ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Neoadjuvant intralesional targeted immunocytokines (daromun) in stage III melanoma

K. C. Kähler[1], J. C. Hassel[2], M. Ziemer[3], P. Rutkowski[4], F. Meier[5,6], L. Flatz[7], C. Gaudy-Marqueste[8], L. Zimmer[9,10,11,12,13], M. Santinami[14], F. Russano[15], I. von Wasielewski[16], T. K. Eigentler[17], M. Maio[18], I. Zalaudek[19], S. Haferkamp[20], P. Quaglino[21], J. Welzel[22,23], C. Röcken[1], A. Enk[2], J.-C. Simon[3], T. Świtaj[4], M. Garzarolli[5,6], T. Amaral[7], N. Malissen[8], E. Livingstone[9,10,11,12,13], G. Elia[24], A. Covelli[25], K. Lorizzo[25], D. Neri[25], S. Mulatto[25], A. Parca[25], B. Pizzichi[25], P. A. Ascierto[26], C. Garbe[7], C. Robert[27], D. Schadendorf[9,10,11,12,13] & A. Hauschild[1]*

[1]University Hospital Schleswig-Holstein, Campus Kiel, Kiel; [2]Department of Dermatology and National Center for Tumor Diseases (NCT), NCT Heidelberg, Medical Faculty Heidelberg, Heidelberg University, Heidelberg; [3]Skin Cancer Center, University Hospital Leipzig, Leipzig, Germany; [4]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [5]Department of Dermatology, University Hospital Carl Gustav Carus, TU Dresden, Dresden; [6]Skin Cancer Center, University Cancer Centre and National Center for Tumor Diseases, Dresden; [7]Department of Dermatology, University Hospital of Tuebingen, Tuebingen, Germany; [8] Dermatology and Skin Cancer Department, APHM, CRCM INSERM U1068, CNRS U7258, La Timone Hospital, Aix-Marseille University, Marseille, France; [9] Westdeutsches Tumorzentrum (WTZ), University Hospital Essen, Essen; [10]National Center for Tumor Diseases (NCT-West), Campus Essen, Essen; [11]German Cancer Consortium, Partner Site Essen, Essen; [12]Research Alliance Ruhr, Research Center One Health, [13]University Duisburg-Essen, Campus Essen, Essen, Germany; [14] Istituto Nazionale dei Tumori (INT), Fondazione IRCCS, Milano; [15]Istituto Oncologico Veneto (IOV), IRCCS, Padua, Italy; [16]Department of Dermatology, Allergology and Venerology, Claudia von Schilling Comprehensive Cancer Center, Hannover Medical School, Hannover; [17]Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [18]Center for Immuno-Oncology, University Hospital of Siena, Siena; [19]Department of Dermatology and Venereology of the Medical University of Triest, Triest, Italy; [20]University of Regensburg, Regensburg, Germany; [21] Dermatologic Clinic, Department of Medical Sciences, University of Turin, Turin, Italy; [22]Department of Dermatology, University Hospital Augsburg, Augsburg; [23]Bavarian Cancer Research Center BZKF, Augsburg, Germany; [24]Philochem AG, Otelfingen, Switzerland; [25]Philogen S.p.A., Siena; [26]Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Naples, Italy; [27]Gustave Roussy and Paris-Saclay University, Villejuif-Paris, France

Available online 7 July 2025

Background: This phase III trial assessed daromun, a combination of two fibronectin-targeting immunocytokines (L19IL2 and L19TNF), as a neoadjuvant treatment for patients with clinically detectable stage IIIB/C melanoma [American Joint Committee on Cancer (AJCC) version 7].

Patients and methods: Patients were randomized to weekly intralesional daromun administrations (13 million IU of L19IL2 and 400 μg of L19TNF) for 4 weeks followed by surgery, or upfront surgery. Pretreatment with approved adjuvant agents was allowed. The primary endpoint was recurrence-free survival (RFS): events were disease recurrence or death from any cause after complete surgical tumor resection (ClinicalTrials.gov NCT02938299).

Results: A total of 246 patients were randomized and included in the intention-to-treat analysis: 74% had undergone two or more prior surgical resections and 35% had received prior systemic therapy. At a median follow-up of 21 months, the neoadjuvant group ($n = 122$) had a significantly longer RFS than the upfront surgery group ($n = 124$), with a median RFS of 16.7 months and 6.8 months, respectively [hazard ratio (HR) 0.59, 95% confidence interval (CI 0.41-0.86), $P = 0.005$, log-rank test]. The risk of distant recurrence was reduced by 40% in the neoadjuvant arm (HR 0.60, 95% CI 0.37-0.95, $P = 0.029$). Grade $\geq$3 treatment-related adverse events (TRAEs) were 6.7% in the surgery-alone arm and 27.1% in the daromun arm, mostly injection site reactions.

Conclusions: Neoadjuvant daromun resulted in a significantly longer RFS than upfront surgery in patients with locally advanced melanoma. TRAEs were transient and manageable. Neoadjuvant daromun is a new therapeutic option for patients with stage III melanoma, including those with locoregional recurrence after surgery and previous adjuvant therapy.

Key words: neoadjuvant, melanoma, resectable, locally advanced, targeted immunocytokines, immunotherapy, intralesional

INTRODUCTION

Recent studies[1,2] have demonstrated a role for systemic neoadjuvant immunotherapy in stage III melanoma.[3,4] In the randomized phase II SWOG-1801 trial, the neoadjuvant—adjuvant pembrolizumab group showed significantly longer event-free survival [EFS; hazard ratio (HR) 0.58, 95%

*Correspondence to: Dr Axel Hauschild, Department of Dermatology, University Hospital (UKSH), Kiel, Germany. Tel: +49 431 50021131
E-mail: ahauschild@dermatology.uni-kiel.de (A. Hauschild).

confidence interval (CI) 0.39-0.87, $P = 0.004$] at a median follow-up of 14.7 months than the adjuvant-only group.[1] In the phase III NADINA trial, at a median follow-up of 9.9 months, the estimated 12-month EFS was 83.7% in the neoadjuvant ipilimumab + nivolumab group and 57.2% in the adjuvant group (HR 0.32, 99.9% CI 0.15-0.66).[2] Both studies specifically enrolled patients with clinically detectable stage III (NADINA) or stage III/IV (SWOG-1801) resectable melanoma at their initial presentation or at the time of the first detected metastases and no prior exposure to systemic immunotherapies [e.g. anti-CTLA-4, Programmed cell death protein 1 (PD-1) or Programmed death-ligand 1 (PD-L1)] or targeted agents [V-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF) and/or mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors].

