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Comparative efficacy and safety of immunotherapies targeting the PD-1/PD-L1 pathway for previously treated advanced non-small cell lung cancer: A Bayesian network meta-analysis

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ABSTRACT

Background: Two PD-1 (pembrolizumab, nivolumab) and one PD-L1(atezolizumab) inhibitors are approved for previously treated advanced non-small cell lung cancer but have not been compared in head-to-head trials.
Method: A network meta-analysis was conducted to compare efficacy/safety of PD-1/PD-L1 inhibitors.
Results: In five-trials (including long-term updates) with docetaxel as common comparator there were no differences in OS and PFS between PD-1/PD-L1 inhibitors. Pembrolizumab (odds ratio(OR) = 2.22, 95%CrI = 1.28–3.70) and nivolumab (OR = 1.92, 95%CrI = 1.15–3.23) had higher ORRs than atezolizumab and at PD-L1 expression ≥50% and ≥1%. Probabilistically, pembrolizumab ranked first in OS and ORR, and in OS sub-analyses for adenocarcinoma, EGFR-mutant, ECOG-score-1, male, and age < 65 years. Nivolumab ranked first in PFS, and in OS sub-analyses for squamous-cell disease, EGFR-wild-type, and ECOG-score-0. Pembrolizumab and nivolumab ranked the best option for most of adverse events.
Conclusion: While pembrolizumab and nivolumab prevailed in rank in OS and ORR benefit, patient characteristics, safety and tolerance should be considered in treatment decision-making.

1. Introduction

Lung cancer is the leading cause of death in both men and women in the United States (US) and worldwide (Ferlay et al., 2015; Siegel et al., 2018). Approximately 1.83 million new cases of lung cancer and 1.59 million related deaths were estimated in 2012 worldwide (Ferlay et al., 2015). In the US in 2018, it is estimated that 234,030 new cases of lung cancer will be diagnosed with 154,050 deaths due to this disease (Siegel et al., 2018). Around 80–85% of lung cancer cases are classified as non-small-cell lung cancer (NSCLC) (Zappa and Mousa, 2016; Molina et al., 2008) and nearly 70% of patients with lung cancer are diagnosed with locally advanced or metastatic disease (Molina et al., 2008). Prognosis for patients with advanced/metastatic NSCLC is poor (Siegel et al., 2018) as surgical options are limited (Molina et al., 2008) and the chemotherapy response rate, whether cytotoxic or platinum doublet-based regimens in first-line or docetaxel in second-line, is only 15–30% (Malhotra et al., 2017). In recent years several immunotherapeutic agents have been approved that have improved treatment outcomes in patients with lung cancer (Wang et al., 2016).

Programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) are proteins expressed on activated T-cells and pro-B cells and tumor cells including NSCLC. Inhibiting the PD-1/PD-L1 pathway has been shown to restore the activity of T-cells to target tumor cells (Shien et al., 2016). Immunotherapies involving monoclonal antibodies (mAB) targeting PD-1 (nivolumab and pembrolizumab) and PD-L1 (atezolizumab) have provided an alternative option for patients with NSCLC in the second-line setting (Shien et al., 2016; Lee et al., 2018). These agents were evaluated in separate pivotal trials that randomized

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patients with previously treated advanced NSCLC to treatment with either a novel mAB or docetaxel (Shien et al., 2016; Hu et al., 2018). There are no prospective head-to-head randomized clinical trials comparing the efficacy of the PD-1 and PD-L1 checkpoint inhibitors, hence choosing the appropriate immunotherapy is driven by provider preference. We performed a Bayesian network meta-analysis of randomized controlled trials to compare the efficacy and safety of pembrolizumab, nivolumab, and atezolizumab in previously treated patients with NSCLC and to estimate the ranking probabilities of these therapies. Bayesian network meta-analyses are an appropriate statistical method to compare therapies by simulating statistically the estimated outcomes of a comprehensive trial comparing all treatment options through common and linked comparators. In addition, Bayesian network meta-analysis can produce ranking probabilities of treatments, which may help clinicians in their clinical decision-making (Hoaglin et al., 2011; Salanti et al., 2011).

2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist with the extension for network meta-analysis (Hutton et al., 2015).

2.1. Search strategy

We identified eligible studies through a comprehensive search of Medline/PubMed, Cochrane Library, and Embase from inception through 31 May 2018 (Table S1). We also searched the websites of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), screened the reference lists of various articles, in addition to including articles known to us.

2.2. Inclusion and exclusion criteria

Eligible were English-language reports of completed phase II/III randomized controlled trials that assessed the efficacy and/or safety of FDA-approved immune checkpoint inhibitors that target PD-1 (nivolumab, pembrolizumab) and its ligand PD-L1 (atezolizumab) in previously treated advanced NSCLC, including updates for these trials. Studies in the pediatric population or comparing alternate treatment doses of the same product were excluded.

2.3. Outcome measures

The primary outcomes of interest were overall survival (OS), progression-free survival (PFS), objective response rate (ORR) based on the Response Evaluation Criteria in Solid Tumors (RECIST) for complete and partial responses, and treatment-related adverse events (AEs; all-grades and grades 3/4) including immune-related AEs (irAEs). Secondary outcomes included OS, PFS, ORR and treatment-related AEs for the FDA-approved doses (pembrolizumab 200 mg every 3 weeks, nivolumab 3 mg/kg every 2 weeks, and atezolizumab 1200 mg every 3 weeks).

2.4. Selection of studies and data extraction

The search strategy was developed by a professional health sciences librarian (J.M.) and executed under her supervision by the lead investigator (A.A.). Publications produced by the search were managed in Endnote® v.7.3 (Clarivate Analytics, Philadelphia, PA, USA). Duplicate records were removed by one investigator (A.A.) and validated by a second investigator (N.A.). Screening of titles and abstracts and subsequent review of retained full-text publications to identify trials meeting inclusion and exclusion criteria was done independently by two investigators (A.A., and N.A.) with any unresolved disagreements escalated to a methodological (I.A.) or clinical expert (A.M.). Data were extracted by one (A.A.) and verified by a second investigator (N.A.) using a pre-specified and tested data extraction worksheet that covered treatments and treatment groups, patient characteristics, treatment duration, and treatment outcomes (efficacy and safety).

2.5. Assessment of the risks of bias

We assessed the potential risks of bias in trials by using the Cochrane Collaboration Risk of Bias Assessment tool (Higgins and Green, 2011). Two investigators (A.A., and N.A.) completed the review independently. Disagreements were resolved by a third investigator (I.A.).

2.6. Statistical analysis

We performed a Bayesian network meta-analysis using WinBUGS 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK) and NetMetaXL (Canadian Agency for Drugs and Technologies in Health, Ottawa, Canada). In addition to overall analyses including all patients, we performed subgroup analyses of OS and PFS for patients with squamous cell carcinoma, adenocarcinoma, epidermal growth factor receptors (EGFR) type (mutant or wild), Eastern Cooperative Oncology Group (ECOG) performance status score (0 or 1), gender, and age < 65 or ≥ 65 years. We also performed analyses for OS, PFS, and ORR based on PD-L1 expression at $< 1\%$, $\geq 1\%$, $\geq 5\%$, and $\geq 50\%$.

OS and PFS outcomes were expressed as hazard ratios (HR) with their 95% credible interval (95%Crl). ORR and AEs were expressed as odds ratios (OR) and their 95%Crl. For each treatment comparison, we ran the model for 60,000 iterations with discarding of the first 30,000 iterations. Fixed-effects models were used due to the small number of trials and the network being based on single study connections (Cameron et al., 2014). Ranking probabilities of treatments were estimated using the surface under the cumulative ranking (SUCRA) probabilities to show the likelihood of therapies in best-to-worst order (Salanti et al., 2011).

3. Results

3.1. Characteristics of selected trials

The search yielded five unique trials that met the inclusion and exclusion criteria as well as three updates for three of these trials (Fig. S1) (Brahmer et al., 2015; Borghaei et al., 2015; Herbst et al., 2016; Rittmeyer et al., 2017; Fehrenbacher et al., 2016; Horn et al., 2017; Vokes et al., 2018; Fehrenbacher et al., 2018). All five trials had docetaxel as the comparator arm and included 3024 patients with advanced NSCLC previously treated with chemotherapy (Fig. S2). All trials reported the primary outcomes of OS, PFS, and ORR. Trials were similar in patients' median age with a slight majority of men (Table 1). The majority of patients had non-squamous NSCLC type, wild type of EGFR, no anaplastic lymphoma kinase (ALK) translocation, PD-L1 expression measured by tumor proportion score (TPS) less than 50%, ECOG performance status score of 1, and one prior line of systemic treatment. Three additional articles provided 2-year and 3-year updates for two nivolumab trials (Checkmate-017, Checkmate-057) (Horn et al., 2017; Vokes et al., 2018) and a 2-year update for an atezolizumab trial (OAK) (Fehrenbacher et al., 2018).

