URN 2426: Neo-adjuvant followed by adjuvant pembrolizumab for stage III macroscopic resectable melanoma

Narrative summary of papers presented for review

One paper was presented for review by NHS England. The paper is a phase II, open-label randomised trial conducted at 90 sites across the USA. Adults (n=313) with clinically detected, resectable stage III or IV melanoma were recruited to receive either intravenous pembrolizumab before surgery, followed by additional pembrolizumab as adjuvant treatment (neoadjuvant–adjuvant group), or surgery followed by adjuvant intravenous pembrolizumab (adjuvant-only group). The median follow-up duration was 14.7 months.

Paper 1: Patel et al 2023. Neoadjuvant-adjuvant or adjuvant-only pembrolizumab in advanced melanoma: a phase II, open-label randomised trial

This paper reports on a phase II, open-label randomised trial that assessed the efficacy and safety of intravenous pembrolizumab before surgery, followed by additional pembrolizumab as adjuvant treatment (n=154; neoadjuvant–adjuvant group) compared to surgery followed by adjuvant intravenous pembrolizumab (n=159; adjuvant-only group). Patients were recruited between February 2019 and May 2022 from 90 sites across the USA. Eligible patients (aged ≥18 years) had histologically confirmed cutaneous, acral, or mucosal melanoma; clinically detectable,[1] measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) and stage IIIB to IIID melanoma or oligometastatic resectable stage IV (M1a, M1b, and M1c) melanoma[2]. Eligibility criteria included patients at initial presentation or at the time of the first detected nodal (including recurrent disease in a previous lymphadenectomy basin), satellite, in-transit, or distant metastases. Patients with metastases in multiple regional nodal basins were eligible for inclusion, as were patients who were positive for human immunodeficiency virus (HIV) if they had stable and adequate CD4 counts (≥350 cells per cubic millimetre) and a serum HIV viral load of less than 25,000 IU per millilitre, regardless of whether they were receiving antiviral treatment. Key exclusion criteria included local recurrences in the scar or surgical bed of the primary melanoma as the sole site of disease, previous immunotherapy for melanoma (previous adjuvant treatment other than immunotherapy, and previous radiotherapy were permitted), active autoimmune disease in patients who had received systemic treatment within two years before trial entry, uveal melanoma, and any history of brain metastasis.

The median age of patients was 64.0 years (range 19.0 to 90.0) in the neoadjuvant-adjuvant group and 62.0 years (range 22.0 to 88.0) in the adjuvant-only group. The majority of patients were male: 92 of 154 (60%) patients in the neoadjuvant-adjuvant group and 111 of 159 (70%) patients in the adjuvant-only group. The proportion of patients with each disease stage was similar in both treatment groups: Stage IIIB: neoadjuvant-adjuvant group (n=62,

[1] Defined as disease that is apparent and measurable on physical examination or on radiographic or magnetic resonance imaging.
[2] Resectable nodal metastases had to have a minimum short-axis diameter of 1.5 cm, while the minimum size for other metastases was 1 cm.

40%), adjuvant-only group (n=64, 40%); stage IIIC: neoadjuvant-adjuvant group (n=69, 45%), adjuvant-only group (n=74, 47%); stage IIID: neoadjuvant-adjuvant group (n=9, 6%), adjuvant-only group (n=10, 6%); stage IV: neoadjuvant-adjuvant group (n=14, 9%), adjuvant-only group (n=11, 7%). The proportion of patients with each primary melanoma subtype was also similar in both treatment groups: cutaneous or unknown (neoadjuvant-adjuvant group; n=143 [93%], adjuvant-only group; n=153 [96%]); acral (neoadjuvant-adjuvant group; n=4 [3%], adjuvant-only group; n=5 [3%]); mucosal (neoadjuvant-adjuvant group; n=4 [3%], adjuvant-only group; n=0 [0%]). The authors stated that the trial population was representative of patients with melanoma in the USA with respect to race and ethnicity. The majority of patients (98% to 99%) in both treatment groups had not received previous BRAF and MEK adjuvant treatment or previous radiotherapy.

