Assessment of a novel vaccine's safety and efficacy in high-grade glioma patients, using MHC I Dextramer® and mass-cytometry-based platform

Mueller S. *et al.* Mass cytometry detects H3.3K27M-specific vaccine responses in diffuse midline glioma. J Clin Invest. 2020, 130 (12) 6325-6337.

Background

Diffuse midline gliomas (DMGs), including diffuse intrinsic pontin glioma (DIPG), are fast-growing, high malignancy brain tumors that often occur in children and result in poor outcomes. H3.3K27M, a uniformly expressed neoantigen shared among patients with DMGs or DIPG, represents a valuable immunotherapy target.

This study is the first pilot trial, assessing a novel H3.3K27M-targeted peptide vaccine's safety and efficacy profile in pediatric patients with high-grade glioma.

Study description

Based on HLA-A*02.01$^+$ and H3.3K27M$^+$ status and adequate organ function, 29 newly diagnosed patients (aged 3-21 years) were enrolled in this study:

- **Stratum A:** 19 patients with DIPG
- **Stratum B:** 10 patients with non-pontine DMGs, including spinal cord DMGs.

The vaccine was administered in combination with the helper tetanus toxoid (TT) peptide and poly-ICLC every 3 weeks for 8 cycles followed by every 6 weeks. 9 patients with DIPG received concurrent oral dexamethasone treatment

HLA-A*02:01-H3.3K27 Dextramer® staining was used to monitor H3.3K27M epitope-specific CD8+ T cells in patient-derived PBMCs using flow and mass cytometry.

Results

- Administration of the H3.3K27M-specific vaccine was well tolerated with no grade-4 treatment-related adverse events (TRAEs)
- Mass cytometry-based detection of H3.3K27M-reactive CD8+ T cells was as sensitive as conventional flow cytometry using H3.3K27 Dextramer® staining (**Fig.1**)
- The expansion of H3.3K27M-reactive CD8+ T cells was associated with prolonged overall survival (OS): Median OS 16.3 months for immunological responders compared with 9.9 months for non-responders
- Dexamethasone treatment was associated with lower vaccine efficacy in patients with DIPG.

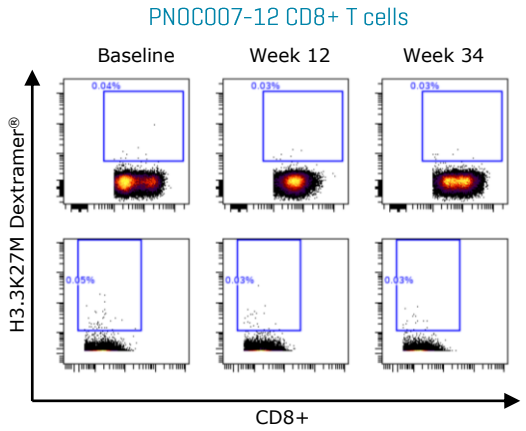

Fig.1. Mass cytometry-based detection of H3.3K27M-reactive CD8+ T cells is as sensitive as conventional flow cytometry using H3.3K27M Dextramer®. CD8+ T cells were detected from the same patient on both flow cytometry (*above*) and mass cytometry (*below*), exhibiting comparable percentages of overall CD8+ T cells that were identified as H3.3K27M-reactive.

Conclusions

- The H3.3K27M-specific vaccine revealed a safe regimen and potent efficacy in overall survival in patients with DMGs and DIPG
- Mass cytometry-based analysis combined with MHC I Dextramer® staining of H3.3K27-specific CD8+ T cells provides a powerful platform for precise cellular immune monitoring of vaccine responses
- MHC I Dextramer® reagents "exhibit higher affinity and specificity for epitope-specific CD8+ T-cell populations in comparison with conventional HLA tetramers"
- MHC I Dextramer® equally ensures higher resolution in both flow and mass cytometry workflows