3.2. Risk of bias

All five trials being open-label, they were all considered at high risk of bias in performance and detection. Two studies were rated at high risk of selection bias because they utilized unmasked allocation methods (Fig. S3) (Rittmeyer et al., 2017; Fehrenbacher et al., 2016).

Table 1
Characteristics of included studies.

Medications	Keynote-010			CheckMate-017		CheckMate-057		OAK		POPLAR	
	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Docetaxel 75 mg/m^2	Nivolumab 3 mg/kg	Docetaxel 75 mg/m^2	Nivolumab 3 mg/kg	Docetaxel 75 mg/m^2	Atezolizumab 1200 mg	Docetaxel 75 mg/m^2	Atezolizumab 1200 mg	Docetaxel 75 mg/m^2
No. patients	344	346	343	135	137	292	290	425	425	144	143
Phase	2/3			3		3		3		2	
Age (median, range)	63 (29–82)	63 (20–88)	62 (33–82)	62 (39–85)	64 (42–84)	61 (37–84)	64 (21–85)	63 (33–82)	64(34–85)	62 (42–82)	62 (36–84)
Men (N, %)	212 (62)	213 (62)	209 (61)	111 (82)	97 (71)	151 (52)	168 (58)	261 (61)	259 (61)	93 (65)	76 (53)
Histology											
Squamous (N, %)	76 (22)	80 (23)	66 (19)	135 (100)	137 (100)	0	0	112 (26)	110 (26)	49 (34)	48 (34)
Non-squamous (N, %)	240 (70)	244 (71)	240 (70)	0	0	292 (100)	290 (100)	313 (74)	315 (74)	95 (66)	95 (66)
PD-L1 TPS											
1–49% (N, %)	205 (60%)	195 (56%)	191 (56%)	NA	NA	NA	NA	169 (40%)	157 (37%)	33 (23%)	46 (32%)
≥50% (N, %)	139 (40%)	151 (44%)	152 (44%)	NA	NA	NA	NA	72 (17%)	65 (15%)	15 (10%)	15 (11%)
< 10% (N, %)	NA	NA	NA	81 (60%	75 (55)	145 (50)	145 (50)	NA	NA	NA	NA
≥10% (N, %)	NA	NA	NA	36 (27)	33 (24)	86 (29)	79 (27)	NA	NA	NA	NA
EGFR status											
Wild-type (N, %)	293 (85%)	288 (83%)	294 (86%)	NA	NA	168 (58%)	172 (59%)	318 (75%)	310 (73%)	72 (50%)	75 (52%)
Mutant (N, %)	28 (8%)	32 (9%)	26 (8%)	NA	NA	44 (15%)	38 (13%)	42 (10%)	43 (10%)	10 (7%)	8 (6%)
ALK translocation											
No (N, %)	307 (89%)	305 (88%)	310 (90%)	NA	NA	113 (39%)	130 (45%)	223 (52%)	201 (47%)	61 (42%)	55 (38%)
Yes (N, %)	2 (1%)	4 (1%)	2 (1%)	NA	NA	13 (4%)	8 (3%)	2 (< 1%)	0	0	3 (2%)
ECOG performance status											
0 (N, %)	112 (33%)	120 (35%)	116 (34%)	27 (20%)	37 (27%)	84 (29)	95 (33%)	155 (36%)	160 (38%)	46 (32%)	45 (32%)
1 (N, %)	229 (67%)	225 (65%)	224 (65%)	106 (79%)	100 (73%)	208 (71%)	194 (67%)	270 (64%)	265 (62%)	96 (68%)	97 (68%)
No. of prior systemic regimens											
1 (N, %)	243 (71%)	235 (68%)	235 (69%)	134 (99%)	137 (100%)	256 (88%)	259 (89%)	320 (75%)	320 (75%)	93 (65%)	96 (67%)
2 (N, %)	66 (19%)	69 (20%)	75 (22%)	1 (1%)	0	35 (12%)	31 (11%)	105 (25%)	105 (25%)	51 (35%)	47 (33%)

ALK: anaplastic lymphoma kinase, ECOG: Eastern Cooperative Oncology Group performance status, EGFR: epidermal growth factor receptor, PD-L1: programmed death-ligand 1, TPS: tumor proportion.

Table 2
Primary outcomes: OS and PFS expressed as HR and 95%CrI, and ORR expressed as OR and 95%CrI.

	Pembrolizumab vs. Docetaxel	Nivolumab vs. Docetaxel	Atezolizumab vs. Docetaxel	Nivolumab vs. Pembrolizumab	Pembrolizumab vs. Atezolizumab	Nivolumab vs. Atezolizumab
Results based on the original published trials						
OS (HR,95%CrI)	0.66 (0.57 – 0.76)*	0.68 (0.57 – 0.80)*	0.73 (0.63 – 0.85)*	1.03 (0.82 – 1.29)	0.90 (0.72 – 1.11)	0.93 (0.74 – 1.15)
PFS (HR,95%CrI)	0.83 (0.74 – 0.94)*	0.82 (0.70 – 0.95)*	0.95 (0.83 – 1.08)	0.98 (0.81 – 1.18)	0.88 (0.74 – 1.05)	0.86 (0.70 – 1.05)
ORR (OR,95%CrI)	2.19 (1.46 – 3.34)*	1.91 (1.31 – 2.83)*	1.00 (0.71 – 1.40)	0.87 (0.50 – 1.54)	2.22 (1.28 – 3.70)*	1.92 (1.15 – 3.23)*
Results based on the updates of the trials (Checkmate-017/Cheackmate-057, and OAK)						
OS‡ (HR,95%CrI)	0.66 (0.57 – 0.76)*	0.71 (0.61 – 0.82)*	0.75 (0.65 – 0.87)*	1.07 (0.87 – 1.33)	0.88 (0.71 – 1.08)	0.95 (0.77 – 1.17)
OS† (HR,95%CrI)	0.66 (0.57 – 0.76)*	0.70 (0.61 – 0.81)*	0.75 (0.65 – 0.87)*	1.07 (0.87 – 1.31)	0.88 (0.71 – 1.08)	0.94 (0.77 – 1.15)
PFS† (HR,95%CrI)	0.83 (0.74 – 0.94)*	0.80 (0.69 – 0.92)*	0.93 (0.82 – 1.06)	0.96 (0.79 – 1.15)	0.89 (0.75 – 1.07)	0.85 (0.70 – 1.04)
ORR‡ (OR,95%CrI)	2.19 (1.46 – 3.34)*	1.91 (1.31 – 2.83)*	1.06 (0.76 – 1.48)	0.87 (0.50 – 1.54)	2.07 (1.22 – 3.54)*	1.81 (1.09 – 3.02)*

* Statistically significant (95%CrI does not include 1), CrI: credible interval, HR: hazard ratio, OR: odds ratio, ORR: objective response rate, OS: overall survival, PFS: progression-free survival.
‡ Results using the 2 years updates for Checkmate-017/Cheackmate-057, and OAK.
† Results using the 3 years updates for Checkmate-017/Cheackmate-057, and 2 years updates for OAK.

3.3. Overall survival

In pairwise comparisons to docetaxel, all three PD-1/PD-L1 immune checkpoint inhibitors showed statistically significant OS benefits as indicated by the respective HRs and associated 95%CrIs not crossing unity (Table 2). In pairwise comparisons to each other, pembrolizumab, nivolumab, and atezolizumab did not show statistically significant OS benefits relative to each other as indicated by the respective HRs with associated 95%CrIs crossing unity. Pembrolizumab was ranked the best therapy in terms of OS with a probability of 53% based on data from the original published trials and 68–70% when incorporating data from the recent updates on the nivolumab and atezolizumab trials (Fig. S4).

