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Comparative efficacy and safety of nivolumab versus relevant treatments in pretreated advanced non-small cell lung cancer: a systematic literature review and indirect treatment comparison of randomized controlled trials

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Introduction

- Lung cancer is the second most common cancer in both men and women, and is the leading cause of cancer-related death in the world.[1] Non-small cell lung cancer (NSCLC), the most common form of lung cancer, comprises approximately 80% of all such malignancies.
- Treatments of choice in advanced NSCLC include concurrent chemoradiation using platinum-based treatments (PBTs).[2,3] Following disease progression on the first-line PBT, recommended subsequent therapies include systemic immune checkpoint inhibitors (ICIs), other targeted therapies, or cytotoxic regimens. Despite these recommended regimens, uncertainty remains regarding the optimal treatment for advanced NSCLC patients with disease progression following first-line PBT.
- In a previous study by Armoiry et al.[4], a systematic literature review (SLR) and a network meta-analysis (NMA) were conducted to estimate the comparative efficacy and safety of conventional interventions in patients with advanced NSCLC with disease progression on or after first-line PBT.
- In light of the recent results[5] from the phase III CheckMate 078 randomized controlled trial (RCT) of nivolumab versus docetaxel, the current study aimed to compare the efficacy and safety of nivolumab versus the comparators analyzed in Armoiry 2018 in advanced NSCLC patients with disease progression following first-line PBT.

Objective

- To compare the efficacy and safety of nivolumab versus comparator treatments for advanced NSCLC patients with disease progression on or after first-line PBT

Methods

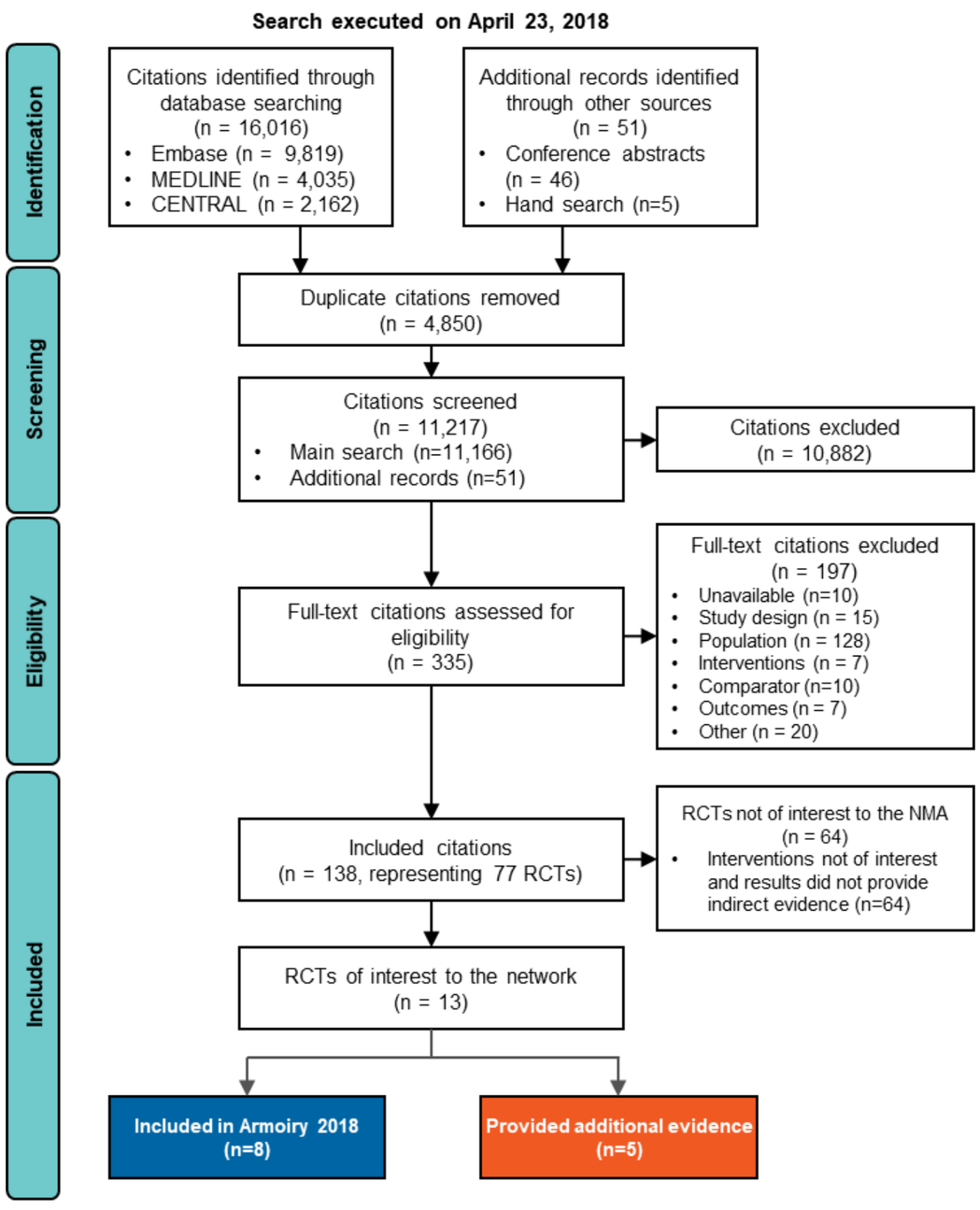
Systematic literature review (SLR)

