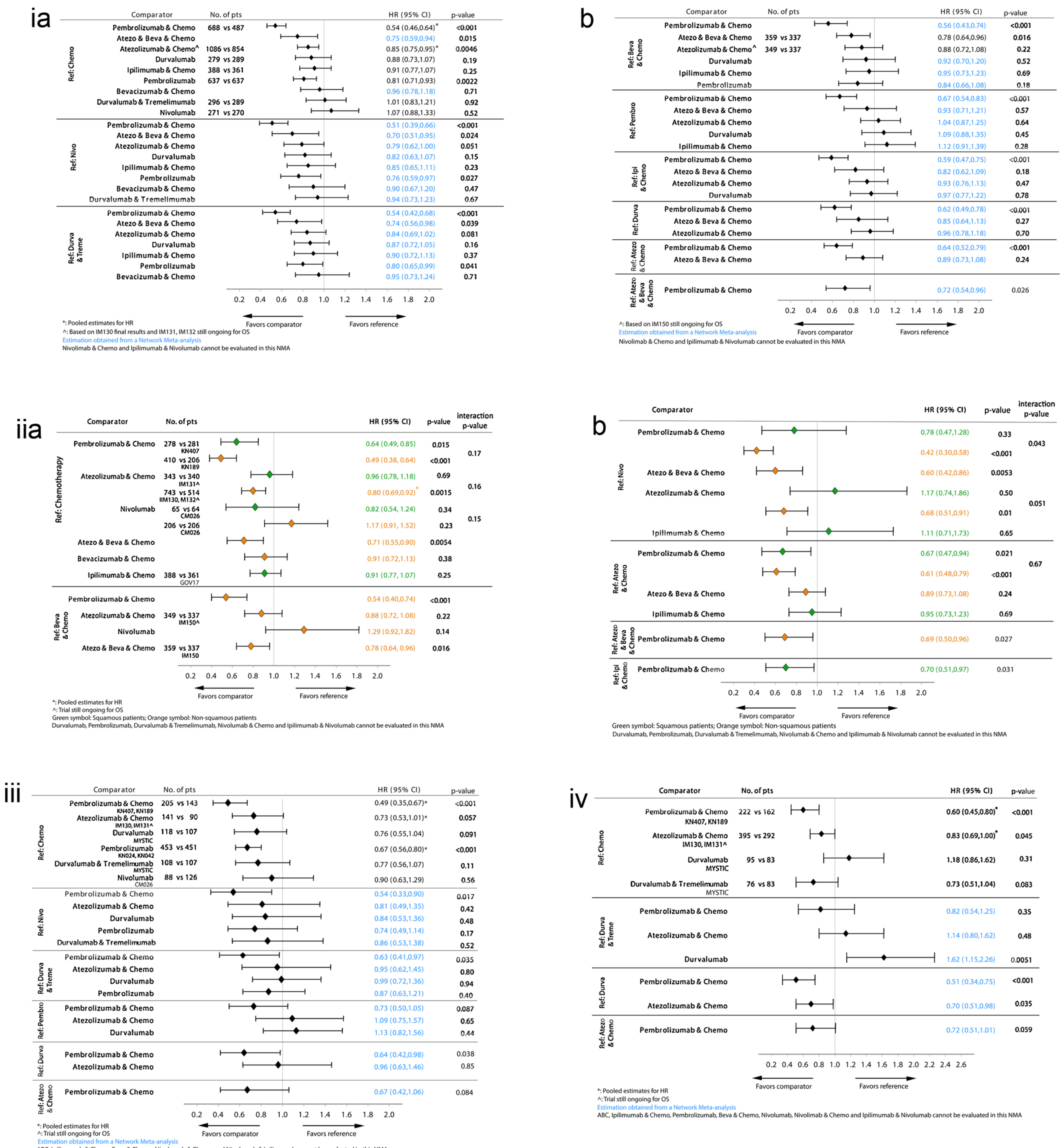


Fig. 6. Forest plots for OS HRs for direct and indirect comparisons **i.a,b:** Overall cohorts; **ii.a,b:** By histology; **iii:** PD-L1-high; **iv:** PD-L1-negative

tremelimumab). The combination of pembrolizumab/chemotherapy is not significantly different than the combination treatments of either atezolizumab/chemotherapy or durvalumab/tremelimumab (Fig. 6iv).

