The relationship between pre-operative ipilimumab and nivolumab pharmacokinetics and treatment outcome in locoregionally advanced urothelial cancer

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Introduction

- In the NABUCCO trial, patients with locoregionally advanced urothelial cancer (UC) received pre-operative ipilimumab and nivolumab [1-3].

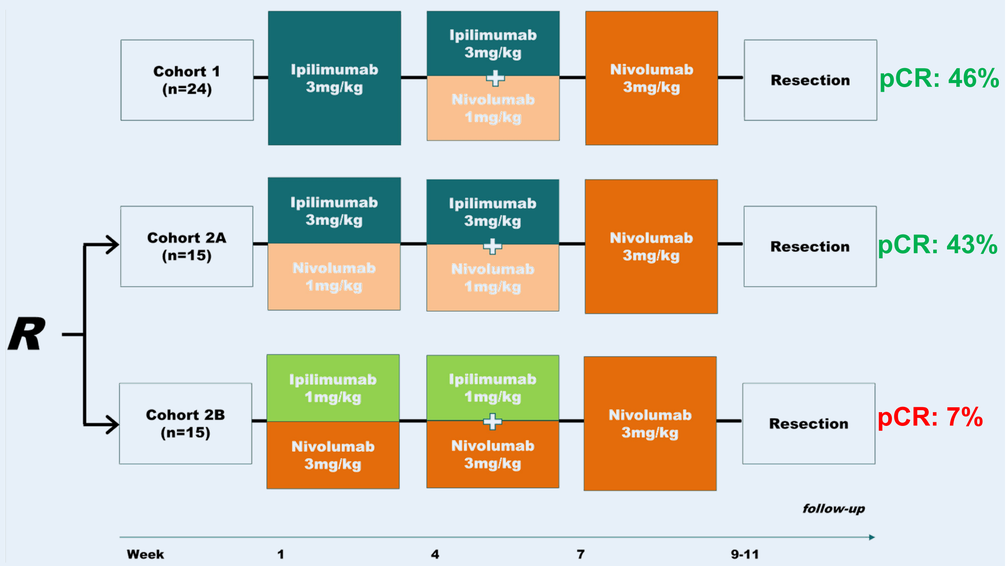

Figure 1. Treatment schedule of the NABUCCO trial. pCR: pathological complete response.

- The trial outcomes suggested the existence of a dose-response relationship for ipilimumab, while nivolumab dose did not appear to be related to response.
- In this treatment setting, the pharmacokinetics (PK) of ipilimumab and nivolumab and its relation with treatment response have not been defined yet.

Aims

1. Describe the PK of ipilimumab and nivolumab in patients with locoregionally advanced UC.
2. Assess the existence of clearance (CL)- and exposure-response relationships in this treatment setting.

Methods

- Ipilimumab and nivolumab serum concentrations were quantified in NABUCCO patient samples using a validated UPLC-MS/MS method [4].
- A joint population PK model for ipilimumab and nivolumab was developed by use of the $PRIOR subroutine in NONMEM (version 7.5) [5-7].
- Individual Bayesian estimates of baseline clearance (CL_0) and total area under the curve (AUC) were derived for both drugs and related to pathologic response at resection. This was done in exploratory plots and by a logistic regression model using equations 1-3:

$$COMBVAR = \frac{Individual\ AUC_{Ipilimumab}}{Population\ median\ AUC_{Ipilimumab}} * SF + \frac{1}{\frac{Individual\ CL0_{Nivolumab}}{Population\ median\ CL0_{Nivolumab}}} \quad \text{Eq. 1}$$

$$f = B_0 + B_1 * COMBVAR \quad \text{Eq. 2}$$

$$P_{Response} = \frac{\exp(f)}{1 + \exp(f)} \quad \text{Eq 3.}$$

Results

1. Population PK model

Table 1. Patient characteristics.

Characteristic	
Patients (n)	52
Samples (n)	139
Age (years (median, sd))	67.8 (7.6)
Male sex (n, %)	40 (76.9)
Baseline body weight (kg (median, sd))	80.6 (12.6)
Baseline performance status (n, %)	
0	38 (73.1)
1	14 (26.9)
Clinical stage (n, %)	
cT3-4aN0M0	28 (53.8)
cT1-4aN1-3M0	24 (46.2)

Table 2. Parameter estimates of the final population PK model.