Neoadjuvant intralesional therapy with talimogene laherparepvec (T-VEC), an oncolytic genetically engineered herpes simplex virus 1 that produces granulocyte-macrophage colony-stimulating factor, was evaluated in resectable stage IIIB to IVM1a melanoma. In a randomized phase II study (NCT02211131), at a median follow-up of 63.3 months, the 5-year recurrence-free survival (RFS) was 22.3% in arm 1 (neoadjuvant T-VEC plus surgery) and 15.2% in arm 2 (surgery alone) (HR 0.76, 80% CI 0.60-0.97).[5]

Daromun, the combination of L19IL2 and L19TNF, has been studied in locally advanced melanoma: its mechanism of action is based on the specific activities of the two cytokines, each fused to L19, a fully human antibody fragment that binds to the alternatively spliced extra- domain B (EDB) of fibronectin (FN),[6] a known marker of neoangiogenesis.[7,8] A moderate to strong, diffuse expression of EDB FN can be observed in the majority of metastatic melanoma lesions. Conversely, a weak expression of EDB characterizes most primary melanoma lesions, and no expression of such isoform is detected in normal skin.[9] Antibody—cytokine fusions with the L19 moiety are preferentially anchored to the tumor stroma:[10,11] their residence time in the injected lesions is much longer ($\geq$72 h) than that of nontargeted cytokines ($<$24 h).[11]

In a phase II study in 22 patients with unresectable stage III-IVM1a melanoma, intralesional daromun resulted in a high proportion of objective responses even in noninjected melanoma lesions [objective response, 69%, complete response, 54%], suggesting a local and systemic immune response.[12]

Here we report the results of the phase III PIVOTAL trial, which evaluated the efficacy and safety of neoadjuvant intralesional daromun followed by surgery versus upfront surgery, in patients with resectable locally advanced melanoma, most of whom had recurrence after prior surgery and/or adjuvant therapy, a more advanced population, to our knowledge, than the patients typically enrolled in other neoadjuvant trials in stage III melanoma.

METHODS

Trial design

PIVOTAL is an open-label, randomized, controlled, multicenter phase III trial (ClinicalTrials.gov NCT02938299) (see Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.06.014 for a visual representation of the study design). The trial was conducted at 22 sites in four countries (Germany, Italy, France, and Poland) from July 2016 to August 2023. Adult patients with locally advanced malignant melanoma of the skin who had at least one skin or nodal lesion eligible for complete surgical resection were enrolled. Prior antitumor treatment including surgery, radiotherapy, and approved systemic therapy was allowed.

Patients were randomly assigned in a 1 : 1 ratio to receive either neoadjuvant daromun followed by surgery (arm 1) or upfront surgery (arm 2). In the experimental arm 1, daromun—a mixture of 13 million IU of L19IL2 and 400 µg of L19TNF—was administered intratumorally to all injectable skin and nodal tumors of the patients, once a week (q1W) for up to 4 weeks, followed by surgery within 4 weeks after last treatment. Patients randomized to the control arm 2 underwent surgical resection of all existing melanoma tumor lesions within 4 weeks from randomization.

Post-operative treatment with European Medicines Agency-approved adjuvant therapies was allowed in both arms at the discretion of the treating physician (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.06.014—Study design).

Patients were observed for disease recurrence until the first recurrence (or unacceptable toxic effects, withdrawal of consent, or death, whichever occurred first) was documented or up to 36 months after randomization. Thereafter, patients were monitored for survival for up to 60 months after randomization.

Data on adverse events (AEs) were collected throughout the trial until 90 days after completion or discontinuation of treatment and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Comprehensive data regarding clinical, laboratory, and imaging tumor assessments is included in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2025.06.014.

Patient population

The study's participants were adults (aged $\geq$18 years) with locally advanced malignant melanoma of the skin [defined as stage IIIB and IIIC according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system]. Patients had to have measurable disease and be candidates for intralesional therapy with at least one injectable skin or nodal melanoma lesion ($\geq$10 mm in longest diameter) or multiple injectable lesions with a combined longest diameter $\geq$10 mm. Prior antitumor treatments, including surgery, radiotherapy, and approved systemic treatments (e.g. adjuvant immune checkpoint inhibitors, BRAF/MEK inhibitors, etc.) were allowed. An Eastern Cooperative Oncology Group (ECOG) performance status $\leq$1 and a life expectancy of $\geq$24 months were prerequisites for enrollment. The range of acceptable laboratory values at screening was as follows: absolute neutrophil

count $>1.5 \times 10^9$/l, hemoglobin >9.0 g/dl, platelets $>100 \times 10^9$/l, total bilirubin ≤30 μmol/l (or ≤2.0 mg/dl), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × the upper limit of normal (ULN), serum creatinine <1.5 × ULN, and a serum lactate dehydrogenase (LDH) level ≤1.5 × ULN.

Patients with a diagnosis of uveal or mucosal melanoma, melanoma of unknown primary, or the presence of distant metastases at the time of screening were excluded from the study. The following criteria were used to determine exclusion from the study: the presence of other previous or concurrent cancers (with the exception of cervical carcinoma *in situ*, treated basal cell carcinoma, superficial bladder tumors, second primary melanoma *in situ*, or any cancer curatively treated ≥5 years before study entry), the presence of active infections (e.g. requiring antimicrobial therapy), cardiac disease or abnormalities, uncontrolled hypertension, ischemic peripheral vascular disease (grade IIb-IV), severe diabetic retinopathy, history of organ allograft or stem cell transplantation, and autoimmune disease. A comprehensive list of inclusion and exclusion criteria can be found in the protocol and summary of amendments (Supplementary Appendix 1, available at https://doi.org/10.1016/j.annonc.2025.06.014).

Study assessments

All patients underwent a screening visit within 2 weeks before randomization and were required to undergo 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) imaging at the screening visit. Confirmatory biopsies of clinically diagnosed regional melanoma metastases were not mandatory.

Patients randomized to the experimental arm 1 underwent a tumor assessment at the scheduled end of daromun treatment and before surgery (within week 5-8 of starting neoadjuvant treatment). Digital photography was used to document the evolution of cutaneous injected lesions at the conclusion of the treatment period. Histopathology was assessed at the treating site on all excised lesions. A review of institutional pathology reports on surgical specimens from patients in arm 1 was carried out to assess the rate of pathological complete response. Furthermore, a subset of patients underwent immunohistochemical analysis of tumor-infiltrating lymphocyte populations.

Assessment of human antifusion protein antibody (HAFA) formation against L19IL2 and L19TNF was carried out in arm 1 patients before the first and second dose, on the day of the safety visit, and at the first follow-up visit (Supplementary Appendices 1 and 2, available at https://doi.org/10.1016/j.annonc.2025.06.014).

For both arms, tumor assessments were then carried out every 3 months after randomization (6 months for imaging by FDG-PET/CT) for a maximum of 36 months after randomization or until evidence of disease progression or until the withdrawal of consent. At each tumor assessment visit, a complete physical examination and regional lymph node sonography were carried out. Digital photography was used to document the appearance of local cutaneous recurrences. FDG-PET/CT scans were routinely recorded every 6 months or whenever, in the opinion of the treating physician, the occurrence of new visceral lesions was suspected. The recurrence of these lesions was subsequently confirmed by retrospective blinded independent central review (BICR) of the imaging data. Furthermore, follow-up visits or telephone contacts (for patients with disease progression) were conducted at least every 6 months up to 60 months to ascertain OS.