3.8.3.3. Intermediate PD-L1 (1 ≤ PD-L1 ≤ 49%) Cohort. : Results for PD-L1-intermediate patients, are available only for five studies and three experimental treatments (Fig.S4) on 1,511 patients. The combination of pembrolizumab/chemotherapy is estimated to be significantly better than chemotherapy and the other two treatments. It should be noted, that once more for the atezolizumab/chemotherapy combination, OS data is based on two trials with one providing only non-significant interim results (IM131).

3.8.4. OS-NMA by sex

OS results were reported separately for 1,052 females and 2,596 males from five studies (KN407,KN189,KN042,GOV17,CM026). Results are analogous to the corresponding PFS-NMA (Fig.S5a,b), noting that the atezolizumab/chemotherapy combination is not evaluable here.

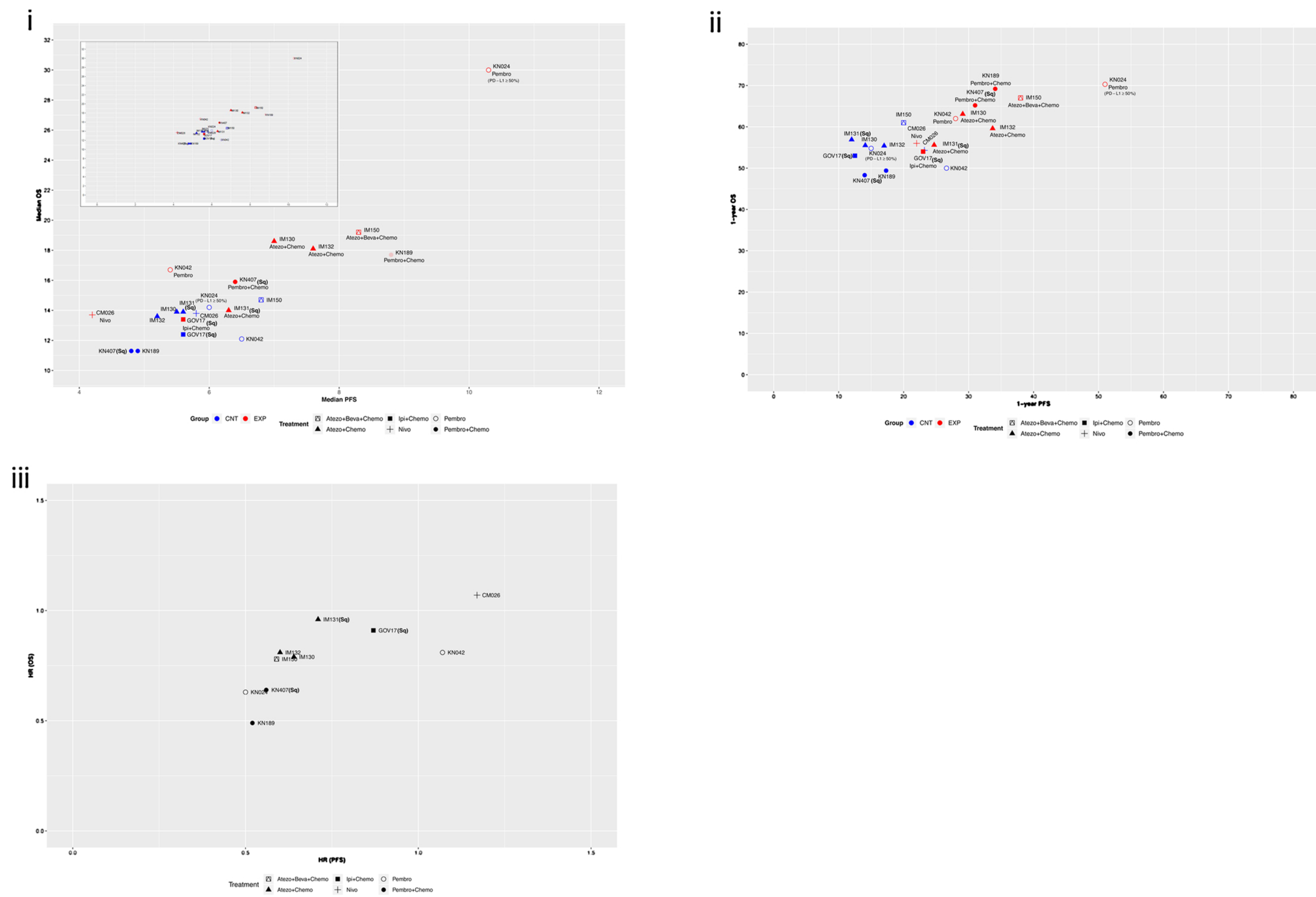


Fig. 7. i Scatterplot of median OS versus PFS by study; Note: For KN189 the median OS for the EXP group is reported as not reached (NR). The estimate is *(1/HR)*(Median in the CNT group)*; ii: Scatterplot of 1-year OS rate versus PFS rate by study; Note: The following 1-year estimates have been derived based on visual inspection of the reported Kaplan-Meier plot: KN024 (PFS), GOV17 (PFS), KN407 (PFS), KN042 (OS); iii: Scatterplot of HRs OS versus PFS by study; CNT: Control arm, EXP: Experimental arm, Sq: Squamous patients

