Comparative Efficacy of Second- and Subsequent-line Treatments for Metastatic NSCLC: A Fractional Polynomials Network Meta-analysis of Cancer Immunotherapies

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Abstract

Cancer immunotherapies have advanced the second-line treatment of non–small-cell lung cancer. Evaluating the relative effect of these therapies requires methods accounting for the delayed clinical effect and longer-term survival rates that have been observed in anti-programmed death-ligand 1/programmed cell death protein 1 therapy trials. This study applied advanced statistical methods to compare clinical trial results across all second-line treatments. The immunotherapies offered superior efficacy in non–small-cell lung cancer.

Background: Extended onset of treatment effect and longer-term survival with anti–programmed death-ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) immunotherapies, atezolizumab, nivolumab, and pembrolizumab, have changed the landscape of second- or subsequent-line (2L+) treatments for adults with non–small-cell lung cancer (NSCLC). This systematic literature review included phase I to IV randomized, controlled trials of 2L+ NSCLC therapies from MEDLINE, Embase, and secondary sources. **Materials and Methods:** Studies of treatments approved in the European Union or United States had to be in English with ≥ 10 patients per arm. A fractional polynomials network meta-analysis (NMA) was conducted because traditional NMA of hazard ratios does not account for delayed onset of clinical effect or long-term survival observed in PD-L1/PD-1 inhibitor trials. Adjusted analyses accounted for treatment switching in the atezolizumab OAK trial. Expected survival time reflected area under the curve over the time horizon. Expected overall survival (OS) was ranked by median ranking with 95% credible intervals and by surface under the cumulative ranking curve. Of 25,115 screened records, 28 studies were included in the quantitative analyses of OS and progression-free survival. **Results:** PD-L1/PD-1 inhibitors had comparable expected 5-year OS; all performed better than other treatment options. In unadjusted analyses, surface under the cumulative ranking curve ranked nivolumab first (87.9%), followed by atezolizumab (85.8%) and pembrolizumab (82.8%). Analyses adjusted for patients switching from docetaxel to immunotherapy ranked atezolizumab first (89.6%), followed by nivolumab (86.5%) and pembrolizumab (81.9%). **Conclusion:** This NMA applied an appropriate approach for indirect comparisons, including cancer immunotherapies, and supported robustness of PD-L1/PD-1 immunotherapies for 2L+ treatment of NSCLC.

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Introduction

Lung cancer remains a leading cause of cancer-related death worldwide.[1] Non–small-cell lung cancer (NSCLC) accounts for 85% of all lung cancers, and more than one-half of patients with NSCLC are diagnosed at advanced stages.[2,3] Surgical resection is the primary treatment approach, with pre- and postoperative

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chemotherapy recommended for patients who can tolerate it.[4] Second- and subsequent-line (2L+) therapies have historically included a range of treatment options depending on histology (squamous or nonsquamous cell carcinomas), genetic alterations, patient fitness for chemotherapy, and expression of programmed cell death 1 ligand 1 (PD-L1).[4] Positive molecular tests for epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements determine the appropriate targeted treatment pathway, particularly regarding the likelihood of response to tyrosine kinase inhibitor therapy.[4] Anti–PD-L1/programmed cell death 1 protein (PD-1) immunotherapies atezolizumab, nivolumab, and pembrolizumab have changed the 2L+ treatment landscape for patients with NSCLC, with an extended onset of treatment effect and longer survival.[5-9]

It is important for clinicians and policy makers to understand the comparative benefits and risks of different NSCLC treatments and to ensure that their assessments account for the defining attributes of each intervention. Considering the infeasibility of a randomized, controlled trial that includes all 2L+ NSCLC treatments, network meta-analyses (NMA) have been conducted in order to evaluate their relative efficacy.[10,11] However, statistical approaches used in traditional NMAs of chemotherapy and other treatments do not account for differences in survival patterns observed with the newer immunotherapies.[12] Specifically, the extended onset of treatment effect and greater long-term survival observed in some patients treated with PD-L1/PD-1 inhibitors violate the proportional hazards assumption of survival functions used in traditional NMAs of time-to-event outcomes, such as overall survival (OS) and progression-free survival (PFS).[13] Such a violation of the proportional hazards assumption based on even a single parameter can greatly bias calculated estimates; therefore, a multidimensional approach to estimating treatment effect may be more appropriate in such cases.[13] To this end, a Bayesian fractional polynomials approach that accounted for the extended onset of PD-L1/PD-1 inhibitors was deemed suitable.[12]

We conducted a systematic literature review and used a fractional polynomials NMA to evaluate the relative efficacy of 2L+ therapies for NSCLC, an approach that accounted for the clinical and statistical considerations specific to PD-L1/PD-1 inhibitors.

Materials and Methods

Systematic Literature Review and Network Selection

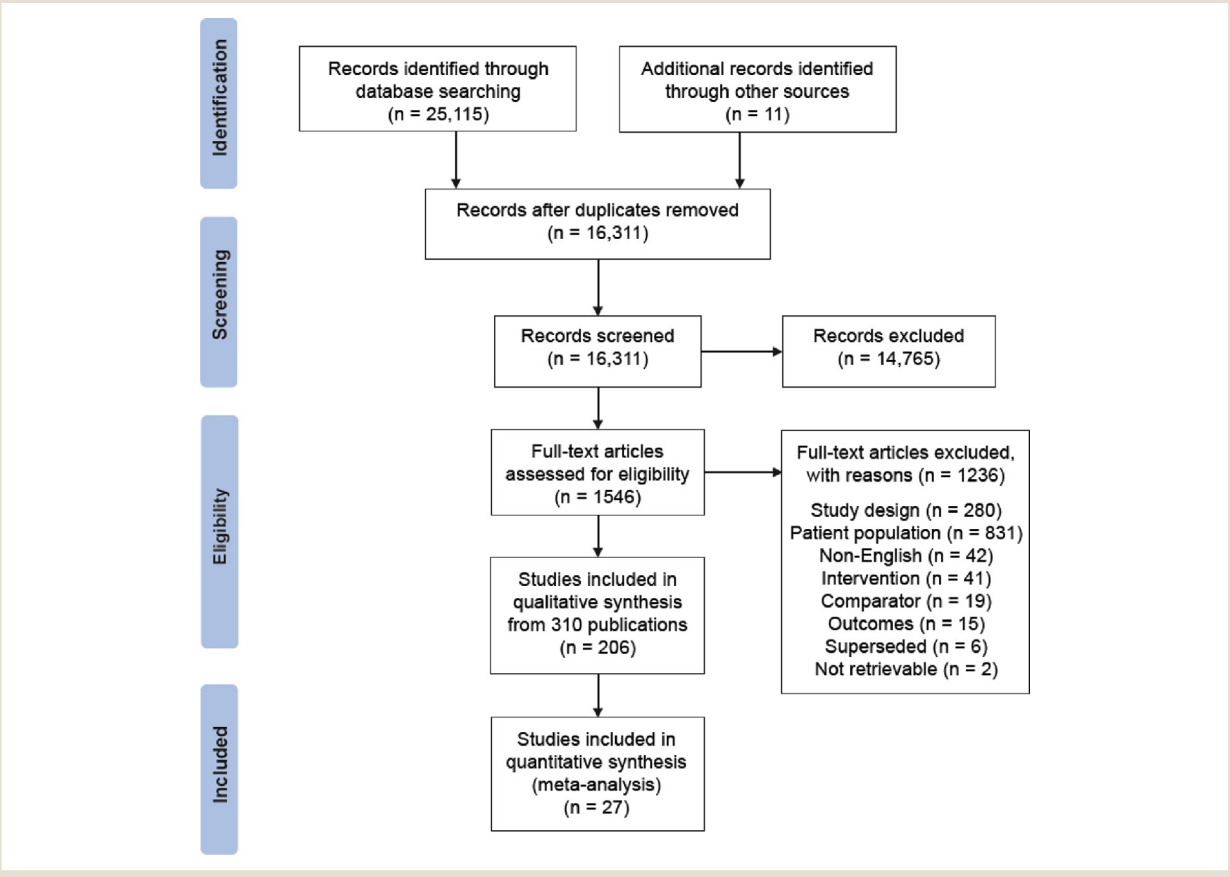
A systematic literature search of randomized, controlled trials of 2L+ treatments published through March 6, 2017 from database inception was conducted using MEDLINE and Embase and supplemented by a search of the Cochrane Database of Systematic Reviews and relevant scientific conference presentations (no published protocol). Eligible records included phase II to IV clinical trials of 2L+ NSCLC treatments for adults (≥ 18 years) with advanced or metastatic NSCLC who had received ≥ 1 prior systemic therapy. Trials with a phase I component were not included. Studies with non-adult participants were included if information specific to adults was reported separately. Included records had to be in English, reporting results for 2L+ NSCLC treatments licensed in the United States or European Union at the time the search was conducted, with ≥ 10 patients per study arm. Studies were included even if the investigational dose was not the approved treatment dose. Treatments specifically targeting EGFR- or ALK-positive patients were excluded in order to avoid enriching the overall population for EGFR/ALK status, because it would likely be an effect modifier. Although a range of outcomes were included in data extraction, the main outcomes of interest were time-to-event OS and PFS, to align with primary endpoints utilized in this treatment landscape. Safety outcomes were not analyzed because the NMA method applies only to time-to-event data. Two independent researchers (J.F., C.M.) screened the records according to predefined criteria. Discrepancies were adjudicated by a third reviewer. For the quality assessment, the Cochrane Risk of Bias Assessment tool was used. Details of the search strategy, study selection process, data extraction methods, and other procedures are in Supplemental Table 1 (in the online version).