3.4. Progression-free survival

In pairwise comparisons to docetaxel, pembrolizumab and nivolumab but not atezolizumab showed a statistically significant PFS benefit as indicated by the respective HRs and associated 95CrIs (Table 2). In pairwise comparisons to each other, pembrolizumab, nivolumab, and atezolizumab did not evidence statistically significant PFS benefits relative to each other as indicated by the respective HRs with associated 95%CrIs crossing unity. Nivolumab was ranked the best therapy in terms of PFS with a probability of 59% based on data from the original published trials and 67% when incorporating data from the recent updates on the nivolumab and atezolizumab trials (Fig. S4).

3.5. Objective response rate

In pairwise comparisons to docetaxel, pembrolizumab and nivolumab but not atezolizumab showed statistically significant ORRs as indicated by the respective ORs and associated 95CrIs (Table 2). In pairwise comparisons to each other, pembrolizumab and nivolumab did not show statistically significant differences in ORR as indicated by ORs with associated 95%CrIs crossing unity. However, both agents showed better ORR outcomes than atezolizumab as indicated by the respective ORs and associated 95%CrIs not crossing unity. Pembrolizumab was ranked the best therapy in terms of ORR with a probability of 68% (Fig. S4).

3.6. Adverse events

Results from all-grade AEs are presented in Table 3. Compared to docetaxel, pembrolizumab, nivolumab, and atezolizumab showed significant risk reduction in alopecia, anemia, diarrhea, dysgeusia, fatigue, febrile neutropenia, myalgia, nausea, neutropenia, peripheral edema, peripheral neuropathy, stomatitis, and treatment-related AEs leading to discontinuation. In addition, pembrolizumab was associated with a reduced risk of asthenia, infusion-related reaction, increased lacrimation, leukopenia, decreased neutrophil count, palmar-plantar erythrodysesthesia syndrome, paresthesia, urticaria, vomiting, and decreased white blood cell count; but with an increased risk of elevated alanine aminotransferase level, back pain, elevated blood creatinine, elevated blood thyroid stimulating hormone, colitis, hyperthyroidism, hypothyroidism, pneumonitis, pruritus, rash, and maculopapular rash. Nivolumab was associated with a reduced risk of asthenia, constipation, decreased appetite, hypersensitivity, increased lacrimation, leukopenia, mucosal inflammation, decreased neutrophil count, pain, paresthesia, pyrexia, vomiting, and decreased white blood cell count; but with an increased risk of elevated aspartate aminotransferase level, elevated blood thyroid stimulating hormone, hyperthyroidism, hypothyroidism, pneumonitis, pruritus, and rash. Atezolizumab was associated with an increased risk of elevated alanine aminotransferase and aspartate aminotransferase levels, back pain, cough, musculoskeletal pain, pneumonitis, and pyrexia.

Nivolumab showed a significantly lower risk of anemia and nausea than pembrolizumab and atezolizumab; lower risk of leukopenia than pembrolizumab; and lower risk of constipation, decreased appetite, diarrhea, neutropenia, peripheral edema, peripheral neuropathy, pneumonitis, pyrexia, and vomiting than atezolizumab. Pembrolizumab showed a lower risk of urticaria than nivolumab; a lower risk of asthenia, neutropenia, peripheral edema, peripheral neuropathy, pyrexia, and vomiting than atezolizumab. Atezolizumab did not show any lower risk of AEs when compared to nivolumab and pembrolizumab.

When nivolumab, pembrolizumab and atezolizumab were compared to each other or separately to docetaxel, there was no difference in the rate of treatment-related death. The 2-year and 3-year updates of the nivolumab trials revealed that the rates of diarrhea at these extended time points were similar to those for atezolizumab.

Nivolumab ranked best for reducing the risk of 22 out of 52 all-grades AEs, atezolizumab for 2 AEs, pembrolizumab for 13 AEs, and docetaxel for 15 AEs (Fig. S5).

Table 4 summarizes the grade3/4 AEs results. Compared to docetaxel, the three immune checkpoint inhibitors had a significantly lower risk of neutropenia and febrile neutropenia. In addition, pembrolizumab and nivolumab were associated with a reduced risk of asthenia, fatigue, leukopenia, decreased neutrophil count, and decreased white blood cell count. Nivolumab and atezolizumab were associated with a reduced risk of anemia, decreased appetite, peripheral neuropathy, and stomatitis. Pembrolizumab and atezolizumab were associated with a reduced risk of diarrhea; pembrolizumab with a higher risk of pneumonitis; and nivolumab with a lower risk of asthenia and fatigue versus atezolizumab.

Out of 50 grade 3/4 AEs included in the analysis, nivolumab was the best option for reducing the risk of 28 AEs, pembrolizumab for 10 AEs,

Table 3
Adverse events (all grades), expressed as OR and 95%CrI.

