SYSTEMATIC LITERATURE REVIEW AND NETWORK META-ANALYSIS OF IMMUNOTHERAPY, TARGETED AGENTS, OR COMBINATION REGIMENS IN TREATMENT-NAÏVE UNRESECTABLE OR METASTATIC MELANOMA

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Abstract: 114114

INTRODUCTION

- Immune checkpoint inhibitors and BRAF and MEK inhibitors have significantly improved treatment outcomes in patients with *BRAF*^{V600} mutation-positive metastatic melanomas.
- The phase III IMspire150 randomized controlled trial (RCT) was a double-blind, randomized (1:1), placebo-controlled, multicenter trial (NCT02908672) in 514 patients and was the first to show improved progression-free survival (PFS) with a triplet therapy (atezolizumab+cobimetinib+vemurafenib [ACV]) versus cobimetinib+vemurafenib (CV) in treatment-naïve (TN) unresectable stage IIIC or IV *BRAF*^{V600} mutation-positive (BRAF+) melanoma.[1] ACV is indicated for BRAF+ unresectable or metastatic melanoma patients.
- Given the lack of head-to-head clinical trials, the comparative effectiveness of ACV versus other guideline-recommended therapies in TN unresectable or metastatic melanoma is unknown.

OBJECTIVE

- To compare the efficacy and safety of ACV relative to other therapies for TN adults with unresectable or metastatic melanoma.

METHODS

Systematic Literature Review

- A systematic literature review (SLR) to identify RCTs was conducted in February 2021 to identify evidence for TN adults with metastatic or unresectable stage IIIc and/or stage IV melanoma. Treatments considered were those recommended by guidelines and included ACV, CV, nivolumab (as monotherapy or in combination with ipilimumab), pembrolizumab, dabrafenib in combination with trametinib, encorafenib in combination with binimetinib and prolgolimab.
- Outcomes of interest included overall survival, survival rate, PFS, time to progression, response rates, disease control rate, proportion who discontinued treatment due to adverse events (%$_{disc}$) and all grade 3/4 adverse events. Titles and abstracts of publications were reviewed in duplicate; included articles were reviewed in duplicate as well.

Feasibility Assessment

- A feasibility assessment was conducted for all endpoints, for both the overall population and the subpopulation of RCTs reporting on BRAF+ patients.
- Based on the available data, the final endpoints included were PFS, objective response rate (ORR) and %$_{disc}$.
- Whenever multiple publications were available for a single RCT, the most updated information was used.

Network Meta-Analysis

- NMAs using a Bayesian framework were conducted for the overall population based on the feasible networks identified from the SLR.
- Analyses were implemented using JAGS (version 4.3.0) called through R using R packages *rjags, gemtc*, and *bugsnet*. Additional packages using to output the results include *ggmcmc* and *ggplot2*.
- Vague or flat priors were used for study-specific baselines and treatment effect parameters.
- For PFS, hazard ratios (HRs) were estimated via linear models with identity link functions. For ORR and %disc, binomial distributions with complementary log-log functions were used to account for differences in follow-up across studies.
- HRs, corresponding to 95% credible intervals (CrIs), and the probability to be ranked either the best treatment option were evaluated.
- A subgroup analysis was conducted including only those RCTs who limited inclusion to patients who were BRAF+.

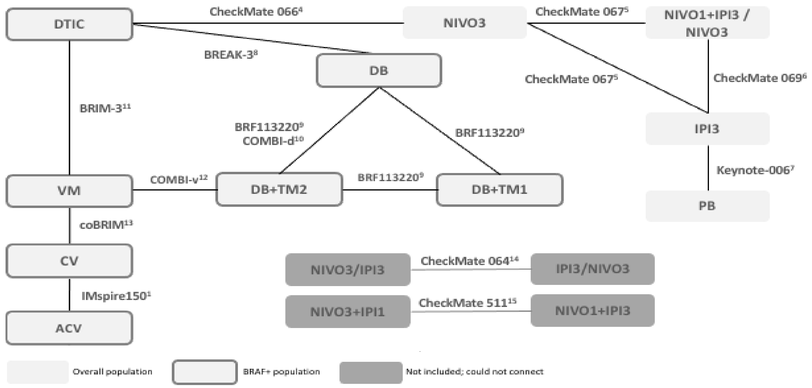
Sensitivity and Inconsistency Analyses

- For all analyses, both fixed effects and random effects were considered. For random effects models, NMAs with priors for between study variance with different parameter values were tested to ensure priors did not have significant influence on posterior distributions.
- The deviance information criteria (DIC) was used to compare the relative fit of competing models; models with lower DIC were preferred.
- Given that closed loops were present in the networks of evidence obtained in the analysis, the consistency assumption was assessed via implementation of an inconsistency model.

RESULTS

- The SLR identified a total of 13 unique RCTs which were included for the feasibility analysis and determined similar enough for comparison **(Figure 1**). Notable exclusions included the COLUMBUS trial[2] (patients were not required to be TN and results were not stratified by line of therapy), and the MIRACULUM trial[3] (patients were included for stage II – IV unresectable or metastatic melanoma).
- A network from the 11 connected RCTS was used to assess all three endpoints in the overall population.