The search identified 25,115 studies for screening and evaluation (Figure 1). Studies had to be connected in an evidence network by common comparators. Two hundred six studies reported in 310 publications were assessed, 171 of which were excluded, leaving 34 studies for further consideration. Of note, we opted to include the KEYNOTE-010 trial of pembrolizumab, even though participants had to express PD-L1/PD-1 on ≥ 1% of tumor cells, a requirement absent from other PD-L1/PD-1 trials. This exception was made for the sake of relevance to real-world treatment decisions and practices and was tested in sensitivity analyses. Three single histology studies of treatments only approved for single-histology populations were excluded because their restricted approval suggested that histology would likely be an effect modifier for these treatments and would thus violate NMA assumptions (afatinib in squamous-cell carcinoma,[14] afatinib in adenocarcinoma,[15] and pemetrexed in adenocarcinoma[16]). Four studies did not report a Kaplan-Meier curve for OS, and 14 did not report one for PFS. Therefore, the final extended NMA (with pembrolizumab) included 27 clinical trials reporting OS and 18 trials reporting PFS. The predominance of docetaxel as comparator arm among the studies reflects its role as standard-of-care for NSCLC during the time period in which the trials were conducted. Data from regimens of docetaxel given once weekly (QW) and 3 times a week (Q3W) were pooled owing to the large number of similar doses studied. The study by Chen and colleagues included 2 docetaxel arms QW (docetaxel 35 mg/m^2 and 40 mg/m^2).[17] In order to distinguish the doses while retaining the Chen study in the network, data from the docetaxel 40 mg/m^2 arm was included in a separate treatment node, and data from the docetaxel 35 mg/m^2 arm was included in the pooled docetaxel QW data. Separate analyses were conducted, one without including pembrolizumab in the network (base case) and another that included pembrolizumab (extended network).

Statistical Analysis

This Bayesian fractional polynomials NMA was based on methods described by Jansen and colleagues using time-to-event OS and PFS.[13] Atezolizumab was used as the reference treatment for reporting based on individual patient-level data from the phase III OAK and phase II POPLAR trials, which investigated atezolizumab versus docetaxel in patients with previously treated NSCLC.[5,6] The OAK trial was originally designed to enroll 850 patients in the intent-to-treat (ITT) population, which served as the primary efficacy analysis population.[5] However, the sample size was increased to

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Study Identification and Selection Flow Chart



1225 patients in order to power an OS comparison among patients with high PD-L1 expression. This NMA used the original ITT primary analysis population of the first 850 randomized participants. Survival curves from all other studies were extracted from published reports and digitized using DigitizeIt (Braunschweig, Germany), and the Guyot algorithm was used to convert the digitized data for analysis.[18]

In the OAK trial, 17% of patients in the docetaxel arm switched to an immunotherapy at some point during follow-up. This switching may have led to confounded survival estimates not representative of the true effectiveness of atezolizumab. Thus, we used rank-preserving structural failure time models to adjust for estimating the true survival time of patients in the docetaxel arm as if they had stayed on docetaxel for the duration of follow-up.[19] Results of this switch-adjusted analysis for expected OS are included. Base-case and extended network analyses were performed for OS, switch-adjusted OS, and PFS. Data necessary to perform analyses of mid-trial switching to immunotherapy was not available for other studies.

The NMA was performed on the parameters of the fractional polynomials that modeled the hazard over time from each study arm to obtain an overall set of estimated parameters for each treatment. Several models were evaluated: first- and second-order fractional polynomials and fixed and random effects. First-order random effects models with $p1 = 0$ (Weibull) were selected as the best-fitting models according to deviance information criterion and visual examination of fitted curves and were used for all analyses.

Posterior distributions of the model parameters were summarized with point estimates and 95% credible intervals (CrIs). Expected survival was based on the area under the survival curve generated from these parameters for each treatment. The expected survival time reflected the area under the survival curve over the time horizon. A time horizon of 5 years was used to model expected OS, and 2.5 years was used for expected PFS, in order to minimize extrapolation beyond the period for which data was observed. The relative differences in expected OS and PFS, as well as hazard ratios over time for atezolizumab versus each comparator, were estimated.

The probability that each treatment would be ranked at a certain position among all interventions was calculated and summarized using median ranking with 95% CrI and presented with rankograms. Effectiveness of treatments was also estimated using the surface under the cumulative ranking (SUCRA) line, where a SUCRA value of 100% indicated the treatment was certain to be best and 0% that it was certain to be worst.

Analyses were conducted using JAGS (Just Another Gibbs Sampler) with 50,000 iterations, of which 12,500 were discarded, as

well as a thinning parameter of 25 with 2 chains. Uninformative priors were used for all parameters according to equation 9 of Jansen[14]: multivariate normal with 0 mean and covariance and 10,000 variance for d and μ parameters; uniform (0,2) for σ.

Results

Studies and treatments included in the base-case and extended network analyses are presented in Table 1. The all-evidence network, which is the same for the unadjusted OS and switch-adjusted OS extended networks, is presented in Figure 2. The extended networks are identical to those of the base case with the addition of pembrolizumab, and the PFS extended network is presented in Supplemental Figure 1 (in the online version).

OS

Expected OS over 5 years was comparable among PD-L1/PD-1 inhibitors in the unadjusted base-case analysis as well as in the unadjusted extended network analysis that included pembrolizumab (Figure 3A). All PD-L1/PD-1 inhibitors performed better than other treatments. In the extended network, nivolumab showed the longest expected OS at 19.99 months (95% CrI, 14.55-27.19 months), followed by atezolizumab at 19.41 months (95% CrI, 14.19-25.70 months) and pembrolizumab at 19.34 months (95% CrI, 12.25-28.74 months).

