ORIGINAL REPORT

Perioperative Pembrolizumab in Locally Advanced Melanoma: A Real-world Single-centre Retrospective Study

Simon GOLLER[1†], Tassilo DEGE[1†], Patrick SCHUMMER[1], Lukas HAUG[2], Michael MEIR[3], Thomas GEHRKE[4], Detlef KLEIN[5], Matthias GOEBELER[1], Hermann KNEITZ[1], Bastian SCHILLING[6], Anja GESIERICH[1†] and Valerie GLUTSCH[1*†]

[1]Department of Dermatology, Venereology and Allergology, University Hospital Würzburg, Würzburg, Germany, [2]Dr. Senckenberg Institute of Pathology, University Hospital Frankfurt, Frankfurt am Main, Germany, [3]Department of General, Visceral, Transplant, Vascular and Paediatric Surgery, University Hospital Würzburg, Würzburg, Germany, [4]Department of Oto-Rhino-Laryngology, Plastic, Aesthetic and Reconstructive Head and Neck Surgery, University Hospital Würzburg, Würzburg, Würzburg, Germany, [5]Institute for Diagnostic and Interventional Radiology, University Hospital Würzburg, Würzburg, Germany, and [6]Department of Dermatology, Venereology and Allergology, University Hospital Frankfurt, Frankfurt am Main, Germany

†These authors contributed equally to this work.

Perioperative immune-checkpoint inhibition (ICI) using pembrolizumab (3 doses of pembrolizumab 200 mg every 3 weeks before surgery and 15 doses afterwards) in advanced resectable melanoma has shown substantial pathological response rates and improved event-free survival (EFS) compared to postoperative (adjuvant) ICI. Real-world evidence on efficacy and safety of perioperative ICI in melanoma remains limited. In this retrospective single-centre study, 20 patients with resectable stage IIIB–IV melanoma were treated with perioperative pembrolizumab. Radiological and pathological responses, early survival outcomes and treatment-related adverse events were analysed at a median follow-up of 13.9 months. Eighteen patients (18/20) underwent surgery. A pathological complete response was observed in 44% (8/18), while 56% (10/18) showed a pathological non-response. No patient (0/18) had a pathological partial response. One-year EFS was 66.5% (95% confidence interval (CI) 47.3–93.3), 1-year relapse-free survival 77.6% (95% CI 57.9–100) and 1-year overall survival 89.2% (95% CI 76.0–100, identical with 1-year melanoma-specific survival). Immune-related adverse events occurred in 50% of the patients (≥grade 3 in 15%). Our study confirms the feasibility of perioperative pembrolizumab in a real-world setting and shows promising efficacy and tolerability in melanoma. Pathological response may guide surgical and adjuvant strategies.

Key words: melanoma; neoadjuvant therapy; immunotherapy; pembrolizumab; retrospective studies; surgery.

Submitted Sept 7, 2025. Accepted after revision Oct 23, 2025

Published Jan 19, 2026.
DOI: 10.2340/actadv.v106.adv-2025-0009

Acta Derm Venereol 2026; 106: adv-2025-0009.

SIGNIFICANCE

In advanced resectable melanoma, perioperative immunotherapy with pembrolizumab (immunotherapy is initiated before surgery and continued afterwards) has shown improved outcomes compared to adjuvant immunotherapy (immunotherapy after surgery). Real-world evidence on this approach remains limited. In this retrospective single-centre study, 20 patients with resectable stage IIIB–IV melanoma were treated with perioperative pembrolizumab. Our results demonstrate that perioperative immunotherapy with pembrolizumab is a feasible and well-tolerated treatment approach in routine clinical practice. The observed pathological responses, survival outcomes and manageable safety profile underline its effectiveness and support its implementation beyond controlled clinical trial settings.

Corr: Valerie Glutsch, Department of Dermatology, Venereology and Allergology, University Hospital Würzburg, Josef-Schneider-Str. 2, Würzburg, Germany. Email: glutsch_v@ukw.de

Therapy of advanced melanoma has undergone a drastic change in the last decade with the emergence of immune-checkpoint inhibitors (ICI) (1) and targeted therapy (TT) with BRAF/MEK inhibitors (2). Starting in an advanced and mostly palliative setting, the treatment time point was gradually shifted earlier into the adjuvant (3) setting and has recently been extended to the presurgical setting for resectable stage III and IV melanoma (4). Presurgical immunotherapy targeting the PD-1/PD-L1 pathway is emerging as a promising strategy to enhance antitumour immunity and overcome resistance in advanced cancers by leveraging higher tumour burden and lymphocyte infiltration to better prime T cells before surgery (5).

