

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

CCO Independent Conference Coverage*

of the ESMO 2022 Annual Congress; September 9-13, 2022; Paris, France

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Supported by educational grants from AstraZeneca; Bristol Myers Squibb; Exelixis, Inc.; Gilead Sciences, Inc.; and Merck Sharp & Dohme Corp.



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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 resection¹
 - Trial met both primary endpoints of improving DFS in ITT (HR: 0.70; $P < .001$) and PD-L1 $\geq 1\%$ (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 resection²
- 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 trial⁸

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CheckMate 274 Exploratory Analysis: Study Design¹

■ 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

*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.

■ 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

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

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 $\geq 1\%$ status

CheckMate 274 Exploratory Analysis: Investigators' Conclusions

- Positive association found for DFS and biomarkers of preexisting antitumor immunity¹
 - Gene signature for *IFN-γ* and gene expression for *CD4* found predictive of clinical benefit with adjuvant nivolumab²
 - CD8 infiltration was observed to be prognostic of DFS²
- Efficacy with nivolumab was positively associated with TMB and DFS²
- Investigators concluded that these results reinforce mechanism for benefit with immunotherapy²
 - 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

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