AE data were collected throughout the study until 90 days after completion or discontinuation of treatment and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

A comprehensive array of hematological analyses were conducted, encompassing platelet count, red blood cell count, white blood cell count, hemoglobin, and hematocrit. In addition, chemical parameters such as creatinine, blood urea nitrogen, creatine kinase, potassium, sodium, uric acid, chloride, total protein, albumin, LDH, calcium, glucose, phosphorus, and magnesium were measured. Liver function tests (AST and ALT, total bilirubin, gamma glutamyl transferase, and alkaline phosphatase) and coagulation [prothrombin time, activated partial thromboplastin time, and international normalized ratio (INR)] were carried out for both arms during screening within 2 weeks before randomization and at the time of surgery. For arm 1, these analyses were also carried out at each treatment visit and on the day of the safety assessment (at 1 week after the last daromun dose). Pregnancy tests (by serum, when appropriate) were carried out at screening in both arms and repeated at the safety visit in arm 1 only.

Primary and secondary endpoints

The primary endpoint was RFS as assessed by BICR and defined as the time from the date of randomization to the date of the first documented disease recurrence or death from any cause after complete surgical resection of the tumor. Patients who did not undergo surgery or were found to have noncompletely resectable disease at surgery were censored at the date of the last assessment.

Two interim analyses of RFS were planned at ∼24 events (25% information fraction), and at 48 events (50% information fraction). The Lan—DeMets alpha spending function was implemented to determine the required nominal alpha level given the information fraction at the time of the analysis.

Secondary endpoints encompassed OS, distant metastasis-free survival (DMFS), and pathologically documented response (pathological response). OS was defined as the time from randomization to death from any cause: alive subjects were censored at the date of last assessment. DMSF was defined as the time from randomization to first distant metastasis or death without recurrence, whichever came first. Subjects alive and without distant metastasis were censored at the date of last assessment. This endpoint

may be affected by informative censoring as patients with first local recurrence were not followed up for distant metastases.

Histopathological analysis of tumor response to neoadjuvant treatment was carried out on all surgically removed lesions. Given the absence of specific guidance for assessing the pathological response and the lack of a centralized pathology review, a review of institutional pathology reports on surgical specimens from arm 1 patients was carried out to assess the rate of pathological complete response.

Full details and a full list of secondary and exploratory endpoints can be found in the protocol and summary of amendments (Supplementary Appendices 1 and 2, available at https://doi.org/10.1016/j.annonc.2025.06.014).

Trial oversight

The study was funded by Philogen S.p.A. The original protocol and all amendments were approved by the institutional review board or independent ethics committee at each participating site and by the relevant national authorities. Written informed consent was obtained from study participants and approved by the institutional review board at each site. The trial was conducted in accordance with ethical guidelines including Good Clinical Practice standards and the principles of the Declaration of Helsinki.

The study design was reviewed by external scientific experts and by personnel of the sponsor (Philogen S.p.A.). The sponsor funded the study, maintained the study database, and was involved in data collection, data analysis, data interpretation, and the writing of this report. The data were analyzed and interpreted by the authors, who wrote the article without any additional writing assistance.

All the authors had access to the full data used in the manuscript and vouch for the accuracy and completeness of the data and for the trial's adherence to the protocol.

Statistical analysis

The primary endpoint, RFS, defined as the time from the date of randomization to the date of the documented first disease recurrence or death from any cause after complete surgical resection of the tumor, was assessed in the intention-to-treat population (ITT), which included all randomized patients.

To rule out a potential systemic bias, i.e. censoring imbalance between study arms, a simple reverse Kaplan—Meier analysis was carried out. To assess the censoring rates of the survival curves with the reverse Kaplan—Meier approach, the status of the time-dependent outcome for individual patients is flipped: censoring is treated as the 'event' (i.e. pseudo-event) of interest and the original event as 'censored' (i.e. pseudo-censoring).[13] The resulting reversed Kaplan—Meier plot represents the cumulative probability of individuals being censored at a certain follow-up time. In addition, this method allows the use of the Cox proportional hazards modeling to compare the censoring rates between study arms.

RFS curves were estimated using the Kaplan—Meier method and compared using the log-rank test. Ninety-five events would provide an 85% power with a two-sided alpha level of 5% to demonstrate superiority of the neoadjuvant arm for the final analysis, assuming a median RFS of 19.3 months in the neoadjuvant group and 10.4 months in the surgery-only group.

OS was a key secondary objective. The median OS time was assumed to be 40 months and 72 months for the control and the neoadjuvant arms, respectively, giving an HR of 0.557. For a log-rank test to compare Kaplan—Meier curves for OS with a two-sided alpha level of 0.05 and 85% of power, 104 death events were required, giving a total sample size of 214 (107 + 107) subjects, assuming a censoring rate of 10%.

Sample size calculations for this study design were carried out using R 3.6.1 (package gsDesign version 3.0-1).

Full details of the planned statistical analysis can be found in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2025.06.014.

RESULTS

Patients

Three hundred and fifty-four patients were screened between June 2016 and May 2023: 246 patients were randomized to one of the study arms and included in the ITT analysis (122 in arm 1, and 124 in arm 2). The reasons for screen failures are detailed in the CONSORT diagram (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.06.014—CONSORT diagram). At the database cut-off date (3 May 2023), 5 patients in arm 1 and 3 patients in arm 2 had not yet undergone surgery; 13 patients in arm 1 (3 disease progression; 3 AEs; 3 consent withdrawal; 2 ineligible; 2 refusal of further treatment) and 5 patients in arm 2 (4 consent withdrawal; 1 disease progression) discontinued before surgery (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.06.014—CONSORT diagram).

The demographic and clinical characteristics of the patients were well balanced between the two arms with respect to age and sex distribution, stage of disease at study entry, number and size of lesions, ECOG performance status, and LDH levels (Table 1). At screening, 55.3% of patients had skin metastases, 52.4% lymph node metastases, and 0.8% soft tissue metastases: 107 patients (43.5%) had two or more lesions. A total of 182 (74%) had undergone two or more prior surgical procedures for prior recurrence and 86 (35%) had received prior systemic therapy, mainly immune checkpoint inhibitors (ICIs) (Table 1).

