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Three-year distant metastasis-free survival of the phase 3 NADINA trial comparing neoadjuvant nivolumab plus ipilimumab versus adjuvant nivolumab in resectable stage III melanoma

S. Witteveen¹, M.W. Lucas², A.M. Menzies³, M. Lopez-Yurda⁴, N. Maher⁵, B. van de Wiel⁶, R. Saw⁷, W. Van Houdt⁸, A. Torres Acosta⁴, M. Boers-Sonderen⁹, G. Hospers¹⁰, M.S. Carlino¹¹, J.W. de Groot¹², E. Kapiteijn¹³, K.P.M. Suijkerbuijk¹⁴, P. Rutkowski¹⁵, S.K. Sandhu¹⁶, A.A.M. van der Veldt¹⁷, G.V. Long¹⁸, C.U. Blank¹⁹

¹ Department of Immunology/Oncology, NKI-AVL - Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, ² Medical Oncology Department, NKI-AVL - Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, ³ Medical Oncology department-Suite 5/6, Melanoma Institute Australia, Wollstonecraft, Australia, ⁴ Biostatistics, NKI-AVL - Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, ⁵ Pathology, Melanoma Institute Australia, Wollstonecraft, Australia, ⁶ Pathology Department, NKI-AVL - Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, ⁷ Department of Melanoma & Surgical Oncology, Royal Prince Alfred Hospital, Camperdown, Australia, ⁸ Surgical Oncology Department, NKI-AVL - Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, ⁹ Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands, ¹⁰ Medical Oncology, UMCG - University Medical Center Groningen, Groningen, Netherlands, ¹¹ Department of Medical Oncology, Crown Princess Mary Cancer Centre Westmead, Westmead, Australia, ¹² Oncology Center Department, Isala Hospital, Zwolle, Netherlands, ¹³ Medical Oncology Dept., Leiden University Medical Center (LUMC), Leiden, Netherlands, ¹⁴ Medical Oncology Dept, UMC-University Medical Center Utrecht, Utrecht, Netherlands, ¹⁵ Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland, ¹⁶ Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia, ¹⁷ Medical Oncology Department, Erasmus MC - University Medical Center, Rotterdam, Netherlands, ¹⁸ Medical Oncology, University of Sydney, Sydney, Australia ¹⁹ Medical Oncology Dept, NKI-AVL - Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Background

Neoadjuvant ipilimumab + nivolumab (IPI+NIVO) followed by response-driven adjuvant treatment has shown at 2y follow-up superior event-free survival (EFS) and distant metastasis-free survival (DMFS) outcomes vs surgery and adjuvant NIVO in resectable stage III cutaneous melanoma. We report here the 3y EFS and DMFS of the NADINA trial.

Methods

As previously reported in detail, the NADINA trial included macroscopic stage III cutaneous melanoma patients randomized (1:1) to either neoadjuvant IPI 80mg + NIVO 240mg (2x, q3w), followed by surgery with response driven adjuvant therapy or surgery with adjuvant NIVO (480mg, 12x, q4w). Those with a major path response (MPR) did not receive adjuvant therapy. Cox regression modelling was used to analyze EFS and DMFS.

Results

At median FU of 36 months at data cutoff 30th of March 2026, the estimated 3y EFS was 72.9% for the neoadjuvant vs 50.0% for the adjuvant group (HR 0.42 [95% CI 0.31-0.59], p<0.0001). The 3y EFS for patients harboring a BRAFV600E/K mutation remained inferior as compared to BRAFwt with 68.9% vs 77.2% in the neoadjuvant arm and 46.9% vs 53.4% in the adjuvant arm. DMFS at 3y was 75.3% for the neoadjuvant vs 57.4% for the adjuvant group (HR 0.46 [95% CI 0.32-0.66], p<0.0001). In the neoadjuvant arm 3y recurrence-free survival and 3y-DMFS according to pathologic response were 91.3% and 93.6% for CR, 62.3% and 69.3% for near-CR, 87.5% and 87.5% for partial response and 43.0% and 39.4% for non-responders, respectively (p<0.0001 and p<0.0001). Across all subgroups, neoadjuvant remains superior to adjuvant. Updated grade ≥3 systemic treatment-related adverse events remained unaltered and were in 31.6% (n=212) vs 15.9% (n=176 pts receiving adj therapy) in the neoadjuvant and adjuvant arm, respectively.