- Study eligibility criteria:
  - Population: Adult patients with advanced or metastatic NSCLC with disease progression on or after first-line PBT
  - Interventions: ICIs and other targeted therapies, chemotherapy
  - Comparators: Interventions of interest, placebo/best supportive care, and any other comparator facilitating an indirect treatment comparison
  - Outcomes: Overall survival (OS), progression-free survival (PFS), and grade 3-5 treatment-related adverse events (TRAEs)
  - Study designs: RCTs only
- Study selection and data extraction was performed by two reviewers independently, with a third reviewer providing arbitration when necessary. Included RCTs were evaluated for quality using the Cochrane Collaboration's Risk of Bias tool.[6]

Network meta-analysis (NMA)

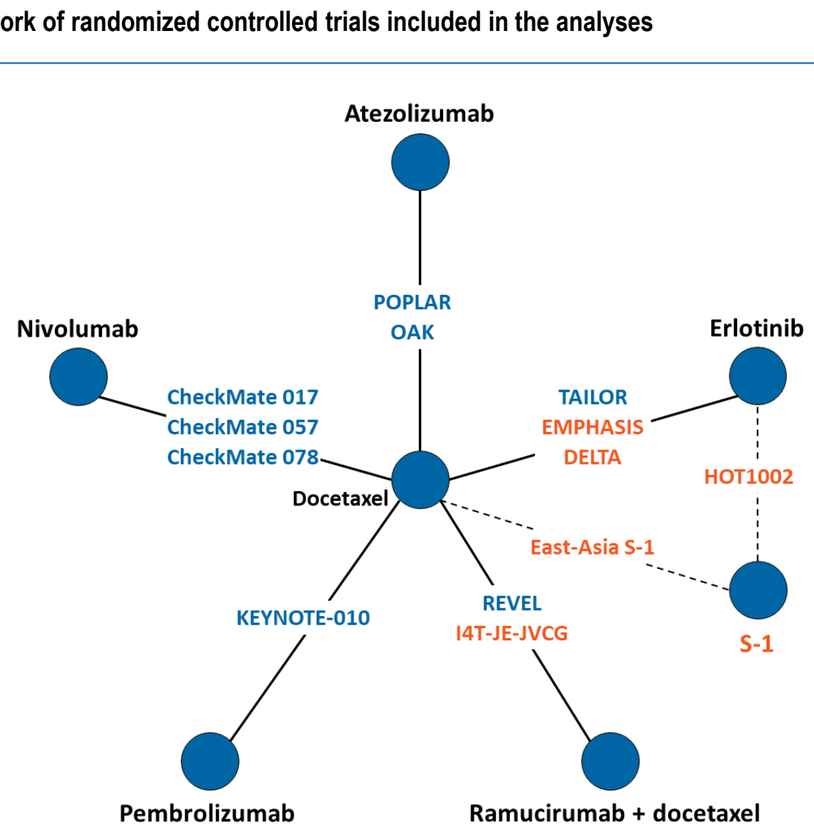
- An NMA was performed in a Bayesian framework using a fixed-effects model (consistent with Armoiry 2018) to assess the comparative efficacy (OS and PFS) and safety (grade 3-5 TRAEs) of nivolumab versus other interventions in the target population.
- Comparators of interest to the NMA were those analyzed in Armoiry 2018: pembrolizumab, atezolizumab, docetaxel, erlotinib and ramucirumab + docetaxel.[4] This was also consistent with other previously published analyses.[4,7-10]
- NMAs were conducted for the overall population (all histologies and programmed death ligand 1 [PD-L1] expression levels), as well as within the PD-L1 expressing population (PD-L1 ≥1%).
- The primary publication was selected as the data source for each trial for the analysis of grade 3-5 TRAEs, as this outcome was less uniformly reported in subsequent publications.
- Relative treatments effects were presented as hazard ratios (HRs) for OS and PFS and relative risks (RRs) for grade 3-5 TRAEs, with 95% credible intervals (CrIs).
- Planned analyses:
  - Base case analysis: The primary network comprised all seven trials included in Armoiry 2018. Additionally, CheckMate 078 was included in this network as it contributed additional data on the ICI class of interventions.
  - Sensitivity analysis: RCTs that were not included in the Armoiry 2018 NMA, but were deemed relevant to the current analyses were included in the context of a sensitivity analysis. These were trials that provided further direct (head-to-head) evidence for the interventions/comparators of interest, as well as studies that provided indirect evidence for the analyses.

