INTRODUCTION

• The multi-center phase 2 PRADO trial (n=99) tested different surgical and adjuvant therapy strategies based on the pathologic response after neoadjuvant ipilimumab 1mg/kg and nivolumab 3mg/kg in clinical stage III melanoma patients [Figure 1].

RESULTS

• The pathologic response rate (pRR ≤50% residual viable tumor) was 72%, including 61% major pathologic responses (MPR: ≤10% viable tumor) [Figure 2].

• After a median follow-up of 28.1 months, the 2-year event-free survival (EFS) rate was 80% [Figure 2].

• Here, we report the pathologic response and EFS data of PRADO according to the IFN-γ signature and TMB, which were found to be independent biomarkers for response and survival in the previous phase 2 OpACIN-neo trial. 2

METHODS

• TMB and the IFN-γ gene expression signature (GES) were examined in baseline tumor biopsies by whole exome sequencing ([n=75]) and mRNA sequencing ([n=83]).

• Associations with pRR, MPR or EFS were examined by univariable Logistic or Cox regression analysis, yielding odds ratio’s (OR) and hazard ratio’s (HR), respectively.

• Cutoffs between IFN-γ or TMB high and low cohorts were calculated using ROC curves.

• P-values were calculated using the 2-sided T-test [t], Log-rank test [l], Chi square test [x] or Spearman’s [r].

• Patients with a high IFN-γ GES had a significantly higher pRR rate and MPR rate than patients with a low IFN-γ GES, and also a higher 2-year EFS rate [Figure 3, Table 1].

• The baseline IFN-γ gene expression score (GES) had a rate and a significantly lower risk of relapse [Figure 4, Table 3].

• IFN-γ GES and logTMB were not correlated (Figure 5).

• CONCLUSIONS

  • The baseline IFN-γ GES and TMB are biomarkers for pathologic response (<50% residual viable tumor) and MPR (<10% residual viable tumor) after neoadjuvant ipilimumab + nivolumab in stage III melanoma.

  • A high IFN-γ GES was associated with significantly improved EFS. However, a high TMB was not associated with improved EFS, possibly owing to the different response-driven surgical and adjuvant therapy strategies in PRADO.

REFERENCES:

1. Reijers et al, Nature Medicine 2022
2. Roosen et al, Nature Medicine 2021

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Fig. 1: PRADO trial design

Fig. 2: Pathologic response and EFS in total cohort

Fig. 3: Association IFN-γ GES and pRR, MPR or EFS

Fig. 4: Association IFN-γ GES and pRR, MPR or EFS

Fig. 5: Correlation between IFN-γ GES and TMB

Fig. 6: Response and MPR rate according to IFN-γ and TMB subgroups

Response and survival according to the interferon-gamma (IFN-γ) signature and tumor mutational burden (TMB) in the PRADO trial testing neoadjuvant ipilimumab and nivolumab in stage III melanoma