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A Machine-Learning Approach to Identify a Peripheral Prognostic Cytokine Signature via Nivolumab Clearance in Patients With Advanced Melanoma

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Background

- Immune checkpoint inhibitors have transformed the treatment landscape for melanoma, a solid tumor type that is known to elicit a strong immune response[1,2]
- Recent data suggest that serum cytokines could function as general prognostic indicators of outcome in patients with advanced melanoma[3]
  - A combination of multiple circulating cytokines into a composite biomarker may provide a more accurate measure than a single cytokine parameter[4]
  - However, there is no clear consensus regarding how or which of these cytokine features could be selected to form a reliable composite biomarker signature to estimate disease prognosis
  - A machine-learning approach is a promising tool to derive composite cytokine signatures to enhance the accuracy of survival prediction[5]
- Drug clearance is significantly associated with the clinical outcome of treatment with the programmed death-1-targeted monoclonal antibodies nivolumab (NIVO)[6] [**Figure 1**] and pembrolizumab[7]
  - The use of baseline clearance to directly predict outcome is not feasible, as the clearance value is determined from post-treatment pharmacokinetic (PK) analysis
  - The effect of NIVO exposure, after accounting for the impact of baseline clearance, shows no association between NIVO exposure and overall survival (OS),[6] thus suggesting NIVO clearance may be a surrogate prognostic biomarker for OS without a confounding effect related to exposure
- Here we investigate a novel machine-learning approach to identify a baseline composite cytokine signature based on the established association between NIVO clearance and OS in advanced melanoma

Methods

Patients and study design

- Primary analyses: phase 3 studies in previously untreated patients with advanced melanoma, CheckMate 066 (NCT01721772) and CheckMate 067 (NCT01844505) [**Table 1**]
- Model validation: phase 3 study in patients with advanced melanoma whose disease progressed following treatment with anti-cytotoxic T lymphocyte antigen-4 (CTLA-4), CheckMate 037 (NCT01721746) [**Table 1**]

Table 1. Summary of clinical studies

Study	Treatment	Dose and schedule	Patients[a] (treated patients), n	Analysis
CheckMate 003 (NCT00730639) Phase 1 dose escalation	NIVO	0.1–10 mg/kg, Q2W	106 [107]	Melanoma cohort; OS and clearance association (**Figure 1**)
CheckMate 037 (NCT01721746) Phase 3	NIVO	3 mg/kg, Q2W	232 [268]	Melanoma, patients progressed following anti–CTLA-4 therapy; test data set in machine-learning approach; NIVO arm used for OS and clearance association in **Figure 1**
	Dacarbazine or carboplatin and paclitaxel	Dacarbazine: 1000 mg/m^2, Q3W Carboplatin: AUC6, Q3W Paclitaxel: 175 mg/m^2, Q3W	57 [102]	
CheckMate 066 (NCT01721772) Phase 3	NIVO	3 mg/kg, Q2W	175 [206]	Melanoma; training data set in machine-learning approach
	Dacarbazine	1000 mg/m^2, Q3W	162 [205]	
CheckMate 067 (NCT01844505) Phase 3	NIVO	3 mg/kg, Q2W	293 [313]	Melanoma; training data set in machine-learning approach

[a]Patients missing cytokine or PK data were excluded from the training and test data sets of the machine-learning model.
AUC6, area under the curve 6.