Figure 1. Study selection flow diagram



RCT, randomized controlled trial.

Figure 2. Network of randomized controlled trials included in the analyses

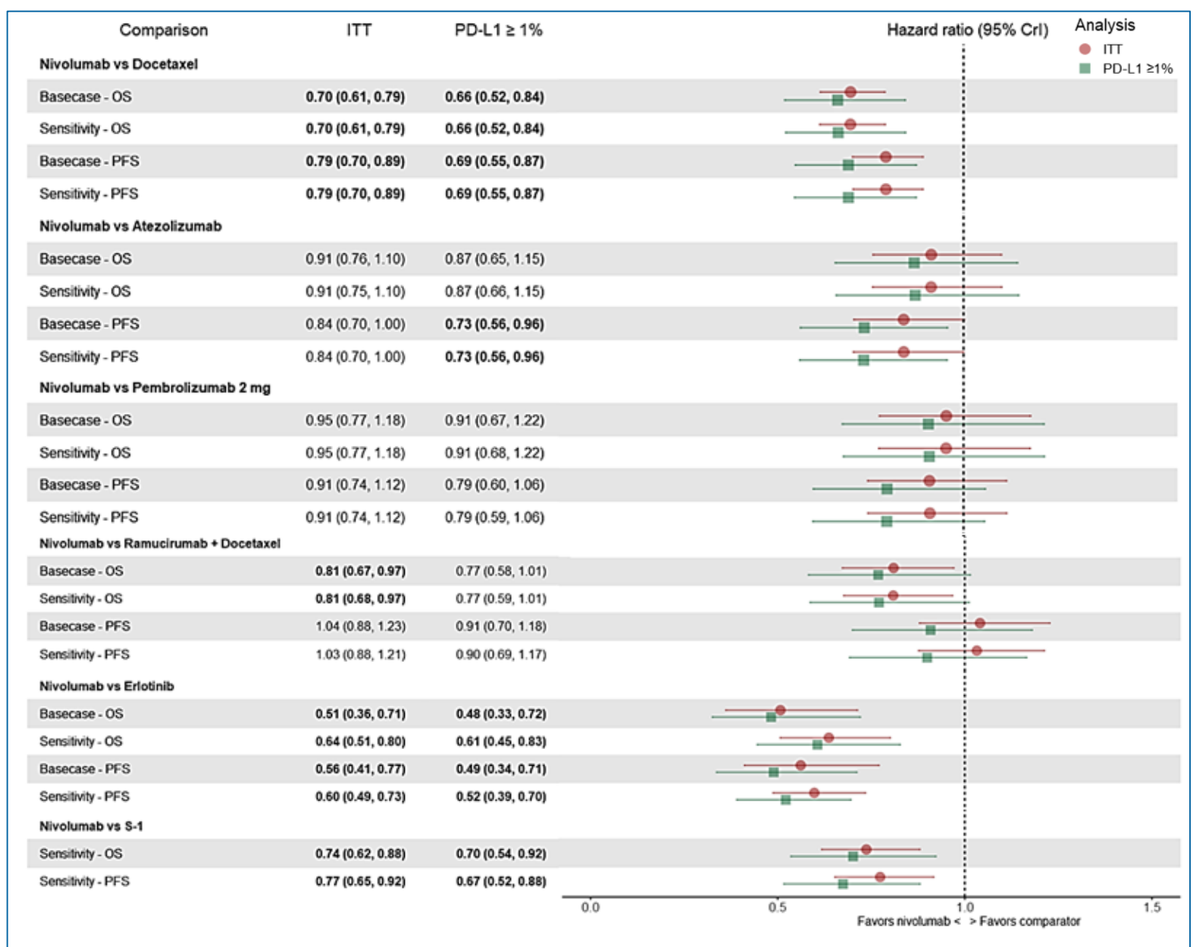


Trials / interventions highlighted in **orange** were only included in the context of a sensitivity analysis.

Results

- A total of 138 citations evaluating 77 RCTs were included in the evidence base **(Figure 1)**. Of these,13 RCTs were deemed suitable for the NMA **(Figure 2)**:
  - **Base case analysis:** CheckMate 017, CheckMate 057, CheckMate 078, OAK, POPLAR, KEYNOTE-010, REVEL, and TAILOR.
  - **Sensitivity analysis:** Base case plus EMPHASIS, DELTA, I4T-JE-JCVG (providing direct evidence), East-Asia S1 and HOT1002 (providing indirect evidence).
- **Figure 3** shows the estimated HRs for OS and PFS from the NMA within the overall and PD-L1 ≥1% populations, for both the base case and the sensitivity analyses.
  - Nivolumab improved OS versus erlotinib (HR: 0.51 [95% CrI: 0.36-0.71]), ramucirumab+docetaxel (HR: 0.81 [95% CrI: 0.67-0.97]), and docetaxel (HR: 0.70 [95% CrI: 0.61-0.79]) in the overall population.
  - Nivolumab also improved PFS versus erlotinib (HR: 0.56 [95% CrI: 0.41-0.77]) and docetaxel (HR: 0.79 [95% CrI: 0.70-0.89]) in the overall population.
  - Estimated HRs for both OS and PFS favored nivolumab versus atezolizumab and pembrolizumab 2 mg/kg, but were not significant.
  - PD-L1 expression in the ICI trials
    - All patients were PD-L1 ≥1% in the KEYNOTE-010 trial, per the trial's patient eligibility criteria
    - Different immunohistochemistry assays were used to measure PD-L1 expression levels in the ICI trials; notably, the tests used to assess PD-L1 expression in the atezolizumab studies (OAK and POPLAR) may have been substantially different from the ones in the trials of nivolumab (the CheckMate trials) and pembrolizumab (KEYNOTE-010), as described in the report from the Blueprint study.[11]
    - Within the PD-L1 expressing population, the NMA results for OS and PFS were generally consistent with the overall population analyses. Results from the sensitivity analyses were also in line with those from the base case analysis.
- **Table 1** shows the incidence of grade 3-5 TRAEs as reported in the included trials. The NMA results suggested that nivolumab was safer than all comparators in terms of grade 3-5 TRAEs. Estimated RRs were similar between the current NMA and Armoiry 2018, as shown in **Table 2**.