Patients were randomly assigned to receive either an intravenous infusion of 200 mg of pembrolizumab every three weeks for a total of three doses before surgery,[3] followed by an additional 15 doses of pembrolizumab as adjuvant treatment (neoadjuvant–adjuvant group), or surgery followed by adjuvant intravenous infusion of 200 mg of pembrolizumab every three weeks for 18 doses (adjuvant-only group) for approximately one year or until disease recurred or unacceptable adverse effects developed. Postoperative radiotherapy was permitted at the discretion of the investigator before the initiation of adjuvant treatment but concomitant use of radiotherapy and pembrolizumab was not permitted. Two patients assigned to the neoadjuvant-adjuvant group and seven patients assigned to the adjuvant-only group withdrew consent prior to treatment but were included in the intention-to-treat (ITT) analyses. At the time that ITT analyses were performed (median follow-up duration 14.7 months), 50 of 154 patients in the neoadjuvant-adjuvant group had completed all protocol treatment, 43 patients were on treatment and 59 had discontinued treatment (n=15 before surgery, n=18 between surgery and adjuvant treatment, and n=26 during adjuvant treatment). Thirty eight patients in the adjuvant-only group had completed all protocol treatment, 41 patients were on treatment and 73 had discontinued treatment (n=1 before surgery, n=21 between surgery and adjuvant treatment and n=51 during adjuvant treatment).

Effectiveness

Overall survival

Patel et al (2023) reported that at the time of data cut-off, 36 patients with advanced melanoma had died: 14 of 154 patients in the neoadjuvant-adjuvant group and 22 of 159 patients in the adjuvant-only group. No statistical measures were reported as the authors stated that the small number of deaths prevented definitive comparison between the two treatment groups.

The included paper (n=313) reported 14 deaths in patients with advanced melanoma treated with neoadjuvant-adjuvant pembrolizumab (n=154) and 22 deaths in patients treated with adjuvant-only pembrolizumab (n=159); no statistical measures were reported.

[3] The interval between the last dose of neoadjuvant pembrolizumab and surgery was expected to be no longer than five weeks, and surgery was expected to be conducted in all patients in the neoadjuvant-adjuvant group regardless of radiologic response to preoperative treatment.

Event-free survival

Patel et al (2023) reported that at a median follow-up of 14.7 months, event-free survival[4] (ITT analysis) was statistically significantly greater in patients with advanced melanoma in the neoadjuvant-adjuvant group (38 events in 154 patients) compared to the adjuvant-only group (67 events in 159 patients); p=0.004[5] (see Table 1).

Table 1: Events in patients with advanced melanoma treated with neoadjuvant-adjuvant pembrolizumab or adjuvant-only pembrolizumab reported by Patel et al 2023

Event type	Neoadjuvant-adjuvant group (n=154)[6]	Adjuvant-only group (n=159)[7]
Failure to receive surgery due to:		
Toxicity	1	0
Progression	12	0
Co-morbidities	1	0
Non-COVID scheduling issue	0	1
Received surgery but did not receive adjuvant treatment due to:		
Patient refusal	1[8]	2
Neo-adjuvant toxicity	3 (colitis, pneumonitis, and polymyalgia rheumatica in 1 patient each)	0
Metastatic disease/disease progression	9	16
Residual disease	1	2
Extended radiation	0	1
Recurrence after starting adjuvant treatment	9	41
Death	1	4
Total events	**38**	**67**

At the time of analysis, 10 of the 313 randomised patients were still receiving neoadjuvant pembrolizumab. Of the remaining patients, 127 of 144 (88%) patients in the neoadjuvant–

[4] Events included disease progression or adverse effects of treatment that prevented surgery; the inability to resect all gross disease; disease progression, surgical complications, or toxic effects of treatment that prevented the initiation of adjuvant treatment within 84 days after surgery; recurrence of melanoma after surgery; or death from any cause.

[5] Data on patients last known to be alive without an event were censored at the date of last contact. To account for differences in time to administration of treatment in the two groups, any events that occurred before adjuvant treatment were assigned the event time of day 84. Patients in the neoadjuvant–adjuvant group who declined surgery due to complete radiographic response were not counted as having had an event and were followed up for recurrence. Data on patients whose surgery or adjuvant treatment was cancelled due to coronavirus disease 2019 (Covid-19)–related trial limitations were censored at the time of withdrawal without an event.

[6] N=154 patients includes the two patients who withdrew consent after randomisation.

[7] N=159 includes the seven patients who withdrew consent after randomisation.

[8] The authors stated that four additional patients did not receive adjuvant treatment due to clinical trial closure because of COVID-19 (n=1), concerns regarding exposure to COVID-19 (n=1), and disease other than melanoma identified at surgery (n=2). There is therefore a discrepancy in the number of patients reported by the authors not to have received adjuvant treatment (i.e. 18 patients and not the stated 14 patients).

adjuvant group and 151 of 159 (95%) patients in the adjuvant-only group had undergone definitive surgery.

At two years, event-free survival was greater in patients with advanced melanoma in the neoadjuvant-adjuvant group (72%; 95% confidence interval [CI] 64.0 to 80.0) compared to patients in the adjuvant-only group (49%; 95% CI 41.0 to 59.0); the difference was 23% (95% CI 11.0 to 35.0), but no other statistical measures were reported. The authors reported similar between-treatment group results for two-year event-free survival according to subgroups (including age, sex, Zubrod's performance-status score[9], lactate dehydrogenase (LDH) level, disease stage, ulceration, and BRAF mutation status).

