Updated follow-up data and biomarker analysis of pre-operative ipilimumab and nivolumab in locoregional advanced urothelial cancer (NABUCCO)

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Introduction

- Pre-operative platinum-based chemotherapy improves 5-year (yr) overall survival (OS) in only 5% in muscle-invasive bladder cancer (MIBC)[1]
- NABUCCO is a phase 1b trial studying pre-operative combination checkpoint inhibition (CPI) in MIBC[2] (**Figure 1**)
- Currently, there are no biomarkers to predict response to pre-operative CPI
- Circulating tumor DNA (ctDNA) has potential for clinical utility
- Plasma ctDNA was undetectable after pre-operative treatment in 13/14 responders and in 4/10 non-responders (p=0.0088; presented AACR 2022)

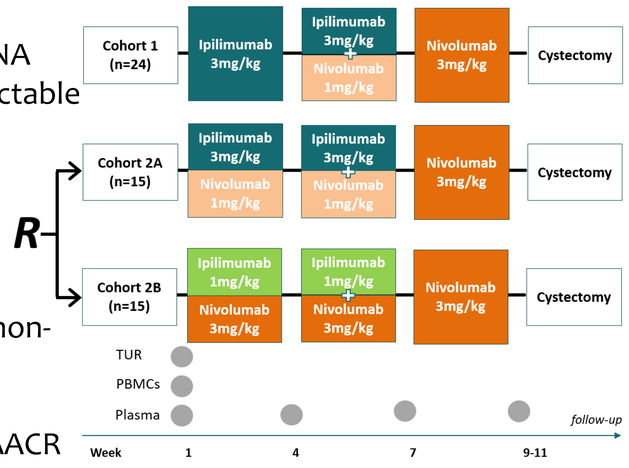


Figure 1. Study design NABUCCO trial (R: Randomization)

Study aims

- Provide clinical follow-up in cohorts 1 and 2
- Confirm pre-operative plasma ctDNA detection to predict response in cohort 2
- Provide an exploratory biomarker analysis to better understand the difference between ipi-low and ipi-high

Methods

- Cut-off date for updated survival analysis is March 2022
- PD-L1 positivity (CPS>10) was determined by immunohistochemistry (22C3 pharmDx test)
- Pathological complete response (pCR) was defined as ypT0/Tis/Ta/T1
- DNA from baseline formalin-fixed, paraffin-embedded (FFPE) tumor tissue and germline DNA (PBMCs) was used for whole-exome sequencing
- Plasma ctDNA detection: RaDaR® assay panel workflow (**Figure 2**)

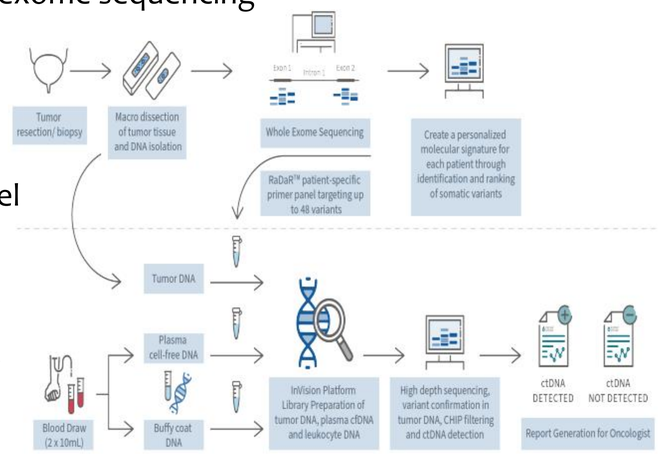


Figure 2. RaDaR workflow for plasma ctDNA detection

Results

PFS is numerically better in the ipi-high cohorts (**Figure 3a**)
OS is similar in ipi-high and ipi-low cohorts (**Figure 3b**)