When the analysis was conducted using switch-adjusted OS results from the OAK study, expected OS was comparable among atezolizumab and the other PD-L1/PD-1 inhibitors in the extended network (Figure 3B). Atezolizumab had the longest expected switch-adjusted OS in both the base-case and extended networks.

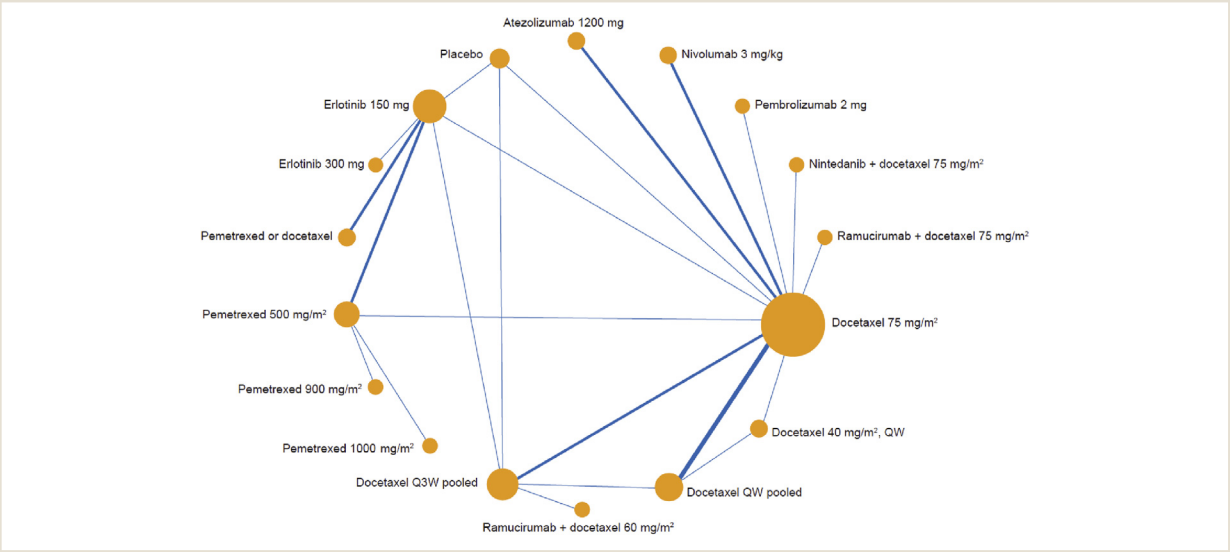
Modeled OS probability was similar among PD-L1/PD-1 inhibitors in both the unadjusted and switch-adjusted analyses (Figure 4). In the unadjusted analysis, the SUCRA ranking was highest for nivolumab, followed by atezolizumab and pembrolizumab; in the switch-adjusted analysis, the SUCRA ranking was highest for atezolizumab, followed by nivolumab and pembrolizumab (Table 2).

Table 1 Studies and Treatments in the Fractional Polynomials Network Meta-analyses

Study	Reference Treatment	Comparator(s)	Contributing to Analyses
Borghaei 2015 (CheckMate 057)[7]	Nivolumab 3 mg/kg	Docetaxel 75 mg/m^2	OS, PFS, OS-switch
Brahmer 2015 (CheckMate 017)[8]	Nivolumab 3 mg/kg	Docetaxel 75 mg/m^2	OS, PFS, OS-switch
Camps 2006[20]	Docetaxel QW pooled	Docetaxel 75 mg/m^2	OS, OS-switch
Chen 2006[17]	Docetaxel 75 mg/m^2	(1) Docetaxel 40 mg/m^2 QW (2) Docetaxel QW pooled	OS, OS-switch
Ciuleanu 2012 (TITAN)[21]	Pemetrexed or docetaxel	Erlotinib 150 mg	OS, PFS, OS-switch
Cullen 2008 (H3E-MC-JMGX)[22]	Pemetrexed 900 mg/m^2	Pemetrexed 500 mg/m^2	OS, PFS, OS-switch
Fossella 2000 (TAX 320)[23]	Docetaxel 75 mg/m^2	Docetaxel Q3W pooled	OS, OS-switch
Garassino 2013 (TAILOR)[24]	Erlotinib 150 mg	Docetaxel 75 mg/m^2	OS, PFS, OS-switch
Garon 2014 (REVEL)[25]	Ramucirumab + docetaxel 75 mg/m^2	Docetaxel 75 mg/m^2	OS, PFS, OS-switch
Gregorc 2014 (PROSE)[26]	Pemetrexed or docetaxel	Erlotinib 150 mg	OS, PFS, OS-switch
Gridelli 2004 (DISTAL 01)[27]	Docetaxel QW pooled	Docetaxel 75 mg/m^2	OS, OS-switch
Hanna 2004[28]	Pemetrexed 500 mg/m^2	Docetaxel 75 mg/m^2	OS, PFS, OS-switch
Herbst 2015 (KEYNOTE-010)[9]	Pembrolizumab 2 mg	Docetaxel 75 mg/m^2	OS, PFS, OS-switch[a]
Karampeazis 2013 (HORG)[29]	Pemetrexed 500 mg/m^2	Erlotinib 150 mg	OS, OS-switch
Kawaguchi 2014 (DELTA, UMIN000002314)[30]	Erlotinib 150 mg	Docetaxel Q3W pooled	OS, PFS, OS-switch
Lai 2005[31]	Docetaxel QW pooled	Docetaxel Q3W pooled	OS, PFS, OS-switch
Lee 2013[32]	Pemetrexed 500 mg/m^2	Erlotinib 150 mg	OS, PFS, OS-switch
OAK individual patient-level data[5]	Docetaxel 75 mg/m^2	Atezolizumab 1200 mg	OS, PFS, OS-switch
Ohe 2008[33]	Pemetrexed 500 mg/m^2	Pemetrexed 1000 mg/m^2	OS, OS-switch
POPLAR individual patient-level data[6]	Docetaxel 75 mg/m^2	Atezolizumab 1200 mg	OS, PFS, OS-switch
Quoix 2004[34]	Docetaxel 75 mg/m^2	Docetaxel Q3W pooled	OS, OS-switch
Reck 2014 (LUME-Lung 1)[35]	Nintedanib + docetaxel 75 mg/m^2	Docetaxel 75 mg/m^2	OS, PFS, OS-switch
Schuette 2005[36]	Docetaxel QW pooled	Docetaxel 75 mg/m^2	OS, OS-switch
Shepherd 2000 (TAX 317)[37]	Docetaxel 75 mg/m^2	(1) Docetaxel Q3W pooled (2) Placebo	OS, OS-switch
Shepherd 2005 (BR.21)[38]	Placebo	Erlotinib 150 mg	OS, PFS, OS-switch
Smit 2016 (CurrentS)[39]	Erlotinib 300 mg	Erlotinib 150 mg	OS, PFS, OS-switch
Yoh 2016[40]	Ramucirumab + docetaxel 60 mg/m^2	Docetaxel Q3W pooled	OS, PFS, OS-switch

Abbreviations: DELTA = Docetaxel and erlotinib lung cancer trial; HORG = Hellenic Oncology Research Group; PFS = progression-free survival; PROSE = Predictive value of proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy; OS = overall survival; Q3W = every 3 weeks; QW = once weekly REVEL = Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy; TAILOR = Tarceva Italian lung optimization trial; TITAN = Tarceva in treatment of advanced NSCLC.
[a]Herbst 2015 (KEYNOTE-010) was included only in the extended network analyses.

Figure 2 All-evidence Network of Included Studies. Edge Width Is Proportional to the Number of Trials for Each Comparison



Abbreviations: Q3W = every 3 weeks; QW = once weekly.

