NeoPeLe: A Phase 2 Trial of Neoadjuvant Pembrolizumab Combined with Lenvatinib In Resectable Stage III Melanoma

Georgina V Long[1–4,8], Andrew Spillane[1–4], Thomas Pennington[1,2,4,5], Kerwin F Shannon[1,2,4–7], Jonathon R Stretch[1,2,4,5], Maria Gonzalez[1], Robyn PM Saw[1,2,4,5], Serigne Lo[1,2], Richard A Scolyer[1,2,5,8,9], Alexander M Menzies[1–4]

1. Melanoma Institute Australia, The University of Sydney, 2. Faculty of Medicine and Health, The University of Sydney, 3. Royal North Shore Hospital, 4. Mater Hospital, 5. Royal Prince Alfred Hospital, 6. Chris O'Brien Lifehouse, 7. Concord Repatriation Hospital, 8. Charles Perkins Centre, The University of Sydney, 9. NSW Health Pathology

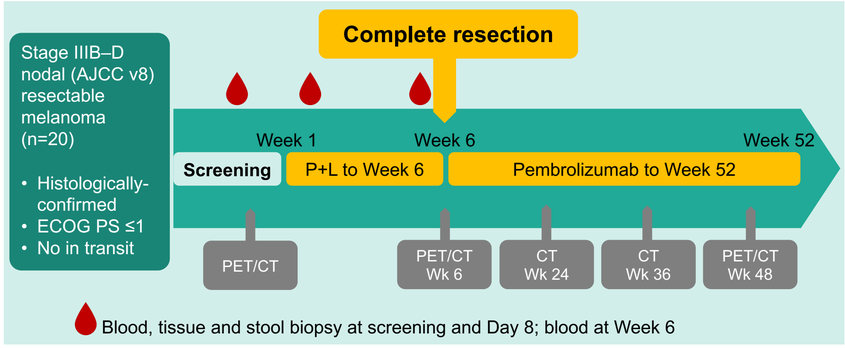
Background

- Neoadjuvant anti-PD-1 induces pathological complete response (pCR) in 20% and any pathological response (pRR) in 34% of patients with stage III melanoma.[1]
- Combination pembrolizumab and lenvatinib (P+L) is active in patients with melanoma who have progressed on anti-PD-1 alone (LEAP-004).[2] Adding lenvatinib to anti-PD-1 could enhance clinical benefit in the neoadjuvant setting, and provide melanoma tissue to gain translational insights into impact of lenvatinib on the tumour microenvironment.
- NeoPeLe (NCT04207086) is a phase II, open label, single arm study of 20 patients with resectable stage III melanoma treated with neoadjuvant P+L.

Objectives

- Primary: To determine the the pathological response rate to 6 weeks of neoadjuvant pembrolizumab plus lenvatinib.
- Key Secondary: To determine the RECIST and metabolic response at Wk 6, the relapse free survival and to evaluate the effects on tumour tissue and peripheral blood.

Methods



Primary endpoints
1. Pathological response rate at Week 6
2. Anti-tumoural immune response

Secondary endpoints
1. Objective clinical (RECIST) response
2. Metabolic response rate
3. Event-free survival (EFS, from therapy), relapse-free survival (RFS, form surgery), overall survival (OS)
4. Surgical morbidity
5. Operability
6. Safety

Treatment
- Neoadjuvant (pre-surgery): Pembrolizumab 200 mg IV on Day 1 and Day 22 plus lenvatinib 20 mg daily for 5 weeks
- Adjuvant (post surgery): Pembrolizumab 200 mg IV 3 weekly for 46 weeks

Assessments
- CT/PET scans at screening, Wk 6 and Wk 48
- CT Scans 12 weekly
- Tissue biopsy at screening and Day 8, and therapeutic lymph node dissection at Wk 6
- Blood for biomarkers at screening, Day 8, and Wk 6
- Surgical operability questionnaire screening and Wk 6 pre-operatively
- Pathologic response determined as per INMC criteria[3] and defined as complete (pCR), near complete, partial (pPR) or no response (pNR)

- 20 patients enrolled from 20 Nov 2020 – 19 Jul 2021
- Data cut off 29 July 2022, median follow up was 14 mo (95% CI 13.6-17.3)

