Network Meta-Analysis (NMA) of immuno-oncology (IO) treatments for First-Line (1L) Advanced or metastatic Melanoma

CO62

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INTRODUCTION

- In the United States (US), an estimated 90,000+ new cases of melanoma were diagnosed in 2018, with advanced melanoma being responsible for most skin-cancer related deaths.[1-3] However, immune checkpoint inhibitors (ICIs) have transformed treatment outcomes in patients with advanced melanoma. [4-8]
- Key ICIs approved for the treatment of treatment-naïve patients with advanced, unresectable stage III/IV melanoma include: ipilimumab (IPI) 3mg/kg, nivolumab (NIVO) 3mg/kg, pembrolizumab (PEM) 2mg/kg, atezolizumab (ATZ) 840 mg, and combination regimen of NIVO 1mg/kg plus IPI 3mg/kg with United States [US] Food and Drug Administration [FDA] approvals of March 2011, December 2014, December 2015, July 2020, and January 2016, respectively.
- Based on data from the RELATIVITY-047 trial (NCT03470922), a new combination treatment consisting of a fixed-dose combination of relatlimab (RELA/BMS-986016), an anti-lymphocyte activation gene-3 (LAG-3) monoclonal antibody, and NIVO, an anti-PD-1 antibody, was approved by the US FDA for patients with unresectable or metastatic melanoma (March 2022) and by the European Medicines Agency (EMA) for first-line (1L) treatment of patients with advanced melanoma and a tumor cell PD-L1 expression of less than 1% (September 2022).[9]

OBJECTIVES

Using evidence identified from a systematic literature review (SLR), the objective of the study was to conduct an NMA of approved 1L IO treatment regimens in metastatic melanoma to assess the relative efficacy and safety of fixed-dose combination nivolumab + relatlimab (NIVO+RELA) in both an all-comers and PD-L1<1% population.

METHODS

Systematic literature review

- An SLR was undertaken to identify randomized controlled trials (RCTs) evaluating systemic therapies used for previously untreated unresectable or metastatic melanoma.
- Study selection criteria based on the Population, Intervention, Comparators, Outcomes, and Study design (PICOS) were used to guide study selection and search strategies to identify potentially relevant publications.
  - For the current research objectives, the results of this SLR were focused to the following key comparators in the NMA: NIVO 1 mg/kg + ipilimumab 3mg/kg (NIVO1+IPI3), PEM, and NIVO 3mg/kg (NIVO3) as presented in **Table 1**.
- Searches of Medical Literature Analysis and Retrieval System Online (MEDLINE), the Excerpta Medica database (EMBASE), and Cochrane Central Register of Controlled Trials from inception to November 2022 as well as relevant conference proceedings from 2017 to 2022 were conducted.
- The European Union Clinical Trials Register (EUCTR), Health Canada Clinical Trials Database, US National Institutes of Health Clinical Trial Registry, and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) were also searched to identify completed clinical trials not yet published that met the criteria with results available.
- Data on key study and patient characteristics along with related clinical outcomes were extracted as reported.

