CheckMate 274: Exploratory Analysis of DFS According to Select Biomarkers in Patients With High-Risk Muscle-Invasive Urothelial Carcinoma Receiving Adjuvant Nivolumab

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CheckMate 274 Exploratory Analysis: Background

- Phase III CheckMate 274 trial evaluated adjuvant nivolumab vs placebo in patients with high-risk muscle-invasive urothelial carcinoma following radical resection[1]
  - Trial met both primary endpoints of improving DFS in ITT (HR: 0.70; *P* <.001) and PD-L1 ≥1% (HR: 0.55; *P* <.001) patient populations
  - Adjuvant treatment with nivolumab is now approved for patients with high-risk muscle-invasive urothelial carcinoma following radical resection[2]
- Clinical trial data from immunotherapy studies in urothelial carcinoma suggest predictive association with PD-L1, TMB, immune infiltration (CD8 and CD4), and activation signatures (eg, IFN-γ)[3-7]
- This exploratory biomarker analysis assessed clinical association of pretreatment tumor and immune features with DFS in patients with muscle-invasive urothelial carcinoma receiving adjuvant nivolumab in CheckMate 274 trial[8]

1. Bajorin. NEJM. 2021;384:2102. 2. Nivolumab PI. 3. Wang. Nature Commun. 2018;9:3503.
4. van Dijk. Nat Med. 2020;26:1839. 5. Zheng. Front Genet. 2021;12:764184.
6. Sharma. Lancet Oncol. 2017;18:312. 7. Galsky. Clin Can Res. 2020;26:5120. 8. Necchi. ESMO 2022. Abstr 1737MO.

CheckMate 274 Exploratory Analysis: Study Design[1]

- **Patient Population**
  - CheckMate 274 (n = 699)
    - Minimum follow-up: 11.0 mo
    - Median follow-up: 23.3 mo
  - Patient baseline characteristics similar between all-treated and biomarker-evaluable populations
  - All patient groups (all treated, biomarker evaluable, and biomarker not evaluable) had similar DFS

- **Exploratory Analyses**
  - RNA-seq*: gene signature (IFN-γ[2]; n = 323; 46%) and gene expression (CD4; n = 323; 46%)
  - WES: TMB† (n = 458; 66%)
  - IHC: CD8‡ (n = 445; 64%)
- **Continuous-Scale Analyses**
  - Cox proportional hazard models including biomarker, treatment arm, biomarker by arm interaction, and nodal status

*RNA-seq analysis of CD4 gene expression and IFN-γ gene signature performed using hybridization protocol to enrich for coding RNAs from total RNA sequencing libraries. †TMB measure by whole exome sequencing and calculated as number of somatic missense mutations in target region of each sample. ‡Performed using anti-CD8 antibody C8/144B.

1. Necchi. ESMO 2022. Abstr 1737MO. 2. Sharma. Lancet Oncol. 2017;18:312.

CheckMate 274 Exploratory Analysis: IFN-γ Signature, CD4 Gene Expression Predict Nivolumab Efficacy

- In *IFN*-γ gene signature score tertiles comparisons (n = 323)
  - *IFN*-γ gene signature score and DFS were positively associated (*P* <.001)
  - *IFN*-γ gene signature score varied with treatment effect (*P* = .013)
    - Higher *IFN*-γ gene signature score was associated with improved DFS with nivolumab but not placebo
- In *CD4* gene expression tertiles comparisons (n = 323)
  - *CD4* gene expression and DFS were positively associated (*P* = .001)
  - *CD4* gene expression varied with treatment effect (*P* <.001)
    - Higher *CD4* gene expression was associated with improved DFS with nivolumab but not placebo

Necchi. ESMO 2022. Abstr 1737MO.

CheckMate 274 Exploratory Analysis: CD8 and TMB Prognostic of Improved DFS

- In CD8 IHC score tertiles comparisons (n = 445)
  - CD8 digital IHC score and DFS were positively associated (*P* <.001)
  - Treatment effect did not appear to vary with CD8 IHC score (*P* = .153)
    - Higher CD8 infiltration associated with improved DFS for both nivolumab and placebo
  - Strong positive correlation was identified between *IFN*-γ gene signature and CD8 digital IHC score (r = 0.80)
- In TMB score tertiles* comparisons (n = 458)
  - TMB score and DFS were positively associated (*P* <.001)
  - Higher TMB score was associated with improved DFS with nivolumab, but evidence that it differed with placebo is limited (*P* = .081)
- Trend for higher *IFN*-γ signature, *CD4* gene expression, and CD8 digital IHC, but not TMB biomarker distribution, with PD-L1 ≥1% status

Necchi. ESMO 2022. Abstr 1737MO.

*TMB tertiles: low (<74 mutations), medium (≥74 and <172), and high (≥ 172).

CheckMate 274 Exploratory Analysis: Investigators' Conclusions

- Positive association found for DFS and biomarkers of preexisting antitumor immunity[1]
  - Gene signature for *IFN*-γ and gene expression for *CD4* found predictive of clinical benefit with adjuvant nivolumab[2]
  - CD8 infiltration was observed to be prognostic of DFS[2]
- Efficacy with nivolumab was positively associated with TMB and DFS[2]
- Investigators concluded that these results reinforce mechanism for benefit with immunotherapy[2]
  - Validation of prior findings in metastatic urothelial carcinoma to adjuvant setting
  - Additional research needed to confirm utility of these findings for clinical trial design and informing treatment decisions in real world

1. Chen. Nature. 2017;541:321. 2. Necchi. ESMO 2022. Abstr 1737MO.

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