	Pembrolizumab vs. Docetaxel	Nivolumab vs. Docetaxel	Atezolizumab vs. Docetaxel	Nivolumab vs. Pembrolizumab	Pembrolizumab vs. Atezolizumab	Nivolumab vs. Atezolizumab
Results based on the original published trials						
Abdominal pain	0.82 (0.24 – 3.29)	0.24 (0.03 – 1.08)	NA	0.28 (0.03 – 2.07)	NA	NA
Alanine aminotransferase increased	2.98 (1.11 – 10.49)*	2.18 (0.78 – 7.20)	24.81 (1.81 – 13310.00)*	0.73 (0.15 – 3.42)	0.12 (0.00 – 2.28)	0.09 (0.00 – 1.59)
Alopecia	0.01 (0.00 – 0.03)*	0.01 (0.00 – 0.03)*	0.01 (0.00 – 0.03)*	0.37 (0.01 – 2.78)	1.27 (0.32 – 4.76)	0.46 (0.02 – 3.45)
Anemia	0.24 (0.14 – 0.41)*	0.07 (0.03 – 0.15)*	0.40 (0.30 – 0.54)*	0.30 (0.11 – 0.72)*	0.60 (0.32 – 1.10)	0.18 (0.07 – 0.15)*
Arthralgia	0.80 (0.45 – 1.49)	0.86 (0.48 – 1.55)	1.22 (0.85 – 1.75)	1.08 (0.46 – 2.44)	0.66 (0.33 – 1.34)	0.71 (0.35 – 1.40)
Aspartate aminotransferase increased	2.85 (0.91 – 12.79)	3.85 (1.15 – 18.35)*	24.61 (1.81 – 16080.00)*	1.35 (0.19 – 9.09)	0.11 (0.00 – 2.48)	0.15 (0.00 – 3.31)
Asthenia	0.48 (0.29 – 0.77)*	0.57 (0.37 – 0.86)*	0.88 (0.67 – 1.15)	1.19 (0.63 – 2.27)	0.54 (0.31 – 0.94)*	1.54 (0.94 – 2.56)
Back pain	18.26 (1.37 – 7767.00)*	NA	1.58 (1.06 – 2.39)*	NA	11.11 (0.83 – 4967.71)	NA
Blood alkaline phosphatase increased	2.94 (0.73 – 21.89)	0.42 (0.05 – 2.36)	NA	0.14 (0.01 – 1.35)	NA	NA
Blood creatinine increased	26.29 (2.10 – 23260.00)*	3.16 (0.91 – 15.24)	NA	0.12 (0.00 – 2.42)	NA	NA
Blood thyroid stimulating hormone increased	39.55 (1.49 – 302100.00)*	29.51 (1.98 – 19920.00)*	NA	0.76 (0.00 – 969.00)	NA	NA
Colitis	32.69 (1.24 – 225500.00)*	5.25 (0.64 – 160.00)	6.63 (0.90 – 196.80)	0.16 (0.00 – 18.82)	4.90 (0.04 – 37693.18)	0.78 (0.01 – 39.32)
Constipation	0.74 (0.38 – 1.51)	0.46 (0.24 – 0.87)*	1.12 (0.84 – 1.52)	0.62 (0.24 – 1.57)	0.66 (0.32 – 1.42)	0.41 (0.20 – 0.82)*
Cough	1.81 (0.54 – 8.58)	NA	1.36 (1.02 – 1.81)*	NA	1.33 (0.38 – 6.67)	NA
Decreased appetite	0.73 (0.50 – 1.07)	0.58 (0.38 – 0.87)*	1.02 (0.80 – 1.31)	0.79 (0.45 – 1.39)	0.71 (0.45 – 1.12)	0.56 (0.35 – 0.91)*
Diarrhea	0.33 (0.21 – 0.49)*	0.29 (0.18 – 0.44)*	0.51 (0.39 – 0.66)*	0.88 (0.48 – 1.61)	0.64 (0.39 – 1.06)	0.57 (0.34 – 0.94)*
Dizziness	1.04 (0.36 – 3.45)	0.24 (0.03 – 1.07)	NA	0.22 (0.02 – 1.47)	NA	NA
Dysgeusia	0.30 (0.13 – 0.65)*	0.16 (0.05 – 0.41)*	0.27 (0.15 – 0.45)*	0.55 (0.14 – 1.88)	1.11 (0.42 – 2.86)	0.60 (0.18 – 1.79)
Dyspnea	0.73 (0.36 – 1.53)	NA	1.00 (0.75 – 1.34)	NA	0.73 (0.34 – 1.62)	NA
Fatigue	0.50 (0.35 – 0.70)*	0.44 (0.31 – 0.62)*	0.63 (0.50 – 0.79)*	0.89 (0.55 – 1.43)	0.79 (0.53 – 1.19)	0.70 (0.46 – 1.05)
Febrile neutropenia	0.01 (0.00 – 0.09)*	0.01 (0.00 – 0.08)*	0.01 (0.00 – 0.05)*	1.28 (0.03 – 100.00)	1.20 (0.01 – 50.00)	1.61 (0.04 – 50.00)
Gamma-glutamyltransferase increased	2.99 (0.41 – 83.51)	6.76 (0.30 – 3271.00)	NA	2.25 (0.02 – 1314.00)	NA	NA
Hypersensitivity	0.12 (0.00 – 1.09)	0.11 (0.00 – 0.80)*	NA	0.96 (0.02 – 48.25)	NA	NA
Hyperthyroidism	197.5 (6.11 – 1413000.00)*	18.94 (1.24 – 10040.00)*	NA	0.10 (0.00 – 122.20)	NA	NA
Hypothyroidism	32.33 (6.01 – 797.10)*	108.20 (9.28 – 144900.00)*	NA	3.28 (0.06 – 4595.00)	NA	NA
Infusion-related reaction	0.27 (0.08 – 0.84)*	0.93(0.36 – 2.46)	NA	3.48 (0.79 – 16.41)	NA	NA
Lacrimation increased	0.04 (0.00 – 0.26)*	0.05 (0.00 – 0.27)*	NA	1.12 (0.03 – 48.72)	NA	NA
Leukopenia	0.19 (0.05 – 0.59)*	0.02 (0.00 – 0.10)*	NA	0.09 (0.00 – 0.84)*	NA	NA
Mucosal inflammation	0.28 (0.03 – 1.90)	0.13 (0.04 – 0.32)*	NA	0.45 (0.05 – 4.71)	NA	NA
Musculoskeletal pain	0.95 (0.29 – 3.75)	NA	2.62 (1.64 – 4.30)*	NA	0.36 (0.10 – 1.54)	NA
Myalgia	0.27 (0.15 – 0.49)*	0.18 (0.08 – 0.35)*	0.36 (0.24 – 0.54)*	0.63 (0.24 – 1.62)	0.75 (0.36 – 1.54)	0.48 (0.20 – 1.07)
Nausea	0.65 (0.44 – 0.98)*	0.36 (0.25 – 0.53)*	0.65 (0.50 – 0.84)*	0.56 (0.32 – 0.97)*	1.01 (0.63 – 1.64)	0.56 (0.35 – 0.89)*
Neutropenia	0.01 (0.00 – 0.05)*	0.01 (0.00 – 0.03)*	0.08 (0.04 – 0.15)*	0.59 (0.06 – 5.89)	0.18 (0.02 – 0.75)*	0.11 (0.01 – 0.43)*
Neutrophil count decreased	0.03 (0.00 – 0.11)*	0.02 (0.00 – 0.13)*	NA	0.77 (0.02 – 10.64)	NA	NA
Pain	0.62 (0.13 – 3.43)	0.24 (0.06 – 0.70)*	NA	0.38 (0.05 – 2.64)	NA	NA
Palmar-Plantar erythrodysesthesia syndrome	0.08 (0.00 – 0.68)*	0.14 (0.01 – 1.05)	NA	1.69 (0.04 – 82.38)	NA	NA
Paresthesia	0.15 (0.05 – 0.36)*	0.22 (0.09 – 0.50)*	NA	1.52 (0.41 – 5.56)	NA	NA
Peripheral edema	0.18 (0.08 – 0.39)*	0.24 (0.11 – 0.47)*	0.59 (0.41 – 0.84)*	1.32 (0.44 – 3.94)	0.31 (0.12 – 0.72)*	0.40 (0.17 – 0.88)*
Peripheral neuropathy	0.07 (0.02 – 0.17)*	0.08 (0.02 – 0.21)*	0.27 (0.17 – 0.42)*	1.14 (0.25 – 5.00)	0.26 (0.08 – 0.72)*	0.30 (0.08 – 0.86)*
Pneumonitis	4.50 (1.51 – 19.93)*	19.21 (3.22 – 486.90)*	41.64 (3.28 – 14600.00)*	4.28 (0.42 – 126.00)	0.11 (0.00 – 2.18)	0.46 (0.00 – 26.36)
Pruritus	5.88 (2.53 – 17.30)*	7.26 (2.74 – 25.52)*	NA	1.24 (0.29 – 5.60)	NA	NA
Pyrexia	0.63 (0.33 – 1.21)	0.47 (0.23 – 0.90)*	1.43 (1.04 – 1.96)*	0.74 (0.29 – 1.84)	0.44 (0.22 – 0.91)*	0.33 (0.15 – 0.68)*
Rash	2.58 (1.48 – 4.89)*	1.99 (1.09 – 3.79)*	NA	0.77 (0.32 – 1.81)	NA	NA
Rash maculopapular	16.87 (1.37 – 6320.00)*	2.02 (0.51 – 10.11)	NA	0.12 (0.00 – 2.47)	NA	NA
Rash pruritic	1.25 (0.25 – 9.82)	3.69 (0.39 – 117.40)	NA	2.98 (0.14 – 126.50)	NA	NA
Stomatitis	0.19 (0.10 – 0.32)*	0.10 (0.02 – 0.31)*	0.26 (0.15 – 0.43)*	0.55 (0.11 – 1.92)	0.71 (0.33 – 1.54)	0.39 (0.08 – 1.36)
Thyroiditis	12.68 (0.36 – 139400.00)	5.24 (0.17 – 3348.00)	NA	0.39 (0.00 – 612.20)	NA	NA

(*continued on next page*)

Table 3 (*continued*)

	Pembrolizumab vs. Docetaxel	Nivolumab vs. Docetaxel	Atezolizumab vs. Docetaxel	Nivolumab vs. Pembrolizumab	Pembrolizumab vs. Atezolizumab	Nivolumab vs. Atezolizumab
Treatment-related Adverse Events Leading to Discontinuation	0.44 (0.26 – 0.74)*	0.29 (0.16 – 0.49)*	0.30 (0.21 – 0.42)*	0.65 (0.30 – 1.37)	1.48 (0.80 – 2.77)	0.96 (0.49 – 1.83)
Treatment-related death	0.54 (0.16 – 1.96)	0.18 (0.01 – 1.45)	0.18 (0.01 – 1.42)	0.32 (0.01 – 3.78)	3.20 (0.27 – 112.80)	1.02 (0.02 – 52.55)
Urticaria	0.06 (0.00 – 0.70)*	2.08 (0.37 – 17.26)	NA	38.46 (1.68 – 5244.00)*	NA	NA
Vomiting	0.45 (0.25 – 0.81)*	0.50 (0.28 – 0.90)*	1.00 (0.72 – 1.39)	1.11 (0.48 – 2.56)	0.45 (0.23 – 0.88)*	0.50 (0.25 – 0.98)*
White blood cell count decreased	0.07 (0.02 – 0.23)*	0.02 (0.00 – 0.12)*	NA	0.28 (0.01 – 2.87)	NA	NA
Results based on the updates of the trials (Checkmate-017/Cheackmate-057)						
Anemia	0.24 (0.14 – 0.41)*	0.08 (0.04 – 0.16)*	0.40 (0.30 – 0.54)*	0.33 (0.13 – 0.78)*	0.60 (0.33 – 1.10)	0.20 (0.09 – 0.41)*
Asthenia	0.48 (0.29 – 0.77)*	0.60 (0.40 – 0.89)*	0.88 (0.67 – 1.15)	1.25 (0.67 – 2.33)	0.54 (0.31 – 0.94)*	0.68 (0.42 – 1.10)
Decreased appetite	0.73 (0.50 – 1.07)	0.60 (0.40 – 0.89)*	1.02 (0.80 – 1.31)	0.82 (0.47 – 1.42)	0.71 (0.45 – 1.12)	0.59 (0.36 – 0.94)*
Diarrhea	0.33 (0.21 – 0.49)*	0.31 (0.20 – 0.47)*	0.51 (0.39 – 0.66)*	0.95 (0.52 – 1.72)	0.64 (0.39 – 1.06)	0.61 (0.37 – 1.00)
Fatigue	0.50 (0.35 – 0.70)*	0.48 (0.34 – 0.66)*	0.63 (0.50 – 0.79)*	0.96 (0.60 – 1.45)	0.79 (0.53 – 1.19)	0.76 (0.51 – 1.13)
Neutropenia	0.01 (0.00 – 0.05)*	0.01 (0.00 – 0.03)*	0.08 (0.04 – 0.15)*	0.58 (0.06 – 5.69)	0.18 (0.02 – 0.75)*	0.10 (0.01 – 0.43)*

* Statistically significant (95%CrI does not include 1), CrI: credible interval, OR: odds ratio.

atezolizumab for 7 AEs, and docetaxel for 5 AEs (Fig.S6).

