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Clinical outcomes and immune responses in a phase I/II study of personalized, neoantigen-directed immunotherapy in patients with advanced MSS-CRC, GEA and NSCLC

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Background

Induction of a strong neoantigen-specific T-cell response may drive tumor lysis and clinical benefit in patients (pts) with poor responses to checkpoint inhibitors (CPI) alone.

Methods

Pts with advanced MSS-CRC (n=10; ≥ 2 lines of therapy), gastroesophageal adenocarcinoma (GEA; n= 10; ≥ 1 line of therapy), and NSCLC (n=2; post-CPI, ≥ 1 line of therapy) were treated with a patient-specific neoantigen-directed heterologous prime/boost vaccine leveraging 20 neoantigens selected using the EDGE^{TM} platform plus 30 mg SC ipilimumab and 480 mg IV nivolumab. Prime is a chimpanzee adenovirus (ChAd) and boosts are self-amplifying mRNA formulated in lipid nanoparticles and a second ChAd administration.

Results

22 pts have been treated. Treatment-related AEs and SAEs were mostly Grade 1-2 and reversible with no DLTs. All evaluated pts have a vaccine-induced, neoantigen-specific T-cell response typically evident after priming and further increased or maintained with boosts. Elicited T-cells were specific for multiple neoantigens (including epitope spreading), cytotoxic and infiltrated the tumor. The best response in 18 evaluable pts per RECIST includes 1 confirmed complete response (GEA; > 4 months [mo]), 4 stable disease (1 CRC >18 mo, 1 CRC > 9 mo, 1 CRC and 1 GEA up to 6 mo), 11 progressive disease (PD), and 2 no measurable disease. $CD8^+$ T-cell responses develop over the first 1-3 mo of vaccination and 8 pts progressed within the first 9 weeks, prior to expected treatment effect. Of 9 pts treated beyond RECIST PD, 4 pts did not have confirmed PD at the next scan. In 9 pts with MSS-CRC with at least one scan, 5 were progression-free per iRECIST beyond 6 mo and 4 of the 5 showed circulating tumor DNA (ctDNA) response (decrease ≥ 50% from baseline) indicating clinical activity in MSS-CRC. Enrollment continues; data will be updated.

Conclusions

Neoantigen-directed prime/boost immunotherapy in combination with CPI is well-tolerated and generates strong and persistent T-cells to multiple neoantigens. Increases in T-cells correlate with a novel pattern of response and clinical benefit characterized by a transient spike then decline in ctDNA, tumor markers, and tumor size, notably in pts with MSS-CRC.

Clinical trial identification

NCT03639714.

Legal entity responsible for the study

Gritstone bio, Inc.

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Disclosure

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