PFS

Among PD-L1/PD-1 inhibitors in the base-case network, expected PFS over 2.5 years was 8.31 months (95% CrI, 4.81-12.93 months) for nivolumab, followed by atezolizumab (6.17 months [95% CrI, 3.37-9.80 months]). In the extended network, nivolumab (8.25 months [95% CrI, 4.28-13.59 months]) was followed by atezolizumab (6.22 months [95% CrI, 3.23-9.91 months]), then pembrolizumab (6.09 months [95% CrI, 2.93-12.02 months]). Among PD-L1/PD-1 inhibitors in the extended network, nivolumab ranked first according to SUCRA probabilities, followed by atezolizumab and pembrolizumab (see Supplemental Table 2 in the online version). Expected PFS over 2.5 years and modeled probability of PFS in the extended network are presented in Supplemental Figures 2 and 3 (in the online version), respectively.

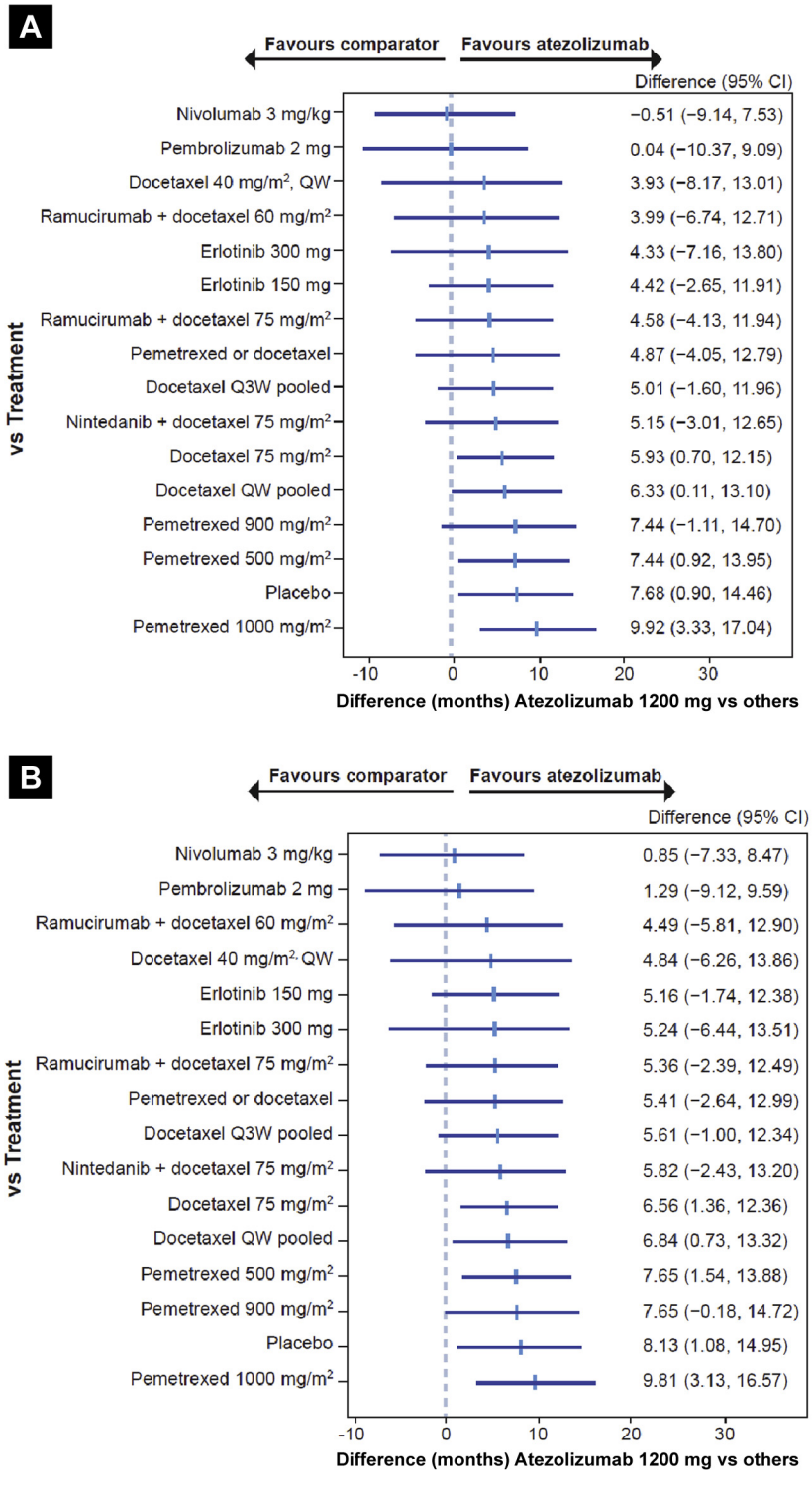
Discussion

This systematic literature review and NMA illustrated the relative OS and PFS benefits of PD-L1/PD-1 inhibitors and other approved options for 2L+ treatments of adults with NSCLC. In a fractional polynomials meta-analysis based on a network of 27 randomized controlled trials, cancer immunotherapies demonstrated greater survival benefits than all other treatments, with comparable modeled OS benefits among PD-L1/PD-1 inhibitors. In unadjusted analyses among PD-L1/PD-1 inhibitors, nivolumab ranked highest for OS (SUCRA, 87.9%), followed by atezolizumab (85.8%) and pembrolizumab (82.8%). The adjusted analysis accounting for midtrial switching from docetaxel to immunotherapy in the OAK trial ranked atezolizumab highest (89.6%), followed by nivolumab (86.5%) and pembrolizumab (81.9%). In both analyses, PD-L1/PD-1 inhibitors were ranked highest, followed by regimens using docetaxel 40 mg/m^2, ramucirumab + docetaxel 60 mg/m^2, and erlotinib 150 mg. Docetaxel was the most common comparator among the trials, driven by the fact that the majority of these studies are pivotal trials designed to demonstrate to regulatory agencies the superiority of the immunotherapy over standard of care.

As cancer immunotherapies and combination therapies become more widely available, it is important to account for treatment switching and the timing of benefits observed with different treatment classes, particularly as various combinations are investigated. Unlike traditional NMAs of hazard ratios, the fractional polynomials NMA approach does not require the assumption of proportional hazards (a constant hazard ratio over time) for the survival functions used in estimating OS and PFS, an assumption that is unlikely to hold for cancer immunotherapies. In our analysis, the fractional polynomials statistical approach and the switching-adjusted analyses, respectively, accounted for cancer immunotherapies' extended onset of treatment effect and the treatment-switching observed in the OAK trial. This analysis also accounted for the fact that during the OAK study, nearly one-fifth (17%) of patients randomized to docetaxel switched to immunotherapy, which would have otherwise biased the true treatment effect of docetaxel (and its comparison with atezolizumab).

This analysis focused on OS and PFS outcomes, as these outcomes are of greatest clinical importance and could be uniquely and appropriately modeled with the fractional polynomial approach. OS was listed as a primary outcome in both the OAK and POPLAR atezolizumab trials and PFS as a secondary outcome, which was widely consistent across comparator trials. According to the most recent United States Food and Drug Administration guidance regarding clinical trial endpoints for cancer drugs and biologics (December 2018), OS is considered the most reliable and usually the preferred cancer trial endpoint.[41] Although safety and side effects are also important outcomes, they are not appropriately modeled using the fractional polynomial approach. This study should be interpreted in the context of certain strengths and limitations. Recent indirect comparisons among 2L+ NSCLC

Figure 3 Expected Overall Survival Difference for Atezolizumab Versus Comparators in the Extended Network (5-Year Time Horizon). A, Unadjusted Analysis; B, Switch-Adjusted Analysis



Abbreviations: CI = confidence interval; Q3W = every 3 weeks; QW = once weekly.

