

Background

The Neo-cuSCC trial will examine whether neoadjuvant combination PD-1 blockade plus lymphocyte-activation 3 (LAG3) checkpoint inhibition will achieve a high rate of pathological complete response with manageable toxicity in patients with resectable stage II-IV (M0) cutaneous SCC (cuSCC).

- cuSCC is the second most common skin cancer worldwide¹.
- While 90% of cases are cured surgically², approx. 5% spread regionally or distantly, with an overall survival (OS) rate <20% at 10 years if regional lymph nodes (LN) are involved³.
- In melanoma, using International Neoadjuvant Melanoma Consortium (INMC) pathological response criteria⁴, a major pathological response to neoadjuvant immunotherapy ($\leq 10\%$ viable tumor) correlates with lower recurrence risk in resectable stage III disease^{5,6} and improved OS and event free survival (EFS) compared to adjuvant therapy^{7,8}.
- Several neoadjuvant anti-PD1 monotherapy trials in patients with resectable cuSCC (N=126) demonstrate high rates (approx. 50%) of pathological complete response (pCR)^{9,10,11}, with one study showing 48% of patients achieved de-escalation of both the extent of surgery and postoperative radiotherapy¹¹.
- Neoadjuvant studies in melanoma⁸ and cuSCC¹² have shown high response rates & manageable toxicity combining PD1 with other immune checkpoint inhibitors, and some data suggests anti-PD1/LAG3 combination may have high activity in this setting¹³.
- The neoadjuvant setting provides early insight into response, informs patients about prognosis, enables personalized management including de-escalation of both surgery and adjuvant therapy regimens, and facilitates collection of specimens to study mechanisms of response and resistance.

INMC Response Criteria⁴

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

Objectives

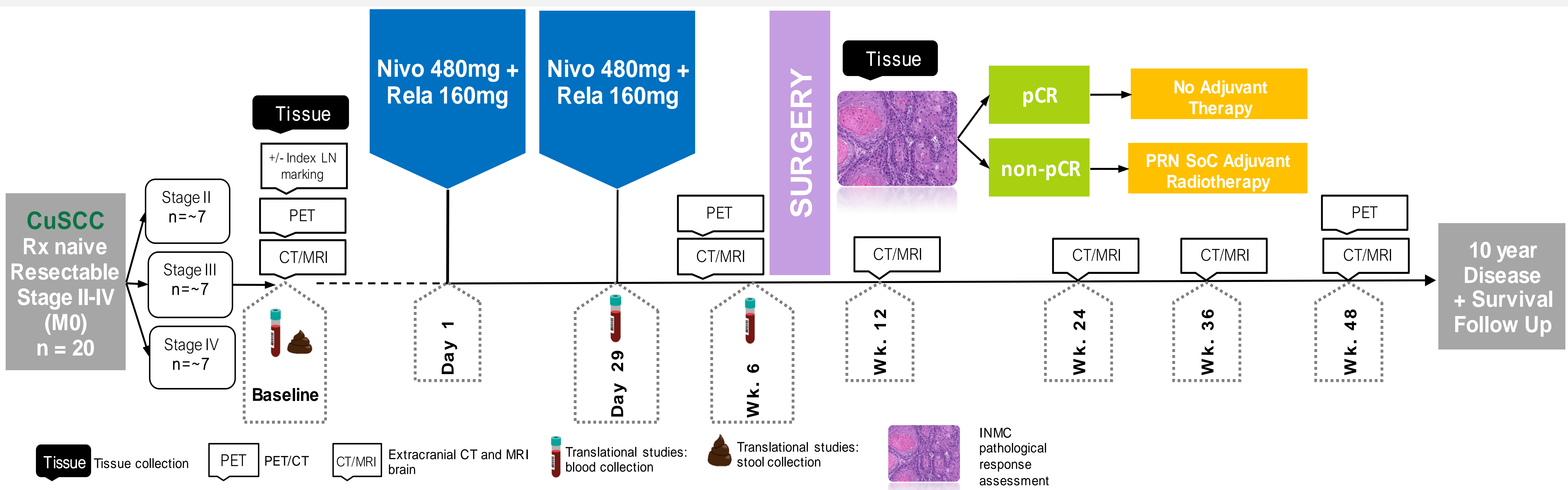
Primary Objective

- Rate of pCR at resection after neoadjuvant therapy using INMC response criteria

Secondary Objectives

- Rate of near-pCR, pPR, and pNR
- RECIST objective response rate (ORR)
- PERCIST metabolic response rate
- Recurrence free survival (RFS), EFS, and OS
- Clinical complete response rate (cCR)
- Assess safety and tolerability
- Describe surgical outcomes
- Quality of life (QoL)
- Rate of surgery and post-operative radiotherapy de-escalation
- Tissue, blood and stool biomarker analyses

Study Design



Key Eligibility Criteria

Inclusion Criteria

- Patients ≥ 18 years of age.
- Histologically confirmed, resectable stage II to IV (M0) cuSCC (AJCC head/neck 8th ed. or UICC non-head/neck 9th ed.).
- In-transit metastases are permitted if they are completely resectable.
- Measurable disease according to RECIST version 1.1 criteria.

Exclusion Criteria

- Clinical or radiographic evidence of distant metastasis.
- Prior anti-PD-1, CTLA-4, PDL-1 or LAG3 antibody exposure, or other experimental local or systemic drug therapy.
- Active autoimmune disease.

Acknowledgements

- Trial sponsored by Melanoma Institute Australia.
- Nivolumab and relatlimab supplied by BMS.
- Patient recruitment is ongoing at Melanoma Institute Australia.

Clinicaltrials.gov
Identifier: NCT06288191

References

1. Bray, F., et.al. 2018; *CA: A Cancer Journal for Clinicians*, 68(6), pp.394-424.
2. Kauvar, A.N., et.al. 2015; *Dermatol Surg*, 41(11), pp. 1214-1240.
3. Ogata, D., et.al. 2019; *Curr Treat Options Oncol* 20(4), p.30.
4. Tetzlaff, M., et.al. 2018; *Annals of Oncology*, 29(8), pp.1861-1868
5. Menzies, A.M., 2021; *Nature Medicine*, 27(2), pp.301-309
6. Long, G.V., et.al. 2024; *Annals of Oncology*, 35, p.S1232.
7. Patel, S.P., et.al. 2023; *New England Journal of Medicine*, 388(9), pp.813-823
8. Blank, C.U., et.al. 2024; *The New England Journal of Medicine*, 391(18), pp.1696-1708
9. Ferrarotto, R., et.al 2021; *Clin Cancer Res*, 27(16): pp.4557-4565
10. Gross, N.D., et.al. 2022; *New England Journal of Medicine*, 387(17), pp.1557-1568.
11. Ladwa, R., et.al. 2024; *JCO*, 42, 9514-9514.
12. Zuur, C.L., et.al 2023; *JCO*, 41, 9507-9507.
13. Amaria, R.N., et.al. 2022; *Nature*, 611(7934), pp.155-160.