3.7. Subgroup analyses

3.7.1. Overall survival

Compared to docetaxel, nivolumab produced significant improvements in OS for all subgroups of interest, except in patients with an EGFR mutation (Table 5). Pembrolizumab showed a significant OS benefit in most subgroups except in patients with squamous NSCLC, ECOG-0, and age ≥65 years. Atezolizumab evidenced a significant OS benefit except in patients with an EGFR mutation, ECOG-0, and age < 65 years. The three immune checkpoint inhibitors did differ in OS in all subgroups. In probability rankings (Fig. S7), pembrolizumab ranked first in the subgroups of adenocarcinoma NSCLC (74%), EGFR mutation (53%), ECOG-1 (58%), males (50%), and age < 65 years (67%). Nivolumab ranked as the best therapy for patients with squamous NSCLC (77%), EGFR-wild-type (40%), and ECOG-0 (68%). Atezolizumab ranked first for females (53%) and patients age ≥65 years (54%).

3.7.2. Progression-free survival

Only the nivolumab and pembrolizumab trials permitted subgroup analyses for PFS (Table 5). PFS was significantly better in nivolumab compared to docetaxel in patients with squamous NSCLC, ECOG-1, males, and age < 65 years. Compared to docetaxel, pembrolizumab improved PFS in EGFR-wild-type, ECOG-1, and male patients. There were no differential PFS benefits in comparisons of nivolumab to pembrolizumab across subgroups. In probability rankings (Fig. S8), nivolumab ranked first in the subgroups of squamous NSCLC (93%), EGFR-wild-type (51%), ECOG-0 (88%), males (68%), females (45%), and patients age < 65 years or ≥65 years (65%); pembrolizumab in the subgroups of adenocarcinoma NSCLC (71%), and ECOG-1 (61%), subgroups; and docetaxel in the case of EGFR mutation (89%).

3.7.3. OS, PFS, and ORR based on PD-L1 expression

Subgroup analyses based on PD-L1 expression < 1% yielded a better OS benefit for atezolizumab compared to docetaxel and similar OS, PFS and ORR benefits compared to nivolumab (Table 6). Nivolumab, pembrolizumab, and atezolizumab produced better OS outcomes at PD-L1 expression ≥1% compared to docetaxel, but there were no differences when compared to each other. In comparison to docetaxel, nivolumab and pembrolizumab evidenced a better PFS benefit at PD-L1 expression ≥1%. Pembrolizumab and nivolumab had significant improvements in ORR in patients with PD-L1 expression ≥1% in comparison to docetaxel and atezolizumab. At PD-L1 expression ≥5%, nivolumab and atezolizumab had significantly better OS, PFS, and ORR benefits compared to docetaxel. There were no statistically significant differences in these outcomes when comparing nivolumab to atezolizumab at this PD-L1 expression level. Pembrolizumab and atezolizumab showed significant improvements in OS, PFS, and ORR in patients with PD-L1 expression ≥50% compared to docetaxel and similar benefits when compared to each other. In probability rankings, nivolumab yielded the best OS (69%, 93%), PFS (96%, 96%) and ORR (100%, 94%) in patients with PD-L1 expression ≥1% and ≥5%, respectively, in comparison to atezolizumab and docetaxel (Figs. S9–S11). Atezolizumab was the first-ranked option for OS (80%) at PD-L1 expression ≥50% while pembrolizumab ranked first for PFS (61%) and ORR (69%) in comparison to atezolizumab and docetaxel at this PD-L1 expression level (Figs. S9–S11).

3.8. OS, PFS, ORR and treatment-related AEs based on the FDA-approved doses

3.8.1. OS, PFS, and ORR

The Checkmate-17, Checkmate-57, POPLAR, and OAK trials used the FDA-approved doses of nivolumab and atezolizumab. The Keynote-

Table 4
Adverse events (grades3/4), expressed as OR and 95%CrI.