Table 1. Study selection criteria to identify trials for the SLR

Criteria	Inclusion Criteria for SLR	Eligibility criteria for analysis set
Population	Adult patients with previously untreated unresectable or metastatic melanoma	
Intervention	NIVO+RELA and any of the following relevant alternative interventions, evaluated as either monotherapy or in combination with other treatments, in the previously untreated setting: *Immunotherapies (IOs):* • Atezolizumab (PD-L1 inhibitor) • Ipilimumab (CTLA-4 inhibitor) • Nivolumab (PD-1 inhibitor) • Pembrolizumab (PD-1 inhibitor) *Targeted therapies:* • Binimetinib (MEK inhibitor) • Cobimetinib (MEK inhibitor) • Dabrafenib (BRAF inhibitor) • Encorafenib (BRAF inhibitor) • Trametinib (MEK inhibitor) • Vemurafenib (BRAF inhibitor) *Chemotherapies:* • Dacarbazine (DTIC)	NIVO+RELA and any of the following IOs in the previously untreated setting: • Nivolumab (PD-1 inhibitor) + Ipilimumab (CTLA-4 inhibitor) • Nivolumab monotherapy • Pembrolizumab (PD-1 inhibitor)
Comparators	• Placebo • Any intervention of interest/Any treatment that facilitates an indirect comparison	• Any intervention of interest
Outcomes	Studies must report at least one of the following *Efficacy outcomes:* • Overall survival (OS) • Progression free survival (PFS) • Time to progression (TTP) • Objective response rate (ORR) • Complete response (CR) • Partial response (PR) • Stable disease (SD) • Progressive disease (PD) • Duration of response (DOR) *Safety outcomes:* • Any grade adverse events (AE) • Grade 3-4 Adverse Events (AEs) • Overall Discontinuations • Discontinuations due to AEs (DAE) • Discontinuations due to treatment-related AEs (DTRAE) • Discontinuation due to PD or death Note: Safety and tolerability outcomes were extracted but were not otherwise part of the outcomes-specific *selection* criteria of studies. In other words, relevant studies from which safety and tolerability data were extracted needed to report on at least one efficacy outcome.	The following outcomes were of interest for the NMA: • OS • PFS • Grade 3/4 AEs • Grade 3/4 treatment-related AEs
Study Design	Randomized controlled trials (RCTs)	
Language	English-language publications	
Geographical regions	No limits	

Notes: Beyond the outcomes of interest listed in the table, the following outcomes were also extracted but not analyzed: duration of response, stable disease rate, progressive disease rate, discontinuations due to progressive disease or death. ***Abbreviations:*** NIVO, nivolumab; NMA, network meta-analysis; RCT, randomized controlled trial; RELA, relatlimab.

Feasibility assessment

- A feasibility assessment was conducted to gauge the appropriateness of proceeding with an NMA where this process evaluated the heterogeneity of the identified RCTs with respect to distribution of trial, patient and treatment characteristics to identify factors that may bias indirect estimates (i.e. effect modifiers).

Network meta-analysis

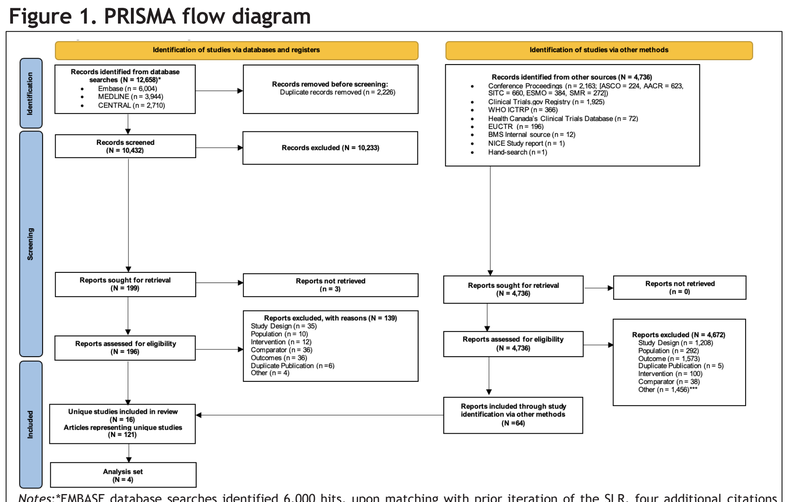
- Where results of the RCTs in the analysis set formed part of one evidence network and were deemed sufficiently similar for each population of interest, they were synthesized by means of a Bayesian NMA.
  - Efficacy outcomes analyzed were OS and PFS; as both efficacy outcomes were time-to-event (or survival) endpoints, tests of proportional hazards (PH) were conducted. Results are presented as hazard ratios (HRs) with associated 95% credible intervals (CrIs) with validation plots showing modeled treatment effects at the trial-level.
    - NMAs assuming constant HRs over time were conducted on the reported HRs.
    - NMAs allowing time-varying HRs were conducted using flexible fractional polynomial models using published Kaplan-Meier data.[10, 11]
    - For efficacy outcomes, the PD-L1 <1% subgroup was also analyzed.
  - Safety outcomes analyzed were all-cause and treatment-related grade 3/4 adverse events (AEs).
    - Analyses were conducted based on number of patients reporting an event and the number of patients in the safety analysis set. Results are presented as odds ratios (ORs) with associated 95% CrIs.