Figure 3. Results from the network meta-analysis (overall and progression-free survival)



All patients were PD-L1 ≥1% in KEYNOTE-010 (pembrolizumab) per the trial's patient eligibility criteria. All bolded values are statistically significant at the 0.05 significance level. The values in parentheses are 95% credible intervals.
CrI, credible interval; ITT, intention-to-treat; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival.

Table 1. Grade 3-5 treatment-related adverse events reported in the included trials

Trial	Arm 1	Safety population	Grade 3-5 TRAEs, n (%)	Arm 2	Safety population	Grade 3-5 TRAEs, n (%)
CheckMate017	Docetaxel	129	74 (57.4)	Nivolumab	131	9 (6.9)
CheckMate057	Docetaxel	268	144 (53.7)	Nivolumab	287	30 (10.5)
CheckMate078	Docetaxel	156	77 (49.4)	Nivolumab	337	39 (11.6)
OAK	Docetaxel	578	248 (42.9)	Atezolizumab	609	90 (14.8)
POPLAR	Docetaxel	135	55 (40.7)	Atezolizumab	142	17 (12)
REVEL	Docetaxel	618	479 (77.5)	Ramucirumab + Docetaxel	627	526 (83.9)
KEYNOTE-010	Docetaxel	309	109 (35.3)	Pembrolizumab 2 mg	339	43 (12.7)

TRAE, treatment-related adverse event.

Table 2. Relative risks estimated from the network meta-analysis (grade 3-5 treatment-related adverse events)

Intervention	Atezolizumab		Pembrolizumab 2 mg		Erlotinib		Docetaxel		Ramucirumab + docetaxel	
	Armoiry 2018	Current NMA	Armoiry 2018	Current NMA	Armoiry 2018	Current NMA	Armoiry 2018	Current NMA	Armoiry 2018	Current NMA
Nivolumab	**0.55 (0.38, 0.79)**	**0.50 (0.36, 0.70)**	**0.52 (0.34, 0.81)**	**0.44 (0.30, 0.66)**	**0.46 (0.29, 0.72)**	--	**0.18 (0.14, 0.25)**	**0.19 (0.14, 0.24)**	**0.17 (0.12, 0.23)**	**0.16 (0.12, 0.20)**
Atezolizumab			0.95 (0.66,1.38)	0.87 (0.61, 1.29)	0.83 (0.55,1.23)	--	**0.34 (0.28, 0.41)**	**0.37 (0.30, 0.45)**	**0.31 (0.25, 0.38)**	**0.31 (0.25, 0.39)**
Pembrolizumab 2 mg					0.87 (0.54,1.39)	--	**0.35 (0.26, 0.48)**	**0.43 (0.31, 0.57)**	**0.32 (0.23, 0.44)**	**0.36 (0.25, 0.48)**
Erlotinib							**0.41 (0.29, 0.58)**	--	**0.37 (0.26, 0.53)**	--
Docetaxel									**0.91 (0.85, 0.97)**	**0.83 (0.75, 0.94)**

Each cell represents the comparison (relative risk) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. The values in parentheses are 95% credible intervals.

Discussion

- Based on a robust SLR, this is the only NMA that includes the phase III CheckMate 078 clinical trial in the network, thereby incorporating the maximum amount of clinical data available for nivolumab efficacy and safety.
- With an evidence base that is synthesized as recent as April 2018, our NMA uses the longest follow-up data from key clinical trials such as CheckMate 017, CheckMate 057, OAK, POPLAR, and KEYNOTE-010.
- The current study is the only NMA that presents comparative results for both the overall NSCLC population and the subgroup of patients with PD-L1 ≥1%
- Although this NMA benefits a single common comparator for many studies in the network and other advantages, it is subject to the limitations of NMA, including differences in study designs and in patient populations in the network.

Conclusions

- NMA results suggest that nivolumab improved survival versus several relevant treatments for pretreated and immunotherapy-naïve advanced NSCLC and was similar to pembrolizumab and atezolizumab in comparable populations.
- Consistent with previous results from Armoiry 2018, the current NMA showed that nivolumab was safer than all comparators of interest in terms of grade 3-5 TRAEs.

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