Conclusions

At 3y FU neoadjuvant IPI+NIVO continues to show a highly significant superior estimated EFS and DMFS as compared to adjuvant NIVO. All subgroups benefit from neoadjuvant IPI+NIVO, although BRAFV600E/K mutant patients have a slightly worse outcome in both arms. With this longer FU, pathologic partial responders appear to achieve an equally good outcome as MPR patients.

Clinical trial identification

NCT04949113.

Legal entity responsible for the study

Christian Blank.

Funding

Bristol Myers Squibb.

Disclosure

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Kapiteijn: Financial Interests, Institutional, Advisory Board: Delcath, Lilly; Financial Interests, Institutional, Invited Speaker: Immunocore; Financial Interests, Institutional, Coordinating PI: BMS, Pierre Fabre, Delcath, Novartis. K.P.M. Suijkerbuijk: Financial Interests, Institutional, Advisory Board: BMS, AbbVie, Pierre Fabre; Financial Interests, Institutional, Other, honoraria for Safety Review Committee: Sairopa; Financial Interests, Institutional, Research Grant: Novartis, Tigenix, Bristol Myers Squibb, Philips, Genmab. P. Rutkowski: Financial Interests, Personal, Invited Speaker, honoraria for lectures: MSD, BMS, Pierre Fabre; Financial Interests, Personal, Advisory Board: MSD, BMS, Pierre Fabre, Merck, Philogen, Medison Pharma, Genesis Pharma, Immunome, Cogent; Financial Interests, Personal, Invited Speaker: Merck, Novartis, AstraZeneca, Genesis Pharma; Financial Interests, Personal, Other, member of IDMC: Erasca; Financial Interests, Institutional, Research Grant, research grant for ISS: Pfizer; Financial Interests, Institutional, Funding, research grant for institution: BMS; Non-Financial Interests, Member of Board of Directors: Polish Society of Surgical Oncology; Non-Financial Interests, Member of Board of Directors, President: Polish Oncological Society; Non-Financial Interests, Officer, Chair of International Affair Committee: ASCO; Non-Financial Interests, Leadership Role: ASCO; Non-Financial Interests, Member: ESSO. S.K. Sandhu: Financial Interests, Institutional, Advisory Board, I have served on advisory boards for MSD. The e contracts for my role are set up with the institution and the funds go to a research fund at Peter MacCallum Cancer Centre.: Merck Sharp and Dohme; Financial Interests, Institutional, Advisory Board, I have served on advisory boards for AstraZeneca. The contracts for my role as an advisor are set up with the institution and the funds go to a research fund at Peter MacCallum Cancer Centre.: AstraZeneca; Financial Interests, Institutional, Advisory Board, I have served on advisory boards for Novartis. The contracts for my role as an advisor are set up with the institution and the funds go to a research fund at Peter MacCallum Cancer Centre.: Novartis; Financial Interests, Institutional, Advisory Board, I have served on an advisory board for Merck Serono. The contracts for my service are set up with the institution and funds go into a research fund at the Peter MacCallum Cancer Centre.: Merck Serono; Financial Interests, Institutional, Advisory Board, I have served on an advisory board for SkylineDx. The contracts for my service are set up with the institution and funds go into a research fund at the Peter MacCallum Cancer Centre.: SkylineDx; Financial Interests, Institutional, Advisory Board, I have served on an advisory board for AbbVie. The contracts for my role are with the institution and funds go into a research fund at the Peter MacCallum Cancer Centre.: AbbVie; Financial Interests, Institutional, Invited Speaker, I have received honoraria for invited speaker role only which is paid to my institution. Funds go into a research fund at the Peter MacCallum Cancer Centre.: Janssen; Financial Interests, Institutional, Advisory Board, I serve on an advisory board for AdvanCell. The contracts for my role are with the institution and funds go into a research fund at the Peter MacCallum Cancer Centre.: AdvanCell; Financial Interests, Personal, Stocks/Shares: AdvanCell; Financial Interests, Institutional, Research Grant, My institution receives grant funding to run an investigator initiated trial that I lead.: Novartis, Genentech, Amgen, AstraZeneca, Merck Serono, Merck Sharp and Dohme; Financial Interests, Institutional, Research Grant, Pfizer are providing funding to my institution for the conduct of an investigator initiated clinical trial.: Pfizer; Financial Interests, Institutional, Research Grant, Senwha are providing funding to my institution for the conduct of an investigator initiated clinical trial.: Senwha; Non-Financial Interests, Other, I serve on the Independent Safety and Data Monitoring committee for 2 of Novartis sponsored studies and don't receive any compensation for this.: Novartis; Non-Financial Interests, Other, I serve on the steering committee for several Janssen sponsored trials and i do not receive compensation for this.: Janssen; Non-Financial Interests, Other, I serve on the steering committee for one AstraZeneca sponsored trial and I do not receive compensation for this.: AstraZeneca; Non-Financial Interests, Other, I serve on the steering committee for one Genentech sponsored trials and I do not receive compensation for this.: Genentech; Non-Financial Interests, Other, I serve on the steering committee for a Bristol Myers Squibb sponsored trial and I do not receive remuneration for this.: Bristol Myers Squibb; Non-Financial Interests, Principal Investigator, I am a principal investigator on several of Janssen sponsored studies and don't receive any remuneration for this.: Janssen; Non-Financial Interests, Principal Investigator, I am a principal investigator on several Novartis sponsored studies and don't receive any remuneration for this.: Novartis; Non-Financial Interests, Principal Investigator, I am a principal investigator on several of Genentech sponsored studies and don't receive any remuneration for this.: Genentech; Non-Financial Interests, Principal Investigator, I am a principal investigator on several of Bristol Myers Squibb sponsored studies and don't receive any remuneration for this.: Bristol Myers Squibb; Non-Financial Interests, Principal Investigator, I am the Principal Investigator for several AstraZeneca sponsored studies and am not remunerated for this.: AstraZeneca; Non-Financial Interests, Principal Investigator, I am a principal investigator on a MacroGenics sponsored study and don't