RESULTS

Evidence base

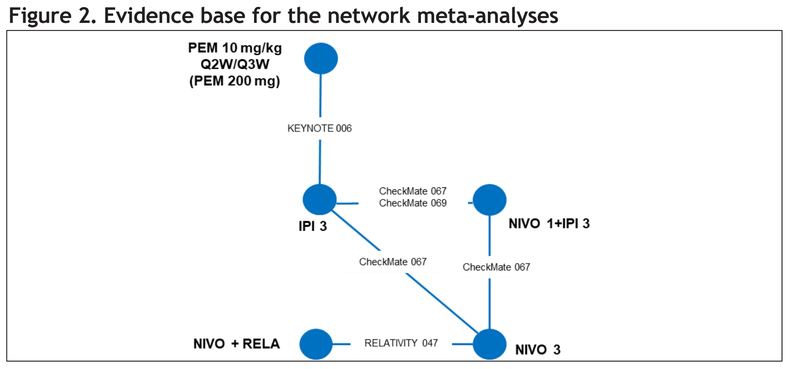
- The overall SLR identified 12,658 citations of which 121 citations reporting on 16 unique trials were included (see **Figure 1**).
- For the purposes of the current NMA, only the trials evaluating IOs (specifically, NIVO+RELA, NIVO1+IPI3, PEM, and NIVO3 monotherapy) in either the all-comers or PD-L1<1% population were deemed of interest. Thus, the evidence base for the NMA comprised of 4 trials as presented in **Figure 2**.
  - All four trials reported HRs (for constant HR NMA), Kaplan-Meier curves (for time-varying HR NMA) and efficacy data for both all-comers and PD-L1 <1% subgroups.
  - KEYNOTE-006 did not report on all-cause grade 3/4 AEs but all four trials reported treatment-related grade 3/4 AEs.

Figure 1. PRISMA flow diagram



Notes:*EMBASE database searches identified 6,000 hits, upon matching with prior iteration of the SLR, four additional citations were identified and added to the evidence base which were excluded as duplicate publications; *CCTR database searches identified 2,708 hits, upon matching with prior iteration of the SLR, two additional citations were identified and added to the evidence base which were excluded as duplicate publications; ***Publications excluded under "Other" evaluated irrelevant interventions and/or irrelevant populations; the exact number was not tracked due to the limitations of the grey literature sources that did not allow for easy export and tracking of decisions for each citation.

Figure 2. Evidence base for the network meta-analyses



Feasibility assessment

- The key result of the feasibility assessment was the higher proportion of stable brain metastases in the KEYNOTE-006 trial (close to 10%) compared to all other trials (<5%).
- Within the remainder of the network of IO-only trials considered here, no major differences were found with respect to patient characteristics, treatment characteristics or outcome definitions that would suggest effect modifiers may bias results of the NMAs.
- For both the OS and PFS networks, at least one trial had a PH violation which implied that the time-varying analyses are more appropriate. For ease of interpretation, the constant HR analyses are also presented.
- Trial level Kaplan-Meier (KM) plots overlayed with fitted NMA survival were generated as a validation that the NMA results reflect what is seen in the observed data.