In several clinical trials, this perioperative/neoadjuvant approach (presurgical plus adjuvant ICI) was compared to adjuvant ICI only. These trials included the OpACIN-neo (6) phase 2 trial, which evaluated 3 neoadjuvant dosing schemes of ipilimumab plus nivolumab (IPI/NIVO) in patients with resectable stage III melanoma to identify a regimen with reduced toxicity and sustained efficacy. The combination of ipilimumab 1 mg/kg and nivolumab 3 mg/kg showed a favourable balance of lower toxicity and high pathological response. The PRADO (Personalized Response-directed Surgery and Adjuvant Therapy after Neoadjuvant Ipilimumab and Nivolumab in High-risk Stage III Melanoma) trial (7) demonstrated that omitting lymph node dissection in patients with a major response to neoadjuvant IPI/NIVO was feasible, reduced morbidity and improved quality of life. Recently, the Southwest Oncology Group (SWOG) Cancer Research Network S1801 trial (8) compared 3 cycles of presurgical pembrolizumab followed by surgery and 15 adjuvant cycles vs surgery followed by 18 cycles of pembrolizumab (200 mg every 3 weeks (q3w)) for up to 1 year or until disease recurrence. This trial demonstrated an event-free survival (EFS) of 72% in the neoadjuvant-adjuvant group compared to 49% in the adjuvant-only group at 2 years, suggesting a shift in paradigm. In 2024, compelling data from the NADINA (Neoadjuvant Ipilimumab plus Nivolumab versus Standard Adjuvant Nivolumab in Macroscopic Stage III Melanoma) trial (9) once again underscored that the future of therapy for patients with metastatic but resectable melanoma lies in neoadjuvant treatment. These patients received 2 cycles of presurgical IPI/NIVO q3w followed by therapeutic lymph node dissection (TLND) and – if no major pathological response was achieved – proceeded either with adjuvant dabrafenib/trametinib or 11 cycles of adjuvant nivolumab (BRAF wild-type patients). In the adjuvant group, patients received upfront lymph-node dissection followed by 12 cycles of adjuvant nivolumab. With a 1-year EFS of 84% in the neoadjuvant group compared to only 57% in the adjuvant group, the neoadjuvant setting appeared to be clearly superior.

While perioperative/neoadjuvant immunotherapy has shown promising efficacy in multiple melanoma trials, its implementation in routine care remains complex. Clinical trials involve selected patients and structured protocols that may not reflect real-world practice. Therefore, real-world data are essential to assess feasibility, timing and safety of perioperative immunotherapy across broader patient populations, including those with comorbidities or logistical constraints. They also help evaluate the variability in immune-related toxicity and surgical outcomes outside of trial settings (10).

Here, we present retrospective data from a single-centre cohort of 20 patients treated with perioperative pembrolizumab 200 mg q3w, focusing on pathological and radiological responses, early survival outcomes and safety signals, providing insights into the clinical feasibility of this approach.

METHODS

In this retrospective cohort study, 20 patients with stage IIIB–IV (M1a) melanoma (according to the Cancer Staging Manual of the American Joint Committee on Cancer, 8th edition (11)), who were treated with perioperative pembrolizumab between February 2023 and June 2025 at the Department of Dermatology of the University Hospital Würzburg, Germany, were identified and retrospectively analysed. Patients received perioperative pembrolizumab 200 mg intravenously q3w according to the "neoadjuvant-adjuvant group" of the SWOG1801 trial (pembrolizumab 200 mg in weeks 0, 3, 6, radiological assessment in week 9 with subsequent surgery, followed by 15 cycles of adjuvant pembrolizumab) (8). Additional adjuvant radiotherapy postoperatively, as well as waiver of adjuvant pembrolizumab or replacement by adjuvant dabrafenib and trametinib, in patients with BRAF V600E/K mutation was permitted. Eligibility included resectable macroscopic nodal and/or in-transit/satellite metastases. Patients with concomitant resectable primary melanoma were also eligible. All cases were reviewed in a multidisciplinary grand round. All patients gave written informed consent regarding off-label perioperative use of pembrolizumab. All patients were alternatively offered immediate surgery and on-label adjuvant therapy.

Radiological response after the preoperative phase of pembrolizumab was assessed via Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 (12) using computed tomography (CT) of the chest and abdomen (and neck in patients with cervical nodal metastasis) and magnetic resonance imaging (MRI) of the brain. The pathological response was categorized into pathological complete response (pCR), pathological partial response (pPR) or pathological non-response (pNR) using the International Neoadjuvant Melanoma Consortium scoring system (13); in case of a divergent response of nodal metastases and synchronous lesions, the poorer response was used as the overall response.

Adverse events (AEs) were graded per CTCAE v5.0. Immune-related (ir) and surgical AEs were recorded. Follow-up included clinical, serological and radiological surveillance as per German guideline

recommendations. Survival outcomes were analysed using R (version 4.4.3; packages *ggplot2, prodlim, ranger, survival, survminer*). Overall survival (OS) and melanoma-specific survival (MSS) were measured from initiation of presurgical ICI to death from any cause or death from melanoma, respectively. Relapse-free survival (RFS) was measured from time of surgery until relapse. EFS was measured from initiation of presurgical ICI to failure to undergo surgery due to disease progression or AEs, failure to initiate adjuvant treatment due to disease progression or AEs, relapse after surgery, or death of any cause (analogous to SWOG S1801). Patients under ongoing treatment were censored at the data cut-off.

RESULTS

Baseline characteristics

The median age was 69 years (range 35–87). Most patients (95%) had stage IIIB/IIIC disease. One patient had resectable iliac nodal metastases without distant metastases (stage IV, M1a). BRAF V600E/K mutations were found in 9 patients (45%). All patients had an Eastern Cooperative Oncology Group performance Status ≤1. Additional synchronous primary melanoma was present in 2 cases (10%). In-transit/satellite metastases were present in 3 cases (15%), including one case without nodal metastasis (ID 18). Eighty percent (16/20) of the patients had measurable disease according to RECIST 1.1. Baseline characteristics are summarized in **Table I**.