At the database lock date of 3 May 2023, a total of 130 of the 246 randomized participants were censored for administrative (64, 26.4%) or nonadministrative (66, 26.8%) reasons in the primary efficacy analysis of RFS. A sensitivity reverse Kaplan—Meier analysis was carried out in which the 57 and 73 censored patients in arm 2 and arm 1, respectively, were considered to have an event at the time of their last observation, while the 116 patients were

Table 1. Baseline demographic and clinical characteristics for the intention-to-treat population at the time of randomization

	Daromun + surgery (n = 122)	Surgery (n = 124)	Total (N = 246)
Age, *n* (%)			
<65 years	60 (49.2)	65 (52.4)	125 (50.8)
≥65 years	62 (50.2)	59 (47.6)	121 (49.9)
Median age (min-max), years	65.0 (23.0-88.0)	63.0 (22.0-91.0)	64.0 (22.0-91.0)
Gender, *n* (%)			
Female	53 (43.4)	55 (44.4)	108 (43.9)
Male	69 (56.6)	69 (55.7)	138 (56.1)
ECOG, *n* (%)			
0	113 (92.6)	120 (96.8)	233 (94.7)
1	9 (7.4)	4 (3.3)	13 (5.3)
LDH level, *n* (%)			
Normal	104 (85.3)	102 (82.3)	206 (83.7)
Elevated	18 (14.8)	22 (17.7)	40 (16.3)
Disease stage, *n* (%) (AJCC 7th version)			
IIIB	33 (27.0)	33 (26.6)	66 (26.8)
IIIC	60 (49.2)	67 (54.0)	127 (51.6)
III unspecified	24 (19.7)	23 (18.6)	47 (19.1)
IV	5 (4.1)	1 (0.8)	6 (2.4)
Disease stage, *n* (%) (AJCC 8th version)			
IIIB	23 (18.9)	26 (21.0)	49 (19.9)
IIIC	84 (68.8)	88 (71.0)	172 (69.9)
IIID	10 (8.2)	5 (4.0)	15 (6.1)
III unspecified	—	4 (3.2)	4 (1.6)
IV	5 (4.1)	1 (0.8)	6 (2.4)
BRAF mutation status, *n* (%)			
Mutated	48 (39.3)	40 (32.3)	88 (35.8)
Wild-type	41 (33.6)	51 (41.1)	92 (37.4)
Unknown	33 (27.1)	33 (26.6)	66 (26.8)
Number of melanoma metastases at study entry			
1	65 (53.3)	74 (59.7)	139 (56.5)
2	26 (21.3)	22 (17.7)	48 (19.5)
≥3	31 (25.4)	28 (22.6)	59 (24.0)
Location of melanoma metastasis, *n* (%)[a]			
Skin (cutaneous and subcutaneous)	72 (59.0)	64 (51.6)	136 (55.3)
Lymph nodes	64 (52.5)	65 (52.4)	129 (52.4)
Soft tissue	1 (0.8)	1 (0.8)	2 (0.8)
Other	2 (1.6)	1 (0.8)	3 (1.2)
Prior surgery, *n* (%)			
None	11 (9.0)	9 (7.3)	20 (8.1)
1	18 (14.8)	26 (21.0)	44 (17.9)
2	44 (36.1)	41 (33.1)	85 (34.6)
≥3	49 (40.2)	48 (38.7)	97 (39.4)
Prior radiotherapy, *n* (%)			
No	115 (94.3)	120 (96.8)	235 (95.5)
Yes	7 (5.7)	4 (3.2)	11 (4.5)
Prior systemic therapy, *n* (%)			
No	79 (64.8)	81 (65.3)	160 (65.0)
Yes	43 (35.3)	43 (34.7)	86 (35.0)
Immunotherapy only	36 (83.7)[b]	30 (69.8)[b]	66 (76.7)
Targeted therapy only	4 (9.3)	5 (11.6)	9 (10.5)
Immunotherapy and targeted therapy	1 (2.3)	3 (7.0)	4 (4.7)
Immunotherapy and chemotherapy	1 (2.3)	2 (4.7)	3 (3.5)
Chemotherapy only	—	2 (4.7)	2 (2.3)
Immunotherapy and clinical trial	1 (2.3)[c]	1 (2.3)[d]	2 (2.3)

The data shown are for the intention-to-treat population, which included all patients who underwent randomization between the two treatment arms (daromun + surgery and surgery without neoadjuvant therapy). A chi-square test indicated that there was no statistically significant difference in the distribution of baseline characteristics between the two arms of the study.

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

Data are *n* (%). Percentages might not total 100 because of rounding.

[a]Patient can have multiple lesions (double counting).

[b]Prior immune checkpoint inhibitor, *n* (%): daromun + surgery 21 (17.2); surgery 19 (15.3).

[c]Pembrolizumab versus placebo.

[d]SGI-110 (DNA methyltransferase inhibitor).

censored at the time of their last observation or event. The resulting plot of reverse Kaplan–Meier curves from randomization for all study participants by arm is shown in Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2025.06.014. The timing and proportion of censoring was comparable between the two study arms. Using a Cox model with treatment group as the only covariate, the HR with 95% CI is 1.00 (0.70-1.43).

