Profiling of the neoantigen-specific T cell response after adjuvant TG4050 individualized therapeutic vaccination in a randomized phase I trial for locally advanced resected HPV-negative HNSCC

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Background:
In the phase I trial TG4050.02 (NCT04183166) evaluating TG4050 in resected, locally advanced HNSCC patients after (chemo)radiation, we showed that patients randomized to immediate vaccination with TG4050 had no relapse after a median follow-up of 30 months versus 3 relapses in the control arm randomized to watchful waiting.

Methods:
Patient-specific neoantigens were predicted from sequencing of tumor material and individualized TG4050 vaccines containing up to 30 neoantigens were manufactured. Patients received weekly doses of TG4050 for 6 weeks, followed by a maintenance period of one dose every 3 weeks for up to a total of 20 doses. In the control arm, the same vaccination regimen was initiated at relapse in combination with standard of care. Apheresis for collection of PBMC was performed at Baseline and 9 weeks after treatment initiation. Blood samples were collected longitudinally up to one year after the end of vaccination. We quantified T cell responses to vaccination by ex vivo IFN-γ ELISpot and pMHC class I tetramer analyses. Using phenotyping, scRNAseq and TCR sequencing, we characterized the CD8 T cells specific to neoantigens and compared them to CD8 T cells specific to viral antigens in the same patient.

Results:
Polyepitopic responses to vaccine neoantigens were detected by ex vivo IFN-γ ELISpot or pMHC class I tetramer analyses in the blood of patients from both treatment groups. These responses were maintained throughout treatment and persisted for over one year after the end of treatment. Vaccine neoantigen-specific CD8 T cells had an effector phenotype at all time-points analyzed, even after end of treatment. At the transcriptomic level, neoantigen-specific CD8 T cells resembled cells specific for the MVA vector. Both kinds of cells displayed higher expression of cytotoxic markers (GZMB, PRF1, GLNY) and markers associated with tissue-resident phenotype (ZNF683, CX3CR1) than CD8 T cells specific for CMV or influenza. TCR repertoire analysis showed that vaccine neoantigen-specific CD8 T cell responses were polyclonal and comprised both de novo responses and expansion of tumor-infiltrating T cell clones.

Conclusion:
Together, this translational data is consistent with the model in which TG4050 induces tumor neoantigen-specific cytotoxic T cell responses that prevent tumor recurrence.