receive any remuneration for this.: MacroGenics; Non-Financial Interests, Principal Investigator, I am a principal investigator on a Regeneron sponsored study and do not receive any remuneration for this.: Regeneron; Non-Financial Interests, Principal Investigator, I am the Principal Investigator on several Merck Sharp and Dohme studies and I do not receive any remuneration for this.: Merck Sharp and Dohme; Non-Financial Interests, Principal Investigator, I am a principal investigator on an IO Biotech study and I do not receive any remuneration for this.: IO Biotech; Non-Financial Interests, Principal Investigator, I am principal investigator on an Evaxion sponsored study and I do not receive any remuneration for this.: Evaxion; Non-Financial Interests, Advisory Role: Daiichi Sankyo, Erasca, Synolo Therapeutics, MacroGenics. A.A.M. van der Veldt: Financial Interests, Institutional, Advisory Board: BMS, MSD, Sanofi, Ipsen, Novartis, Eisai, Pfizer, Roche, Pierre Fabre. G.V. Long: Financial Interests, Personal, Other, Consultant Advisor: BioNTech SE, Boehringer Ingelheim International GmbH, Bristol Myers Squibb, Evaxion Biotech A/S, Immunocore Ireland Limited, Merck Sharp & Dohme, Novartis Pharma AG, Regeneron Pharmaceuticals Inc, Scancell Limited, Fortiva Biologics (USA), Byondis B.V., Iovance Biotherapeutics, Strand Therapeutics Inc, Innovent Biologics (Suzhou) Co. Ltd, Replimune Inc.; Financial Interests, Personal, Advisory Board, Consultant Advisor: GI Innovation; Non-Financial Interests, Principal Investigator, GL is PI on over 40 clinical trials active or in follow up: GL is PI on over 40 clinical trials. C.U. Blank: Financial Interests, Institutional, Advisory Board: BMS, MSD, Roche, Novartis, GSK, AZ, Pfizer, Lilly, GenMab, Pierre Fabre, Hexal/Sandoz; Financial Interests, Personal, Advisory Board: Third Rock Ventures, Senya Therapeutics; Financial Interests, Personal, Stocks/Shares, TNF sensitiser: Flindr Therapeutics; Financial Interests, Institutional, Coordinating PI: NanoString, BMS, Novartis, 4SC; Other, Other, pending patent: WO 2021/177822 A1, US 2023/0114276 A1, EP 4114450 A1, WO 2023/022596 A1, EP 4387683 A1. All other authors have declared no conflicts of interest.