Figure 4 Modeled Overall Survival Probability in the Extended Network: Programmed Death-ligand 1/Programmed Cell Death Protein 1 and Docetaxel. The 95% Credible Intervals for Atezolizumab Is Shown With Dotted Lines and Gray Shading. A, Unadjusted Analysis; B, Switch-Adjusted Analysis

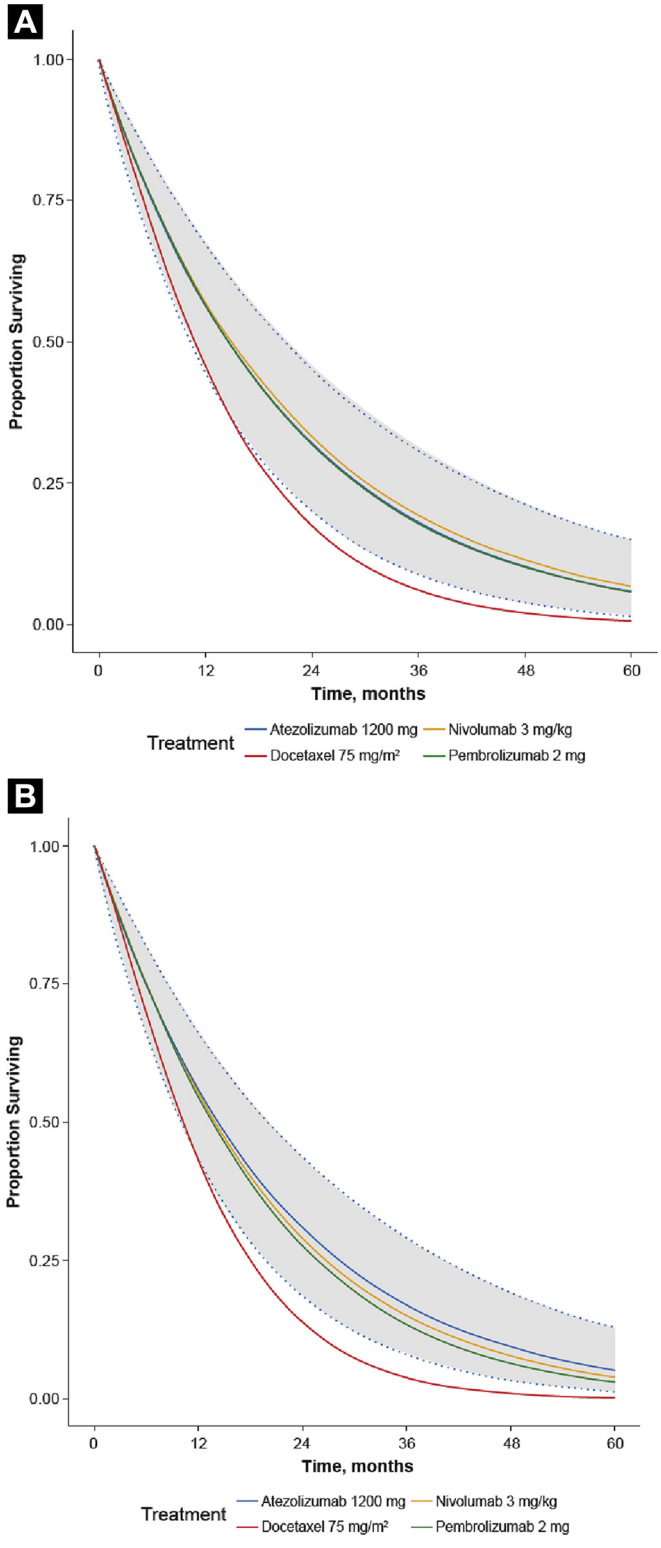


Table 2 Ranking of Expected Overall Survival (5-Year Time Horizon) in the Extended Network

Unadjusted Analysis			Switch-Adjusted Analysis		
	Median Rank (95% CrI)	SUCRA Probability, %		Median Rank (95% CrI)	SUCRA Probability, %
Nivolumab 3 mg/kg	2 (1-8)	87.9	Atezolizumab 1200 mg	2 (1-8)	89.6
Atezolizumab 1200 mg	3 (1-9)	85.8	Nivolumab 3 mg/kg	3 (1-9)	86.5
Pembrolizumab 2 mg/kg	3 (1-13)	82.8	Pembrolizumab 2 mg/kg	3 (1-13)	81.9
Docetaxel QW 40 mg/m^2	7 (1-17)	57.9	Ramucirumab + docetaxel 60 mg/m^2	6 (1-17)	59.9
Ramucirumab + docetaxel 60 mg/m^2	7 (1-17)	57.9	Erlotinib 150 mg	7 (3-13)	57.9
Erlotinib 150 mg	7 (3-13)	57.8	Docetaxel QW 40 mg/m^2	7 (1-17)	55.6
Ramucirumab + docetaxel 75 mg/m^2	8 (2-16)	55.1	Erlotinib 300 mg	8 (1-17)	53.9
Erlotinib 300 mg	8 (1-17)	55.0	Ramucirumab + docetaxel 75 mg/m^2	8 (2-16)	53.5
Docetaxel Q3W pooled	8 (4-15)	51.7	Pemetrexed or docetaxel	8 (2-16)	52.8
Pemetrexed or docetaxel	8 (2-16)	51.5	Docetaxel Q3W pooled	9 (4-15)	51.4
Nintedanib + docetaxel 75 mg/m^2	9 (2-17)	49.8	Nintedanib + docetaxel 75 mg/m^2	9 (2-17)	48.8
Docetaxel 75 mg/m^2	11 (6-14)	40.7	Docetaxel 75 mg/m^2	11 (6-15)	40.0
Docetaxel QW pooled	11 (5-16)	36.4	Docetaxel QW pooled	12 (5-16)	35.6
Pemetrexed 900 mg/m^2	14 (4-17)	26.9	Pemetrexed 900 mg/m^2	14 (4-17)	27.8
Pemetrexed 500 mg/m^2	14 (7-16)	24.5	Pemetrexed 500 mg/m^2	14 (7-16)	25.0
Placebo	14 (7-17)	21.8	Placebo	14 (6-17)	22.1
Pemetrexed 1000 mg/m^2	17 (10-17)	6.4	Pemetrexed 1000 mg/m^2	17 (9-17)	7.8

Abbreviations: CrI = credible interval; OS = overall survival; PFS = progression-free survival; Q3W = every 3 weeks; QW = once weekly; SUCRA = surface under the cumulative ranking curve.

treatment networks used traditional statistical approaches that did not account for the timing of PD-L1/PD-1 inhibitors' treatment effects.[10,11] The previously published assessment of appropriateness and feasibility of this approach demonstrated the importance of incorporating specific treatment-class considerations in the statistical analysis plan of NMA among these therapies.[12] Individual patient-level data were used from the phase III OAK and phase II POPLAR trials of atezolizumab, increasing the accuracy of the input data for these trials and facilitating easier and more accurate subgroup analyses. In this study, histology was population-weighted in the pooled estimates of outcomes. However, further subgroup analysis may be warranted if histology emerges as a source of variability.

Patient-level data were not available for other treatments; thus, we took the customary approach of using data from previously published, digitized Kaplan-Meier curves. Precise information regarding midtrial switching to immunotherapy in other studies was also unavailable, which could have led to an underestimation of modeled outcomes for nivolumab and pembrolizumab. The pembrolizumab KEYNOTE-010 trial, unlike the other PD-L1/PD-1 inhibitor trials, was not a true all-comers study owing to the PD-L1 expression criterion; however, results were consistent in the base-case and extended network analyses conducted with and without pembrolizumab. In the OS analysis, slight visual inconsistency was noted between the direct head-to-head comparisons (in terms of pattern of survival curves) and the direction of treatment effects estimated by the fractional polynomials NMA for some treatment comparisons within closed loops, namely erlotinib 150 mg, docetaxel 75 mg/m^2, and docetaxel Q3W pooled. This slight inconsistency could have been owing to random variation rather than true inconsistency in the network and did not affect comparisons of treatments outside this loop, such as those involving PD-L1/PD-1 inhibitors.

