MSLT-3 / S2601 / EORTC-2519 : A Phase 3 Trial of Selective Index Lymph Node vs. Therapeutic Lymph Node Dissection after Neoadjuvant Immunotherapy for Stage IIIB–D Melanoma

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Background

The MSLT-3 trial will definitively establish whether Selective Index Lymph Node Dissection (ILND) is non-inferior to standard Therapeutic Lymph Node Dissection (TLND) in patients with major pathological response after standard of care neoadjuvant immunotherapy (NAT).

- The phase 2 SWOG-1801 trial showed 72% EFS at 2 years for NAT and 49% for adjuvant pembrolizumab (P = 0.004). [1]
- The phase 3 NADINA trial confirmed superiority of NAT IPI/NIVO over adjuvant NIVO (2-year RFS 83.7% vs 57.2%, HR 0.32).[2]
- Pathological response, particularly major pathological response (MPR), strongly correlates with improved outcomes. The International Neoadjuvant Melanoma Consortium (INMC) pooled analysis (N = 610 immune checkpoint inhibitor patients) demonstrated 3-year RFS of 93% for MPR patients versus 41% for those with no pathological response.[3,4]
- The PRADO proof of concept trial demonstrated that selective index lymph node (ILN) resection can safely de-escalate surgery in MPR patients, with only 4/60 (6.7%) MPR patients recurring after a median follow-up of 28.1 months, all locoregionally. [6]
- ILN resection reduced surgical morbidity and improved quality of life compared to therapeutic lymph node dissection (TLND). [6]
- An international survey of 117 melanoma experts showed that 71% believe a phase 3 randomized controlled trial is needed to change surgical practice. [7]

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

- 2-year recurrence-free survival (RFS) in MPR patients (non-inferiority margin − 5%)

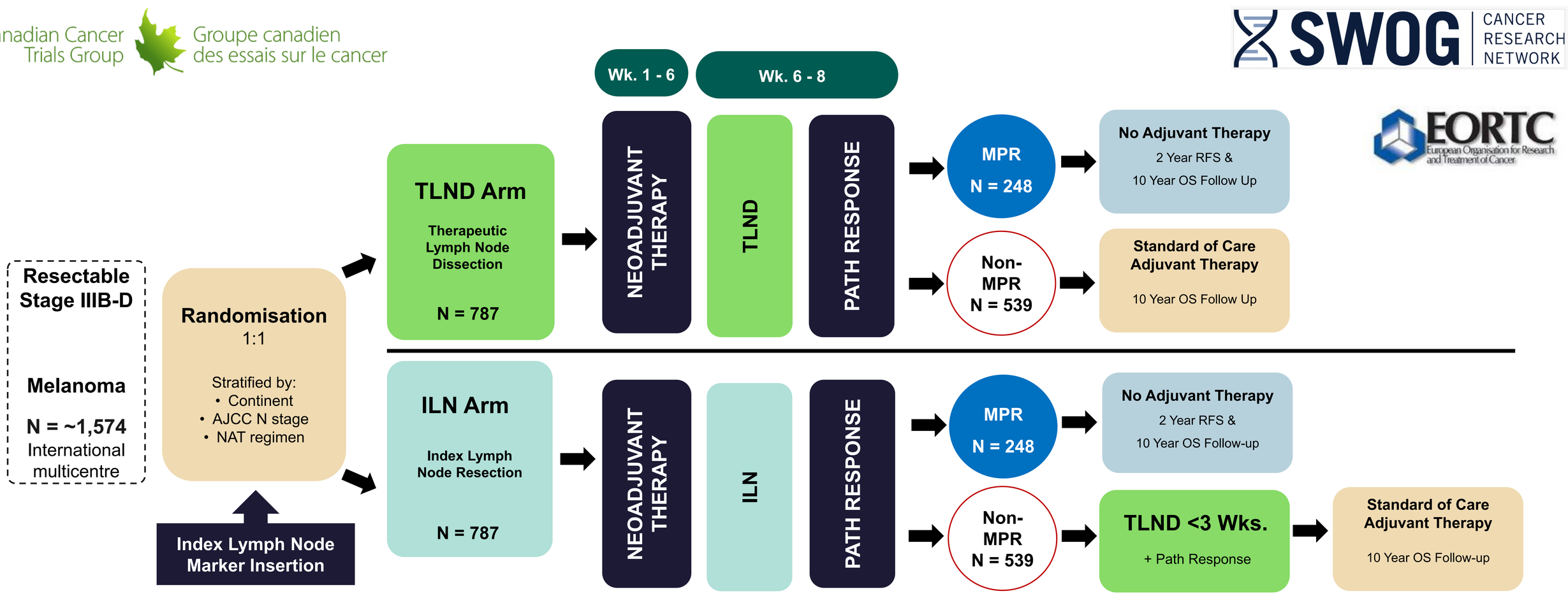
Secondary Endpoints

- Escalation to TLND for isolated nodal recurrence
- Salvage therapy rates
- Distant metastasis-free survival (DMFS)
- Event-free survival (EFS)
- Overall survival (OS)
- Surgery-related adverse events
- Quality of life: QLQ-C30, EQ-5D-5L, FACT-M

Exploratory Endpoints

- Concordance of imaging & ctDNA with pathology
- Health economics & cost-effectiveness

Study Design



Clinicaltrials.gov Identifier: NCT07049276

Eligibility Criteria

Key Inclusion Criteria

- Age ≥18 years & ECOG 0–1
- Resectable stage IIIB–D cutaneous melanoma:
- ≥1 macroscopic LN (groin, axilla or neck): palpable, RECIST-enlarged, or imaging-positive; pathology-confirmed
- ≤3 resectable satellite/in-transit metastases permitted
- Pre-NAT marker placed in largest metastatic node
- Scheduled to receive standard of care NAT (≥1 PD-(L)1 inhibitor; ≤6 weeks)

Key Exclusion Criteria

- Distant metastatic (M1) disease
- Isolated satellite or intransit mets. only
- Uveal or mucosal melanoma
- Active autoimmune disease on systemic treatment
- Prior therapy for current diagnosis
- Contraindication to ICI therapy

References

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