The treatment-specific sex differences observed for PFS are also present for OS with women seeming to derive higher benefit compared to men from the combination of pembrolizumab/chemotherapy versus chemotherapy or any other treatment option (all $p_{interaction} < 0.02$).

3.9. Association of PFS and OS

The association of PFS and OS for both the control and experimental arms is explored in the ten studies providing information on both, in the overall study cohort (Fig.7i-iii; Table-S4). For the ICI-including treatments, a high positive correlation is found for the medians ($\rho_{Spearman} = 0.75$; Fig. 7i), and similarly for the one-year PFS and OS rates ($\rho_{Spearman} = 0.70$; Fig. 7ii). The observed trends are the same, with the highest median and %event-free rate observed with the combinations of chemotherapy with pembrolizumab or atezolizumab (with/without bevacizumab). This is true for the atezolizumab combinations even though OS data is immature in three of the contributing studies. A very high correlation is also describing the association of the summary measure of HR for PFS and OS ($\rho_{Spearman} = 0.91$; Fig. 7iii), indicating good surrogacy of PFS for OS[51].

3.10. Toxicity results

The incidence of any grade ≥ 3 AE is presented, as available per study (of any cause and/or treatment-related; Table-S7).

In the ICI/chemotherapy combinations, no significant difference in incidence of any grade ≥ 3 AE is detected between pembrolizumab/chemotherapy and chemotherapy-alone (any-cause;KN189;KN407) while a significant increase is observed with atezolizumab/chemotherapy (both any-cause and treatment-related AEs; IM131/IM132/IM130) and ipilimumab/chemotherapy (treatment-related AEs; GOV17). For the ABC combination (IM150) no significant increase is detected versus bevacizumab/chemotherapy.

In the two ICI-combinations, a non-significant decrease in treatment-related severe AEs is detected for nivolumab/ipilimumab (CM227), while for durvalumab/tremelimumab this decrease is significant compared to chemotherapy-alone (MYSTIC). Similarly, all ICI-monotherapies of either pembrolizumab (KN024,KN042), nivolumab (CM026), or durvalumab (MYSTIC) exhibit significantly lower incidence of treatment-related severe AEs compared to chemotherapy.

4. Discussion

Since 2011, the randomized exploration of ICI treatments has drawn extensive attention in many patient categories with promising results, as well as potential cure as in the case of selected NSCLC and advanced melanoma patients. Randomized ICI testing in NSCLC, started more recently with first promising results published in 2015 in the second-line treatment, leading to the approval of pembrolizumab, atezolizumab and nivolumab[31–34,52].

Initially, in the indication of frontline therapy, an enrichment strategy design led to the approval of pembrolizumab for PD-L1-high patients([KN024[12]). Almost all subsequent studies included all-comers, either restricted or stratified by histological subtype, stratified or exploring PD-L1 expression level, with only two requiring PD-L1-positivity. All these studies are included in the present NMA.

Platinum-based chemotherapy and the combination of chemotherapy with pembrolizumab are to date the only EMA-approved options for first-line treatment in advanced/metastatic NSCLC wt ALK/EGFR irrespective of PD-L1 status, while the standard of care for PD-L1-high is pembrolizumab-monotherapy, FDA- and EMA-approved. The approved chemotherapy backbones for the pembrolizumab/chemotherapy combination are carboplatin and either paclitaxel or nab-paclitaxel [based on KN407] for squamous, and carboplatin or cisplatin and pemetrexed, for non-squamous [based on KN189]. According to the ESMO guidelines, along with the EMA-approved pembrolizumab-combination, atezolizumab/chemotherapy with/without bevacizumab are recommended treatments for any PD-L1 expression in the treatment algorithm for stage-IV NSCLC[53].

The field is expanding in a very rapid pace, with 17 currently active additional Phase-III studies (clinicaltrials.gov-Oct2018) including, apart from the ICIs already reported, at least one more (avelumab), and different combinations evaluated (Table-S8).

