769 INTERIM CLINICAL AND TRANSLATIONAL DATA FROM NTC-001, A PHASE I STUDY TO EVALUATE THE NON-ENGINEERED NEOANTIGEN-SPECIFIC T CELL PRODUCT BNT221 IN PATIENTS WITH ADVANCED OR METASTATIC MELANOMA

[1]Jessica SW Borgers, [2]Divya Lenkala, [2]Brian McCarthy, [2]Victoria Kohler, [2]Sebastian Hymson, [2]Emily Jackson, [2]Katya Esaulova, [2]Joong Hyuk F Sheen, [2]Olivia Finney, [2]Kristen Balogh, [1]Sebastian Klobuch, [1]Matthijs D Linssen, [1]Cynthia Nijenhuis, [2]Richard B Gaynor, [2]Mark DeMario, [1]John B Haanen, [2]Marit MVan Buuren*. *[1]Netherlands Cancer Institute, Amsterdam, Netherlands; [2]BioNTech US, Cambridge, MA, USA*

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 MHCI- 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 ($\geq 1 \times 10^8$ cells to $\leq 1 \times 10^9$ cells and $>2 \times 10^9$ cells to $\leq 1 \times 10^{10}$ 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.

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Ethics Approval This study was approved by the Central Committee on Research Involving Human Subjects (CCMO), NL72301.000.19.

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