Table 1. Patient Characteristics

	N=20
Female, n (%)	6 (30%)
Age, median (range), years	70 (28–78)
ECOG 0, n (%)	20 (100%)
BRAF V600E	3 (15%)
Disease site, n (%)	
Neck	2 (10%)
Axilla	10 (50%)
Inguinal/ilio-inguinal	7 (35%)
Other	1 (5%)
Primary Melanoma T-category (AJCC v8), n (%)	
T1a/b	12 (60%)
T2a	5 (25%)
T4a/b	2 (10%)
N-stage (AJCC v8), n (%)	
N1b	10 (50%)
N2b/3b/3c	10 (50%)

Table 2. Treatment-related Adverse Events

	N=20
Any treatment-related AE, n (%)	19 (95%)
Grade 3/4 treatment-related AE, n (%)	9 (45%)
Any treatment discontinuation during NAT, n (%)	1 (5%)
Lenvatinib	1
Pembrolizumab	0
Any treatment interruption during NAT, n (%)	5 (25%)
Lenvatinib	5
Pembrolizumab	0
Treatment-related death, n (%)	0

Table 3. Treatment-related Adverse Events ≥ 25%

	N=20	
Treatment-related AE, n (%)	**Any grade**	**Grade 3/4**
Fatigue	9 (45%)	0
Hypertension	8 (40%)	5 (25%)
Flushing	8 (40%)	0
Headache	6 (30%)	0
Anorexia	5 (25%)	0
Dysphonia	5 (25%)	0

References

1. Menzies A, *et al.* Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). *Nat Med.* 2021.
2. Arance A, *et al.* Phase II LEAP-004 study of lenvatinib plus pembrolizumab for melanoma with confirmed progression on a programmed cell death protein-1 or programmed death ligand 1 inhibitor given as monotherapy or in combination. *J Clin Oncol.* 2022.
3. Amaria RN, *et al.* Neoadjuvant systemic therapy in melanoma: Recommendations of International Neoadjuvant Melanoma Consortium. *Lancet Oncol.* 2019.

Acknowledgements

- All MIA staff, patients, and their carers
- Trial sponsored by the Melanoma Institute Australia
- Drug and funding support provided by Merck Sharp & Dohme (Australia) Pty Ltd

melanoma.org.au

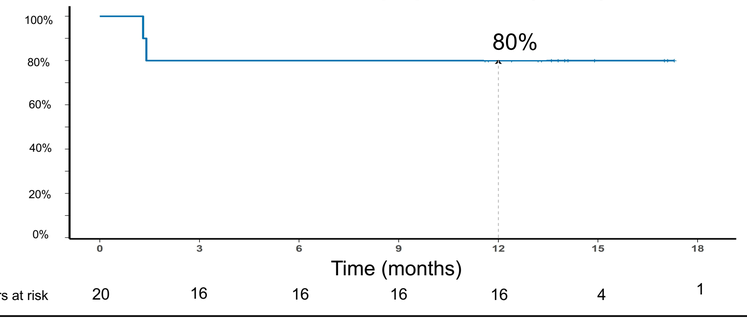
Results

- The majority of patients had a pathological response (75%) and most were a pCR (40%)
- Pathological response did not correlate with the radiological RECIST response prior to surgery at Wk 6
- Surgery was easier than expected in 13/20 (65%) and harder in 7/20 (35%); no correlation with path response

Figure 1. Pathological and Radiological RECIST Response at Week 6

Pathological Response, n (%)	N=20	RECIST Response, n (%)	N=20
Any Pathological Response	**15 (75%)**	**Objective Response Rate**	**7 (35%)**
pCR	8 (40%)	CR	1 (5%)
near-pCR	3 (15%)	PR	6 (30%)
pPR	4 (20%)	SD	11 (55%)
pNR	5 (25%)	PD	2 (10%)

Figure 2. Event-free survival in total population (n=20)



- Three patients (4/20, 20%) had recurred during follow-up;
  - 2 with pNR; 1 with pPR and 1 with pCR
  - 2 distant only, 1 regional only and 1 local then distant.
- Two patients had died at data cut off due to melanoma
  - 1 with pNR; 1 with pPR

Conclusions

- Neoadjuvant pembrolizumab + lenvatinib induced a high pathological response rate of 75% and a high major pathological response (pCR+near-pCR) rate of 55%.
  - These results are higher than response rates reported for PD-1 monotherapy and similar to those reported for PD-1 + CTLA-4 combination therapy.[1]
  - Lenvatinib appears to enhance the activity of PD-1 monotherapy.
- There was a low rate of recurrence in pathological responders (1/15).
- Given this early promising data, recruitment to NeoPeLe was increased to a total of 40 patients and is ongoing.
- Translational studies are underway.