Table I. Baseline characteristics

	Patients n/n (%)
Sex	
Male	16/20 (80)
Female	4/20 (20)
Subtype primary melanoma	
Superficial spreading melanoma	5/20 (25)
Nodular melanoma	6/20 (30)
Lentigo maligna melanoma	2/20 (10)
Acral-lentiginous melanoma	0/20 (0)
Not specified	4/20 (20)
Unknown primary	3/20 (15)
Anatomical region primary melanoma	
Head	4/20 (20)
Trunk	6/20 (30)
Extremities	7/20 (35)
Unknown primary	3/20 (15)
Stage (AJCC 8th edition)	
IIIB	5/20 (25)
IIIC	14/20 (70)
IV[a]	1/20 (5)
BRAF status	
Wildtype	8/20 (40)
V600E or V600K	9/20 (45)
Other[b]	3/20 (15)
NRAS status	
Wildtype	10/20 (50)
Q61R or Q61K	4/20 (20)
Other[c]	1/20 (5)
Not determined	3/20 (15)
ECOG PS	
0	18/20 (90)
1	2/20 (10)
LDH prior to perioperative ICI	
≤ULN	17/20 (85)
>ULN	3/20 (15)
S100 prior to perioperative ICI	
≤ULN	16/20 (80)
>ULN	4/20 (20)
Site of nodal metastases[d]	
Axilla	9/19 (47)
Groin	5/19 (26)
Neck	5/19 (26)
Additional synchronous lesions[d]	
Primary melanoma	2/19 (11)
In-transit or satellite metastases	2/19 (11)
Measurable disease according to RECIST 1.1	
Yes	16/20 (80)
No	4/20 (20)
Median age at start neoICI (years) (range)	69 (35–87)

Percentages may not add up to 100 due to rounding.
[a]One patient had operable iliac nodal metastases (M1a). [b]V600R, N581S, K601E. [c]Exon 4 NRAS mutation. [d]One patient without nodal metastasis (N=19) but satellite metastases.
AJCC:American Joint Cancer Committee; ECOG PS:Eastern Cooperative Oncology Group Performance Status; ICI:immune-checkpoint inhibition; LDH:lactate dehydrogenase; RECIST:Response Evaluation Criteria In Solid Tumours; S100:S100 protein; ULN:upper limit of normal.

Perioperative therapy and pathological and radiological responses

Of the 20 patients included in our analysis, 18 received 3 cycles of presurgical pembrolizumab (90%, **Table II**). Two patients received only 2 cycles due to progressive disease (PD) (ID 11) or due to an AE (ID 16, ir pancreatitis), respectively (**Fig. 1**).

Radiological response after the presurgical phase showed radiological partial response (rPR) in 40% (8/20), radiological stable disease (rSD) in 15% (3/20), radiological progressive disease (rPD) in 30% (6/20, including 1 patient without RECIST-measurable target lesion at baseline and unequivocal progression). Radiological complete response (rCR) was not observed. Three patients (15%) without measurable target lesions according to RECIST 1.1 at baseline were classified as "non-CR, non-PD".

Surgery was performed, and pathological response was assessed in 18 patients (90%). Surgery was not performed in 2 patients: one achieved deep rPR (almost rCR) without subsequent resection (ID 7), the other progressed locally and with new distant metastases to inoperable disease (ID 11). Surgery was performed at a median of 12.4 weeks after the first dose of pembrolizumab. In 1 patient, surgery was delayed due to an irAE (ID 16). Surgery included complete macroscopic tumour resection in 16 patients. In 2 patients (ID 2, ID 18), complete resection was waived after biopsy/selective resection of a representative satellite metastasis yielded pCR.

Pathological assessment showed pCR in 8/18 (44%) and pNR in 10/18 (56%) of our patients. pPR was not observed in our cohort. Radiological–pathological correlation was quite accurate (Table SI): all patients with rPR had a pCR, patients with rSD had pCR (1/3)

Table II. Therapeutic outcome

	Patients n/n (%)
Three cycles of ICI preoperative[a]	18/20 (90)
Radiological response	
CR	0/20 (0)
PR	8/20 (40)
SD	3/20 (15)
PD	6/20 (30)
Non-CR, non-PD[b]	3/20 (15)
Pathological response[c]	
CR	8/18 (44)
PR	0/18 (0)
NR	10/18 (56)
Adjuvant radiotherapy	
Yes	5/20 (25)
No	15/20 (75)
Adjuvant systemic therapy	
Adjuvant ICI	12/20 (60)
Adjuvant TT	2/20 (10)
None	6/20 (30)
Subsequent therapies	
ICI	2/20 (10)
Radiotherapy	1/20 (5)
None	17/20 (85)
Median time-to-surgery (weeks) (range)	12.4 (9.6–16.6)
Median Follow-up (months) (IQR)	13.9 (6.6–19.6)
Relapse-free survival	
One-year rate (%) (95 % CI)	77.6 (57.9–100)
Event-free survival	
One-year rate (%) (95 % CI)	66.5 (47.3–93.3)
Overall survival	
One-year rate (%) (95 % CI)	89.2 (76.0–100)
Melanoma-specific survival	
One-year rate (%) (95 % CI)	89.2 (76.0–100)

Percentages may not add up to 100 due to rounding.
[a]Two patients received only 2 cycles due to PD and escalation of therapy or due to adverse events, respectively. [b]Of 4 patients without target lesions according to RECIST 1.1 prior to ICI, 3 were classified as "non-CR, non-PD" and 1 as unequivocal PD. [c]Two patients were not evaluable for pathological assessment as no surgery was performed. In 1 patient, surgery was not performed due to deep PR (almost CR) on imaging, in the other patient due to PD to inoperable disease.
CI:confidence interval; CR:complete response; ICI:immune-checkpoint inhibition; IQR:interquartile range; NE:not evaluable; NR:non-response; PD:progressive disease; PR:partial response; SD:stable disease; TT:targeted therapy.

