NeoIRENIE: A Phase 2 randomized trial of intensified neoadjuvant therapy for melanoma patients with multi-omic biomarker or clinically predicted poor response to standard immune checkpoint inhibitor (ICI) therapy

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Background

The NeoIRENIE trial evaluates whether intensified ICI regimens improve pathological response in poor prognosis patients identified by multi-omic biomarker prediction, treatment failure, or mucosal histology

- Neoadjuvant immunotherapy (NAT) with immune checkpoint inhibitors (ICI) has emerged as superior treatment for stage III melanoma, demonstrating improved outcomes compared to adjuvant therapy.
- The SWOG-1801 trial showed a 23% event-free survival (EFS) benefit at 2 years for NAT versus adjuvant pembrolizumab (72% vs 49%, P=0.004). [1]
- The NADINA trial confirmed superiority of NAT ipilimumab/nivolumab over adjuvant nivolumab (2-year RFS 83.7% vs 57.2%, HR 0.32). [2]
- Pathological response, particularly major pathological response (MPR; ≤10% viable tumor), strongly correlates with improved outcomes. [3, 4]
- The International Neoadjuvant Melanoma Consortium (INMC) pooled analysis (N=610 ICI patients) demonstrated 3-year RFS of 93% for MPR patients versus 41% for those with no pathological response. [3, 4]
- Standard NAT with IPI (1mg/kg) and NIVO (3mg/kg) achieves MPR in only ~60% of pts. [2]
- Multi-omic biomarkers can predict poor response to anti-PD-1 therapy, identifying patients who may benefit from intensified ICI therapy.

INMC Response Criteria[5]

	Viable Tumour (%)
Major Pathological Response	
Pathological complete response (pCR)	0%
Near-pathological complete response (near-pCR)	≤10%
Non-Major Pathological Response	
Pathological partial response (pPR)	>10% - ≤50%
Pathological non-response (pNR)	>50%

Objectives

Primary Endpoint

- Pathological response rate in each INMC response category (pCR, near-pCR, pPR, pNR)

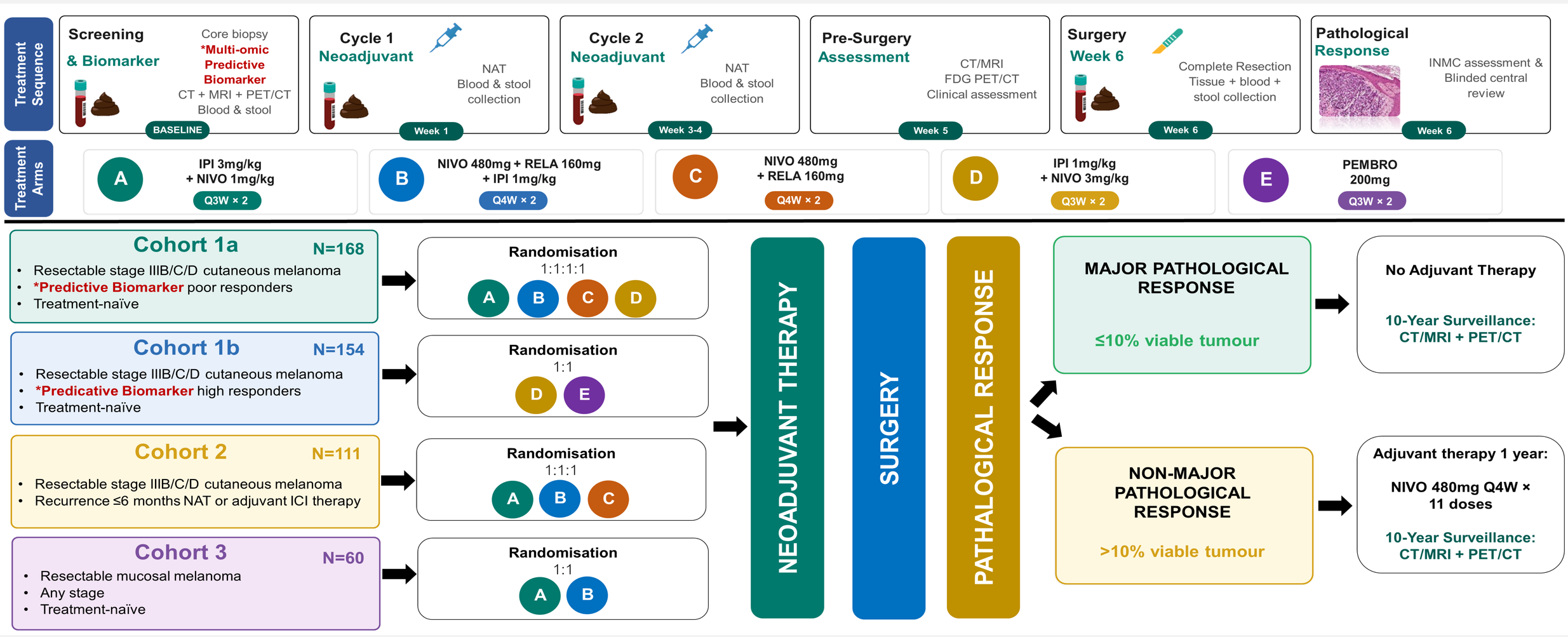
Secondary Endpoints

- Event-free survival (EFS)
- RECIST objective response rate (ORR)
- PERCIST metabolic response rate
- Overall survival (OS)
- Recurrence-free survival (RFS)
- Safety and tolerability
- Surgical outcomes
- Quality of life (QoL)

Exploratory Endpoints

- Biomarker analyses and validation of multi-omic predictive model
- Tissue, blood and stool biomarker analyses

Study Design



Eligibility Criteria

Key Inclusion Criteria

- Patients ≥18 years of age
- Clinically detectable, fully resectable AJCC 8th ed. melanoma (cutaneous and mucosal)
- Tumour amenable to core biopsy for multi-omic predictive biomarker model (cohorts 1a and 1b)
- ECOG PS 0 –1
- Measurable disease per RECIST v1.1 and/or PET imaging
- Adequate organ function

Key Exclusion Criteria

- Uveal melanoma
- Clinical or radiographic evidence of distant metastasis
- Known CNS metastases
- Active autoimmune disease requiring systemic treatment
- Prior CTLA-4 or LAG-3 inhibitor exposure (exceptions for Cohort 2)

References

1. Patel, S.P., et al. 2023; NEJM, 388(9), pp.813-823.
2. Blank, C.U., et al. 2024; NEJM, 391(18), pp.1696-1708.
3. Menzies, A.M., 2021; Nature Medicine, 27(2), pp.301-309.
4. Long, G.V., et al. 2024; Annals of Oncology, 35, p.S1232.
5. Tetzlaff, M., et al. 2018; Annals of Oncology, 29(8), pp.1861-1868.

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