Patient serum cytokine assay

- Cytokines in patient serum samples collected at baseline were measured using Luminex-based technology (custom MAP panel consisting of several multiplex human inflammatory MAP panels, Myriad® RBM)

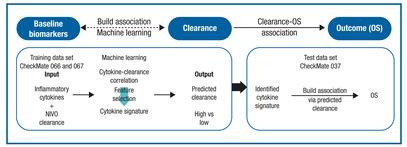
Machine-learning model

- Algorithms: random forest and Boruta
- Training data set: CheckMate 066 and 067 (n = 468) [**Figure 2**]
  - NIVO clearance was estimated from population PK analysis using a linear 2-compartment model, and median of baseline NIVO clearance (9.94 mL/h) was used to define high/low
- Model development and validation (**Figure 2**)
  - A panel of relevant cytokines was selected via Boruta algorithm
  - The random forest model was then built on selected cytokines and evaluated via cross-validation
  - The model was tested on an independent data set (CheckMate 037; n = 158)

Assessment of clinical association

- Association between predicted clearance level and OS was assessed using Kaplan–Meier analysis

Figure 2. Schematic overview of the machine-learning approach used to identify peripheral biomarkers using clearance as a bridge



Results

- A receiver operating characteristic curve analysis showed the out-of-sample performance for the machine-learning model with an average area under the curve of 0.76 (**Figure 3A**)
- The 2 × 2 confusion matrix that described the performance of the concordance between the actual clearance vs the predicted clearance showed a relatively high accuracy of 0.7 (**Figure 3B**)
- Selected cytokine features from the machine-learning model were based on measured importance (Boruta algorithm) [**Figure 4**]
- In the training data set (CheckMate 066 and 067)
  - Patients with low clearance of NIVO had significantly improved OS compared with patients with high clearance ($P < 0.0001$) [**Figure 5A**]
  - The patient group predicted to have low clearance of NIVO using the selected cytokine signature was also associated with significantly longer survival ($P < 0.0001$) [**Figure 5B**]

Figure 3. Development of a machine-learning model to identify baseline composite cytokine signature via NIVO clearance: (A) receiver operating characteristic curve analysis, (B) 2 × 2 analysis of actual clearance vs predicted clearance

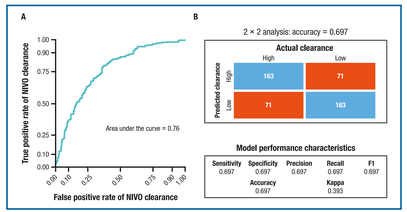


Figure 4. Selected cytokine features from the machine-learning model

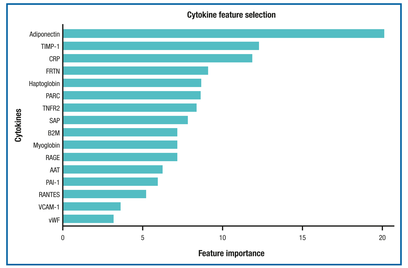
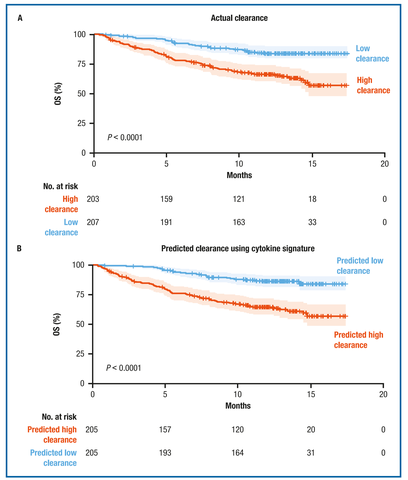


Figure 5. Correlation between predicted clearance from the composite cytokine signature and clinical outcome (OS) of NIVO in the training data set (CheckMate 066 and 067): (A) OS based on actual NIVO clearance data, (B) OS based on predicted NIVO clearance



- Similar correlations of survival with NIVO clearance were observed in the test data set (CheckMate 037) with actual clearance data and the selected cytokine signature clearance approach in patients whose disease progressed following anti–CTLA-4 therapy (**Figure 6A** and **B**)
- The association of low clearance with longer OS was observed in patients randomized to the study control arms and treated with chemotherapy (**Figure 7A** and **B**)

Figure 6. Validation of the cytokine signature from an independent clinical study in the test data set (CheckMate 037): (A) OS based on actual NIVO clearance data, (B) OS based on predicted NIVO clearance