Table III. Adverse events

	Patients n/n (%)
irAE	
Any grade	10/20 (50)
Grade 1–2	7/20 (35)
≥Grade 3	3/20 (15)
≥2 irAE (any grade)	3/20 (15)
≥2 irAE (≥grade 2)	1/20 (5)
Organ system involved	
Endocrine	3/20 (15)
Gastrointestinal	2/20 (10)
Skin	2/20 (10)
Respiratory	1/20 (5)
Hepatic	1/20 (5)
Others[a]	5/20 (25)
Hospitalisation due to irAE	3/20 (15)
Sequelae due to irAE	
Hormone replacement	2/20 (10)
Other[b]	1/20 (5)
AE related to surgery	
Any	6/20 (30)
Lymphatic fistula	2/20 (10)
Wound infection	2/20 (10)
Drain dysfunction	2/20 (10)
Other[c]	3/20 (15)
Time-to-resolution of irAE (weeks), median (range)	30.1 (2.7–60.0)

Percentages may not add up to 100 due to rounding.
[a]Other documented adverse events were lymphopenia, sarcoid-like reaction, myalgia, fatigue and headache. [b]The other sequela due to adverse events was an ongoing myalgia. [c]Other post-surgical adverse events included lymphoedema, lymphocele and incarcerated incisional hernia with burst abdomen.
AE:adverse event; irAE:immune-related adverse event.

or pNR (2/3) and all patients with rPD had pNR. Surprisingly, the pathological response in synchronous lesions was often divergent from nodal metastases (Table SII).

Pembrolizumab was continued after surgery (adjuvant ICI) in 60% (12/20). In 2 patients with pNR and BRAF V600E mutation, adjuvant dabrafenib/trametinib was initiated instead. Five patients with pNR received additional adjuvant radiotherapy.

Survival outcomes

At a median follow-up of 13.9 months, 1-year EFS was 66.5% (95% CI 47.3–93.3), 1-year RFS 77.6% (95% CI 57.9–100) and 1-year OS 89.2% (95% CI 76.0–100, identical with 1-year MSS), respectively (**Fig. 2**).

Safety

Immune-related irAEs occurred in 10/20 patients (50%), with 3 patients (15%) experiencing ≥grade 3 irAEs. The most affected systems were endocrine, skin and gastrointestinal. Three patients (15%) were hospitalized due to an irAE. Immune-related AE resolution occurred within a median of 30.1 weeks.

Surgery-related AEs occurred in 6 patients (30%), including lymphatic fistulae, drain and wound complications. No treatment-related deaths occurred. Full safety data are provided in **Table III**.

DISCUSSION

This study presents one of the first real-world analyses of perioperative pembrolizumab in resectable stage III/IV melanoma, confirming the efficacy, feasibility and safety of this regimen outside clinical trials. Our observed pCR rate of 44% is very encouraging compared to SWOG S1801 (8), where pCR was achieved in only 21% of patients. Unfortunately, the pPR rate is not reported for the published cohort. Since we did not observe pPRs in our cohort, this might explain the compelling difference of >20%. However, an exploratory analysis (LBA48 (14)) of 89 patients of the SWOG S1801 cohort reported a pCR rate of 40% which is in line with our findings, whereby this analysis additionally showed 11% of near pCR and 29% of pPR. Also very similar to our results, to our knowledge, the only other real-world analysis of perioperative pembrolizumab reported 45% pCR (15, 16), and a real-world study of

neoadjuvant nivolumab monotherapy reported 35% pCR (17). These promising findings have to be interpreted in the context of differences in patient selection and, importantly, in pathology review procedures. The exploratory SWOG S1801 analysis incorporated centralized, blinded pathology review, which may yield higher pCR estimates due to standardized interpretation. A well-trained pathologist familiar with the methodology and guidelines is, therefore, essential for the pathological assessment of neoadjuvantly treated metastases, especially in the case of pathology-driven treatment decisions. The relevance of the pathological response assessment is underscored by the fact that none of our 8 patients with pCR relapsed so far, as seen in another real-world analysis of perioperative immunotherapy (18).

Early EFS in our real-world cohort – with a 1-year EFS of 66.5% – was somewhat lower than observed in the SWOG S1801 trial, which reported a 1-year EFS of approximately 75–80% and a 2-year EFS of 72%. A comparison of our real-world cohort to the SWOG S1801 trial reveals both overlaps and important differences in patient characteristics. The median age of our patients was older (69 vs 64 years), and our cohort included a higher proportion of patients with stage IIIC disease (70% vs 45%). These differences might therefore, at least in part, explain the differences in early survival outcomes, along with limitations in sample size and follow-up. Our analysis suggests that older patients may have a poorer outcome and were under-represented in clinical trial settings. This observation aligns with prior reports indicating that older individuals are frequently under-represented in pivotal melanoma trials such as NADINA and SWOG S1801, where the median age was typically below 65 years (19). The combination of age-related comorbidity, frailty and exclusion criteria likely contributes both to reduced inclusion and to inferior response rates in real-world populations. Similarly, for real-world neoadjuvant nivolumab, the reported 1-year EFS of 72% is somewhat inferior to SWOG S1801 (17). Of note, our 1-year RFS of 77.6%, which is not reported for the SWOG 1801 cohort, is slightly better than for real-world neoadjuvant nivolumab, which is reported