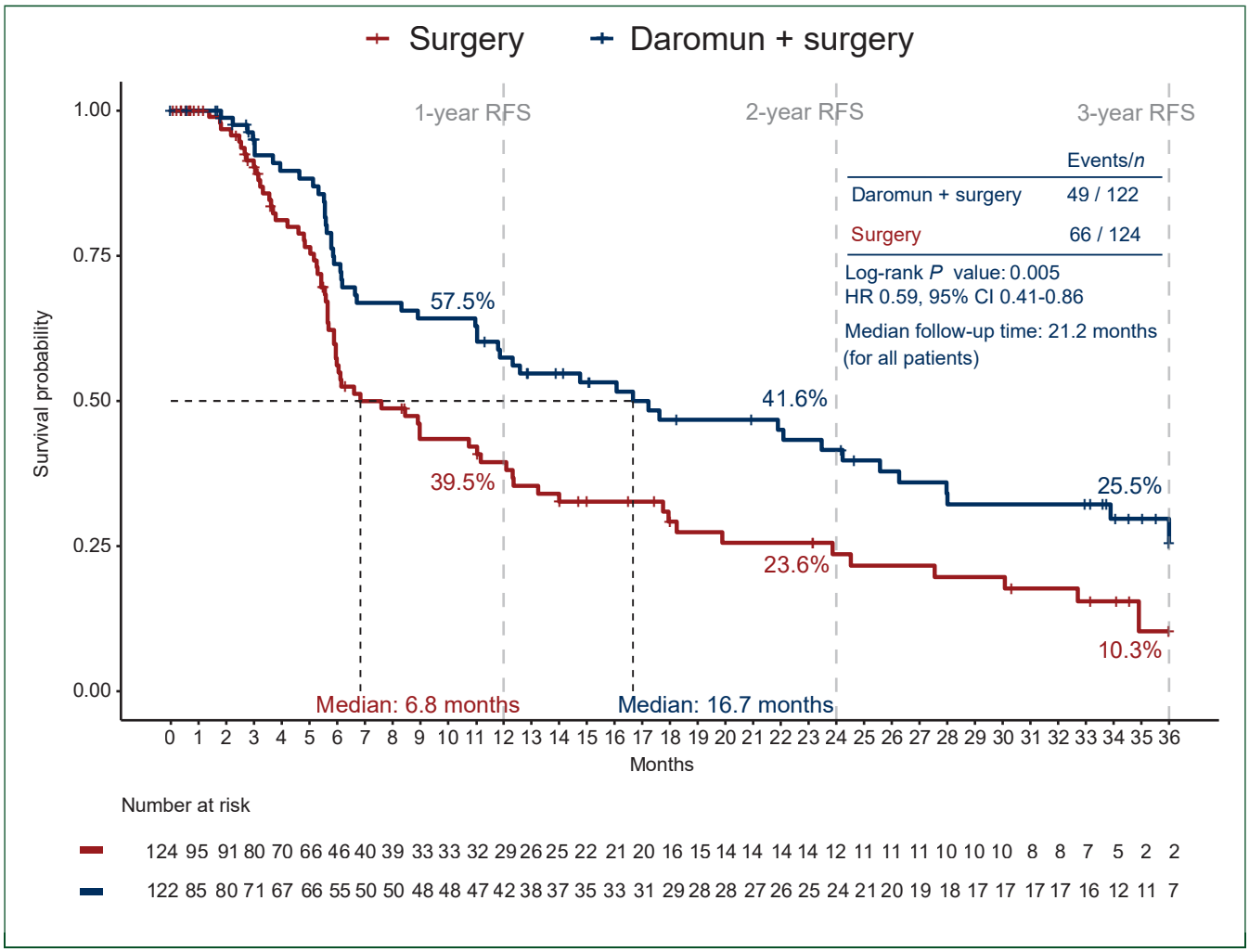

Figure 1. Kaplan–Meier estimates of recurrence-free survival (RFS) in the intention-to-treat (ITT) population. Shown are estimates of RFS for 246 patients in the study (ITT population) stratified by treatment group. The results were assessed by retrospective blinded independent central review (BICR). Tick marks show data censored at the time of last disease assessment. The hazard ratio (HR) in the table results from a univariate Cox regression with the treatment arm as the covariate. The proportional hazards assumption was verified using Schoenfeld residuals.
CI, confidence interval.

Efficacy

Two interim analyses were carried out at 25% and 50% of the expected RFS events. An independent data safety monitoring board concluded that the criteria for futility were not met and recommended that the study continue as planned. The final RFS analysis was carried out when the preplanned 95 events, as adjudicated by the local investigators, were reported. However, a BICR identified 20 more events (8 in arm 1 and 12 in arm 2) than the investigators at the database cut-off date.

At a median follow-up of 22.2 months for arm 1 and 20.2 months for arm 2, 49 events (32 distant and 17 local recurrences) were observed in the daromun arm and 66 (37 distant and 26 local recurrences, and 3 non-treatment-related deaths) in the control arm.

RFS was significantly longer in the neoadjuvant arm than in the upfront surgery arm [Figure 1; median RFS 16.7 months versus 6.8 months; estimated 2-year RFS 41.6% (95% CI 31.4% to 55.1%) versus 23.6% (95% CI 15.4% to 36.2%); HR 0.59, 95% CI 0.41-0.86, log-rank $P = 0.005$]. The investigator-assessed RFS was consistent with the primary analysis by the BICR. Median RFS was 24.2 months in the experimental arm and 10.7 months in the control arm, with a 39% reduction in the risk of recurrence or death in patients treated with daromun (HR 0.61, 95% CI 0.41-0.92, log-rank $P = 0.018$) (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2025.06.014).

Because of the difference in the time between randomization and surgery in the two arms (median time to surgery: 6.6 weeks in arm 1 and 2.3 weeks in arm 2), a time-dependent bias in the assessment of events cannot be ruled out. In a sensitivity landmark analysis at 3 months after randomization, when 99% of surgery had been carried out in both arms, the estimated RFS at 2 years was 37.9% (95% CI 27.4% to 52.3%) in the neoadjuvant-treated group and 24.0% (95% CI 15.2% to 37.8%) in the surgery-only group (HR 0.60, 95% CI 0.41-0.89) (Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2025.06.014).

Subgroup	Daromun + surgery	Surgery	HR (95% CI)
All patients	49/122	66/124	0.6 (0.4-0.9)
Age			
<65 years	23/60	34/65	0.5 (0.3-0.9)
≥65 years	26/62	32/59	0.7 (0.4-1.1)
Gender			
Male	33/69	37/69	0.7 (0.4-1.1)
Female	16/53	29/55	0.5 (0.3-0.9)
ECOG – PS			
0	44/113	65/120	0.6 (0.4-0.9)
1	5/9	1/4	N/A
LDH level			
Normal	43/104	53/102	0.6 (0.4-0.9)
Elevated	6/18	13/22	0.7 (0.3-1.9)
Disease stage – AJCC 7th			
III B	11/33	16/33	0.4 (0.2-0.8)
III C	26/60	38/67	0.6 (0.4-1.0)
III unspecified	11/24	12/23	0.9 (0.4-2.2)
IV	1/5	0/1	N/A
BRAF mutation status			
Mutated	18/48	16/40	0.8 (0.4-1.6)
Wild type	17/41	31/51	0.4 (0.2-0.8)
Unknown	14/33	19/33	0.7 (0.3-1.4)
Lesions (*n*)			
1	29/65	34/74	0.7 (0.4-1.1)
2	9/26	16/22	0.6 (0.2-1.3)
=3	11/31	16/28	0.4 (0.2-0.9)
Prior surgery			
None	4/11	4/9	0.7 (0.2-2.7)
1	5/18	18/26	0.3 (0.1-1.0)
2	18/44	19/41	0.7 (0.3-1.3)
≥3	22/49	25/48	0.6 (0.3-1.0)
Prior RT			
No	45/115	62/120	0.6 (0.4-0.9)
Yes	4/7	4/4	0.6 (0.1-2.5)
Prior systemic therapy			
No	30/79	43/81	0.6 (0.4-1.0)
Yes	19/43	23/43	0.5 (0.3-1.0)

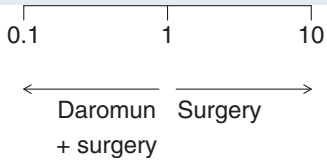

Figure 2. Forest plot of recurrence-free survival across subgroups according to baseline characteristics. Recurrence-free survival in prespecified subgroups in the intention-to-treat population for daromun plus surgery (arm 1) versus surgery (arm 2). For each group, hazard ratio (HR) and 95% confidence interval (CI) are estimated using a univariate Cox regression model with assigned arm as a covariate. The x-axis is on a logarithmic scale and the size of the squares is proportional to the number of events in each group.

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; N/A, not applicable; RT, radiotherapy.