	Pembrolizumab vs. Docetaxel	Nivolumab vs. Docetaxel	Atezolizumab vs. Docetaxel	Nivolumab vs. Pembrolizumab	Pembrolizumab vs. Atezolizumab	Nivolumab vs. Atezolizumab
Abdominal pain	2.22 (0.01 – 40060.00)	0.19 (0.00 – 5.93)	NA	0.06 (0.00 – 58.91)	NA	NA
Alanine aminotransferase increased	19.26 (0.58 – 254100.00)	3.89 (0.40 – 130.60)	14.46 (0.86 – 7371.00)	0.26 (0.00 – 23.16)	1.30 (0.00 – 23980.00)	0.20 (0.00 – 29.50)
Alopecia	0.09 (0.00 – 1.31)	0.42 (0.01 – 5.41)	0.20 (0.00 – 5.79)	4.76 (0.06 – 856.80)	0.46 (0.00 – 303.77)	2.19 (0.02 – 1357.40)
Anemia	0.35 (0.08 – 1.40)	0.06 (0.00 – 0.37)*	0.38 (0.20 – 0.71)*	0.16 (0.00 – 1.78)	0.93 (0.19 – 4.27)	0.16 (0.01 – 1.12)
Arthralgia	3.39 (0.15 – 1759.00)	1.01 (0.03 – 42.44)	3.64 (0.39 – 100.00)	0.26 (0.00 – 36.57)	0.94 (0.01 – 650.62)	0.25 (0.00 – 21.49
Aspartate aminotransferase increased	3.21 (0.14 – 1408.00)	0.96 (0.03 – 37.37)	11.22 (0.65 – 5094.00)	0.26 (0.00 –36.49)	0.28 (0.00 – 222.57)	0.07 (0.00 – 9.28)
Asthenia	0.21 (0.04 – 0.84)*	0.06 (0.00 – 0.37)*	0.57 (0.22 – 1.37)	0.28 (0.01 – 3.31)	0.37 (0.06 – 1.99)	0.10 (0.00 – 0.84)*
Back pain	1.33 (0.02 – 716.40)	NA	1.72 (0.50 – 6.89)	NA	0.77 (0.01 – 447.43)	NA
Blood alkaline phosphatase increased	3.34 (0.15 – 1564.00)	0.20 (0.00 – 5.67)	NA	0.04 (0.00 – 6.21)	NA	NA
Blood creatinine increased	2.10 (0.01 –29140.00)	1.01 (0.03 – 41.10)	NA	0.42 (0.00 – 343.50)	NA	NA
Blood thyroid stimulating hormone increased	2.21 (0.01 – 41130.00)	1.08 (0.00 – 806.40)	NA	0.39 (0.00 – 2386.00)	NA	NA
Colitis	26.19 (0.82 – 337600.00)	3.82 (0.41 – 115.40)	5.36 (0.17 – 3394.00)	0.14 (0.00 – 20.29)	5.25 (0.00 – 89686.10)	0.71 (0.00 – 90.99)
Constipation	2.06 (0.01 – 29140.00)	0.25 (0.01 – 2.31)	2.28 (0.18 – 71.89)	0.10 (0.00 – 43.70)	0.92 (0.00 –15320.97)	0.10 (0.00 – 3.32)
Cough	1.43 (0.01 – 2974.00)	NA	2.31 (0.18 – 78.28)	NA	0.63 (0.00 – 1658.10)	NA
Decreased appetite	0.62 (0.13 – 3.38)	0.40 (0.01 – 5.27)	0.18 (0.02 – 0.76)*	0.63 (0.01 – 13.19)	3.57 (0.40 – 50)	2.27 (0.05 – 50)
Diarrhea	0.11 (0.01 – 0.50)*	0.28 (0.04 – 1.30)	0.32 (0.09 – 0.97)*	2.50 (0.20 – 33.33)	0.35 (0.03 – 2.57)	0.87 (0.09 – 6.62)
Dizziness	0.18 (0.00 – 5.09)	1.01 (0.00 – 676.00)	NA	6.09 (0.00 – 15810.00)	NA	NA
Dysgeusia	2.19 (0.01 – 36160.00)	1.06 (0.00 – 885.30)	1.03 (0.00 – 723.40)	0.40 (0.00 – 2444.00)	2.58 (0.00 – 170794.19)	1.03 (0.00 – 8989.00)
Dyspnea	0.45 (0.10 – 2.02)	NA	1.02 (0.48 – 2.17)	NA	0.44 (0.08 – 2.34)	NA
Fatigue	0.40 (0.17 – 0.98)*	0.15 (0.04 – 0.40)*	0.69 (0.36 – 1.30)	0.36 (0.08 – 1.38)	0.59 (0.20 – 1.74)	0.21 (0.05 –0.70)*
Febrile neutropenia	0.01 (0.00 – 0.09)*	0.02 (0.00 – 0.08)*	0.01 (0.00 – 0.05)*	1.35 (0.03 – 100.00)	1.20 (0.01 – 50.00)	1.54 (0.04 – 50.00)
Gamma-glutamyltransferase increased	0.45 (0.01 – 17.98)	6.85 (0.31 – 2872.00)	NA	17.61 (0.12 – 15660.00)	NA	NA
Hypersensitivity	2.16 (0.01 – 38010.00)	0.42 (0.01 – 5.39)	NA	0.16 (0.00 – 81.39)	NA	NA
Hyperthyroidism	7.49 (0.15 – 166400.00)	1.04 (0.00 – 798.50)	NA	0.10 (0.00 – 289.60)	NA	NA
Hypothyroidism	2.10 (0.01 – 29140.00)	1.01 (0.03 – 41.10)	NA	0.42 (0.00 – 343.50)	NA	NA
Infusion-related reaction	2.09 (0.01 – 27960.00)	0.41 (0.01 – 5.31)	NA	0.16 (0.00 – 80.05)	NA	NA
Lacrimation increased	2.21 (0.01 – 41130.00)	1.07 (0.00 – 806.40)	NA	0.39 (0.00 – 2386.00)	NA	NA
Leukopenia	0.04 (0.00 – 0.26)*	0.02 (0.00 – 0.13)*	NA	0.56 (0.01 – 23.76)	NA	NA
Mucosal inflammation	0.18 (0.00 – 4.99)	0.12 (0.00 – 0.81)*	NA	0.62 (0.01 – 100.20)	NA	NA
Musculoskeletal pain	2.12 (0.01 – 41360.00)	NA	5.03 (0.64 – 159.90)	NA	0.40 (0.00 – 8764.24)	NA
Myalgia	2.10 (0.01 – 32740.00)	4.90 (0.17 – 2030.00)	0.18 (0.01 – 1.43)	2.44 (0.00 – 6975.00)	14.47 (0.03 – 303674.46)	33.46 (0.49 – 24000.00)
Nausea	1.75 (0.19 – 50)	0.43 (0.05 – 2.41)	2.08 (0.37 – 16.67)	0.23 (0.00 – 4.24)	0.86 (0.04 – 39.18)	0.20 (0.01 – 2.39)
Neutropenia	0.01 (0.00 – 0.04)*	0.01 (0.00 – 0.04)*	0.03 (0.01 – 0.08)*	1.14 (0.17 – 16.67)	0.31 (0.01 – 2.72)	0.35 (0.04 – 2.39)
Neutrophil count decreased	0.01 (0.00 – 0.07)*	0.03 (0.00 – 0.16)*	NA	3.19 (0.07 – 403.60)	NA	NA
Pain	2.21 (0.01 – 41130.00)	1.07 (0.00 – 806.40)	NA	0.39 (0.00 – 2386.00)	NA	NA
Palmar-Plantar erythrodysasthesia syndrome	2.10 (0.01 – 29140.00)	1.01 (0.03 – 41.10)	NA	0.42 (0.00 – 343.50)	NA	NA
Paresthesia	2.10 (0.01 – 29140.00)	1.01 (0.03 – 41.10)	NA	0.42 (0.00 – 343.50)	NA	NA
Peripheral edema	2.15 (0.01 – 41350.00)	0.41 (0.01 – 5.31)	0.25 (0.01 – 2.29)	0.16 (0.00 – 80.00)	10.90 (0.02 – 278473.96)	1.71 (0.03 – 112.16)
Peripheral neuropathy	0.18 (0.00 – 5.03)	0.19 (0.01 – 1.49)	0.03 (0.00 – 0.40)*	0.99 (0.01 – 174.50)	6.31 (0.03 – 4655.49)	6.07 (0.09 – 3104.63)
Pneumonitis	7.76 (1.28 – 234.60)*	5.03 (0.63 – 143.70)	18.89 (1.36 – 8815.00)*	0.63 (0.01 – 27.91)	0.42 (0.00 – 28.11)	0.26 (0.00 – 18.14)
Pruritus	0.18 (0.00 – 5.04)	1.02 (0.03 – 40.94)	NA	6.21 (0.04 – 2101.00)	NA	NA
Pyrexia	0.45 (0.01 – 16.59)	0.41 (0.01 – 5.29)	0.94 (0.02 – 36.62)	0.85 (0.01 – 76.05)	0.48 (0.00 – 77.28)	0.41 (0.00 – 36.19)
Rash	3.31 (0.15 – 1660.00)	0.40 (0.01 – 5.13)	NA	0.10 (0.00 – 7.26)	NA	NA
Rash maculopapular	7.45 (0.15 – 159900.00)	1.01 (0.03 – 39.98)	NA	0.11 (0.00 – 29.51)	NA	NA
Rash pruritic	2.21 (0.01 – 41130.00)	1.07 (0.00 – 806.40)	NA	0.39 (0.00 – 2386.00)	NA	NA
Stomatitis	0.12 (0.00 – 1.06)	0.11 (0.00 – 1.93)	0.06 (0.00 – 0.38)*	0.90 (0.00 – 79.73)	1.96 (0.04 – 100.00)	1.79 (0.00 – 100.00)
Thyroiditis	2.21 (0.01 – 41130.00)	1.07 (0.00 – 806.40)	NA	0.39 (0.00 – 2386.00)	NA	NA
Urticaria	2.10 (0.01 – 29140.00)	1.01 (0.03 – 41.10)	NA	0.42 (0.00 – 343.50)	NA	NA
Vomiting	0.19 (0.01 – 2.41)	0.41(0.01 – 5.28)	0.43 (0.05 – 2.38)	2.22 (0.03 – 100.00)	0.43 (0.01 – 11.83)	0.96 (0.02 – 25.00)
White blood cell count decreased	0.02 (0.00 – 0.15)*	0.04 (0.00 – 0.21)*	NA	2.08 (0.04 – 263.50)	NA	NA

* Statistically significant (95%CrI does not include 1), CrI: credible interval, OR: odds ratio.

Table 5
OS and PFS by subgroup, expressed as HR and 95%CrI.