Figure 1: Network of evidence



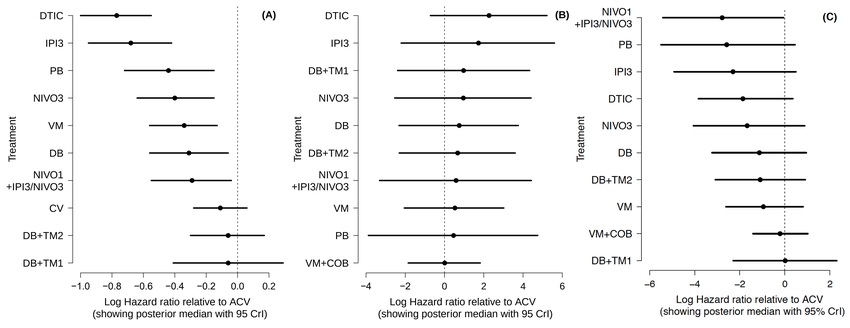
Progression-free survival, overall population

- ACV numerically prolongs PFS relative to all comparators (**Figure 2A**), using a fixed effects analysis. The result was statistically significant for most comparators, including NIVO1+IPI3/NIVO3 (HR [95% CrI]: 0.75 [0.58 – 0.97]).
- ACV was considered the most effective treatment in 51.9% of all simulations.

Objective response rate

- ACV was numerically superior in ORR relative to all comparators using a random effects for the analysis. This result was not statistically significant as compared to any treatment in the analysis (**Figure 2B**).
- ACV was ranked the best treatment option in 28.7% of all simulations.

Figure 2: Forest plot for ACV versus other treatments for PFS (A), ORR (B) & %$_{disc}$ (C), overall population



Note: values below 0 favor ACV and above 0 favor the comparator

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RESULTS (continued)

Proportion discontinued due to adverse events

- Using the random effects for the analysis, ACV was associated with better %$_{disc}$ and was numerically superior to all comparators with the exception of DB+TM1. A statistically significant difference was found versus NIVO1+IPI3/NIVO3 (HR [95% CrI]: 0.06 [0.00 – 0.94]) (**Figure 2C**).
- ACV is considered the most effective treatment in 39.1% of all simulations being the second most likely treatment to have the lowest %$_{disc}$.

BRAF+ subpopulation

- A network of seven RCTs was used to assess the evidence in the BRAF+ subpopulation (**Table 1**).
- ACV was numerically superior to all comparators and was statistically superior to DTIC, VM and DB for PFS.
- For ORR and %$_{disc}$, ACV was numerically superior to all comparators; no statistical differences were found.

Table 1: HR for ACV versus other treatments in the BRAF+ subpopulation

	PFS		ORR		%$_{disc}$	
Comparator	HR	95% CrI	HR	95% CrI	HR	95% CrI
DTIC	**0.46**	**0.37-0.58**	9.95	0.55-165.99	0.15	0.02-1.09
VM	**0.71**	**0.57-0.88**	1.75	0.15-19.22	0.36	0.08-1.78
DB	**0.73**	**0.57-0.94**	2.19	0.12-39.60	0.31	0.04-2.02
DB+TM2	0.94	0.74-1.19	1.99	0.12-34.55	0.33	0.05-1.96
CV	0.90	0.76-1.07	1.03	0.18-5.88	0.70	0.26-2.42
DB+TM1	0.94	0.66-1.34	2.74	0.11-69.38	0.99	7.85

Note: estimates in bold indicate statistical difference (α = 0.05) in comparison to ACV

LIMITATIONS

- Some treatments that may be used in TN patients with unresectable or metastatic melanoma were excluded due to SLR inclusion criteria; the population of the SLR, however, aligns with the study population of the RCT.
- Estimating hazard ratios from binary data modeled using binomial distributions resulted in wider CrIs; given the low levels of heterogeneity assessed, the wide credible intervals are more likely from the indirectness of the evidence and/or sparseness of data.

CONCLUSIONS

- ACV had the highest PFS benefit and a low rate of treatment discontinuation compared with other therapies evaluated in the NMA for TN unresectable or metastatic melanoma for both the overall TN and BRAF+ subpopulation.
- ACV is most likely to be ranked the best treatment option in terms of PFS and ORR versus other available treatments.

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ABBREVIATIONS

%$_{disc}$: proportion who discontinued treatment due to adverse events; ACV: atezolilzumab+cobimetinib+vemurafenib; BRAF+: *BRAF*^{V600} mutation-positive; CrI: credible interval; CV: cobimetinib+vemurafenib; DB: dabrafenib; DIC: deviance information criteria; DTIC: dacarbazine; HR: hazard ratio; IPI3: ipilimumab 3 mg; IPI3/NIVO3: ipilimumab 3mg followed by nivolumab 3 mg; NIVO1: nivolumab 1 mg; NIVO3: nivolumab 3 mg; NIVO3/IPI3: nivolumab 3 mg followed by ipilimumab 1 mg; NMA: network meta-analysis; ORR: objective response rate; PB: pembrolizumab; PFS: progression-free survival; RCT: randomized controlled trial; SLR: systematic literature review; TM1: trametinib 1 mg; TM2: trametinib 2 mg; TN: treatment-naïve; VM: vemurafenib

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