485 LONG TERM RESULTS FROM A PHASE 1 TRIAL OF GEN-009, A PERSONALIZED NEOANTIGEN VACCINE, COMBINED WITH PD-1 INHIBITION IN ADVANCED SOLID TUMORS

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Background GEN-009 adjuvanted personalized cancer vaccine contains up to 20 neoantigens selected by ATLAS™, an ex vivo bioassay screening autologous T-cells for immune responses against both neoantigens and Inhibigens™. Inhibigen-specific T-cells suppress immunity, have been shown to accelerate tumor progression in mice, and are excluded from GEN-009. In cohort A, all patients immunized in the adjuvant setting with GEN-009 monotherapy developed immune responses. Ninety-nine percent of selected peptides were immunogenic: ex vivo CD4+ and CD8+ fluorospot responses specific for 51% and 41% of immunized peptides, respectively.[1] Six of 8 patients continue without progression with a median follow up >2 years.

Methods GEN-009 was administered to patients with advanced cancer who received standard-of-care (SOC) PD-1 inhibitor as monotherapy or in combination therapy during vaccine manufacturing. Five vaccine doses were administered over 24 weeks in combination with single agent anti-PD-1. Patients who progressed prior to vaccination received salvage therapy followed by GEN-009 in combination. Peripheral T-cell responses were measured by ex vivo and in vitro stimulated fluorospot assays. Circulating tumor (ct) DNA levels were evaluated in a subset of patients pre- and post-GEN-009 administration.

Results 15 patients received GEN-009 in combination with PD-1 inhibitor; 1 patient received GEN-009 monotherapy. Median number of neoantigens per vaccine was 14 (range 5–18). GEN-009-related adverse events were limited to vaccine injection site reactions, mild myalgias or fatigue. Sequential vaccination with GEN-009 had an additive effect on the magnitude of ex vivo T-cell responses, that persisted in some patients for 12+ months post first vaccine dose. An association between proportion of peptides eliciting significant cytokine responses and RECIST response is apparent. Epitope spread was detected in CD8+ T-cells from CPI-sensitive patients, but not refractory patients. Four patients who responded to PD-1 inhibition followed by disease stabilization then demonstrated further tumor reduction after GEN-009 vaccination. Seven of 9 CPI responsive patients are progression-free 7 to 18 months after first vaccine dose. Three of 7 CPI-refractory patients have experienced unexpected prolonged stable disease, with 2 PR and 1 SD after vaccination lasting up to 10 months. Plasma ctDNA kinetics mirrored RECIST responses in each tested patient; in some responders, all evidence of ctDNA disappeared, including non-targeted antigens.

Conclusions Vaccination with GEN-009 alone or in combination with anti-PD-1 was well tolerated. Preliminary data demonstrate induction of robust, durable neoantigen-specific immune responses and epitope spreading in the presence of PD-1 CPI. Broad immunity against tumor specific targets and encouraging patient outcomes support further study.

Trial Registration ClinicalTrials.gov identifier: NCT03633110

REFERENCES

1. Lam H, et al. An empirical antigen selection method identifies neoantigens that either elicit broad anti-tumor response or drive tumor growth. *Cancer Discovery* 2021 March;**11**(3):696–713.

Ethics Approval This study was approved by Western Institutional Review Board, approval number 1-1078861-1

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