	Pembrolizumab vs. Docetaxel	Nivolumab vs. Docetaxel	Atezolizumab vs. Docetaxel	Nivolumab vs. Pembrolizumab	Pembrolizumab vs. Atezolizumab	Nivolumabvs. Atezolizumab
OS (HR,95%CrI)						
Squamous	0.74 (0.50 – 1.09)	0.59 (0.44 – 0.79)*	0.75 (0.58 – 0.96)*	0.80 (0.49 – 1.30)	0.99 (0.62 – 1.57)	0.79 (0.54 – 1.16)
Adenocarcinoma	0.63 (0.50 – 0.79)*	0.72 (0.59 – 0.89)*	0.72 (0.61 – 0.86)*	1.15 (0.85 – 1.57)	0.87 (0.65 – 1.16)	1.00 (0.77 – 1.31)
EGFR-mutant	0.87 (0.45 –1.70)	1.18 (0.69 – 1.99)	1.25 (0.71 – 2.18)	1.35 (0.57 – 3.15)	0.70 (0.29 – 1.67)	0.94 (0.44 – 2.03)
EGFR-wild	0.66 (0.55 – 0.80)*	0.66 (0.51 – 0.86)*	0.69 (0.57 – 0.83)*	1.00 (0.72 – 1.38)	0.96 (0.74 – 1.25)	0.96 (0.70 – 1.33)
ECOG-0	0.73 (0.52 – 1.02)	0.60 (0.43 – 0.84)*	0.78 (0.58 – 1.04)	0.83 (0.52 – 1.33)	0.94 (0.60 – 1.46)	0.78 (0.50 – 1.20)
ECOG-1	0.63 (0.51 – 0.78)*	0.69 (0.58 – 0.84)*	0.69 (0.56 – 0.84)*	1.10 (0.83 – 1.46)	0.92 (0.68 – 1.23)	1.01 (0.77 – 1.33)
Male	0.65 (0.52 – 0.81)*	0.66 (0.54 – 0.81)*	0.79 (0.64 – 0.97)*	1.02 (0.75 – 1.37)	0.82 (0.61 – 1.11)	0.84 (0.62 – 1.12)
Female	0.69 (0.51 – 0.94)*	0.76 (0.58 – 0.98)*	0.65 (0.49 – 0.85)*	1.09 (0.73 – 1.64)	1.07 (0.71 – 1.61)	1.17 (0.80 – 1.71)
Age ≥ 65	0.76 (0.57 – 1.02)	0.69 (0.54 – 0.89)*	0.66 (0.52 – 0.83)*	0.91 (0.62 – 1.34)	1.16 (0.80 – 1.68)	1.06 (0.75 – 1.49)
Age < 65	0.63 (0.50 – 0.79)*	0.70 (0.56 – 0.86)*	0.80 (0.64 – 1.00)	1.11 (0.81 – 1.52)	0.78 (0.57 – 1.08)	0.87 (0.64 – 1.18)
PFS (HR,95%CrI)						
Squamous	0.86 (0.62 – 1.20)	0.62 (0.47 – 0.81)*	NA	0.71 (0.47 – 1.10)	NA	NA
Adenocarcinoma	0.85 (0.71 – 1.03)	0.92 (0.77 – 1.11)	NA	1.08 (0.83 – 1.40)	NA	NA
EGFR-mutant	1.79 (0.94 – 3.41)	1.46 (0.90 – 2.36)	NA	0.81 (0.36 – 1.83)	NA	NA
EGFR-wild	0.83 (0.71 – 0.98)*	0.83 (0.65 – 1.06)	NA	0.99 (0.74 – 1.33)	NA	NA
ECOG-0	1.08 (0.82 – 1.43)	0.80 (0.60 – 1.07)	NA	0.74 (0.50 – 1.11)	NA	NA
ECOG-1	0.76 (0.63 – 0.91)*	0.79 (0.66 – 0.94)*	NA	1.04 (0.71 – 1.59)	NA	NA
Male	0.78 (0.64 – 0.94)*	0.72 (0.60 – 0.88)*	NA	0.93 (0.71 – 1.23)	NA	NA
Female	1.01 (0.78 – 1.32)	0.98 (0.76 – 1.24)	NA	0.96 (0.67 – 1.38)	NA	NA
Age ≥ 65	0.93 (0.72 – 1.19)	0.85 (0.68 – 1.08)	NA	0.92 (0.66 – 1.30)	NA	NA
Age < 65	0.84 (0.69 – 1.02)	0.80 (0.65 – 0.97)*	NA	0.95 (0.72 – 1.25)	NA	NA

* Statistically significant (95%CrI does not include 1), CrI: credible interval, ECOG: Eastern Cooperative Oncology Group performance status, EGFR: epidermal growth factor receptor, HR: Hazard ratio, NA: not available, OS: overall survival, PFS: progression free survival.

10 trial evaluated 2 doses of pembrolizumab (2 mg/kg or 10 mg/kg) while the FDA-approved dose is a flat dose of 200 mg. Since the 2 mg/kg dose is the closest to the FDA-approved dose, we used the outcomes for pembrolizumab 2 mg/kg in the secondary outcomes analysis. Results for OS and ORR were similar to the main results. However nivolumab became the first ranked treatment for OS (55%). For PFS, only nivolumab was statistically better than docetaxel and there were no differences between PD-1 and PD-L1 inhibitors when compared to each other (Table S2, Fig. S12). OS and ORR results based on PD-L1 expression ≥1% and ≥50% as well as PFS at PD-L1 expression ≥50% were similar to the main results. Nivolumab was the only agent with a significant PFS benefit compared to docetaxel at PD-L1 expression ≥1% but similar to other agents (Table S3). Ranking positions at PD-L1 expression ≥ 1% and ≥50% were similar to the main results (Fig. S12).

3.8.2. Adverse events

Results for all-grade AEs were similar to the primary results (Table S4) except for a few. Pembrolizumab was associated with a higher risk of elevated blood alkaline phosphatase compared to docetaxel and nivolumab. In the primary analysis, pembrolizumab had lower rates of nausea, palmar-plantar erythrodysesthesia syndrome, and urticaria than docetaxel, but rates were similar when using the FDA-approved dose. The 2-year and 3-year updates for nivolumab showed no difference compared to atezolizumab in the risk of diarrhea. Pembrolizumab replaced nivolumab as the first ranked option for reducing the risk of decreased neutrophil count (Fig. S13).

Results for grade 3/4 AEs were similar to the primary results (Table S5). There were some changes in the ranking of therapies. Pembrolizumab ranked first instead of nivolumab for reducing the risk of arthralgia, increased blood creatinine, hypothyroidism, palmar-plantar erythrodysesthesia syndrome, paresthesia, and urticaria; pembrolizumab ranked first instead of docetaxel for reducing the risk of cough and musculoskeletal pain; pembrolizumab and atezolizumab ranked first instead of atezolizumab for reducing the risk of stomatitis; and nivolumab ranked first instead of pembrolizumab for reducing the risk of neutropenia (Fig. S14).

Table 6
Subgroup analysis for OS, PFS, and ORR based on PD-L1 expression.

PD-L1 Expression	Pembrolizumab vs. Docetaxel	Nivolumab vs. Docetaxel	Atezolizumab vs. Docetaxel	Pembrolizumab vs. Atezolizumab	Nivolumab vs. Pembrolizumab	Nivolumab vs. Atezolizumab
OS (HR,95%CrI)						
< 1%	NA	0.78 (0.61 – 1.02)	0.80 (0.64 – 0.99)*	NA	NA	0.98 (0.70 – 1.38)
≥ 1%	0.66 (0.55 – 0.78)*	0.63 (0.48 – 0.82)*	0.69 (0.56 – 0.84)*	0.95 (0.73 – 1.24)	0.96 (0.70 – 1.32)	0.91 (0.66 – 1.27)
≥ 5%	NA	0.46 (0.34 – 0.63)*	0.63 (0.48 – 0.81)*	NA	NA	0.74 (0.49 – 1.10)
≥ 50%	0.53 (0.40 – 0.70)*	NA	0.43 (0.29 – 0.63)*	1.23 (0.77 – 1.97)	NA	NA
PFS (HR,95%CrI)						
< 1%	NA	0.97 (0.76 – 1.24)	1.02 (0.84 – 1.25)	NA	NA	0.95 (0.69 – 1.30)
≥ 1%	0.82 (0.70 – 0.95)*	0.69 (0.54 – 0.87)*	0.89 (0.75 – 1.06)	0.91 (0.73 – 1.15)	0.85 (0.64 – 1.12)	0.78 (0.58 – 1.03)
≥ 5%	NA	0.54 (0.41 – 0.72)*	0.75 (0.59 – 0.94)*	NA	NA	0.73 (0.51 – 1.04)
≥ 50%	0.58 (0.46 – 0.74)*	NA	0.62 (0.45 – 0.86)*	0.94 (0.63 – 1.41)	NA	NA
ORR (OR,95%CrI)						
< 1%	NA	0.88 (0.44 – 1.75)	0.77 (0.40 – 1.45)	NA	NA	1.14 (0.45 – 2.92)
≥ 1%	2.19 (1.46 – 3.36)*	2.79 (1.61 – 5.00)*	1.12 (0.75 – 1.68)	1.95 (1.10 – 3.51)*	1.27 (0.63 – 2.60)	2.49 (1.25 – 5.06)*
≥ 5%	NA	3.76 (1.97 – 7.61)*	1.93 (1.12 3.38)*	NA	NA	1.96 (0.83 – 4.77)
≥ 50%	5.05 (2.73 – 10.15)*	NA	3.88 (1.82 – 8.96)*	1.30 (0.46 – 3.63)	NA	NA

* Statistically significant (95%CrI does not include 1), CrI: credible interval, HR: hazard ratio, NA: not available, OR: odds ratio, ORR: objective response rate, OS: overall survival, PD-L1: programmed death ligand-1, PFS: progression free survival.