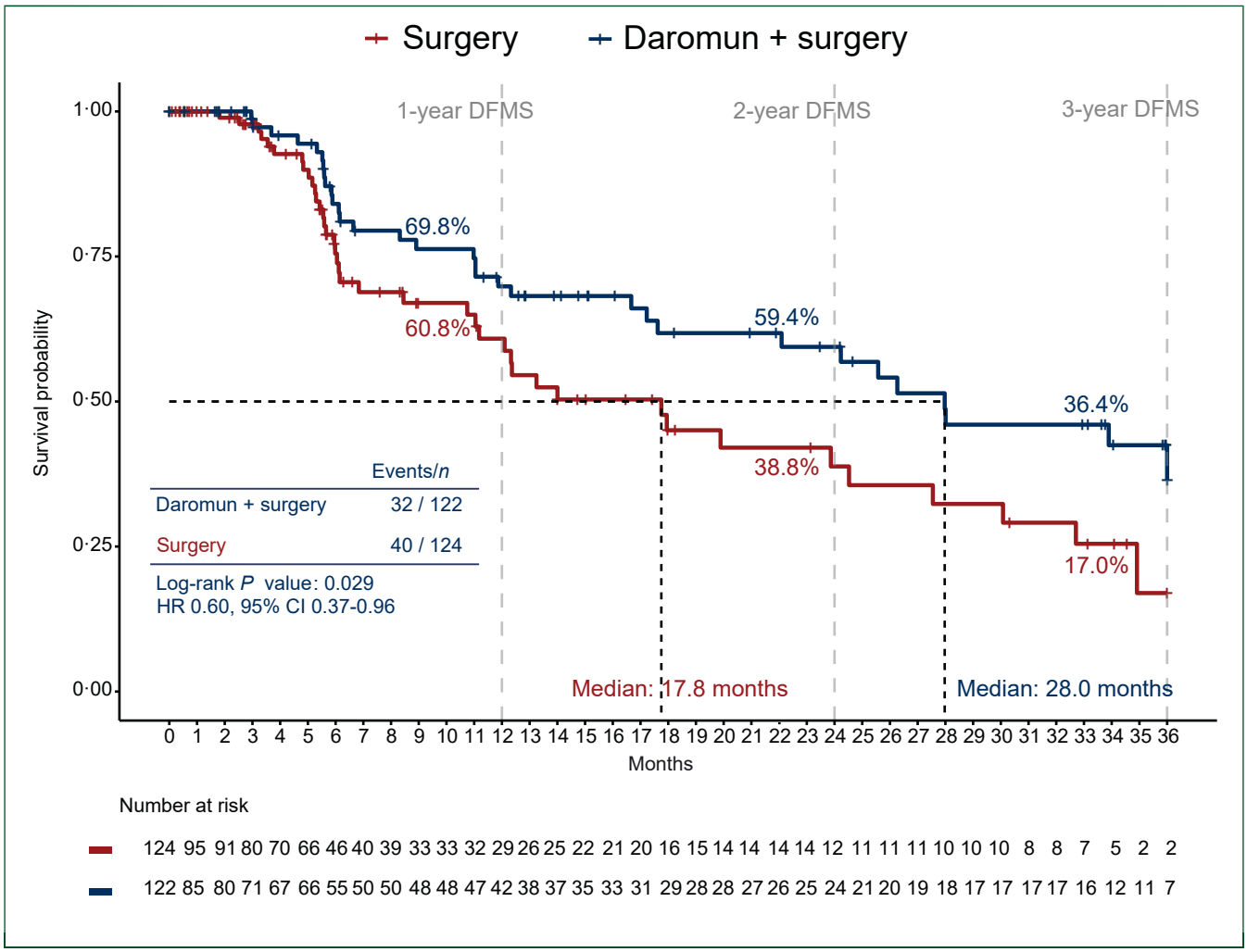

Figure 3. Kaplan–Meier estimates of distant metastasis-free survival (DMFS) in the intention-to-treat (ITT) population. Kaplan–Meier estimates of DMFS were assessed by retrospective blinded independent central review (BICR). Tick marks show data censored at the time of last disease assessment. DMFS is defined as the time from randomization to distant metastasis without prior local metastasis or death from any cause without recurrence.

The use of post-operative adjuvant therapies was allowed at the discretion of the treating physician in both arms: 31 patients in arm 1 and 47 in arm 2 received post-operative adjuvant therapy (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.06.014). In a planned sensitivity analysis, patients who had been treated with neoadjuvant daromun appeared to have a longer RFS than patients without neoadjuvant treatment both in the patients with post-operative adjuvant therapy (estimated 2-year RFS 47.2% in arm 1 versus 35.2% in arm 2), and in the patients without post-operative treatment (estimated 2-year RFS 31.7% in arm 1 versus 13.3% in arm 2) (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.06.014).

Subgroup analysis was carried out to evaluate the effect of baseline characteristics such as age, gender, stage, number of lesions, BRAF V600 mutation status, and prior treatment on the primary endpoint. The benefit of neoadjuvant daromun was consistent across all patient subgroups (Figure 2).

The benefit of neoadjuvant daromun was observed also in DMFS. The estimated DMFS at two years was 59.4% (95% CI 48.0% to 73.6%) in the neoadjuvant-treated group and 38.8% (95% CI 26.9% to 56.0%) in the surgery-alone group (Figure 3). The median time to distant metastases was 28 months (95% CI 22.1 months-not reached) in the daromun arm compared with 17.7 months (95% CI 11.2-30.1 months) in the control arm (HR 0.60, 95% CI 0.37-0.95, $P = 0.029$). In accordance with the protocol, data were obtained only for the first disease recurrence, whether local or distant.

OS was another secondary endpoint: 40 deaths had been reported by the database cut-off date. This small number of deaths precluded a definitive comparison between the groups with respect to OS.

A review of the institutional pathology reports confirmed a complete pathological response (defined as no viable tumor in the surgical specimen including skin and nodal lesions) in 22 of 104 patients (21%) who had undergone surgery after neoadjuvant therapy.