To our knowledge, our NMA is the first systematic review, encompassing the entirety of publicly available results from first-line Phase-III randomized studies testing ICIs and their combinations in this cohort, including information reported as recently as in April 2019. The focus is on frontline chemotherapy-naïve patients, not eligible for targeted therapies, thus excluding patients with known ALK/EGFR mutations. The relative benefit on PFS/OS irrespective of PD-L1-positivity, and by PD-L1 levels, were explored. Of importance, the TMB classification could not be examined in this NMA.

The use of five approved anti-PD-L1 IHC assays corresponding to each different ICI tested, is a well-known limitation, and for IMP studies, the "positive" test for PD-L1 expression, is based not only on TCs but also on tumor infiltrating immune cells[54,55]. In our NMA, this is of no consequence for the primary overall cohort analysis, but we recognize it as an important limitation for the analyses by PD-L1 level since the subgroup breakdowns are reported in each study based on the different approved assays. The histology mix is different across studies, and is confounded with a higher proportion of males in squamous cohorts and different backbone chemotherapy. A separate analysis by histology addressed this issue, while also PD-L1 levels and sex are evaluated as effect modifiers through subgroup analysis. Other patient and cohort characteristics are similar across studies, and importantly the study control arms exhibit similar median PFS and OS, supporting the validity of the indirect and mixed comparisons described by the NMA.

In the primary NMA in the overall cohort, the PFS of three combination treatments, pembrolizumab/chemotherapy, atezolizumab/chemotherapy and nivolumab/ipilimumab fare better than chemotherapy. The PFS benefit of the ICI combinations with chemotherapy is significantly higher than any other treatment examined, with pembrolizumab/chemotherapy faring better than atezolizumab/chemotherapy. This difference is not significant when examined by histology, with both combinations shown to be the better treatments for both squamous and non-squamous. Interestingly, in the one negative study on nivolumab included in this NMA, a differential effect of nivolumab between squamous and non-squamous histology is apparent ($p_{interaction} = 0.074$). A detrimental effect of nivolumab in non-squamous patients is detected (HR = 1.29[1.2-1.63]), that is not discussed as such in the original publication (CM026[17]).

When examining OS, again the combination of pembrolizumab/chemotherapy is the better treatment, followed first by the ABC combination, then pembrolizumab-monotherapy and atezolizumab/chemotherapy, all no different between them. ABC is only present in the OS-NMA for the full cohort, with a significantly higher OS also to nivolumab, the combination of durvalumab/tremelimumab and bevacizumab/chemotherapy. The OS benefit shown for the combinations of atezolizumab is mainly driven from the non-squamous subtype. Of note, the OS-NMA could be under-estimating the OS benefit of atezolizumab/chemotherapy, by using non-significant interim data from three of four still ongoing studies (IM150[24,48],IM131[19],IM132[20]). Sensitivity analysis, exploring this bias did not show different results.

For PD-L1-high patients, pembrolizumab-monotherapy, the standard of care, does provide statistically significant PFS benefit over chemotherapy, but again the combination of chemotherapy with atezolizumab or pembrolizumab are overall the better treatments regarding PFS. For OS, pembrolizumab/chemotherapy and pembrolizumab-alone are significantly better than chemotherapy, while no different than atezolizumab/chemotherapy.

In the PD-L1 negative cohort, importantly, all three combinations with chemotherapy examined (pembrolizumab, atezolizumab, nivolumab) exhibit superior PFS to chemotherapy-alone, without an apparent separation between the three combinations. For OS, a different set of treatments is available, now including durvalumab and its combination with tremelimumab (MYSTIC[28]). The combination of pembrolizumab/chemotherapy and atezolizumab/chemotherapy are superior to chemotherapy-alone while no different between them and durvalumab/tremelimumab. Durvalumab-alone is clearly less efficacious than any combination treatment. We again note that the combination atezolizumab/chemotherapy is at a disadvantage, with OS data partly based on a non-significant interim analysis (IM131[19]).

Lastly, in the PD-L1-intermediate subgroup, the combination of pembrolizumab/chemotherapy and atezolizumab/chemotherapy, provide statistically significant benefit in PFS compared to chemotherapy, while this is verified in OS only for pembrolizumab/chemotherapy, with again partly non-significant data used for the atezolizumab combination (IM131[19]).

Sex is also explored for a possible differential effect on PFS/OS treatment benefit, and again the same treatment combinations qualify. Interestingly, pembrolizumab/chemotherapy seems to benefit more women than men.

