

Model-based meta-analysis (MBMA) of efficacy and safety of anti-PD1 compounds in melanoma

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Introduction

- Several immuno-oncology (IO) agents are currently approved for the treatment of melanoma
- No global evaluation of the treatment landscape is available due to the heterogeneity of trial designs and population

Objective:

- Quantify the efficacy and safety of the IO treatment landscape in melanoma
- Quantify the impact of important covariate effects.

Methodology

Data: 16 publicly available summary-level clinical trials

Drugs: anti-PD1, anti-CTLA4, anti-PD1+anti-CTLA4, chemo

endpoints:

- Efficacy: overall response rate – ORR (# 45)
- Safety: incidence of grade 3+ adverse events [AEs] (#26)

PD-L1 expression: 5% threshold, selection of the stratified arm when available

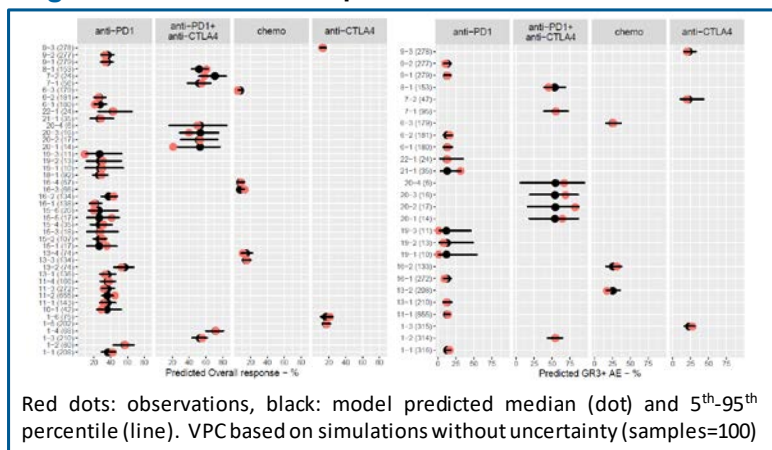
Modeling: non-linear mixed effects MBMA – Monolix 2018.

$$\text{logit}(\text{End}_{ijk}) = \text{DEF}_{ij} + \text{Cov}_{ik} + \eta_{1i} + \varepsilon_{ijk}$$

End_{ij} : probability of the endpoint (ORR or AE) of strata k of arm j of trial i ;
 DEF_{ij} : drug/drug class effect for arm j of trial i ; Cov_{ij} : covariate effect for strata k of trial i ; η_{1i} : random inter-trial variability; ε_{ijk} : residual variability – normalized by $\sqrt{N_{\text{obs}}}$

Results

Figure 1a and b: Forest plot-VPC for ORR and AE



- Final models correctly describe the data (Figure 1a and b)

- ORR and AE incidence are quantified per drug class

Based on this model:

- Efficacy of anti-PD1 and anti-PD1+anti-CTLA4 increases with % of PD-L1 positive patients (figure 2)
- Efficacy of all drug classes evaluated decreases with increasing line of therapy
- Anti-PD1 is the drug class associated with the lower incidence of AEs

Figure 2: Head-to-head simulation for efficacy and safety

Conclusion

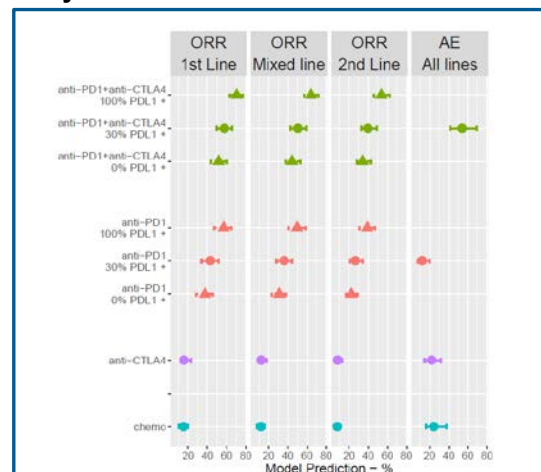
This MBMA framework enables quantification of:

- the efficacy and safety of IO and non-IO drug classes in melanoma
- the impact of PD-L1 expression and line of therapy on efficacy

This MBMA can be used to simulate head-to-head comparisons between compounds in development and currently available IO therapies in melanoma prior to conducting a clinical trial.

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Model simulations for 100 trials including 100 patients per arm.

Median and 5th-95th percentile interval are represented in the graph.