Table 2. Adverse events (AEs) in the safety-evaluable population

AE, *n* (%)	Daromun + surgery ($n = 118$)[a]			Surgery ($n = 119$)[a]		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any AEs	113 (95.8)	34 (28.8)	3 (2.5)	58 (48.7)	13 (10.9)	—
Any SAEs	18 (15.3)	12 (10.2)	2 (1.7)	10 (8.4)	8 (6.7)	—
Any TRAEs	110 (93.2)	31 (26.3)	1 (0.8)	40 (33.6)	8 (6.7)	—
Any TRSAEs	10 (8.5)	8 (6.8)	—	5 (4.2)	4 (3.4)	—
irAEs[b]	3 (2.5)	—	—	0	—	—
TRAEs in >10% of patients, *n* (%)						
Injection site reaction	79 (66.9)	13 (11.0)	—	0	—	—
Pyrexia	57 (48.3)	1 (0.8)	—	0	—	—
Chills	57 (48.3)	—	—	0	—	—
Nausea	26 (22.0)	—	—	0	—	—
Fatigue	18 (15.3)	1 (0.8)	—	0	—	—
Headache	16 (13.6)	—	—	0	—	—
Influenza-like illness	14 (11.9)	—	—	0	—	—
Vomiting	14 (11.9)	—	—	0	—	—
Alanine aminotransferase increased	12 (10.2)	1 (0.8)	—	0	—	—

The safety population included all patients who were randomly assigned to either of the two study arms and who had received at least one dose of daromun and/or underwent surgery (arm 1) or who underwent surgery (arm 2). Data are *n* (%) of patients who experienced AEs.
SAE, serious adverse event; irAE, immune-related adverse event; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.
[a]Safety population of both arms also included patients who were scheduled for surgery at the database cut-off date: five patients in arm 1 and three patients in arm 2.
[b]In a retrospective analysis, three patients treated with one or more doses of daromun (2.5%) experienced an episode of irAE characterized by mild [Common Terminology Criteria for Adverse Events (CTCAE) grade 1] severity: immune-mediated thyroiditis, dermatitis, and maculopapular rash.

Safety

AEs of any cause of grade ≥3 were reported in 37 patients (31.3%) in the neoadjuvant arm and in 13 patients (10.9%) in the control arm (Table 2). Grade 3 treatment-related AEs (TRAEs) were reported in 26.3% of patients in the daromun arm with only one grade 4 (neutropenia) (0.8%), while in the control arm grade 3 TRAEs were reported in 6.7% of patients without any grade 4 (Table 2). The most commonly reported grade 3 TRAE in patients treated with daromun was injection site reaction (11% of patients). Three immune-related (ir)AEs were reported in the neoadjuvant arm, which were grade 1 and transient, and there were no treatment-related deaths.

DISCUSSION

Neoadjuvant and perioperative immunotherapies are gaining ground in clinical practice for resectable stage III melanoma, as reflected in the latest European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines.[3,4,14,15] Data from prospective randomized trials have demonstrated a significant EFS benefit for ICIs in treatment-naïve patients with resectable disease[1,2] whereas OS data in these studies were immature at the time of reporting. Intralesional neoadjuvant immunotherapy with T-VEC was also evaluated in a randomized phase II trial:[5] sustained, although not statistically significant, improvements in 5-year RFS and OS were reported with neoadjuvant T-VEC plus surgery compared with standard surgery.

PIVOTAL is the first phase III trial of intralesional neoadjuvant targeted immunocytokines, daromun followed by surgery versus upfront surgery in patients with resectable clinical stage III melanoma, many of whom had experienced multiple recurrences (74% with two or more prior surgeries) and had received prior systemic treatments (35%). The population of patients in the PIVOTAL trial is different from that in the SWOG 1801 or NADINA trials. In fact, in the latter studies, prior immunotherapy with ICIs was an exclusion criterion, whereas in the SWOG-1801 only 4 out of 313 patients (1.3%) had received prior targeted therapy with BRAF/MEK inhibitors.[1,2] In the T-VEC phase II study, only 4% of the patients had received prior systemic immunotherapy.[5] Finally, 40.6% of patients in PIVOTAL had in-transit metastases, which have adverse prognostic implications,[12] while 10.4% of patients in NADINA had in-transit metastases.

The prognostic significance of the study population is underscored by the strikingly short median RFS observed in the control arm—5.3 months in patients who received no post-operative adjuvant therapy and 11.7 months in those who received post-operative adjuvant therapy. Both median RFSs are significantly shorter than RFS benchmarks in recent adjuvant trials (e.g. COMBI-AD >2.8 years[16]; KEYNOTE-054 >15 months[17]). This fact underlines that PIVOTAL investigated a high-risk population that was not represented in previous neoadjuvant trials, which enrolled relatively homogeneous, treatment-naïve populations and excluded patients with prior systemic therapy.

Despite the more advanced patient population, PIVOTAL showed a significant improvement in RFS with a 41% reduction in the risk of recurrence or death in patients treated with daromun. In the prespecified analysis of DMFS, daromun significantly reduced the risk of distant metastasis by 40% compared with the control arm. These findings suggest that daromun triggers a systemic immune response, even when administered locally.

The open-label design of PIVOTAL and the lack of risk factor stratification may be of potential concern. Although the long enrollment period and the lack of stratification

criteria may have increased the likelihood of heterogeneity between the two arms, there is no imbalance between the two arms in terms of baseline patient characteristics. In addition, the forest plot in Figure 2 shows that none of the factors considered appear to affect the activity of intralesional daromun. The results of an additional analysis regarding the distribution of patients with/without prestudy systemic treatments and with/without post-operative adjuvant treatment between the two arms are detailed in the Supplementary Material (Table S3 and Figure S6, available at https://doi.org/10.1016/j.annonc.2025.06.014).

The longer time from randomization to surgery in the neoadjuvant arm compared with the control arm may have introduced a time-dependent bias in the observation of events for the primary efficacy analysis. A *post hoc* landmark analysis accounting for the longer time to surgery in the neoadjuvant arm still shows a >50% increase in 2-year RFS in the neoadjuvant group compared with the upfront surgery group.

Patients could not be stratified by planned post-operative adjuvant therapy: adjuvant ICI was only allowed at the treating physician's discretion after its approval in Europe in mid-2018. In a sensitivity analysis, *post hoc* stratification was carried out and, when RFS for patients with or without post-operative adjuvant systemic therapy was analyzed using Kaplan—Meyer curves, the prolongation of RFS with neoadjuvant daromun appeared to be maintained both in patients receiving adjuvant ICI and in those without post-operative treatment.

Patients who receive neoadjuvant therapy are at risk of losing the opportunity for curative surgery due to disease progression or treatment-related serious AEs before surgery. Evidence to date suggests that ∼5% of patients enrolled in neoadjuvant trials with stage III disease at initial assessment will progress to distant metastatic disease before surgery.[18,19] Only 4.9% of patients in the neoadjuvant daromun arm experienced disease progression (three patients) or AEs (three patients) leading to inability to undergo surgery.

From a safety standpoint, daromun was well tolerated, with most AEs limited to local injection site reactions. irAEs were infrequent (2.5%) and mild. In contrast to systemic neoadjuvant regimens, which have reported grade ≥3 AEs in up to 47% of patients (e.g. NADINA), daromun demonstrated a favorable safety profile with significantly lower rates of high-grade toxicity (28.8%) and serious AEs (10.2%).

Neoadjuvant daromun represents a well-tolerated and effective therapeutic option for patients with pretreated, recurrent stage III melanoma. Its favorable safety profile and clinical efficacy support its potential role as a complementary or alternative strategy to systemic immunotherapy, particularly in high-risk patients or those ineligible for ICIs.