Conclusions

This NMA showed that PD-L1/PD-1 inhibitors had the highest expected 5-year OS compared with all other 2L+ treatments for NSCLC. Because OS estimates are influenced by the timing of treatment effects and by active treatment switching in clinical trials, a fractional polynomials meta-analytic approach that accounted for treatment switching was appropriate for assessing the relative clinical benefit of current treatment options. In this analysis, PD-L1/PD-1 inhibitors had similar modeled OS. In the unadjusted OS model, nivolumab ranked highest, followed by atezolizumab and pembrolizumab. When the analysis was adjusted for chemotherapy treatment switching in the OAK trial, atezolizumab ranked highest, followed by nivolumab and pembrolizumab. This analysis used an appropriate approach for meta-analysis of this diverse treatment network and supported the robustness of PD-L1/PD-1 inhibitors in the context of 2L+ options for patients with NSCLC.

Clinical Practice Points

- Anti—PD-L1/PD-1 immunotherapies atezolizumab, nivolumab, and pembrolizumab have changed the 2L+ treatment landscape for patients with NSCLC. The clinical data that have emerged are complex, with heterogeneous results across the landscape. Interpretation may be further complicated because the treatments often have different response dynamics than previous standard of care. Furthermore, outcomes in comparator arms can be complicated by switching to follow-up therapies. There is a need to synthesize this wealth of information, not only to educate clinicians but to inform the broader health care system. Payers in the system often drive the need for Health Technology Assessments across the treatment landscape. NMAs are conducted to evaluate the relative efficacy of therapies when randomized controlled trials are not appropriate or

possible. Statistical approaches used in traditional NMAs of chemotherapy and other treatments do not account for differences in survival patterns observed with the newer immunotherapies. The extended onset of treatment effect and greater long-term survival observed in some patients treated with PD-L1/PD-1 inhibitors violate the proportional hazards assumption of survival functions used in traditional NMAs of time-to-event outcomes. We conducted a systematic literature review and used a fractional polynomials NMA to evaluate the relative efficacy of 2L+ therapies for NSCLC.

- Cancer immunotherapies demonstrated greater survival benefits than all other treatments, with comparable modeled OS benefits among PD-L1/PD-1 inhibitors. In unadjusted analyses among PD-L1/PD-1 inhibitors, nivolumab ranked highest for OS, followed by atezolizumab and pembrolizumab. The adjusted analysis accounting for mid-trial switching from docetaxel to immunotherapy in the OAK trial ranked atezolizumab highest, followed by nivolumab and pembrolizumab. In both analyses, PD-L1/PD-1 inhibitors were ranked highest, followed by regimens using docetaxel 40 mg/m^2, ramucirumab + docetaxel 60 mg/m^2, and erlotinib 150 mg. The statistical approach used in our analysis accounted for cancer immunotherapies' extended onset of treatment effect and the treatment-switching observed in the OAK trial, which is more appropriate than traditional NMA methods.

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Disclosure

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Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2019.06.017.

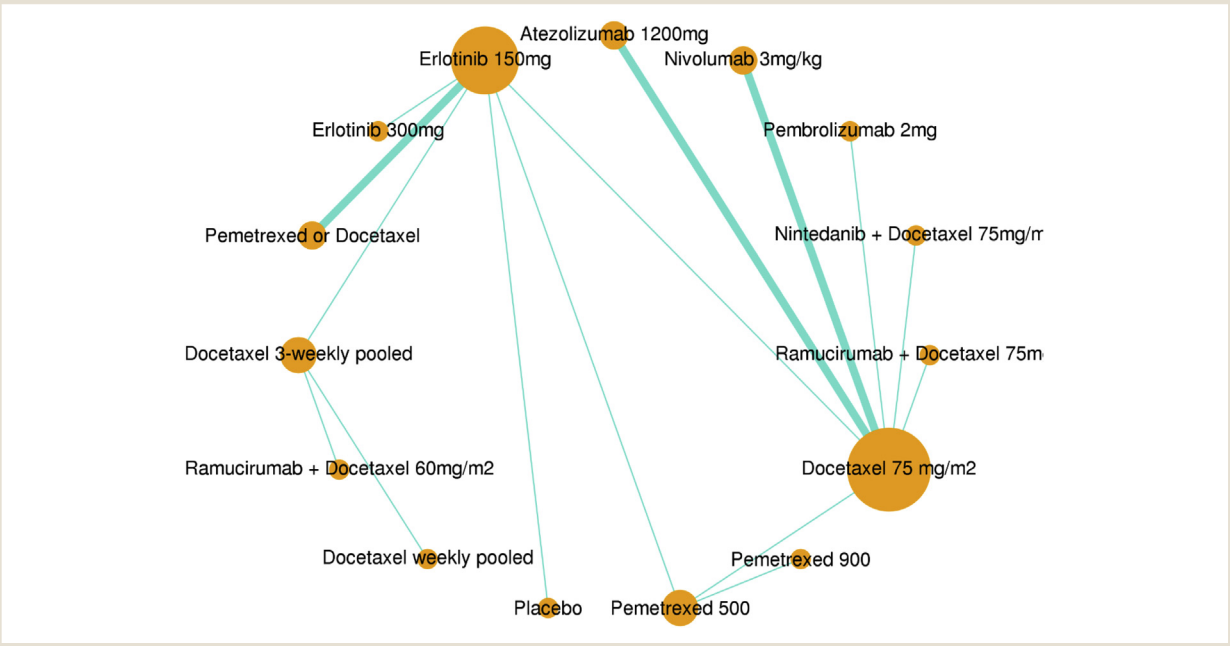
References

1. World Health Organization. International Agency for Research on Cancer. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. Available at: http://globocan.iarc.fr/Pages/fact_ sheets_cancer.aspx?cancer=lung. Accessed: July 16, 2018.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65:87-108.
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; 62:10-29.
4. Novello S, Barlesi F, Califano R, et al, ESMO Guidelines Committee. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; 27:v1-27.
5. Rittmeyer A, Barlesi F, Waterkamp D, et al, OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; 389:255-65.
6. Fehrenbacher L, Spira A, Ballinger M, et al, POPLAR Study Group. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016; 387:1837-46.
7. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *N Engl J Med* 2015; 373:1627-39.
8. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. *N Engl J Med* 2015; 373:123-35.
9. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; 387:1540-50.
10. Créquit P, Chaimani A, Yavchitz A, et al. Comparative efficacy and safety of second-line treatments for advanced non-small cell lung cancer with wild-type or unknown status for epidermal growth factor receptor: a systematic review and network meta-analysis. *BMC Med* 2017; 15:193.
11. Institute for Clinical and Economic Review. Treatment options for advanced non-small cell lung cancer: effectiveness, value and value-based price benchmarks. 2016. Available at: https://icer-review.org/wp-content/uploads/2016/10/MWCEPAC_NSCLC_Final_Evidence_Report_Meeting_Summary_110116.pdf. Accessed: August 1, 2018.
12. Chu P, Watkins CL. Fractional polynomial modelling in network meta-analyses of cancer immunotherapies in advanced non-small cell lung cancer (NSCLC). Presented at: 20th Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research; 4-8 November 2017; Glasgow, Scotland [abstract PRM150].
13. Jansen JP. Network meta-analysis of survival data with fractional polynomials. *BMC Med Res Methodol* 2011; 11:61.
14. Soria JC, Felip E, Cobo M, et al, LUX-Lung 8 Investigators. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2015; 16:897-907.
15. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012; 13:528-38.
16. Li N, Ou W, Yang H, et al. A randomized phase 2 trial of erlotinib versus pemetrexed as second-line therapy in the treatment of patients with advanced EGFR wild-type and EGFR FISH-positive lung adenocarcinoma. *Cancer* 2014; 120:1379-86.
17. Chen YM, Shih JF, Perng RP, Tsai CM, Whang-Peng J. A randomized trial of different docetaxel schedules in non-small cell lung cancer patients who failed previous platinum-based chemotherapy. *Chest* 2006; 129:1031-8.
18. Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012; 12:9.
19. Latimer NR, Abrams KF, National Institute for Health and Care Excellence (NICE). NICE DSU Technical Support Document 16: adjusting survival time estimates in the presence of treatment switching. 2014. Available at: https://www.ncbi.nlm.nih.gov/books/NBK310374/. Accessed: October 6, 2018.
20. Camps C, Massuti B, Jiménez A, et al, Spanish Lung Cancer Group. Randomized phase III study of 3-weekly versus weekly docetaxel in pretreated advanced non-small-cell lung cancer: a Spanish Lung Cancer Group trial. *Ann Oncol* 2006; 17:467-72.
21. Ciuleanu T, Stelmakh L, Cicenas S, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. *Lancet Oncol* 2012; 13:300-8.
22. Cullen MH, Zatloukal P, Sörenson S, et al. A randomized phase III trial comparing standard and high-dose pemetrexed as second-line treatment in patients with locally advanced or metastatic non-small-cell lung cancer. *Ann Oncol* 2008; 19:939-45.
23. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000; 18:2354-62.