Structural parameters	Final parameter estimate (RSE %)	
	Ipilimumab	*Nivolumab*
CL (mL/hour)	12.0 (4.4)	13.0 (4.8)
V1 (L)	3.95 (0.6)	4.27 (0.7)
Q (mL/hour)	28.7 (7.2)	34.6 (6.8)
V2 (L)	3.15 (2.5)	2.72 (2.4)
Inter-individual variability		
CL (CV%)	29.8 (22.6)	29.9 (24.3)
V1 (CV%)	39.0 (54.8)	50.0 (48.5)
CL : V1 (-)	0.0400 (64.1)	0.0432 (63.7)
CL_{IPI} : CL_{NIVO} (corr)	0.57 (30.8)	
Residual unexplained variability		
Proportional error (%)	23.6 (10.2)	16.2 (18.0)
Additional error (µg/mL)	1.5 (fixed)	1.5 (fixed)

2. PK-response relationships

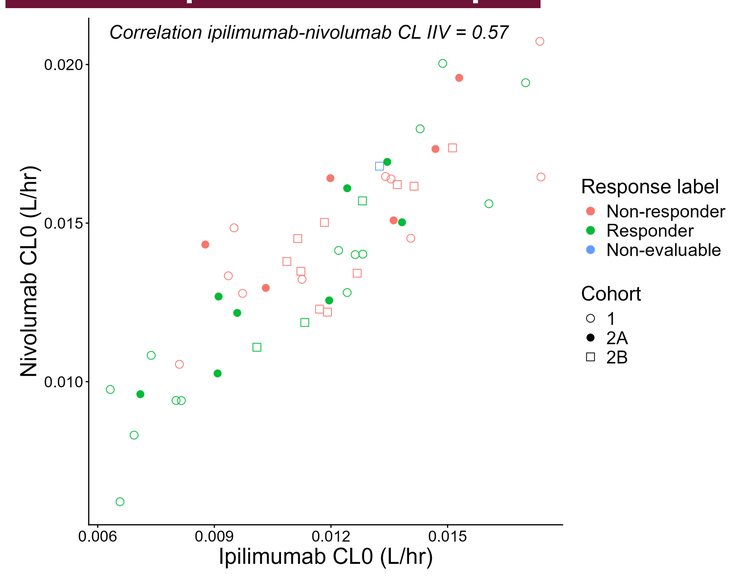

Figure 2. Relationship between ipilimumab and nivolumab CL_0, and response.

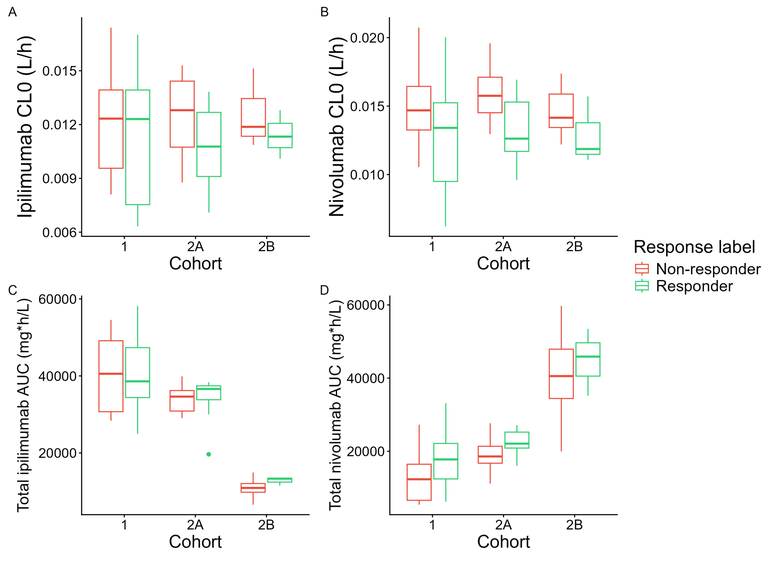

Figure 3. Individual estimates per cohort splitted by response label, for ipilimumab CL_0 (A), nivolumab CL_0 (B), total ipilimumab AUC (C) and total nivolumab AUC (D).

