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A POPULATION MODEL FOR THE RESPONSE OF PATIENTS WITH ADVANCED MELANOMA TO THE TREATMENT BY IMMUNE CHECKPOINT INHIBITORS, BASED ON THE REAL-WORLD DATA

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ABSTRACT

Immune checkpoint inhibitors (ICI) have brought an unprecedented improvement in the treatment of cancer, especially advanced melanoma, increasing 5-year survival rates to > 40% with anti-PD1-based monotherapy and > 50% for combined therapy. Yet, nearly half of the patients do not respond to ICI treatment, emphasizing the need to identify patients that have higher probability to benefit from it. Unfortunately, no single biomarker has been found that can define the subpopulation of likely responders.

Despite numerous clinical trials of various ICI treatments, there is no clear picture which combination of patients' characteristic and treatment protocols will be optimal. The number of possible experimental arms is limited, and extensive analysis is needed, in order to answer the important clinical questions. Usually the analysis of the clinical data is carried out using simple statistical models, such as logistic regression and Cox survival models. Even when augmented by modern learning techniques, these approaches oversimplify the complicated trajectories of the diseases interacting with the immune system and the treatment, representing them as static distributions of a single value of interest (e.g., Time to Progression).

We suggest using instead the dynamic models (e.g., implemented by ODEs) for representing these interactions and predicting the individual response (e.g., size of tumour lesions) as it develops in time, under the patient-specific conditions. This naturally leads to the concept of population model, where the individual patients are represented by vectors of parameters of the dynamic models, following a populational distribution, with possible dependence on known covariates. We have used real-world dataset of patients with advanced melanoma treated by Pembrolizumab, to develop such population model, using the mixed-effects model formalism. The model was fitted using a modification of SAEM algorithm that allows application of advanced machine learning for modelling the effect of covariates.

We report the results of fitting the population model, and show examples of clinical insights and questions that can be answered using simulations of this model.