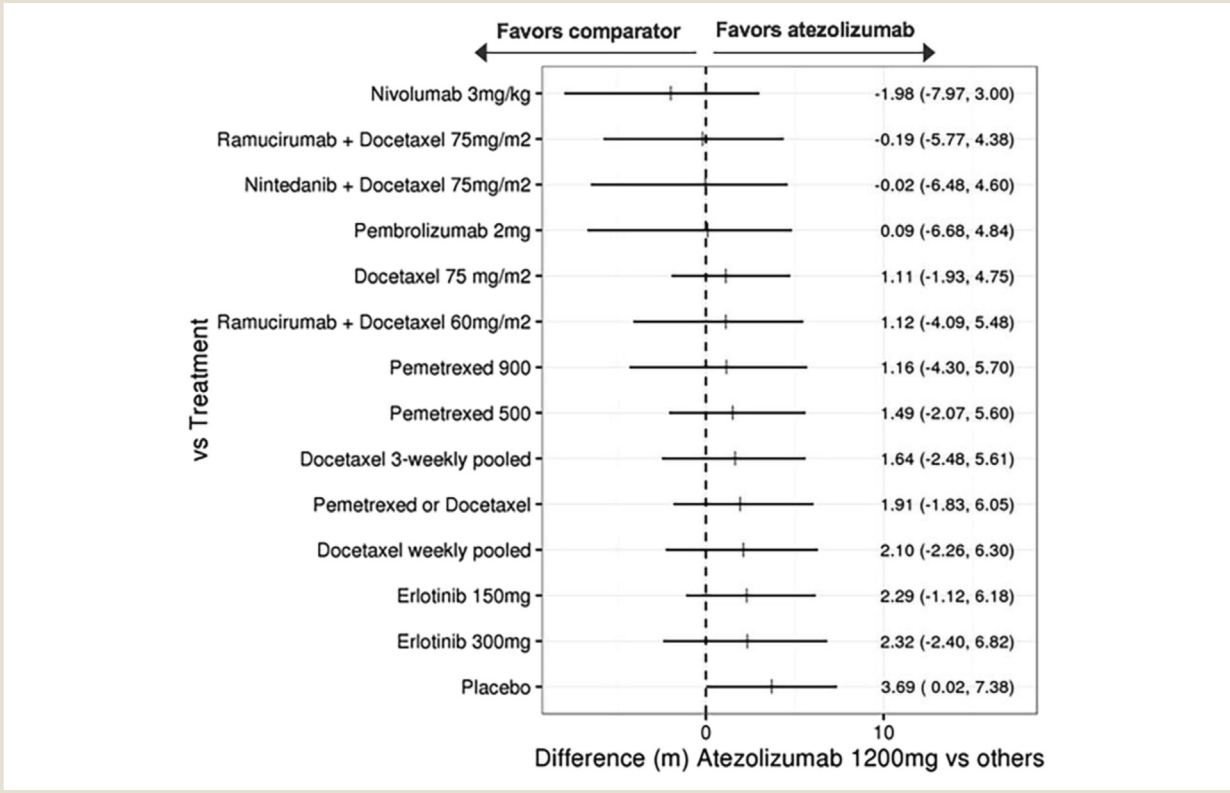
24. Garassino MC, Martelli O, Broggini M, et al, TAILOR trialists. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. *Lancet Oncol* 2013; 14:981-8.
25. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014; 384:665-73.
26. Gregorc V, Novello S, Lazzari C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker-stratified, randomised phase 3 trial. *Lancet Oncol* 2014; 15:713-21.
27. Gridelli C, Gallo C, Di Maio M, et al. A randomised clinical trial of two docetaxel regimens (weekly vs 3 week) in the second-line treatment of non-small-cell lung cancer. The DISTAL 01 study. *Br J Cancer* 2004; 91:1996-2004.
28. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; 22:1589-97.
29. Karampeazis A, Voutsina A, Souglakos J, et al. Pemetrexed versus erlotinib in pretreated patients with advanced non-small cell lung cancer: a Hellenic Oncology Research Group (HORG) randomized phase 3 study. *Cancer* 2013; 119:2754-64.
30. Kawaguchi T, Ando M, Asami K, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). *J Clin Oncol* 2014; 32:1902-8.
31. Lai CL, Tsai CM, Chiu CH, et al. Phase II randomized trial of tri-weekly versus days 1 and 8 weekly docetaxel as a second-line treatment of advanced non-small cell lung cancer. *Jpn J Clin Oncol* 2005; 35:700-6.
32. Lee DH, Lee JS, Kim SW, et al. Three-arm randomised controlled phase 2 study comparing pemetrexed and erlotinib to either pemetrexed or erlotinib alone as second-line treatment for never-smokers with non-squamous non-small cell lung cancer. *Eur J Cancer* 2013; 49:3111-21.
33. Ohe Y, Ichinose Y, Nakagawa K, et al. Efficacy and safety of two doses of pemetrexed supplemented with folic acid and vitamin B12 in previously treated patients with non-small cell lung cancer. *Clin Cancer Res* 2008; 14:4206-12.
34. Quoix E, Lebeau B, Depierre A, et al. Randomised, multicentre phase II study assessing two doses of docetaxel (75 or 100 mg/m^2) as second-line monotherapy for non-small-cell lung cancer. *Ann Oncol* 2004; 15:38-44.
35. Reck M, Kaiser R, Mellemgaard A, et al, LUME-Lung 1 Study Group. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung-1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol* 2014; 15:143-55.
36. Schuette W, Nagel S, Blankenburg T, et al. Phase III study of second-line chemotherapy for advanced non-small-cell lung cancer with weekly compared with 3-weekly docetaxel. *J Clin Oncol* 2005; 23:8389-95.
37. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; 18:2095-103.
38. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al, National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; 353:123-32.
39. Smit EF, Wu YL, Gervais R, et al. A randomized, double-blind, phase III study comparing two doses of erlotinib for second-line treatment of current smokers with advanced non-small-cell lung cancer (CurrentS). *Lung Cancer* 2016; 99:94-101.
40. Yoh K, Hosomi Y, Kasahara K, et al. A randomized, double-blind, phase II study of ramucirumab plus docetaxel vs placebo plus docetaxel in Japanese patients with stage IV non-small cell lung cancer after disease progression on platinum-based therapy. *Lung Cancer* 2016; 99:186-93.
41. United States Department of Health and Human Services. Clinical trial endpoints for the approval of cancer drugs and biologics: guidance for industry. Available at: https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf. Accessed: January 23, 2019.