Network meta-analysis

Efficacy analysis:

Overall survival:

- All-comers:
  - In the constant HR analysis, for the comparison of NIVO+RELA versus PEM and NIVO3, the point estimate favored NIVO+RELA, although the upper bound of the 95% CrI crossed one (HR [95% CI] 0.72 [0.50, 1.05] and 0.82 [0.67, 1.01], respectively).
  - For the comparison with NIVO1+IPI3, NIVO+RELA had similar risk of death (95% CrIs cross one) versus NIVO1+IPI3 yielding a HR of 0.96 [0.72, 1.27].
  - Results of the time-varying NMA were similar to the constant HR analysis where 95% CrIs crossed one; point estimate HRs for NIVO+RELA versus all comparators fell below one (i.e. favoring NIVO+RELA) with the exception of NIVO1+IPI3 at 18 months and onwards where the HR point estimate was above one.
- PD-L1 <1%:
  - In the constant HR analysis for the PD-L1<1%, for the comparison of NIVO+RELA versus PEM and NIVO3, the point estimate favored NIVO+RELA, although the upper bound of the HR 95% CrI crossed one (0.84 [0.46, 1.52] and 0.83 [0.64, 1.08], respectively).
  - For the comparison with NIVO1+IPI3, constant HR analysis was similar to that of the all-comers where NIVO+RELA showed similar survival compared to NIVO1+IPI3 with a HR of 1.14, [0.75, 1.72], although 95% CrIs were wide owing to the smaller sample sizes available in this subgroup.
  - Similar to the all-comers analysis, results of the time-varying analysis were consistent with those of the constant HR analysis with no statistically significant HRs for NIVO+RELA versus comparators and all point estimates below one with the exception of versus NIVO1+IPI3 6 months onwards where the HR was above one.

Table 2: OS, constant hazard ratio, all-comers (blue) and PD-L1 <1% (green)

Hazard Ratio (Fixed Effects)			
NIVO3	0.99 (0.58, 1.69)	**0.73 (0.53, 1.00)**	0.83 (0.64, 1.08)
1.14 (0.83, 1.55)	**PEM**	0.74 (0.43, 1.25)	0.84 (0.46, 1.52)
0.86 (0.70, 1.04)	0.76 (0.56, 1.02)	**NIVO1+IPI3**	1.14 (0.75, 1.72)
0.82 (0.67, 1.01)	0.72 (0.50, 1.05)	0.96 (0.72, 1.27)	**NIVO+RELA**

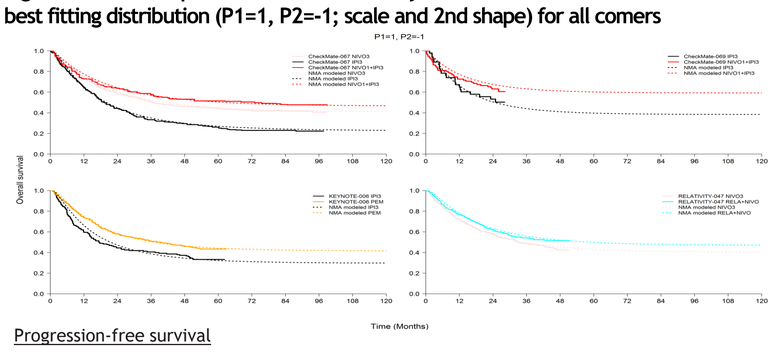
Note: Blue highlighted cells represent all-comers population HR (95% CrI) of row treatment versus column treatment; DIC: 12.59; Deviance: 6.6. Green highlighted cells represent PD-L1 <1% population HR (95% CrI) of column treatment versus row treatment; DIC: 10.74; Deviance: 5.73. All bolded values are statistically significant at the 0.05 significance level.