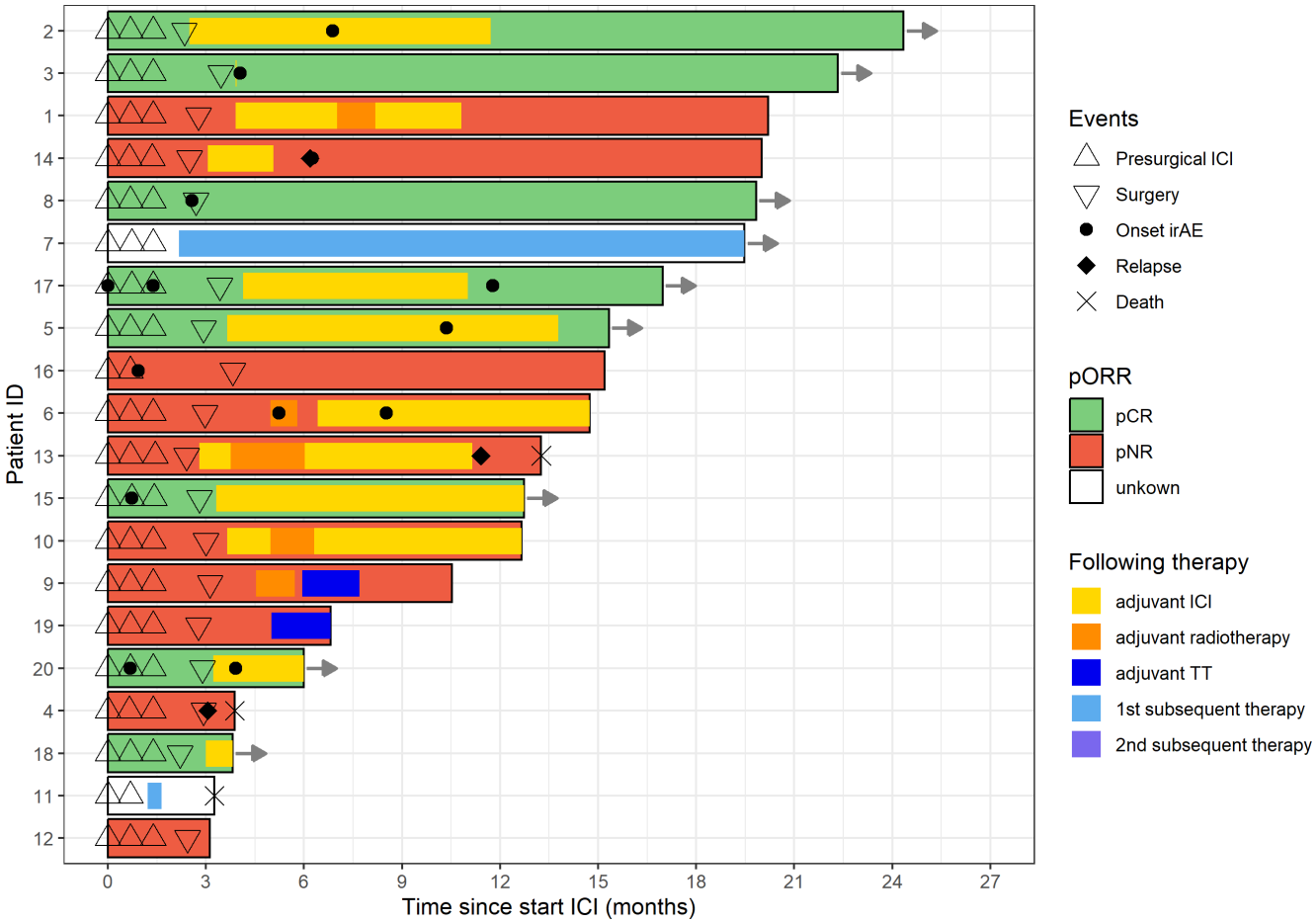

Fig. 1. Swimmer plot demonstrating outcome since initiation of perioperative ICI (n=20). ICI, immune checkpoint inhibition. irAE, immune-related adverse event. pORR, pathological overall response rate. pCR, pathological complete response. pNR, pathological non-response. TT, targeted therapy. The arrows indicate ongoing response at data cut-off. For ID 14, no information on following therapies was available due to change to another center (only survival status).

