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Personalized combination of neoadjuvant domatinostat, nivolumab (NIVO) and ipilimumab (IPI) in stage IIIB-D melanoma patients (pts) stratified according to the interferon-gamma signature (IFN-γ sign): The DONIMI study

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Background

Neoadjuvant (neoadj) IPI + NIVO induces high pathologic response rates (pRR 72-78%) in stage IIIB-D melanoma which is strongly associated with long-term relapse-free survival (RFS). Pts with a low baseline IFN-γ sign are less likely to respond. The class I histone deacetylase inhibitor domatinostat (DOM) increased intratumoral T cell infiltration and IFN-γ sign expression in melanoma. DONIMI tests neoadj combinations of NIVO ± IPI with DOM stratified according to IFN-γ sign from tumor biopsies.

Methods

This phase 1b study tested the safety/feasibility of neoadj NIVO ± DOM ± IPI in stage III RECISTv1.1 measurable melanoma. It also prospectively tested the IFN-γ sign for the first time, randomizing IFN-γ sign high pts to arm A (2 cycles NIVO 240mg q3w) or arm B (2 cycles NIVO 240mg + DOM 200mg BID, d1-14, q3w), and IFN-γ sign low pts to arm C (same treatment regimen as arm B) or arm D (2 cycles NIVO 240mg + IPI 80mg + DOM 200mg QD, d1-14, q3w). Surgery was planned after 6 wks. Adjuvant NIVO 480mg q4w or dabrafenib + trametinib (non-responding BRAFV600 mutated pts) started at week 12 for 52 wks.

Results

Between Jan 2020 - Apr 2021, 40 pts were enrolled (10 pts in each arm). Baseline characteristics were comparable. All treatment regimens were feasible as surgery was performed on time in all pts (wk 6 ± 1 wk). Gr 3-4 systemic treatment-related AEs (trAEs) during the first 12 wks occurred in 0% in arm A, 20% in arm B, 40% in arm C and 20% in arm D. Except for gr 2-3 DOM-related rash, no unexpected trAEs were observed. pRR was 90% in arm A, 80% in arm B (both IFN-γ sign high pts), 30% in arm C and 40% in arm D (both IFN-γ sign low pts). 2 pts in arm D developed distant metastases before surgery. At data cutoff (Jul 7, median FU 8.9 months), estimated 6-month RFS rate was 100% in IFN-γ sign high pts and 79.4% in IFN-γ sign low pts.

Conclusions

Neoadj NIVO ± DOM ± IPI appears safe and feasible. DONIMI shows prospectively the discriminative ability of the IFN-γ sign algorithm. It adequately identified pts who can benefit from NIVO ± DOM alone (IFN-γ high pts) vs pts who might need an alternative scheme (IFN-γ low pts). Standard DOM dosing (200mg BID d1-14) plus IPI + NIVO is currently being tested.

Clinical trial identification

NCT04133948.

Legal entity responsible for the study

Netherlands Cancer Institute (PI: Christian Blank).

Funding

4SC.

Disclosure

C.U. Blank: Financial Interests, Institutional, Advisory Board: BMS; Financial Interests, Institutional, Advisory Board: MSD; Financial Interests, Institutional, Advisory Board: Roche; Financial Interests, Institutional, Advisory Board: Novartis; Financial Interests, Institutional, Advisory Board: GSK; Financial Interests, Institutional, Advisory Board: AstraZenica; Financial Interests, Institutional, Advisory Board: Pfizer; Financial Interests, Institutional, Advisory Board: Lilly; Financial Interests, Institutional, Advisory Board: Genmab; Financial Interests, Institutional, Advisory Board: Pierre Fabre; Financial Interests, Personal, Advisory Board: Third Rock Ventures; Financial Interests, Institutional, Research Grant: BMS; Financial Interests, Institutional, Research Grant: Novartis; Financial Interests, Institutional, Research Grant: Nanostring; Financial Interests, Institutional, Research Grant: 4SC; Financial Interests, Personal, Ownership Interest: Immagene BV. A.M. Menzies: Financial Interests, Institutional, Advisory Board: BMS; Financial Interests, Institutional, Advisory Board: MSD; Financial Interests, Institutional, Advisory Board: Novartis; Financial Interests, Institutional, Advisory Board: Roche; Financial Interests, Institutional, Advisory Board: Pierre-Fabre; Financial Interests, Institutional, Advisory Board: QBiotics. R.P.M. Saw: Financial Interests, Institutional, Advisory Board: MSD; Financial Interests, Institutional, Advisory Board: Novartis; Financial Interests, Institutional, Advisory Board: QBiotics; Financial Interests, Institutional, Invited Speaker: BMS; Financial Interests, Institutional, Invited Speaker: Novartis. A.J. Spillane: Non-Financial Interests, Institutional, Advisory Board: QBiotics; Financial Interests, Personal, Other, fees for professional services: Stryker. B.A. van de Wiel: Non-Financial Interests, Institutional, Advisory Board: BMS. R.A. Scolyer: Financial Interests, Institutional, Other, professional services: QBiotics; Financial Interests, Institutional, Other, professional services: Novartis; Financial Interests, Institutional, Other, professional services: MSD; Financial Interests, Institutional, Other, professional services: NeraCare; Financial Interests, Institutional, Other, professional services: Amgen Inc; Financial Interests, Institutional, Other, professional services: BMS; Financial Interests, Institutional, Other, professional services: Myriad Genetics; Financial Interests, Institutional, Other, professional services: GSK. A.C.J. van Akkooi: Financial Interests, Institutional, Advisory Board: Amgen; Financial Interests, Institutional, Advisory Board: BMS; Financial Interests, Institutional, Advisory Board: Novartis; Financial Interests, Institutional, Advisory Board: MSD; Financial Interests, Institutional, Advisory Board: Merck-Pfizer; Financial Interests, Institutional, Advisory Board: Sanofi; Financial Interests, Institutional, Advisory Board: Sirius Medical; Financial Interests, Institutional, Advisory Board: 4SC; Financial Interests, Institutional, Research Grant: Amgen; Financial Interests, Institutional, Research Grant: Merck-Pfizer. G.V. Long: Financial Interests, Institutional, Advisory Board: Aduro Biotech Inc; Financial Interests, Institutional, Advisory Board: Amgen Inc; Financial Interests, Institutional, Advisory Board: Array Biopharma Inc; Financial Interests, Institutional, Advisory Board: Boehringer Ingelheim International GmbH; Financial Interests, Institutional, Advisory Board: BMS; Financial Interests, Institutional, Advisory Board: Highlight Therapeutics S.L.; Financial Interests, Institutional, Advisory Board: MSD; Financial Interests, Institutional, Advisory Board: Novartis Pharma AG; Financial Interests, Institutional, Advisory Board: Pierre-Fabre; Financial Interests, Institutional, Advisory Board: QBiotics Group Limited; Financial Interests, Institutional, Advisory Board: Regeneron Pharmaceuticals Inc. All other authors have declared no conflicts of interest.