Table 3: OS, time-varying hazard ratio, all-comers (blue) and PD-L1 <1% (green), presented as HRs over time for RELA + NIVO versus comparators

RELA + NIVO vs.	Time-varying HR (95% CrI)					
	3 months	6 months	12 months	24 months	36 months	48 months
All-comers						
NIVO3	0.78 (0.57, 1.06)	0.82 (0.66, 1.01)	0.83 (0.67, 1.05)	0.84 (0.66, 1.08)	0.84 (0.66, 1.09)	0.85 (0.65, 1.10)
PEM	0.85 (0.50, 1.42)	0.74 (0.52, 1.06)	0.69 (0.48, 1.02)	0.67 (0.45, 1.02)	0.66 (0.43, 1.02)	0.66 (0.43, 1.03)
NIVO1 + IPI3	0.84 (0.56, 1.26)	0.93 (0.69, 1.26)	0.98 (0.72, 1.35)	1.01 (0.72, 1.43)	1.02 (0.72, 1.45)	1.02 (0.72, 1.47)
PD-L1 <1%						
NIVO3	0.67 (0.43, 1.03)	0.78 (0.59, 1.04)	0.87 (0.66, 1.16)	0.94 (0.66, 1.33)	0.98 (0.66, 1.44)	1.00 (0.66, 1.51)
PEM	0.93 (0.40, 2.14)	0.87 (0.48, 1.55)	0.83 (0.44, 1.54)	0.81 (0.37, 1.72)	0.79 (0.33, 1.82)	0.79 (0.32, 1.90)
NIVO1 + IPI3	0.91 (0.49, 1.70)	1.05 (0.69, 1.61)	1.17 (0.75, 1.80)	1.25 (0.74, 2.11)	1.29 (0.73, 2.30)	1.32 (0.72, 2.43)

Note: Cells shaded in grey indicate estimates based on model extrapolations; All bolded values are statistically significant at the 0.05 significance level; Abbreviations: CrI – credible interval; HR – hazard ratio. For all-comers: model presented is P1=1, P2=-1, scale and 2nd shape, fixed effect; For PD-L1 <1%: model presented is P1=0, P2=-0.5, scale and 2nd shape, fixed effect.

Figure 3: OS trial-specific KM curves overlayed with modeled survival curves from best fitting distribution (P1=1, P2=-1; scale and 2nd shape) for all comers



Progression-free survival

- All comers:
  - In the constant HR analysis, NIVO+RELA had improved PFS versus NIVO3 while for the comparison with PEM, the point estimate favored NIVO+RELA, although the upper bound of the 95% CrI crossed one.
  - For the comparison of NIVO+RELA versus NIVO1+IPI3, similar risk of progression was seen.
  - Results of the time-varying NMA were similar to the constant HR NMA versus NIVO3 and NIVO1+IPI3; however, results differed from the constant HR analysis versus PEM where NIVO+RELA showed improved risk of progression 6 months onwards. HR point estimates were below one versus NIVO3 at all time points and above one versus NIVO1+IPI3 from 6 months onwards.
- PD-L1 <1%:
  - For the PD-L1<1% population, results of the PFS NMA favored NIVO+RELA when compared with both NIVO3 (consistent with the all-comer results but with greater improvement in PFS) and PEM.
  - NIVO+RELA was comparable to NIVO1+IPI3, similar to the all-comers results.
  - For the time-varying analysis, comparative PFS were similar to those of the all-comer results but only favored NIVO+RELA over NIVO3 between 3 and 9 months, PEM at all time points, and had HR point estimates above one versus NIVO1+IPI3 at all time points.