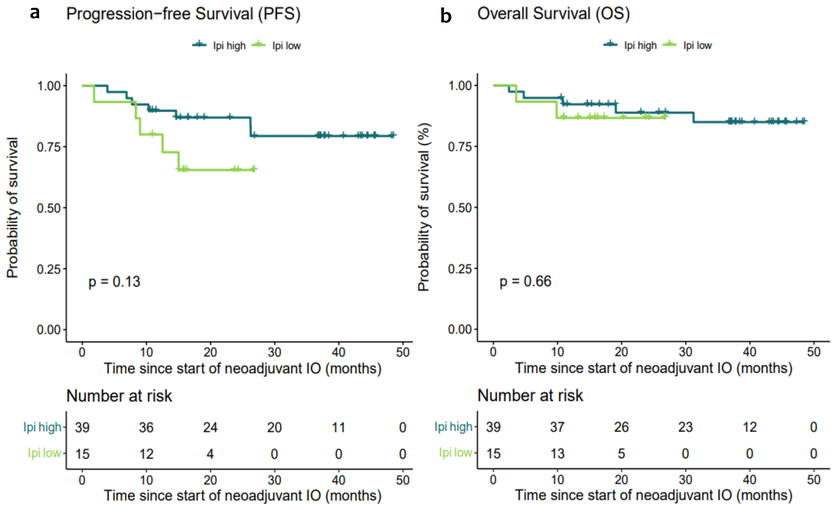
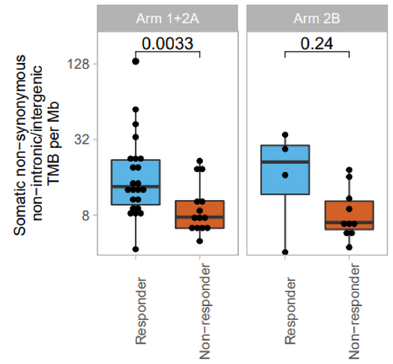


Figure 3. PFS (a) and OS (b) since start of neoadjuvant checkpoint inhibition in ipi high cohorts (cohort 1+2A) and the ipi-low cohort (cohort 2B)

Response rates based on PD-L1 expression are comparable between ipi-high (p=0.1691) and ipi-low (p=0.5594) (**Table 1**)

Table 1. Response rates based on PD-L1 expression	**Ipi-high (cohort 1+2A)**	**Ipi-low (cohort 2B)**
pCR PD-L1 positive	16/23 (70%)	3/7 (43%)
pCR PD-L1 negative	6/14 (43%)	1/7 (14%)



Responders to ipi-high show a higher tumor mutational burden (TMB) compared to non-responders (**Figure 4**)

Figure 4. TMB in responders versus non-responders in ipi-high and ipi-low

Absence of plasma ctDNA after treatment was associated with response and with favorable PFS in cohort 1 and 2 (**Figure 5**)

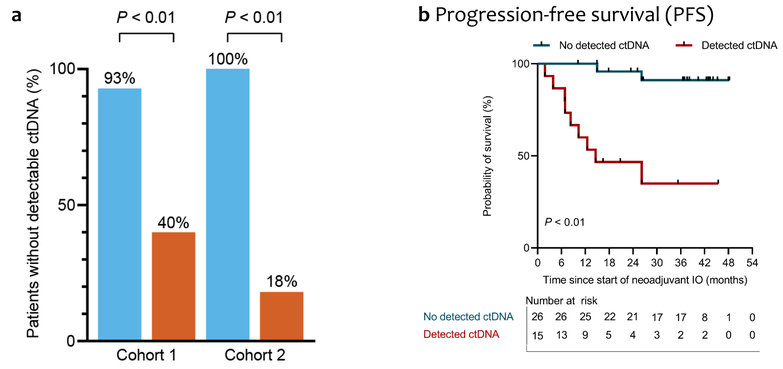


Figure 5. Plasma ctDNA in responders (blue) versus non-responders (orange) in cohort 1 and 2 (**a**) and PFS in detected vs no detected plasma ctDNA prior to surgery (**b**)

Conclusions

- Encouraging clinical outcome for ipi-high
- PD-L1 is not predictive for response upon ipi-high or ipi-low
- TMB is associated with response to ipi-high
- Clearance of plasma ctDNA positively associates with ipi/nivo response and PFS

References
[1] The ABC meta analysis collaboration, *Eur Urol* 2005
[2] Van Dijk et al, *Nat Med* 2020

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