Supplemental Data

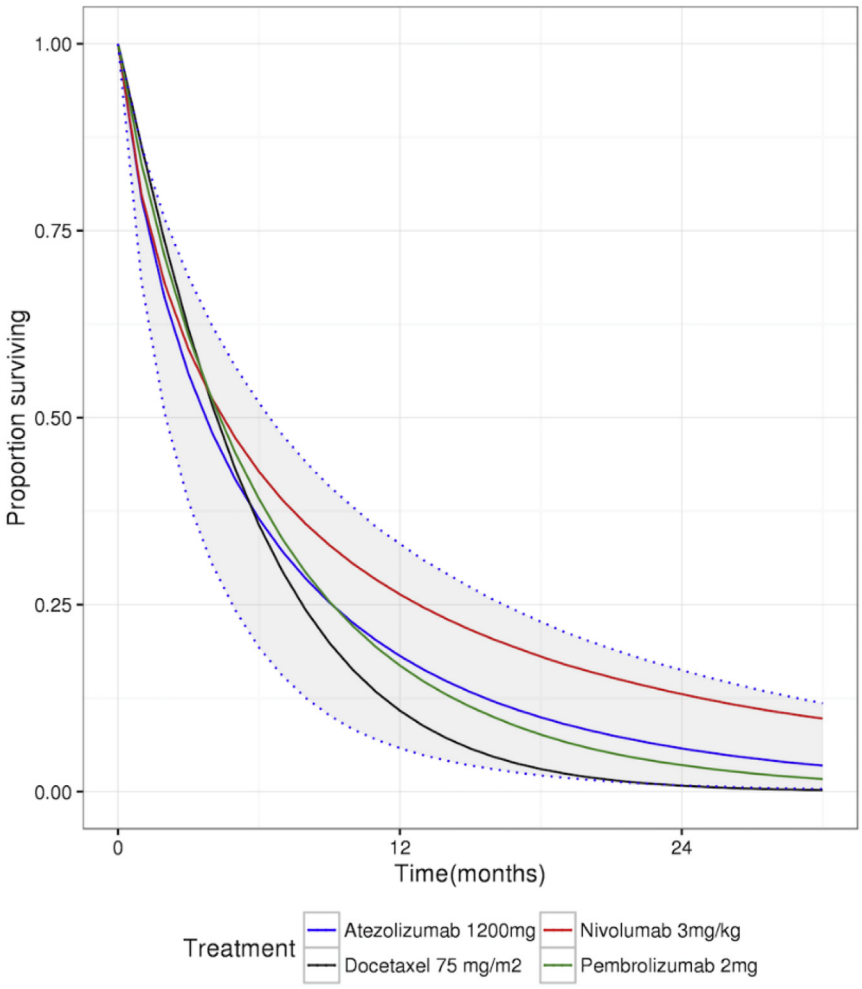
Supplemental Figure 1 Unadjusted Progression-free Survival Extended Evidence Network. Edge Width Is Proportional to the Number of Trials for Each Comparison



Supplemental Figure 2 Expected Progression-free Survival Difference (Months) for Atezolizumab Versus Comparators in the Extended Network (2.5-Year Time Horizon)



Supplemental Figure 3 Modeled Progression-free Survival Probability in the Extended Network, Programmed Death-ligand 1/Programmed Cell Death Protein 1, and Docetaxel. The 95% Credible Interval for Atezolizumab Is Shown With Dotted Lines and Gray Shading



Supplemental Table 1 Systematic Literature Search Criteria and Terms

	Search Term	Results
Search strategy for MEDLINE		
1	exp Carcinoma, Non-Small-Cell Lung/	40,764
2	Lung neoplasms/ and non small cell.ti,ab.	33,963
3	nsclc.ti,ab.	29,143
4	non small cell.ti,ab.	45,271
5	(carcinom$ or cancer$ or neoplas$).ti,ab.	1,832,431
6	lung$.ti,ab.	541,502
7	1 or 2 or 3 or (4 and 5 and 6)	55,964
8	randomized controlled trial.pt.	448,634
9	controlled clinical trial.pt.	91,926
10	randomized.ab.	380,814
11	placebo.ab.	181,410
12	clinical trials as topic.sh.	181,437
13	randomly.ab.	266,646
14	trial.ti.	170,882
15	or/8-14	1,086,393
16	exp animals/ not humans.sh.	4,324,702
17	15 not 16	1,001,234
18	7 and 17	8059
Search strategy for EMBASE		
1	exp non small cell lung cancer/	49,563
2	lung cancer/ and non small cell.ti,ab.	20,923
3	nsclc.ti,ab.	51,506
4	non small cell.ti,ab.	69,448
5	(carcinom$ or cancer$ or neoplas$).ti,ab.	2,484,909
6	lung$.ti,ab.	746,640
7	1 or 2 or 3 or (4 and 5 and 6)	102,176
8	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/	547,201
9	(random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).ti,ab.	1,753,292
10	8 or 9	1,844,562
11	(animal$ not human$).sh,hw.	4,081,856
12	10 not 11	1,690,561
13	7 and 12	11,207
Search strategy for Cochrane CENTRAL and CDSR		
1	exp Carcinoma, Non-Small-Cell Lung/	2270
2	Lung Neoplasms/ and non small cell.ti,ab.	2088
3	nsclc.ti,ab.	4111
4	non small cell.ti,ab.	5293
5	(carcinom$ or cancer$ or neoplas$).ti,ab.	83,376
6	lung$.ti,ab.	25,568
7	1 or 2 or 3 or (4 and 5 and 6)	6044
8	limit 7 to yr="2011-2017"	2639
9	7 not 8	3405
10	remove duplicates from 8	2509
11	remove duplicates from 9	3340
12	10 or 11	5849

Abbreviations: ab = abstract; exp = explodes; hw = subject heading word; nsclc = non–small-cell lung cancer; pt = publication type; sh = MeSH subject heading; ti = title.

Supplemental Table 2 Ranking for Expected Progression-free Survival (2.5-Year Time Horizon) in the Extended Network

	Median Rank (95% CrI)	SUCRA Probability, %
Nivolumab 3 mg/kg	1 (1-9)	92.1
Ramucirumab + docetaxel 75 mg/m^2	4 (1-12)	77.2
Nintedanib + docetaxel 75 mg/m^2	4 (1-13)	74.2
Atezolizumab 1200 mg	4 (1-13)	73.0
Pembrolizumab 2 mg	4 (1-14)	70.2
Docetaxel 75 mg/m^2	7 (4-12)	54.5
Ramucirumab + docetaxel 60 mg/m^2	7 (1-14)	54.4
Pemetrexed 900 mg/m^2	8 (1-15)	51.1
Pemetrexed 500 mg/m^2	9 (3-14)	43.8
Docetaxel Q3W pooled	9 (3-14)	41.8
Pemetrexed or docetaxel	11 (4-14)	35.0
Docetaxel QW pooled	11 (3-15)	30.3
Erlotinib 300 mg	12 (3-15)	26.4
Erlotinib 150 mg	12 (7-14)	22.6
Placebo	15 (10-15)	3.5

Abbreviations: CrI = credible interval; Q3W = every 3 weeks; QW = once weekly; SUCRA = surface under the cumulative ranking curve.