Table 4: PFS, constant hazard ratio, all-comers (blue) and PD-L1 <1% (green)

Hazard Ratio (Fixed Effects)			
NIVO3	1.46 (0.89, 2.40)	**0.61 (0.45, 0.83)**	**0.68 (0.54, 0.86)**
1.03 (0.78, 1.36)	**PEM**	**0.42 (0.26, 0.69)**	**0.47 (0.27, 0.80)**
0.79 (0.65, 0.94)	0.76 (0.58, 1.00)	**NIVO1+IPI3**	1.11 (0.76, 1.63)
0.81 (0.67, 0.97)	0.79 (0.56, 1.10)	1.03 (0.79, 1.34)	**NIVO+RELA**

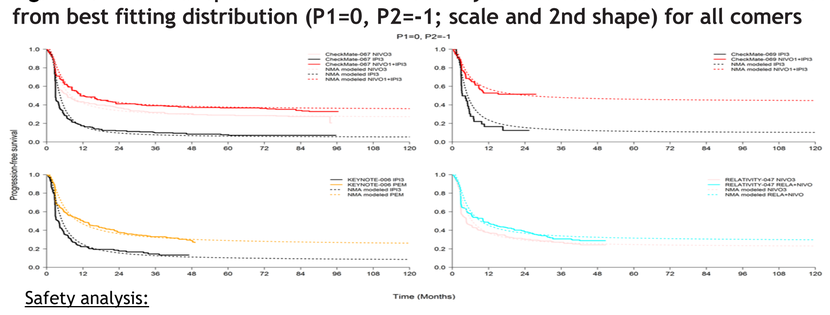
Note: Blue highlighted cells represent all-comers population HR (95% CrI) of row treatment versus column treatment; DIC: 11.63; Deviance: 5.65. Green highlighted cells represent PD-L1 <1% population HR (95% CrI) of column treatment versus row treatment; DIC: 11.37; Deviance: 5.37. All bolded values are statistically significant at the 0.05 significance level.

Table 5: PFS, time-varying hazard ratio, all-comers (blue) and PD-L1 <1% (green), presented as HRs over time for RELA + NIVO versus comparators

RELA + NIVO vs.	Time-varying HR (95% CrI)					
	3 months	6 months	12 months	24 months	36 months	48 months
All-comers						
NIVO3	**0.78 (0.65, 0.93)**	0.83 (0.68, 1.02)	0.86 (0.67, 1.10)	0.88 (0.67, 1.14)	0.88 (0.67, 1.16)	0.88 (0.67, 1.16)
PEM	0.79 (0.56, 1.12)	**0.67 (0.46, 0.98)**	**0.62 (0.40, 0.97)**	**0.60 (0.37, 0.97)**	**0.59 (0.36, 0.97)**	**0.59 (0.35, 0.97)**
NIVO1 + IPI3	0.99 (0.75, 1.30)	1.05 (0.78, 1.42)	1.09 (0.77, 1.55)	1.11 (0.75, 1.62)	1.11 (0.75, 1.65)	1.12 (0.74, 1.66)
PD-L1 <1%						
NIVO3	**0.65 (0.52, 0.82)**	**0.71 (0.54, 0.92)**	0.73 (0.53, 1.01)	0.75 (0.53, 1.06)	0.76 (0.53, 1.08)	0.76 (0.53, 1.09)
PEM	**0.44 (0.25, 0.77)**	**0.41 (0.21, 0.79)**	**0.39 (0.18, 0.84)**	**0.39 (0.17, 0.88)**	**0.38 (0.16, 0.89)**	**0.38 (0.16, 0.90)**
NIVO1 + IPI3	1.02 (0.68, 1.53)	1.03 (0.66, 1.60)	1.03 (0.60, 1.72)	1.03 (0.58, 1.80)	1.03 (0.57, 1.83)	1.03 (0.56, 1.84)

Note: Cells shaded in grey indicate estimates based on model extrapolations; All bolded values are statistically significant at the 0.05 significance level; Abbreviations: CrI – credible interval; HR – hazard ratio. For all-comers: model presented is P1=0, P2=-1, scale and 2nd shape, fixed effect; For PD-L1 <1%: model presented is P1=0, P2=-1, scale and 2nd shape, fixed effect

Figure 4: PFS trial-specific KM curves overlayed with modeled survival curves from best fitting distribution (P1=0, P2=-1; scale and 2nd shape) for all comers



Safety analysis:

- For all-cause grade 3/4 AEs, treatment with NIVO+RELA was associated with lower odds of events compared to NIVO1+IPI3, but no statistical difference versus NIVO3.
- For treatment-related grade 3/4 AEs, treatment with NIVO+RELA was associated with lower odds of event versus NIVO1+IPI3 but higher odds versus both NIVO3 and PEM.