Table 3. Parameter estimates of the final logistic regression model.

Parameter	Estimate	RSE (%)	95% CI
Intercept (B_0)	-2.84	37.6	-4.93 to -0.75
Slope (B_1)	1.44	37.7	0.38 to 2.50

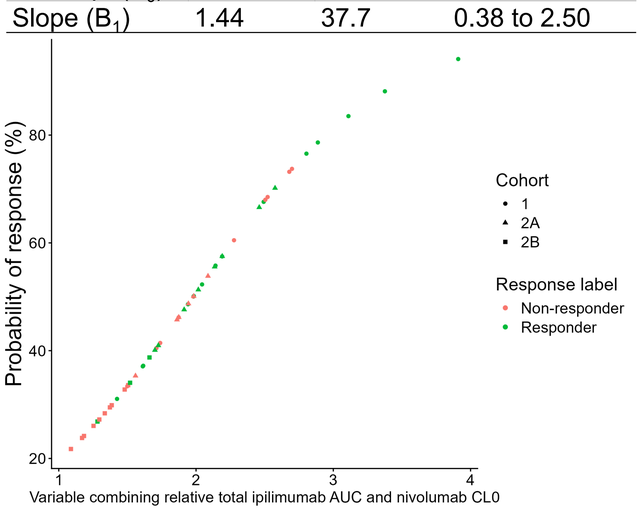

Figure 4. Relationship between the logistic regression model dependent variable combining the relative total ipilimumab AUC and inverse nivolumab CL_0, and the predicted probability of response.

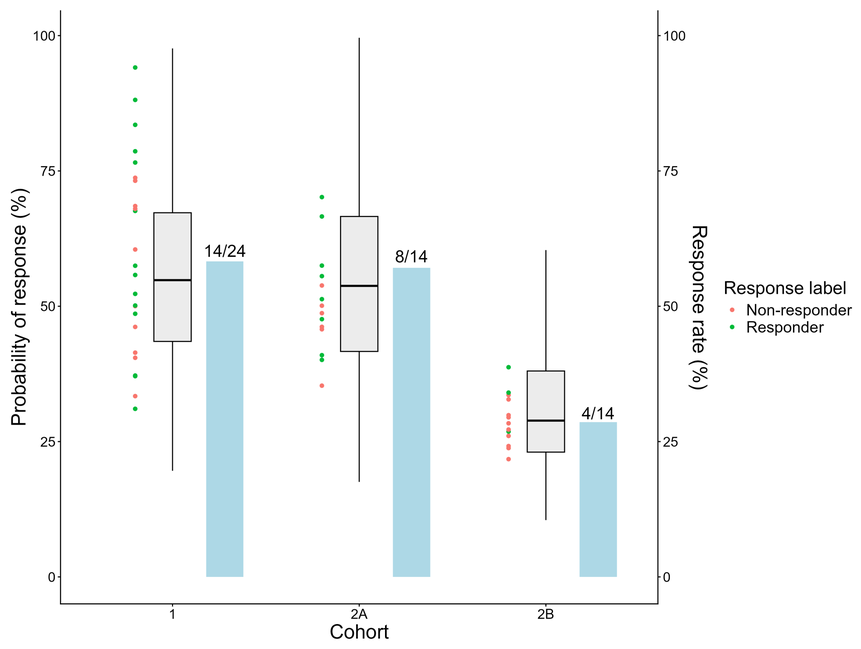

Figure 5. Model predicted probability of response (left y-axis) for NABUCCO trial patients colored by response label (dots) and simulated patients (25-75 boxplot), and the observed response rate (right y-axis) in the NABUCCO trial per cohort (blue bars (responders/total patients on top)).

Conclusions

- For the first time, the pre-operative PK of ipilimumab and nivolumab were described and, related to treatment response in patients with locoregionally advanced UC.
- Individual ipilimumab exposure and nivolumab CL_0 estimates were predictive for treatment response.
- Administration of a relatively high ipilimumab dose (such as 3 mg/kg) should be prioritized during dose selection of ipilimumab-nivolumab regimens in locoregionally advanced UC.
- A predicted probability of response, calculated with the help of an individual's PK estimates, could be part of treatment decision making.

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