PERIPHERAL AND TUMORAL IMMUNE ACTIVITY IN THE EXPANSION PART OF THE FIRST-IN-HUMAN DUOBODY®-PD-L1×4-1BB (GEN1046) TRIAL

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Background DuoBody-PD-L1×4-1BB (GEN1046) is a class-defining, bispecific immunotherapy designed to induce an anti-tumor immune response by simultaneous and complementary PD-L1 blockade and conditional 4-1BB stimulation. Encouraging clinical activity and manageable safety were observed during dose escalation in the ongoing phase 1/2a trial in patients with advanced solid tumors (NCT03917381). We report exploratory pharmacodynamic analyses and potential biomarkers of response in an expansion cohort of patients with PD-(L)1-R/R NSCLC.

Methods Patients with metastatic/unresectable NSCLC who had multiple lines of prior systemic therapy, including a checkpoint inhibitor, received flat-dose DuoBody-PD-L1×4-1BB (100 mg) intravenously every 3 weeks. Immunophenotyping of peripheral blood and measurements of soluble immune mediators were evaluated in serial blood samples in cycles 1–2. Tumor PD-L1 and 4-1BB expression and additional immune markers were evaluated by immunohistochemistry in core needle tumor biopsy specimens collected before treatment and at cycle 2.

Results As of May 2021, 40 patients with PD-(L)1-R/R NSCLC were enrolled (median age, 63 years). Treatment with DuoBody-PD-L1×4-1BB elicited pharmacodynamic modulation of immune endpoints within the first 2 cycles. Induction of peripheral IFN-γ, CXCL9/10, and expansion of peripheral CD8+ effector memory T cells and activated NK cells were observed starting at cycle 1 (>2-fold from baseline) and maintained or increased through cycle 2. Based on 9 paired tumor biopsy samples, increased PD-L1 and 4-1BB expression and cytotoxic CD8+/GZMB+ cell density were detected following treatment. In a subset of patients with clinical response (n=5 confirmed PRs), a trend of greater induction of IFN-γ, CXCL9/10, and activated NK cells was observed vs nonresponders. Disease control rates were higher in patients who had progressed on prior anti-PD-1 therapy within 8 months (64% [16/25]) from the first dose of DuoBody-PD-L1×4-1BB. As expected, among patients with evaluable baseline tumors (n=26), most with any degree of tumor reduction (best change, <0%) harbored PD-L1+ tumors (≥1% tumor positive score; 7/10) and showed close spatial proximity between PD-L1+ and 4-1BB+ cells. Conversely, most patients without any degree of tumor reduction presented with PD-L1– tumors (12/16).

Conclusions In patients with NSCLC who progressed on PD-(L)1 therapy, DuoBody-PD-L1×4-1BB elicited pharmacodynamic effects consistent with its proposed mechanism of action. Relationships between disease control and PD-L1 tumoral expression, as well as time from last prior anti-PD-1

therapy, were observed. These findings support that patient selection and/or anti-PD-1 combination therapy may lead to improved clinical efficacy. Further analyses are ongoing and updated results will be presented.

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Trial Registration NCT03917381

Ethics Approval This trial is undertaken following full approval of the final protocol, amendments, informed consent form, applicable recruiting materials, and subject compensation programs by the Independent Ethics Committee/Institutional Review Board.

Consent Written informed consent, in accordance with principles that originated in the Declaration of Helsinki 2013, current ICH guidelines including ICH-GCP E6(R2), applicable regulatory requirements, and sponsor policy, was provided by the patients.

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