Table 6: Overall (green) and treatment-related (blue) grade 3/4 adverse events fixed effects network meta-analysis results

Odds Ratios (Fixed Effects)			
NIVO3		**2.86 (2.06, 4.00)**	1.31 (0.98, 1.77)
1.05 (0.62, 1.78)	**PEM**		
4.83 (3.45, 6.83)	**4.61 (2.82, 7.53)**	**NIVO1+IPI3**	**0.46 (0.29, 0.72)**
2.08 (1.39, 3.14)	**1.99 (1.01, 3.87)**	**0.43 (0.25, 0.73)**	**NIVO+RELA**

Note: Blue highlighted cells represent treatment-related grade 3/4 adverse event OR (95% CrI) of row treatment versus column treatment; DIC: 19.62; Deviance: 9.63. Green highlighted cells represent overall grade 3/4 adverse events OR (95% CrI) of column treatment versus row treatment; DIC: 37.75; Deviance: 20.77. All bolded values are statistically significant at the 0.05 significance level. Grey highlighted cells reflect unavailability of comparative estimate.

DISCUSSION

- For the all-comer population in the constant HR analysis, NIVO+RELA had improved PFS versus NIVO3, and similar risk of death and progression versus NIVO1+IPI3.
  - Generally, results of the time-varying OS and PFS NMAs were consistent with the constant HR NMA.
- For the PD-L1<1% constant HR analysis, NIVO+RELA had similar risk of death versus NIVO1+IPI3; and improved PFS versus NIVO3 (consistent with the all-comers analysis) and PEM.
  - Results of the time-varying OS and PFS NMAs were generally similar to the constant HR NMA results.
- Safety analyses showed better odds of both treatment-related and all-cause grade 3/4 AEs for NIVO+RELA versus NIVO1+IPI3 but mixed results versus NIVO3 (no statistical difference for all-cause but statistical difference for treatment-related). Safety data for PEM was only available for treatment-related grade 3/4 AEs where it showed better odds of events versus NIVO+RELA.

LIMITATIONS

- Though this study conducted a thorough SLR to inform the evidence base, limitations exist with this process present in many SLRs; notably, the use of published data/conference abstracts, restriction to English language, and date of searches where new data may be available for some comparators.
- The following considerations should be taken into account when interpreting results of the NMA:
  - The NMA assumes that there are no important differences in effect modifiers between trials.
  - Given KEYNOTE-006 had a higher proportion of patients with brain metastases than other patients, comparisons to PEM may be biased.
  - For time-varying NMA, only the best fitting model is presented and is required to be the same across all included trials and may thus not reflect all complexities in the hazards over time.
  - The NMA utilized clinical trial data from RCTs which have specific eligibility criteria for trial inclusion, which may not be generalizable to the broader patient population.
  - Given that there are differences in dates that trials were conducted, this may lead to bias in the form of eligibility creep or differences in prior adjuvant or subsequent therapy. It was assumed that these differences (if they existed) do not act as treatment effect modifiers. Where data was available to assess this assumption, it was done so within the feasibility assessment and found no differences.

CONCLUSION

- NIVO + RELA provides an important dual-IO treatment option for 1L advanced melanoma and those with tumors expressing PD-L1<1% expression levels.
- Findings of the comparative analysis suggested that NIVO+RELA showed similar efficacy with a lower odds of grade 3/4 AEs compared with NIVO1 + IPI3 and a better PFS as compared to IO monotherapies such as NIVO3 and PEM.

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