Finally, the question on whether treatment efficacy is different for patients with and without liver metastases was explored through direct meta-analysis, for the atezolizumab studies and the more recently presented KN189 subgroup results. A differentiating effect of liver metastasis on the PFS benefit of the atezolizumab/chemotherapy combination was found, which is cancelled when ABC is added to the treatments. When the effect of both the pembrolizumab/chemotherapy and atezolizumab/chemotherapy treatments is explored in the meta-analysis, a beneficial effect of the ICI/chemotherapy combination is observed for both liver metastasis subgroups, with an apparent higher benefit in the subgroup without liver metastasis ($p_{interaction} = 0.087$).

The clear aim of this study was to use the entirety of available information to date. Thus, even data based on interim analyses of ongoing studies were incorporated in the analysis. This, as already noted, could have under-estimated the pembrolizumab-monotherapy PFS benefit and the atezolizumab/chemotherapy OS benefit, and it is important to recognize that upcoming information might affect the present conclusions. Other limitations due to data availability include that not all patients and treatments evaluated in the overall cohort are present in the analysis by histology and/or in other analyses. As an example, data on durvalumab and durvalumab/tremelimumab was provided only for the OS-NMA and not the primary PFS-NMA, while ABC was evaluated only for OS in the overall cohort with information stemming from non-squamous patients.

NMA results should always be interpreted with caution since they are partly based on indirect comparisons, and thus subject to satisfying both a.the transitivity assumption and b.the consistency assumption between direct and indirect evidence. The former is satisfied here since patient populations and effect modifiers are comparable in the included trials and/or addressed in subgroup analyses while the latter could not be verified due to lack of direct evidence from head-to-head trials[56].

Another possible NMA limitation, is the use of HRs as efficacy measure across studies, while the PFS hazards are not necessarily proportional. An indication of the lack of proportionality for PFS, is seen by the comparison of the marginal improvement in median PFS, vis-à-vis the almost doubling of %PFS improvement at one-year, for the six of the seven studies with statistically significant PFS HR in the overall cohort (KN407,CM227,IM150, IM131,IM132,IM130). This discrepancy between magnitude of benefit in medians versus one-year survival, is not apparent for OS, pointing out that the problem of non-proportionality in PFS does not translate to a similar problem for OS.

In addition, PFS was used as outcome in our primary NMA, while a debate on the surrogacy of PFS regarding OS exists in most tumour types. The issue cannot be considered settled although recently PFS is more acceptable as surrogate outcome in advanced NSCLC[57]. Allowing crossover to the experimental arm for patients progressing in the control arm is a common and ethical practice, which further complicates the issue by casting doubt on the purity of OS outcome. In seven of the ten studies reporting both PFS and OS results, the significance of the reported effect is the same for both endpoints (both non-significant:2 studies; both significant:5). Surprisingly, PFS (secondary endpoint) is non-significant while OS is significant in one study still ongoing for the final analysis of PFS (KN042,[16]). In the two studies testing the atezolizumab/chemotherapy combination versus chemotherapy, PFS is significant while OS is not, but the OS results are immature and follow-up continues.

The level of association, and the similar trends observed regarding median PFS/OS, one-year PFS/OS, and corresponding HRs, indicate that PFS is a good surrogate for OS in this cohort and the family of ICI-including treatments, as well as that the PFS HR non-proportionality and the crossover did not particularly affect the results. Thus, the limitation of the PFS HR non-proportionality, the surrogacy issue and the crossover issue are apparently surpassed for the current NMA since the conclusions stemming from either PFS or OS are consistent regarding the relative importance of treatments.

In addition, the conclusion that the specific ICI-chemotherapy combinations are the most promising treatments is robust, being reached across different PD-L1 cut-offs, as well as in the examined subgroups by histology and sex. Also importantly, observed toxicity is generally acceptable compared to the toxicity observed for the chemotherapy-alone option.

6. Conclusion

A very strong message comes from this systematic review and NMA of ICI treatments as first-line, demonstrating the evidence-based definition of new standards of care for advanced NSCLC. First, chemotherapy is clearly inferior of any ICI and chemotherapy combination. Second, in ICI treatment combinations a backbone of chemotherapy is preferred than another ICI. The addition of chemotherapy to ICIs has enhanced the treatment efficacy as first-line treatment for advanced NSCLC patients. The NMA, subject to the limitations described, consistently suggests as preferred treatments, the combination of pembrolizumab/chemotherapy and of atezolizumab/chemotherapy without or with bevacizumab (ABC: only OS available in non-squamous patients in the overall cohort). Pembrolizumab-monotherapy benefit in high-PD-L1 is also confirmed, inferior to pembrolizumab/chemotherapy for PFS but not different for OS in this specific subgroup of patients.