The included paper (n=313) reported that at a median follow-up of 14.7 months, event-free survival was statistically significantly greater in patients with advanced melanoma treated with neoadjuvant-adjuvant pembrolizumab (38 events in 154 patients) compared to patients treated with adjuvant-only pembrolizumab (67 events in 159 patients).

Disease recurrence

Patel et al (2023) reported that at the time of data cut-off, nine patients with advanced melanoma in the neoadjuvant-adjuvant group and 41 patients in the adjuvant-only group had disease recurrence during or after the adjuvant pembrolizumab treatment phase (see Table 1). Of the patients in the neoadjuvant-adjuvant group, 50 completed all adjuvant treatment cycles and none had subsequent disease recurrence. Of the patients in the adjuvant-only group, 38 patients completed all adjuvant cycles and four (11%) had subsequent disease recurrence; no statistical measures were reported.

The included paper (n=313) reported no subsequent disease recurrence in the 50 patients with advanced melanoma who completed all adjuvant treatment cycles in the neoadjuvant-adjuvant group, while 11% of patients who completed all adjuvant treatment cycles in the adjuvant-only group had subsequent disease recurrence; no statistical measures were reported.

Overall response to treatment[10]

Patel et al (2023) reported that after completion of neoadjuvant treatment in the neoadjuvant-adjuvant group, nine of 142 (6%) evaluable patients[11] with advanced melanoma had a complete imaging-based response and 58 (41%) evaluable patients had a partial response. The authors reported that a review of the institutional pathology reports indicated that 28 of 132 (21%) patients had a complete pathological response (i.e. no viable tumour) after neoadjuvant treatment.

The included paper (n=142 evaluable patients) reported that after completion of neoadjuvant pembrolizumab treatment in the neoadjuvant-adjuvant group, 6% of

[9] Zubrod's performance-status scores range from 0 to 5, with higher scores indicating greater disability; a score of 0 indicates that the patient is fully active, 1 that the patient is restricted in strenuous activity but is ambulatory, and 2 that the patient is unable to work but is ambulatory and capable of self-care and up and about more than 50% of waking hours.

[10] Overall response was defined as the percentage change in tumour measurement from baseline using objective response (≥30% decrease) and disease progression (>20% increase) according to Response Evaluation Criteria in Solid Tumours.

[11] N=142 evaluable patients excludes the 10 patients still receiving neoadjuvant treatment and the two patients who withdrew consent after randomisation.

evaluable patients with advanced melanoma had a complete imaging-based response and 41% of evaluable patients had a partial response.

Safety

Patel et al (2023) reported that in patients with advanced melanoma who received neoadjuvant-adjuvant treatment, 11 of 152 (7%) evaluable patients had at least one grade 3 or 4 adverse event (e.g. fever, diarrhoea, sepsis) that was considered to be related to pembrolizumab, nine of 127 (7%) evaluable patients who completed surgery in the neoadjuvant-adjuvant group had at least one grade 3 or 4 adverse event (e.g. increase in alanine aminotransferase level, infections or infestations, wound infection) considered to be related to surgery. In patients with advanced melanoma in the adjuvant-only group, five of 141 (4%) evaluable patients had at least one grade 3 adverse event (e.g. chest-wall pain, seroma, skin infection) that was considered to be related to surgery (no grade 4 adverse events were noted). The authors reported that the number of adverse events of grade 3 or higher were similar in both treatment groups during adjuvant pembrolizumab treatment (12% in the neoadjuvant-adjuvant group and 14% in the adjuvant-only group). No deaths due to pembrolizumab were reported.

The included paper (n=313) reported that during neoadjuvant pembrolizumab treatment in the neoadjuvant-adjuvant group, 7% of evaluable patients (n=152) with non-advanced melanoma experienced at least one pembrolizumab-related grade 3 or 4 adverse event and 7% of evaluable patients (n=127) experienced a grade 3 or 4 adverse event related to surgery. Of the evaluable patients in the adjuvant-only group (n=141), 4% had at least one grade 3 adverse event related to surgery (no grade 4 adverse events were noted). Adverse events of grade 3 or higher were reported to be similar during adjuvant pembrolizumab treatment in both treatment groups. No deaths due to pembrolizumab were reported.

References

- Patel, S.P. et al. (2023) 'Neoadjuvant-adjuvant or adjuvant-only pembrolizumab in advanced melanoma,' The New England Journal of Medicine, 388(9), pp. 813-823. https://doi.org/10.1056/nejmoa2211437.