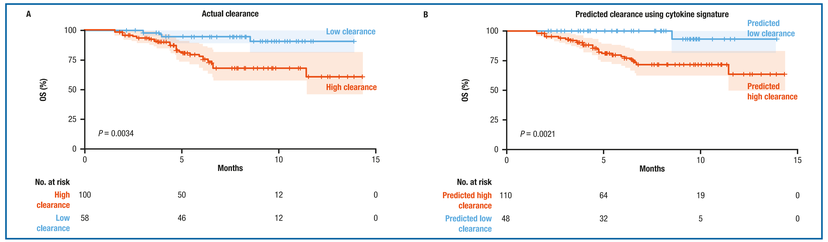
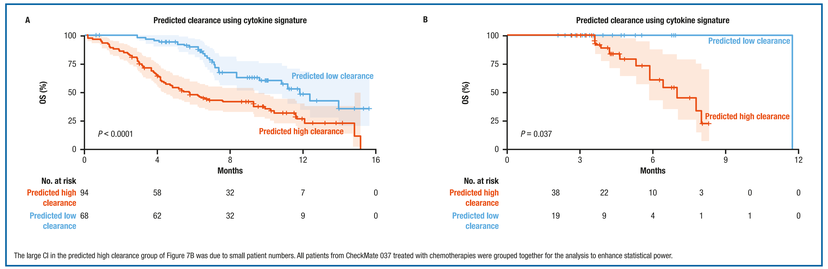
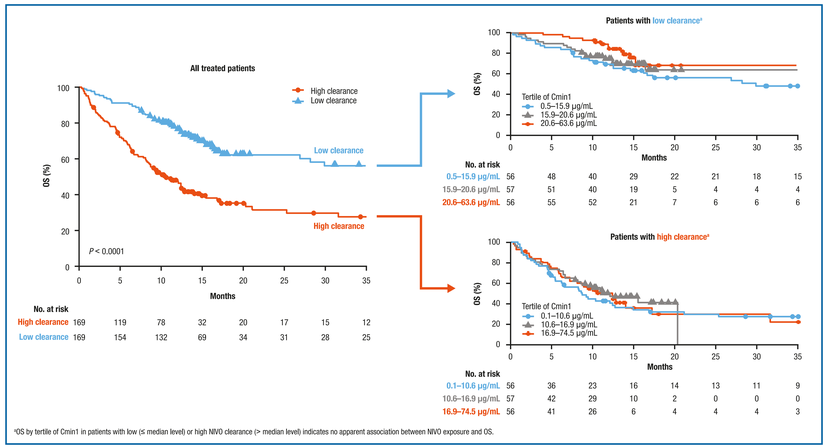


Figure 7. Evaluation of the selected prognostic cytokine signature in patients treated with chemotherapy (control arms): (A) OS based on predicted clearance in CheckMate 066 (dacarbazine), (B) OS based on predicted clearance in CheckMate 037 (dacarbazine or carboplatin and paclitaxel)



The large CI in the predicted high clearance group of Figure 7B was due to small patient numbers. All patients from CheckMate 037 treated with chemotherapies were grouped together for the analysis to enhance statistical power.

Figure 1. OS of patients with melanoma treated with NIVO in CheckMate 003 and 037 studies by NIVO clearance (at baseline)



[a]OS by tertile of Cmin1 in patients with low (≤ median level) or high NIVO clearance (> median level) indicates no apparent association between NIVO exposure and OS.

Conclusions

- Our study established a machine-learning model to characterize the relationship between baseline cytokine features and NIVO clearance in treatment-naïve or previously treated (post–CTLA-4) patients with advanced melanoma
- The selected cytokine signature was strongly associated with clinical efficacy for NIVO or chemotherapy, suggesting its potential utility as a prognostic biomarker
- These results demonstrate the potential to apply the prognostic composite cytokine signature in clinical studies as a potential stratification factor to balance the treatment arms; further study is warranted

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