Appendix 2. Supporting clinical trials

The table below summarises clinical trials that serve as supporting studies for this assessment. Although there are elements of the study design that do not fully align with this treatment under consideration, the evidence supplements the findings of the pivotal NADINA study.

The trials include patients with resectable stage III melanoma with ≥1 lymph node metastasis and with a mutational status of either V600 BRAF positive or wild type. The table only reports data relating to patients that were treated with 2 cycles of neoadjuvant nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV every 3 weeks for 2 cycles), which is comparable to the dose proposed by the Group. No adjuvant treatment was given to the patients whose outcome data is represented in the table.

A key difference to note is that the exclusion criteria for these studies included patients with in-transit metastasis within the last 6 months, whereas the treatment under consideration is for patients with up to 3 in-transit metastases.

<table>
<tr><th>Author (Year)</th><th>Study Design</th><th>Number of treated patients (age)</th><th>Number (%) patients achieving MPR</th><th>Longer-term outcomes</th><th>Safety</th><th>Key differences from current assessment</th></tr>
<tr><td>Rozeman et al (2019)[18]</td><td rowspan="2">OpACIN-Neo.

Phase II multicentre, open-label, randomised controlled trial.

3 treatment arms in study: only group B reported as most relevant.</td><td rowspan="2">30
(≥ 18 years)</td><td>19 (63.3%)</td><td>Median follow-up 8.3 months: no relapse in patients achieving a MPR or pPR.</td><td rowspan="2">Within the first 12 weeks, grade 3–4 immune-related adverse events were observed in 6 (20%) patients.</td><td rowspan="3"><u>Both studies</u>

Treatment dose (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg).

Patients with a history of in-transit metastasis within last 6 month were excluded.

<u>PRADO study</u>

Surgery was not intended for patients achieving MPR following neoadjuvant treatment.</td></tr>
<tr><td>Versluis et al (2023)[19]

47 month follow-up</td><td>N/A</td><td>Estimated 3-year rates (not stratified by pathological response):

RFS: 79%
EFS: 77%
DMFS: 86%
OS: 93%</td></tr>
<tr><td>Reijers et al (2022)[17]</td><td>PRADO extension cohort of OpACIN-Neo.

Phase II, multicentre study.

No blinding or randomisation.</td><td>99
(≥ 18 years)</td><td>60 (61%)</td><td>Estimated 24-month rates:

MPR RFS: 93%
MPR DMFS: 98%

pPR RFS: 64%
pPR DMFS: 64%

pNR RFS: 71%
pNR DMFS: 76%</td><td>Within the first 12 weeks, grade 3–4 immune-related adverse events were observed in 22 patients (22%; 95% CI; 14-32%).</td></tr>
</table>

Author (Year)	Study Design	Number of treated patients (age)	Number (%) patients achieving MPR	Longer-term outcomes	Safety	Key differences from current assessment
Pathological response is assessed according to the International Neoadjuvant Melanoma Consortium (INMC) criteria. Major pathological response (MPR): ≤ 10% residual viable tumour which includes patients with a complete pathological response (pCR) (0% residual viable tumour) and those with a near-complete pathologic response (> 0% - ≤ 10% residual viable tumour). Pathological partial response (pPR): > 10% - ≤ 50% residual viable tumour. Pathologic non-response (pNR): > 50% residual viable tumour. BRAF: B-Raf proto-oncogene, serine/threonine kinase; DMFS: distant metastasis-free survival; EFS: event-free survival; IV: intravenous; OS: overall survival; RFS: recurrence-free survival; CI: confidence interval.						