A randomized phase II trial of TG4001 plus avelumab versus avelumab alone in recurrent/metastatic (R/M) Human Papilloma Virus (HPV)-16 positive anogenital cancers

AACR 2023
Poster CT045

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BACKGROUND

TG4001 is a vaccine using an attenuated and modified poxvirus (MVA) as a vector expressing the HPV-16 E6 and E7 proteins (rendered non-oncogenic) and interleukin-2. As a monotherapy, it was shown to achieve histological resolution and viral clearance in patients with cervical precancerous lesions (CIN 2/3, Harper DM et al. 2019). Immune checkpoint inhibitors targeting the PD1/PD-L1 axis like avelumab have made a breakthrough in advanced solid tumors, however, only a minority of patients experience durable responses. In a phase Ib/II single-arm study, the combination of TG4001 and avelumab demonstrated a clinically relevant tumor activity in heavily pre-treated patients with HPV-16 positive cervical, anal, oropharyngeal and genital cancers. Presence of liver metastases had a profound impact on outcome in terms of ORR and PFS. In patients without liver metastases an ORR of 32% and median PFS of 5.6 months was achieved. The treatment regimen was associated with changes in tumor microenvironment such as increase in immune infiltrates and expression of genes associated with activation of the immune system. Furthermore, increased expression of PD-L1 was observed which may be the basis of a synergy between TG4001 and avelumab (Le Tourneau et al., 2020).

STUDY DESIGN

The current part of the study is designed as a randomized open-label, two-arm trial evaluating the efficacy of the combination of TG4001 and avelumab versus avelumab alone (NCT03260023) .

➔ Patients are currently being recruited into two cohorts (A and B).

➔TG4001 is administered at a dose of $5x10^7$ pfu SC weekly for 6 weeks, every 2 weeks up to Month 6, and every 12 weeks thereafter.

➔Avelumab is given IV at 800 mg every 2 weeks starting one week after the first vaccine dose.

STUDY OBJECTIVES

PRIMARY

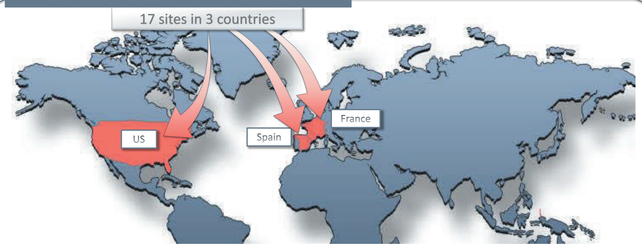
- Progression-Free Survival (PFS) according to RECIST1.1

CT-scan every 6 weeks during 9 months and every 12 weeks thereafter until progression

SECONDARY

- Overall Response Rate (ORR)
- Disease Control Rate (DCR)
- Overall Survival (OS)
- Percentage of early progressors for ancillary cohort (B)
- Safety
- Blood- and tumor-based immune parameters

PARTICIPATING COUNTRIES



KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria

❑ Metastatic or refractory/recurrent HPV-16+ cancer including cervical, vulvar, vaginal, penile and anal cancer

❑ HPV-16 positivity determined in central laboratory by nested PCR with HPV-16 specific probes and retest of negative results by sequencing.

❑ No more than one prior line of chemotherapy for recurrent/metastatic disease

❑ All levels of PD-L1 expression

❑ For patients with hepatic metastases
- no more than 3 hepatic lesions in total
- maximum size of hepatic target disease ≤ 30 mm according to RECIST 1.1

Key Exclusion Criteria

❑ Prior exposure to cancer immunotherapy including anti-cancer vaccines, any antibody targeting T cell co-regulatory proteins such as anti-PD-L1, anti-PD1, or anti-CTLA-4 antibodies

❑ CNS metastases

❑ ECOG Performance status ≥ 2

❑ Chronic treatment with systemic corticosteroids

ADAPTIVE DESIGN

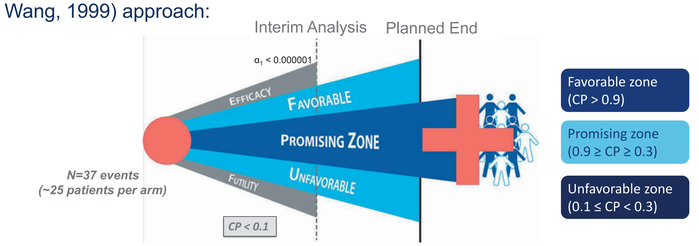
Statistical design for the main cohort (A)

The goal is to compare the efficacy of TG4001 in combination with avelumab compared to avelumab alone.

Primary endpoint: Progression-Free Survival (PFS) evaluated based on RECIST 1.1.

A two-stage group sequential design is used with log-rank test and boundary for efficacy and futility with Conditional Power (CP) at 10% with EAST 6.5® software. CP is the probability for significant result at final analysis, based on the data obtained at the interim analysis (Mehta CR, Pocock SJ, 2011).

At the interim analysis, sample size will be adjusted according to the following decision rules, using CHW (Cui, Hung and Wang, 1999) approach:



Interim analysis is planned after 37 PFS events corresponding to approximately 50 randomized patients allowing sample size re-estimation.

Statistical analysis for the ancillary cohort (B)

The percentage of progressors at Day 43 will be defined for the combination arm (TG4001 with avelumab) and for the monotreatment arm (avelumab only). Supported by the binomial probability calculations and given that the expected proportion of progressors is 80%, threshold will be calculated to obtain at least 80% of actual results observed.

STUDY STATUS

➔ With this randomized, controlled two-arm trial we aim to confirm the results observed in a phase Ib/II single-arm study.

➔ As planned per protocol, interim analysis has been performed in the main cohort (A) in September 2022 and results allowed to continue the trial with sample size adjustment.

➔ For final analysis, a maximum of 120 patients will be enrolled in the main cohort (A).

➔ Completion of recruitment is foreseen for H1 2024.

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ACKNOWLEDGEMENTS

The authors wish to thank all patients, families, caregivers and all technical staff involved in the project.

This trial is sponsored by Transgene.

Avelumab is provided by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945), as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.