Conflict of Interest statement

Urania Dafni, Zoi Tsourti and Katerina Vervita declare that there is no conflict of interest.

Solange Peters has received education grants, provided consultation, attended advisory boards and/or provided lectures for the following organizations, from whom she has received honoraria:

- Consultation fees: Abbvie, Amgen, AstraZeneca, Bayer, Biocartis, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F. Hoffmann-La Roche, Foundation Medicine, Illumina, Janssen, Merck Sharp and Dohme, Merck Serono, Merrimack, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics and Takeda
- Talk in a company's organized public event: AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Illumina, Merck Sharp and Dohme, Novartis, Pfizer, Sanofi, Takeda
- Receipt of grants/research supports: (Sub)investigator in trials (institutional financial support for clinical trials) sponsored by Amgen, AstraZeneca, Biodesix, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, F. Hoffmann-La Roche, Illumina, Merck Sharp and Dohme, Merck Serono, Novartis, and Pfizer.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.05.029.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA: A Cancer Journal for Clinicians 68 (6) (2018) 394–424.
[2] P. Goldstraw, K. Chansky, J. Crowley, et al., The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer, Journal of Thoracic Oncology 11 (1) (2016) 39–51.
[3] Y. Iwai, M. Ishida, Y. Tanaka, et al., Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade, Proceedings of the National Academy of Sciences of the United States of America 99 (19) (2002) 12293–12297.
[4] D.R. Leach, M.F. Krummel, J.P. Allison, Enhancement of antitumor immunity by CTLA-4 blockade, Science (New York) 22 (271) (1996) 1734–1736.
[5] D.M. Pardoll, The blockade of immune checkpoints in cancer immunotherapy, Nature Reviews. Cancer 12 (4) (2012) 252–264.
[6] L.B. Alexandrov, S. Nik-Zainal, C. Wedge, et al., Signatures of mutational processes in human cancer, Nature 500 (7463) (2013) 415–421.
[7] T.A. Chan, E. Jaffee, M. Yarchoan, et al., Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic, Annals of Oncology 30 (1) (2019) 44–56.
[8] L. Mhanna, J. Milia, A. Lusque, et al., Efficacy of immune-checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) patients harboring activating molecular alterations, ASCO Annual Meeting (2018).
[9] L. Fehrenbacher, J. von Pawel, K. Park, et al., Updated Efficacy Analysis Including Secondary Population Results for OAK: A Randomized Phase III Study of Atezolizumab versus Docetaxel in Patients with Previously Treated Advanced Non-Small Cell Lung Cancer, Journal of Thoracic Oncology 13 (8) (2018) 1156–1170.
[10] E. Felip Font, S.N. Gettinger, M.A. Burgio, et al., Three-year follow-up from CheckMate 017/057: Nivolumab versus Docetaxel in Patients With Previously Treated Advanced Non-Small Cell Lung Cancer (NSCLC), Annals of Oncology 28 (suppl_5) (2017) 1301PD.
[11] R.S. Herbst, P. Baas, D.-W. Kim, et al., Factors associated with better overall survival (OS) in patients with previously treated, PD-L1–expressing, advanced NSCLC: Multivariate analysis of KEYNOTE-010, Journal of Clinical Oncology 35 (15_suppl) (2017) 9090.
[12] M. Reck, D. Rodríguez-Abreu, A.G. Robinson, et al., Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer, The New England Journal of Medicine 375 (19) (2016) 1823–1833.
[13] R.S. Herbst, P. Baas, D.W. Kim, et al., Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial, Lancet 387 (10027) (2016) 1540–1550.
[14] R. Brody, Y. Zhang, M. Ballas, et al., PD-L1 expression in advanced NSCLC: Insights into risk stratification and treatment selection from a systematic literature review, Lung Cancer 112 (2017) 200–215.
[15] M. Reck, D. Rodríguez–Abreu, A.G. Robinson, et al., Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced

Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater, Journal of Clinical Oncology 37 (7) (2019) 537–546.
[16] G. Lopes, Pembrolizumab vs Platinum-Based Chemotherapy as Firts-Line Therapy for Advanced/Metastatic NSCLC With a PD-L1 TPS&=1%: Open-Label, Phase 3 KEYNOTE-042 Study, ASCO Annual Meeting (2018).
[17] D.P. Carbone, M. Reck, L. Paz-Ares, et al., First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer, The New England Journal of Medicine 376 (25) (2017) 2415–2426.
[18] F. Cappuzzo, M. McCleod, et al., IMpower130: efficacy and safety from a randomized phase 3 study of carboplatin and nap-paclitaxel with or without atezolizumab in 1L advanced non-squamous NSCLC, ESMO 2018 Congress (2018).
[19] R. Jotte, IMpower131:Primary PFS and Safety Analysis of a Randomized Phase III Study of Atezolizumab + Carboplatin +Paclitaxel or Nab-Paclitaxel vs Carboplatin + Nab-Paclitaxel AS 1L Therapy in Advanced Squamous NSCLC, ASCO Annual Meeting (2018).
[20] V.A. Papadimitrakopoulou, IMpower132: PFS and Safety Results with 1L Atezolizumab + Carboplatin/Cisplatin + Pemetrexed in Stage IV Non-Squamous NSCLC, IASCL 19th World Conference on Lung Cancer (2018).
[21] L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, et al., Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer, The New England Journal of Medicine 378 (22) (2018) 2078–2092.
[22] L. Paz-Ares, A. Luft, D. Vicente, et al., Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer, The New England Journal of Medicine 379 (21) (2018) 2040–2051.
[23] H.L. West, M. McCleod, M. Hussein, et al., IMpower130: Progression-free survival (PFS) and safety analysis from a randomized phase 3 study of carboplatin + nab-paclitaxel (CnP) with or without atezolizumab as first-line (1L) therapy in advanced non-squamous NSCLC, AACR Annual Meeting (2019).
[24] M.A. Socinski, R.M. Jotte, F. Cappuzzo, et al., Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC, The New England Journal of Medicine 378 (24) (2018) 2288–2301.
[25] M.D. Hellman, Nivolumab+ Ipilimumab vs Platinum-Doublet Chemotherapy as First-line Treatment for Advanced Non-Small Cell Lung Cancer: Initial Results From CheckMATE 227, American Association for Cancer Research (2018).
[26] M.D. Hellmann, T.-E. Ciuleanu, A. Pluzanski, et al., Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden, The New England Journal of Medicine 378 (22) (2018) 2093–2104.
[27] R. Govindan, A. Szczesna, M.J. Ahn, et al., Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non-Small-Cell Lung Cancer, Journal of Clinical Oncology 35 (30) (2017) 3449–3457.
[28] N. Rizvi, B.C. Cho, N. Reinmuth, et al., Durvalumab with or without tremelimumab vs platinum-based chemotherapy as first-line treatment for metastatic Non-Small Cell Lung Cancer: MYSTIC, ESMO Immuno-Oncology Congress, (2018).
[29] S. Peters, B.C. Cho, N. Reinmuth, et al., Tumor mutational burden (TMB) as a biomarker of survival in metastatic non-small cell lung cancer (mNSCLC): Blood and tissue TMB analysis from MYSTIC, a Phase III study of first-line durvalumab ± tremelimumab vs chemotherapy, AACR Annual Meeting (2019).
[30] J.D. Wolchok, A. Hoos, S. Day, et al., Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria, Clinical Cancer Research 15 (23) (2009) 7412.
[31] G.-W. Zhou, Y. Xiong, S. Chen, et al., Anti-PD-1/PD-L1 antibody therapy for pretreated advanced nonsmall-cell lung cancer: A meta-analysis of randomized clinical trials, Medicine 95 (35) (2016) e4611-e4611.
[32] A. Ramos-Esquivel, A. van der Laat, R. Rojas-Vigott, et al., Anti-PD-1/anti-PD-L1 immunotherapy versus docetaxel for previously treated advanced non-small cell lung cancer: a systematic review and meta-analysis of randomised clinical trials, ESMO Open 2 (3) (2017) e000236.
[33] P.S. Tan, P. Aguiar Jr, B. Haaland, G. Lopes, Comparative effectiveness of immune-checkpoint inhibitors for previously treated advanced non-small cell lung cancer – A systematic review and network meta-analysis of 3024 participants, Lung Cancer 115 (2018) 84–88.
[34] W. You, M. Liu, J.-D. Miao, et al., A Network Meta-analysis Comparing the Efficacy and Safety of Anti-PD-1 with Anti-PD-L1 in Non-small Cell Lung Cancer, Journal of Cancer 9 (7) (2018) 1200–1206.
