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Two-year clinical update and first biomarker analyses of the phase III NADINA trial comparing neoadjuvant nivolumab plus ipilimumab versus adjuvant nivolumab in resectable stage III melanoma

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Background

The phase 3 NADINA trial showed superior event-free survival (EFS) with neoadjuvant (neoadj) ipilimumab (IPI) + nivolumab (NIVO) followed by surgery and response-driven adjuvant treatment, vs surgery and adj NIVO in resectable, stage III melanoma (83.7% vs 57.2% at 1y, p<0.0001). Here we report the updated EFS, distant metastasis-free survival (DMFS) and the first biomarker analyses.

Methods

RNA/DNA were isolated from baseline frozen tumor samples and PD-L1 expression was scored on baseline FFPE samples (79% of evaluable samples scored). Whole Genome Sequencing data were processed on the nf-core/sarek pipeline. The threshold for tumor mutational burden (TMB) was set at 10 mut/Mb and for PD-L1 at ≥1%. The cutoff for the 10-gene interferon gamma signature (IFNy) was based on Youden J statistics on major pathologic response.

Results

At data cutoff 14 April 2025, all 423 pts had reached EoT. With a median follow up (FU) of 25 mo, the estimated 2y EFS rates were 77.3% vs 55.7% for the neoadj vs adj arm (HR 0.40 [95% CI 0.28-0.57]). Estimated 2y DMFS rates were 82.8% vs 63.9%, respectively (HR 0.43 [95% CI 0.29-0.64]). RFS at 2y for neoadj pts with pathologic partial- or non-response was 67.2% with adj dabrafenib + trametinib (BRAFV600; n=43) and 37.7% with adj NIVO (BRAFWt; n=21). Grade ≥3 systemic treatment related adverse events were observed in 31.1% for the neoadj arm and 15.9% for the adj arm. Biomarkers above threshold (favorable) were associated with improved EFS compared to below threshold (unfavorable; TMB adj arm pending, planned for presentation). EFS at 24 mo was even higher for IFNy-high+TMB-high (96.4%; n=28) and PD-L1-high+TMB-high (100%; n=14) in the neoadj arm.Table: LBA57

Biomarker	Arm	No. of pts	Favorable	24mo EFS (95% CI)	No. of pts	Unfavorable	24mo EFS (95% CI)	HR (95% CI)	Nominal	p-value
IFNy	Neoadj	74	87.7%	(79.9-96.3)	59	65.4%	(53.8-79.6)	0.29 (0.13-0.64)	0.002	
IFNy	Adj	85	66.8%	(57.2-77.9)	67	36.6%	(26.3-50.9)	0.41 (0.25-0.67)	<0.001	
PD-L1	Neoadj	70	87.6%	(79.7-96.2)	60	73.3%	(62.4-86.0)	0.39 (0.17-0.90)	0.028	
PD-L1	Adj	61	67.2%	(56.0-80.6)	51	32.0%	(21.4-47.9)	0.32 (0.18-0.56)	<0.001	
TMB	Neoadj	59	91.5%	(84.7-98.9)	78	62.0%	(51.4-74.8)	0.25 (0.10-0.62)	0.002	

Conclusions

With an additional 10 months FU, neoadj IPI + NIVO continues to demonstrate superior outcomes to adj NIVO in resectable stage III melanoma. IFNy, PD-L1, and TMB serve as predictive biomarkers for improved treatment outcomes.

Clinical trial identification

NCT04949113.

Legal entity responsible for the study

The Netherlands Cancer Institute.

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Disclosure

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