Background Neoantigens, tumor-specific antigens derived from the mutanome, elicit antitumor immune responses. The interim results of a phase I study (NCT04625205) evaluating a personalized, non-engineered, neoantigen-specific T-cell product (BNT221) targeting multiple neoantigens are presented.

Methods Nine patients with checkpoint- and, if applicable, BRAFi-resistant metastatic melanoma received BNT221, completing dose-escalation enrollment. Up to sixty immunogenic MHC-I- and MHCII-restricted neoantigens were selected with our RECON® bioinformatics platform for use in an ex vivo induction process (NEO-STIM™) to prime, activate and expand memory and de novo T-cell responses from both the CD4+ and the CD8+ T-cell compartment, using PBMCs collected via leukapheresis.

Two BNT221 doses (≥ 1 × 10^8 cells to ≤ 1 × 10^9 cells and >2 × 10^9 cells to ≤ 1 × 10^10 cells) were evaluated in a 3+3 escalation design. Endpoints included safety and determination of highest tolerable dose (primary) and efficacy per RECIST 1.1 (secondary). Patients were pretreated with lymphodepleting chemotherapy.

Drug product, peripheral blood and tumor samples were collected for immune analysis and sequencing to monitor the composition, functionality, persistence, and tumor trafficking of the induced neoantigen-specific T-cell responses.

Results BNT221 was well-tolerated. No dose-limiting toxicities were observed, with grade 3–4 toxicities post-infusion limited to hematologic toxicities from lymphodepletion. Seven patients showed stable disease as best overall response (12–36+ weeks). Of those, two patients showed tumor reductions at cutaneous and visceral sites and reported quality of life improvements.

All patients received a polyclonal drug product with neoantigen-specific, polyfunctional CD8+ and CD4+ T-cells of central- and effector-memory phenotype (range: 8–13 responses per product). A subset of clonotypes present in the drug product were detected up to six weeks post-infusion. To date, 106 neoantigen-specific clonotypes recognizing 19 different neoantigens across four patients have been identified. Of all reactive T-cell receptors (TCRs) characterized (n = 57), all TCRs but one, exclusively recognized the mutant epitope and the functional avidity ranged from 0.8nM – 8.5μM. Neoantigen-specific clonotypes were detected in post-treatment tumor through TCR sequencing analysis in one patient tested, for whom tumor reduction was observed post BNT221.

Conclusions In this first in human study, BNT221 as a single infusion therapy demonstrated a tolerable safety profile, product persistence, prolonged stable disease, and tumor reductions in patients with checkpoint inhibitor-resistant metastatic melanoma. Translational analysis shows that the generated products contain multiple highly functional tumor-specific T-cell populations against neoantigens. Further clinical investigation of BNT221 in combination with anti-PD-1 is warranted and currently underway.