[35] K. Shen, J. Cui, Y. Wei, et al., Effectiveness and safety of PD-1/PD-L1 or CTLA4 inhibitors combined with chemotherapy as a first-line treatment for lung cancer: A meta-analysis, Journal of Thoracic Disease 10 (12) (2018) 6636–6652.
[36] X. Xu, Z. Huang, L. Zheng, Y. Fan, The efficacy and safety of anti-PD-1/PD-L1 antibodies combined with chemotherapy or CTLA4 antibody as a first-line treatment for advanced lung cancer, International Journal of Cancer 142 (11) (2018) 2344–2354.
[37] R. Chen, X. Hou, L. Yang, D. Zhao, Comparative efficacy and safety of first-line treatments for advanced non-small cell lung cancer with immune checkpoint inhibitors: A systematic review and meta-analysis, Thoracic Cancer (2019) [Epub ahead of print](.
[38] A.M. Frederickson, S. Arndorfer, I. Zhang, et al., Pembrolizumab plus chemotherapy for first-line treatment of metastatic nonsquamous non-small-cell lung cancer: a network meta-analysis, Immunotherapy 11 (5) (2019) 407–428.
[39] B. Hutton, G. Salanti, D.M. Caldwell, et al., The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations, Annals of Internal Medicine 162 (11) (2015) 777–784.
[40] J.P.T. Higgins, D.G. Altman, P.C. Gøtzsche, et al., The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, BMJ 343 (2011) d5928.
[41] G. Salanti, J.P. Higgins, A. Ades, J.P. Ioannidis, Evaluation of networks of randomized trials, Statistical Methods in Medical Research 17 (3) (2008) 279–301.
[42] J.P. Jansen, R. Fleurence, B. Devine, et al., Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1, Value in Health 14 (4) (2011) 417–428.
[43] D.C. Hoaglin, N. Hawkins, J.P. Jansen, et al., Conducting Indirect-Treatment-Comparison and Network-Meta-Analysis Studies: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 2, Value in Health 14 (4) (2011) 429–437.
[44] B.S. Woods, N. Hawkins, D.A. Scott, Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: A tutorial, BMC Medical Research Methodology 10 (1) (2010) 54.
[45] A. Cipriani, J.P.T. Higgins, J.R. Geddes, G. Salanti, Conceptual and Technical Challenges in Network Meta-analysis, Annals of Internal Medicine 159 (2) (2013) 130–137.
[46] C.J. Langer, S.M. Gadgeel, H. Borghaei, et al., Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study, The Lancet Oncology 17 (11) (2016) 1497–1508.
[47] H. Borghaei, C.J. Langer, S. Gadgeel, et al., 24-Month Overall Survival from KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin with or without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous Non-Small Cell Lung Cancer, Journal of Thoracic Oncology 14 (1) (2019) 124–129.
[48] M.A. Socinski, R.M. Jotte, F. Cappuzzo, et al., Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) ± bevacizumab (bev) vs chemo + bev in 1L nonsquamous (NSQ) NSCLC, ASCO Annual Meeting (2018).
[49] H. Borghaei, Nivolumab + Ipilimumab, Nivolumab +Chemotherapy and Chemotherapy in Chemo-Naiove Patients With Advanced Non-Small Cell Lung Cancer and < 1% Tumor PD-L1 Expression: Results From CheckMate 227, ASCO Annual Meeting (2018).
[50] M.C. Garassino, S. Gadgeel, E. Esteban, et al., Outcomes among patients (pts) with metastatic nonsquamous NSCLC with liver metastases or brain metastases treated with pembrolizumab (pembro) plus pemetrexed-platinum: Results from the KEYNOTE-189 study, AACR Annual Meeting (2019).
[51] M. Buyse, G. Molenberghs, T. Burzykowski, et al., The validation of surrogate endpoints in meta-analyses of randomized experiments, Biostatistics 1 (1) (2000) 49–67.
[52] F. Conforti, L. Pala, V. Bagnardi, et al., Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis, The Lancet Oncology 19 (6) (2018) 737–746.
[53] D. Planchard, S. Popat, K. Kerr, et al., Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†, Annals of Oncology 29 (Supplement_4) (2018) iv192–iv237.
[54] K.M. Kerr, M.-S. Tsao, A.G. Nicholson, et al., Programmed Death-Ligand 1 Immunohistochemistry in Lung Cancer: In what state is this art? Journal of Thoracic Oncology 10 (7) (2015) 985–989.
[55] M.S. Tsao, K.M. Kerr, M. Kockx, et al., PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project, Journal of Thoracic Oncology 13 (9) (2018) 1302–1311.
[56] G. Salanti, Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool, Research Synthesis Methods 3 (2) (2012) 80–97.
[57] F. Fiteni, V. Westeel, F. Bonnetain, Surrogate endpoints for overall survival in lung cancer trials: a review, Expert Review of Anticancer Therapy 17 (5) (2017) 447–454.