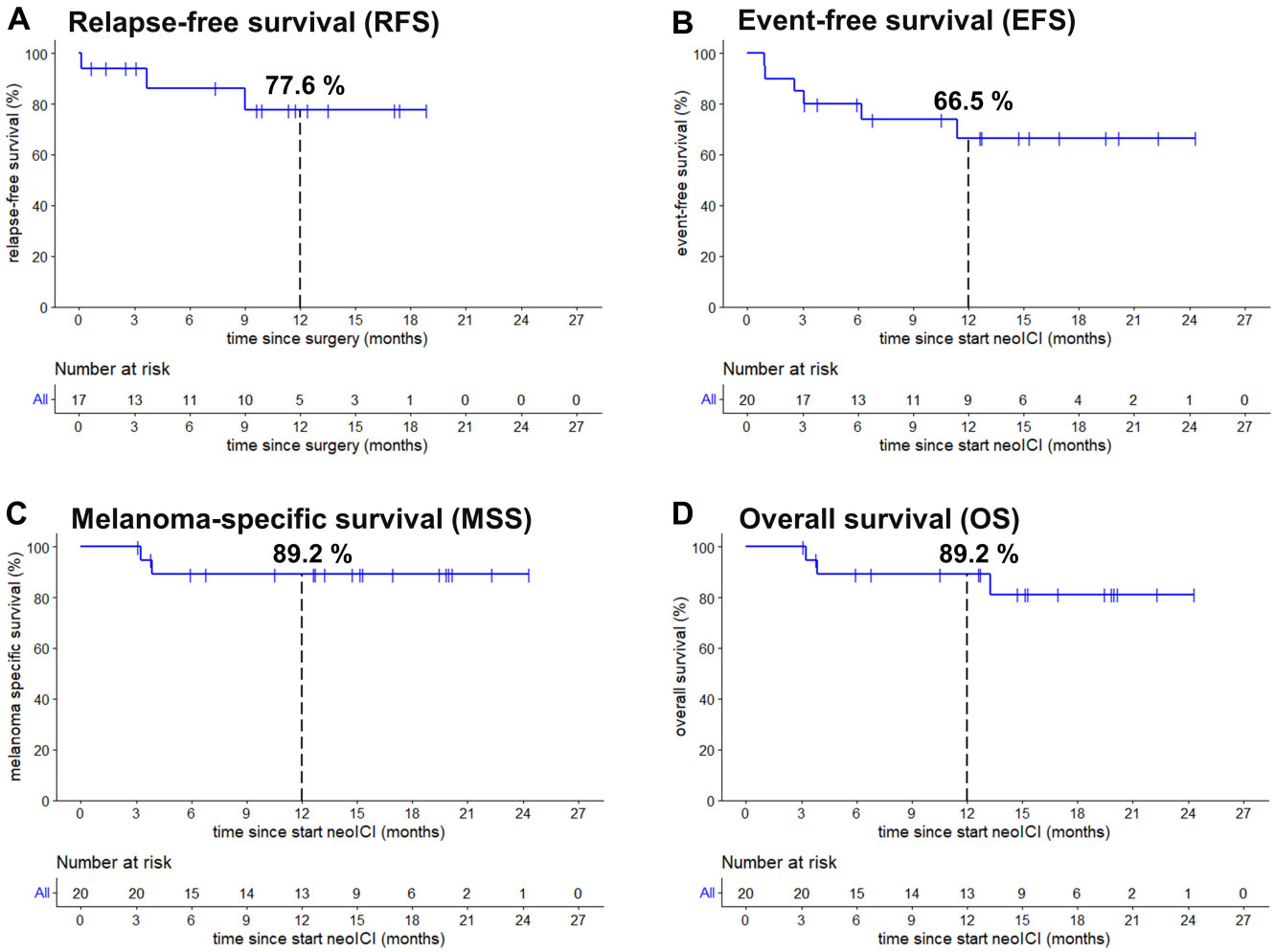

Fig. 2. Kaplan–Meier plots showing (A) relapse-free survival, (B) event-free survival, (C) melanoma-specific survival and (D) overall survival.

with 74% (17). Hence, early EFS and RFS outcomes seem to be comparable across the available retrospective real-world analyses.

Despite these poorer real-world outcomes, perioperative ICI still seems to be clearly superior compared to adjuvant therapy. This applies in comparison to data from clinical trials (1-year EFS of approximately 60% in the adjuvant group of SWOG 1801 compared with 66.5% in our perioperative real-world study), as well as compared to real-world evidence (20). In the real-world analysis recently published by Lodde et al., 1-year RFS was 68.7% in the adjuvant-only setting compared to 77.6% in our study. This supports the perioperative/neoadjuvant therapy approach as the new standard of care in these patients.

Our analysis included 4 patients without RECIST-measurable target lesions. Their lesions were too small (lymph nodes with <15 mm in short axis diameter) according to RECIST 1.1 criteria. Notably, all 4 patients were pathological non-responders. While this observation is based on a small number of patients, it raises the hypothesis that a certain degree of tumour burden may be necessary for effective priming of the antitumour immune response during presurgical therapy. This is in line with preclinical evidence suggesting that sufficient antigen exposure and T cell expansion are required for durable responses to ICI (21). Hence, perioperative treatment should be carefully evaluated for patients with low tumour burden.

In our study, some more special scenarios were addressed. One patient achieved a near rCR after 3 cycles of pembrolizumab (ID 7; follow-up time 19.5 months) and 2 patients achieved a pCR in biopsy/selective resection of a satellite metastasis (ID 2, follow-up time 24.3 months; ID 18, follow-up time 3.8 months). These patients, therefore, did not undergo lymph node dissection. Importantly, none of these 3 patients relapsed during follow-up, and the patient with near rCR showed metabolic CR in the meantime. These cases raise the important clinical consideration of whether complete or near-complete responses to neoadjuvant therapy could justify omitting full lymph node dissection in selected patients. While this approach remains investigational, it is supported by findings from the PRADO trial (7), where omission of TLND was

feasible in patients with major or complete pathological responses based on a pre-marked index node. Marker-based assessment of a single "sentinel" or "index" lymph node (e.g. via seed localization) may serve as a powerful tool to guide surgical extent. The PRADO trial demonstrated that pathological assessment of a single marked node can reliably predict overall pathological response. These cases further support the concept that, in patients with strong radiological or clinical regression, a less invasive surgical approach may be sufficient and should be further explored in prospective real-world settings.

In addition, we have switched the treatment of our patients to TT in the adjuvant setting in 2 patients with pNR and a BRAF V600 mutation. This was aligned with the convincing response-driven approach in the NADINA trial (22). Both patients have not relapsed at data cut-off (ID 9, follow-up time 10.5; ID 19, follow-up time 6.8 months). In this context, an update regarding the RFS and EFS of the NADINA data, as well as a longer follow-up and a higher number of patients in the real-world setting, is necessary to substantiate these encouraging results.