3.9. Treatment cross-over

All trial reports provided information about treatment cross-over after by patients if a treatment to which the patient was randomized was discontinued. Cross-overs between docetaxel and immunotherapies may introduce bias in the intention-to-treat analysis (ITT) which in turn may dilute the OS benefits of a given immunotherapy. We analyzed the cross-over patterns (Fig. S15) and found that generally, the proportion of patients crossing over from immunotherapy to docetaxel was higher than the proportion crossing-over from docetaxel to immunotherapy. However, the 2-year update of the Checkmate-017 trial showed statistically similar rates of, respectively, 8% cross-over from docetaxel to immunotherapy versus 6.7% cross-over from immunotherapy to docetaxel.

4. Discussion

Until 2014, patients with NSCLC who failed first line therapy were limited to docetaxel, pemetrexed and erlotinib as second-line treatment options. Docetaxel had favorable survival benefits over pemetrexed and erlotinib but an unfavorable safety profile (Weiss and Stinchcombe, 2013). Standard second-line therapy has been transformed by the introduction of immunotherapy. These agents provide significant overall survival benefits especially at higher PD-L1 expression levels, as well as better safety profiles (Giroux Leprieur et al., 2017).

This systematic review and network meta-analysis showed superior beneficial effects for pembrolizumab and nivolumab in OS, PFS, and ORR compared to docetaxel in previously treated advanced NSCLC patients, while atezolizumab improved OS only. In general, there were no statistically significant differences between these three immunotherapies in OS and PFS, but pembrolizumab and nivolumab were significantly better than atezolizumab in term of ORRBoth pembrolizumab and nivolumab had better safety profiles than docetaxel and atezolizumab and ranked as the best option for reducing the risk of most AEs. Results from subgroup analyses of OS and PFS showed improvements in many subgroups when comparing PD-1/PD-L1 inhibitors to docetaxel, with no statistically significant differences when comparing PD-1/PD-L1 inhibitors to each other. Both pembrolizumab and nivolumab are approved in the second-line setting, but our findings suggest that pembrolizumab might be the preferred approach relative to OS and ORR.

Our network meta-analysis of trials evaluating PD-1 and PD-L1 inhibitors to docetaxel is not the first such analysis (Giroux Leprieur et al., 2017; Crequit et al., 2017; Tan et al., 2018; Peng et al., 2017; Passiglia et al., 2018). However, it incorporated data from the 2-year and 3-year updates on two nivolumab studies (Checkmate-017 and Checkmate-0.57) and the 2-year update on the atezolizumab trial (OAK). Our analysis also went significantly farther and deeper in assessing the comparative efficacy and safety profiles of these treatments in previously treated patients with advanced NSCLC - and this in patients in general as well as across various subgroups of patients. It also provides evidence on the comparative efficacy and safety of the FDA-approved doses of these agents. In contrast, two prior network meta-analyses, which did not include recently published updates, were limited to subgroups such as wild-type or unknown EGFR status or PD-L1 status (Crequit et al., 2017; Tan et al., 2018). A third prior analysis was an indirect comparison of only pembrolizumab and nivolumab for OS, PFS, and ORR.[27 The most recent analysis reported pairwise indirect comparisons for nivolumab, pembrolizumab, and atezolizumab on OS, PFS, ORR, and grades 3/4 AEs but did not incorporate updated long-term results and relative ranking probabilities between the three agents (Passiglia et al., 2018).

In those analyses of ours that corresponded with these four prior and more selective studies, our results generally are consistent with this prior evidence. In contrast, our study presents a comprehensive evaluation of both the clinical benefits and the safety/risks of PD-1 and PD-L1 inhibitors in general and across several subgroups as well as considering the FDA-approved doses. As such, it provides a more exhaustive comparative assessment of efficacy and safety. Further, by estimating ranking probabilities of the treatments for the various clinical and safety outcomes, our study offers additional guidance to clinicians in selecting the most appropriate therapy for their patients.

There are no authoritative guidelines on the preferred use of pembrolizumab, nivolumab, or atezolizumab in second or later line treatment of advanced NSCLC. All three agents carry category 1 recommendations by the National Comprehensive Cancer Network (NCCN) (Ettinger et al., 2018). Without direct head-to-head trial evidence, differentiating between these therapies is difficult.

Our network meta-analysis remedies this in part. Our indirect comparisons yielded no differences between the three immunotherapies in terms of OS or PFS in general. However, in subgroup analyses, pembrolizumab and nivolumab were found to have better survival outcomes compared to atezolizumab. This was especially true when considering PD-L1 expression levels; the Keynote-10 pembrolizumab trial included only patients with positive PD-L1 expression $\geq$ 1% while other trials did not exclude patients with negative PD-L1 expression. As clinical experience with these agents grows, real-world evidence may further elucidate which treatments best fit specific patient profiles and, specifically, how outcomes may vary based on biomarker expression of PD-L1 and EGFR mutations. Clinical experience may also help understand the association of patient comorbidities with survival and treatment response. Further, immunotherapy regimens have inherent side-effect profiles or immune-related AEs (irAEs), for which therapy-specific management guidelines have been formulated but need to be further validated with data from routine clinical practice (Brahmer et al., 2018). This will enable clinicians to identify the most appropriate therapy that balances patients' likely efficacy response with their known comorbidities and tolerance for AEs and irAEs.

Our network meta-analysis identified some limitations and directions for future research. First, PFS may not be an appropriate efficacy measure due to the mechanism of action of PD-1 and PD-L1 inhibitors that results in pseudo-progression due to the influx of inflammatory cells to the cancer site (Kazandjian et al., 2017). Therefore, PFS results should be interpreted with caution when comparing PD-1 and PD-L1 inhibitors to each other. Second, the included trials used different cut-offs for PD-L1 expression and different assays to measure the level of PD-L1 expression (Cameron et al., 2014; Brahmer et al., 2015; Borghaei et al., 2015; Herbst et al., 2016; Rittmeyer et al., 2017; Fehrenbacher et al., 2016; Hirsch et al., 2017). This too warrants some caution in the interpretation of OS, PFS, and ORR results in subgroups based on PD-L1 expression. Third, the KEYNOTE-10 trial evaluated two doses of pembrolizumab (2 mg/kg and 10 mg/kg) while the FDA-approved dose in NSCLC is 200 mg. We considered the 2 mg/kg because it is the closest dose to the FDA-approved dose and there were no major changes in the efficacy or safety measures (Pembrolizumab (Keytruda) Checkpoint Inhibitor, 2016). Fourth, some AEs are subjective (e.g., fatigue, appetite, nausea, asthenia) and may be subject to observer bias because the trials were open-label.

Although the treatment cross-over and switching are common in oncology, cross-over may lead to underestimating the benefit of the efficacious treatment relative to less efficacious therapy in a standard ITT analysis. Though some statistical methods have been proposed to adjust for cross-over effects (Latimer et al., 2014; Latimer et al., 2015; Ishak et al., 2014), none of the trials in our analysis adjusted for cross-over.

In conclusion, pembrolizumab and nivolumab prevailed in overall OS and ORR benefits over atezolizumab in our overall network meta-analysis. However, our analyses also suggest that clinical (NSCLC type, ECOG status), genomic (EGFR, PD-L1 expression), and demographic (gender, age) patient characteristics, as well as safety and tolerance, should be considered in treatment decision-making about PD-1 and PD-L1 checkpoint inhibitors in previously-treated patients with advanced

NSCLC. Real-world evidence is necessary to complement trial evidence under conditions of greater heterogeneity in patients and treatment settings.

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Author contributions

Study concept and design: Almutairi, McBride, Abraham.
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Critical revision of the manuscript for important intellectual content: Garland, Babiker.
Study supervision: Abraham.

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Almutairi had full access to all of the data in the study and tkes responsibility for the integrity of the data and the accuracy of the data analysis.

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.critrevonc.2019.07.004.

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