Importantly, the safety profile in our real-world cohort was favourable, with irAEs occurring in 50% of patients and only 15% experiencing severe AEs (≥grade 3). No treatment-related deaths were recorded. Only 1 patient (5%) progressed during neoadjuvant therapy to inoperability due to local and distant metastases. These findings compare well to the data from SWOG S1801, where grade ≥3 treatment-related AEs occurred in 12% in the neoadjuvant group. In the NADINA trial, grade ≥3 treatment-related AEs, however, occurred in approximately twice as many patients (29.7%), which confirms the known higher toxicity of neoadjuvant IPI/NIVO. Therefore, neoadjuvant combined immunotherapy is only appropriate after thorough patient selection (preferably for patients with symptomatic disease), despite better efficacy outcomes. The lower toxicity rate and yet low inoperability rate emphasize the clinical safety and feasibility of perioperative anti-PD1 monotherapy with pembrolizumab in routine practice. With careful patient selection and close monitoring, treatment delays or irreversible progression appear to be rare, even outside of trial settings.

The major limitations of this study are the small sample size, the short follow-up and ongoing data collection. In addition, adjuvant therapy was not performed in all patients. Nonetheless, our findings support the continued investigation of de-escalation strategies, such as selective omission of lymph node dissection and tailored adjuvant therapy based on pathological response. However, the reliability of radiological response alone remains limited, and incorporation of minimally invasive nodal sampling techniques may be necessary to confidently guide treatment de-escalation.

In conclusion, the observed response rates, safety profile and feasibility of surgery after presurgical immunotherapy confirm the practicability of perioperative pembrolizumab in a real-world setting. Larger datasets and long-term outcomes will help define optimal patient selection, response assessment tools and adjuvant therapy strategies.

ACKNOWLEDGEMENTS

Simon Goller is supported by TWINSIGHT, a Clinician Scientist Program at the Medical Faculty of the University of Würzburg funded by the Else Kröner-Fresenius Stiftung (project number: TWINSIGHT-10). Tassilo Dege has been supported by the Clinician Scientist Program of the Interdisciplinary Center of Clinical Research (IZKF; project number: Z-2/CSP-25), Medical Faculty, University of Würzburg.

Data availability statement: Data will be shared upon reasonable request to the corresponding author.

Ethics committee: The retrospective analysis of patient data was approved by the Ethics Committee of the University of Würzburg (2025-17-dvh, 2025-92-ka). All patients provided written informed consent.

Conflict of interest: Simon Goller has received travel support from Novartis, Pierre Fabre Pharmaceuticals and Recordati Rare Diseases and reports a speaker's honorarium by Recordati Rare Diseases, outside the submitted work. *Tassilo Dege* has received speaker's honoraria from Leo Pharma and Johnson & Johnson and travel support from Johnson & Johnson, outside the submitted work. *Patrick Schummer* has received honoraria from Bristol-Myers Squibb, an institutional research grant from Novartis, and reports travel support from Bristol-Myers Squibb, Lilly, Sanofi-Aventis, Novartis, Pierre Fabre Pharmaceuticals and Sun Pharmaceuticals, outside the submitted work. *Lukas Haug* has received speaker's honoraria from MSD Sharp & Dohme, outside the submitted work. *Michael Meir* has no conflicts of interest to declare. *Thomas Gehrke* has no conflicts of interest to declare. *Detlef Klein* has no conflicts of interest to declare. *Matthias Goebeler* served as a consultant and/or has received speaker's honoraria and/or reimbursement of travelling expenses from Almirall, Argenx, Biotest, Fresenius, GSK, Janssen, Leo Pharma, Lilly, Novartis, UCB, outside the submitted work. *Hermann Kneitz* has no conflicts of interest to declare. *Bastian Schilling* reports consultancy, speaker fees and/or travel grants from SUN Pharma, Immunocore, Blueprint Medicine, Regeneron, BMS, Sanofi and Pierre Fabre Pharmaceuticals, outside the submitted work. *Anja Gesierich* served as a consultant and/or has received honoraria or travel costs from Allmiral, Amgen, Bristol-Myers Squibb, Immunocore, MSD Sharp & Dohme; Novartis, Pierre Fabre Pharmaceuticals, Pfizer, Regeneron, Roche, Sanofi Genzyme and SUN Pharmaceuticals, outside the submitted work. *Valerie Glutsch* has received honoraria from Bristol-Myers Squibb and Pierre Fabre Pharmaceuticals and reports travel support

from Novartis, Pierre Fabre Pharmaceuticals, Bristol-Myers Squibb, Merck Sharp & Dohme, Sanofi Genzyme and SUN Pharmaceuticals, outside the submitted work.

REFERENCES

1. Wolchok JD, Chiarion-Sileni V, Rutkowski P, Cowey CL, Schadendorf D, Wagstaff J, et al. Final 10-year outcomes with nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2025; 392: 11–22. https://doi.org/10.1056/NEJMoa2407417
2. Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014; 371: 1867–1876. https://doi.org/10.1056/NEJMoa1408868
3. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018; 378: 1789–1801. https://doi.org/10.1056/NEJMoa1802357
4. Boulva K, Apte S, Yu A, Tran A, Shorr R, Song X, et al. Contemporary neoadjuvant therapies for high-risk melanoma: A systematic review. Cancers (Basel) 2021; 13. https://doi.org/10.3390/cancers13081905
5. Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. Science (New York, NY) 2020; 367: eaax0182. https://doi.org/10.1126/science.aax0182
6. Rozeman EA, Menzies AM, van Akkooi ACJ, Adhikari C, Bierman C, van de Wiel BA, et al. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): A multicentre, phase 2, randomised, controlled trial. Lancet Oncol 2019; 20: 948–960. https://doi.org/10.1016/S1470-2045(19)30151-2
7. Reijers ILM, Menzies AM, van Akkooi ACJ, Versluis JM, van den Heuvel NMJ, Saw RPM, et al. Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: The PRADO trial. Nat Med 2022; 28: 1178–1188. https://doi.org/10.1038/s41591-022-01851-x
8. Patel SP, Othus M, Chen Y, Wright GP Jr, Yost KJ, Hyngstrom JR, et al. Neoadjuvant-adjuvant or adjuvant-only pembrolizumab in advanced melanoma. N Engl J Med 2023; 388: 813–823. https://doi.org/10.1056/NEJMoa2211437
9. Blank CU, Lucas MW, Scolyer RA, van de Wiel BA, Menzies AM, Lopez-Yurda M, et al. Neoadjuvant nivolumab and ipilimumab in resectable stage III melanoma. N Engl J Med 2024; 391: 1696–1708. https://doi.org/10.1056/NEJMoa2402604
10. Schummer P, Glutsch V, Haug L, Rosenfeldt M, Lock J, Meir M, et al. Neoadjuvant ipilimumab plus nivolumab in locally advanced melanoma: A real-world single-centre retrospective study. EJC Skin Cancer 2023; 1: 100003. https://doi.org/10.1016/j.ejcskn.2023.100003
11. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017; 67: 472–492. https://doi.org/10.3322/caac.21409
12. Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer 2016; 62: 132–137. https://doi.org/10.1016/j.ejca.2016.03.081
13. Amaria RN, Menzies AM, Burton EM, Scolyer RA, Tetzlaff MT, Antdbacka R, et al. Neoadjuvant systemic therapy in melanoma: Recommendations of the International Neoadjuvant Melanoma Consortium. Lancet Oncol 2019; 20: e378–e389. https://doi.org/10.1016/S1470-(19)30332-8
14. Patel S, Othus M, Wright P, Hyngstrom J, Lao CD, Truong TG, et al. LBA48 Pathologic response and exploratory analyses of neoadjuvant-adjuvant versus adjuvant pembrolizumab (PEM) for resectable stage IIIb-IV melanoma from SWOG S1801. Ann Oncol 2023; 34: S1288. https://doi.org/10.1016/j.annonc.2023.10.042
15. Nardin C, Cavalieri C, Lebbé C, Gérard E, Puyraveau M, Vergara R, et al. Neoadjuvant immune checkpoint inhibitors for patients with resectable stage III/IV melanoma: A nationwide real-life study in France (NEOMEL). Br J Dermatol Br J Dermatol 2025 Jul 14. [Online ahead of print]. https://doi.org/10.1093/bjd/ljaf268
16. Nardin C, Cavalieri C, Lebbe C, Pagès C, Gérard E, Rouanet J, et al. Neoadjuvant immune checkpoint inhibitors for patients with resectable stage III/IV melanoma: A nationwide real-life study in France (NEOMEL). JCO 2024; 42: 9578–9578. https://doi.org/10.1200/JCO.2024.42.16_suppl.9578
17. Nelson A, Krabbe E, Björkström K, Huibers A, Jovanovic B, Blank CU, et al. Neoadjuvant immunotherapy for patients with resectable stage III/IV cutaneous melanoma - A Swedish retrospective real-world study (NEO-MEL). Eur J Cancer 2025; 224: 115485. https://doi.org/10.1016/j.ejca.2025.115485
18. Tomsitz D, Zimmermann P, Kunz WG, Neumann J, Siegmund BJ, Weiss BG, et al. Neoadjuvant treatment with immune checkpoint inhibitors in patients with melanoma: A real-life retrospective study. J Dtsch Dermatol Ges 2025; 23: 600–608. https://doi.org/10.1111/ddg.15632
19. Iacono D, Vitale MG, Basile D, Pelizzari G, Cinausero M, Poletto E, et al. Immunotherapy for older patients with melanoma: From darkness to light? Pigment Cell Melanoma Res 2021; 34: 550–563. https://doi.org/10.1111/pcmr.12917
20. Lodde GC, Hassel JC, von Wasielewski I, Meier F, Mohr P, Kähler K, et al. Long-term follow-up of real-world adjuvant anti-PD1 checkpoint inhibition and targeted therapy in stage III melanoma patients. J Clin Oncol 2025. https://doi.org/10.1200/JCO-1224-02776
21. Cabrita R, Lauss M, Sanna A, Donia M, Skaarup Larsen M, Mitra S, et al. Tertiary lymphoid structures improve immunotherapy and survival in melanoma. Nature New Biol 2020; 577: 561–565. https://doi.org/10.1038/s41586-019-1914-8
22. Blank CU, Lucas MW, Scolyer RA, van de Wiel BA, Menzies AM, Lopez-Yurda MI, et al. Neoadjuvant nivolumab plus ipilimumab versus adjuvant nivolumab in macroscopic, resectable stage III melanoma: The phase 3 NADINA trial. JCO 2024; 42: LBA2–LBA2. https://doi.org/10.1200/JCO.2024.42.17_suppl.LBA2