FUNDING

This work was supported by Philogen S.p.A. (no grant number)

DISCLOSURE

KCK reports research funding to their institution for clinical studies from Philogen; consulting fees from Bristol Myers Squibb (BMS) and Pierre Fabre; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from BMS, Merck Sharp & Dohme (MSD), Pierre Fabre, Immunocore, Philogen, and Delcath; support for attending meetings and/or travel from BMS, MSD, Pierre Fabre, Immunocore, Philogen, and Sun Pharma; and participation on a data safety monitoring board or advisory board from BMS, MSD, Sanofi-Aventis, Novartis, Philogen, and Sun Pharma. JCH reports support for manuscript writing from Philogen; scientific grants to institution from BMS, Sun Pharma, and Sanofi; consulting fees from GSK, Pierre Fabre, and Sun Pharma; consulting fees to institution from BMS, Immunocore, Novartis, Philogen, Sanofi, and MSD; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Amgen, BMS, Delcath, GSK, Immunocore, MSD, Novartis, Pierre Fabre, Sanofi, and Sun Pharma; support for attending meetings and/or travel from BMS, Iovance, and Sun Pharma; participation on a data safety monitoring board or advisory board from Nekvax; leadership or fiduciary role in other board, society, committee, or advocacy group, paid or unpaid: German Dermatologic Cooperative Oncology Group (DeCOG); and receipt of medical writing support fees from BMS. MZ reports the payment of fees for study conduct to institution by Philogen; grants and contracts to their institution for clinical studies from BMS, MSD, Immunocore, Pfizer, Philogen, Regeneron, BioNTech, and Huyabio; advisory boards and consulting (to institution) from Philogen; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Novartis, BMS, Pierre Fabre, SunPharma, AstraZeneca, and Sanofi; and support for attending meetings and/or travel from Pierre Fabre and Sun Pharma; PR reports research funding to their institution from Novartis, Pfizer, Roche, and BMS; consulting fees from BMS, MSD, Novartis, Pierre Fabre, Philogen, Pfizer, Genesis, and Madison Pharma; payment and honoraria from BMS, MSD, Novartis, Pfizer, Pierre Fabre, Sanofi, Merck, and AstraZeneca; honoraria for speakers bureaus from Pfizer, Novartis, Pierre Fabre, MSD, and BMS; and support for attending meetings and/or travel from Orphan Europe and Pierre Fabre. FM reports research funding to their institution for clinical studies from Philogen; consulting fees from Novartis, Pierre Fabre, BMS, MSD, Sanofi, and Immunocore; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Novartis, Pierre Fabre, BMS, MSD, Sanofi, and Immunocore; support for attending meetings and/or travel from Novartis, Pierre Fabre, BMS, MSD, Sanofi, and Immunocore; and participation on a data safety monitoring board or advisory board from Novartis, Pierre Fabre, BMS, MSD, Sanofi, and Immunocore. LF reports grants and contracts to their institution for clinical studies from Hookipa Pharma, Swiss Cancer League, German Research Foundation, Immunophotonics, and Mundipharma; support for attending meetings and/or travel from Philogen and Hookipa Pharma; patents planned, issued, or pending from University of Tübingen,

Hookipa Pharma, and Mundipharma; participation on a data safety monitoring board or advisory board, unpaid: University of Basel (Tumor-Infiltrating Lymphocyte trial); and other financial or nonfinancial interests: founder of Hookipa Pharma, Schmelzberg, Humion, and Abtherix. CG-M reports research funding to their institution for clinical studies (local principal investigator) from Amgen, Astra Zeneca, BMS, Catalyst, Day One Biopharmaceuticals, GSK, Huyabio, IFX, Immunocore, IO Biotech, Jansen, Kartos, Kinnate, MSD, Merck, Novartis, Pfizer, Philogen, Pierre Fabre, Regeneron, Replimmune, Roche, Sairopa, Sanofi, Sotio, DOT Therapeutics, Dragonfly, and Incyte; consulting fees from Pierre Fabre, BMS, and MSD; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Pierre Fabre, BMS, and MSD; support for attending meetings and/or travel from Pierre Fabre, BMS, and MSD; and participation on a data safety monitoring board or advisory board from Sun Pharma and Pierre Fabre. LZ reports payment of honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from BMS, MSD, Pierre Fabre, and Novartis; support for attending meetings and/or travel from Novartis, MSD, BMS, Pierre Fabre, Sun Pharma, and Sanofi; participation on a data safety monitoring board or advisory board from BMS, MSD, Pierre Fabre, Sanofi, and Novartis; and leadership or fiduciary role in other board, society, committee, or advocacy group, unpaid: Committee Survivorship of the 'Arbeitsgemeinschaft für Dermatologische Onkologie'. IvW reports consulting fees from Novartis, BMS, MSD, Kyowa Kirin, Stemline, and Sanofi; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Novartis, BMS, MSD, Stemline, and Kyowa Kirin; payment for expert testimony from BMS, MSD, and Sanofi; and support for attending meetings and/or travel from Novartis, BMS, MSD, Pierre Fabre, Stemline, Kyowa Kirin, and Sanofi. TKE reports research funding to their institution for clinical studies from Philogen; consulting fees from Merck; payment for expert testimony from BMS, MSD, Anaveon, Pierre Fabre, Regeneron, CureVac, Novartis, and Philogen; participation on a data safety monitoring board or advisory board from Philogen; and stock or stock option ownership from CureVac. MM reports consulting fees from GSK, BMS, Astra Zeneca, Roche, MSD, Merck, Pierre Fabre, Alfasigma, Eli Lilly, Sanofi, Amgen, Sciclone, and Incyte; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from GSK, BMS, AstraZeneca, Roche, MSD, Merck, Pierre Fabre, Alfasigma, Eli Lilly, Sanofi, Amgen, Sciclone, and Incyte; support for attending meetings and/or travel from GSK, BMS, AstraZeneca, Roche, MSD, Merck, Pierre Fabre, Alfasigma, Eli Lilly, Sanofi, Amgen, Sciclone, and Incyte; and stock or stock option ownership from Epigen Therapeutics and Theravance. IZ reports grants and contracts to their institution from Philogen, Regeneron, and Sun Pharma; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sanofi, Regeneron, MSD, Sun Pharma, La Roche Posay, Fotofinder, Pierre Fabre, Almirall, and Novartis; support for attending meetings and/or travel from La Roche Posay; participation on a data safety monitoring board or advisory board from Philogen, Sanofi, Regeneron, and Sun Pharma; and leadership or fiduciary role in other board, society, committee, or advocacy group, paid or unpaid: Treasurer of the Melanoma World Society and past President of the International Dermoscopy Society. PQ reports grants to their institution from BMS; consulting fees from BMS, MSD, Pierre Fabre, Sun Pharma, and Sanofi; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from BMS, MSD, Pierre Fabre, Sun Pharma, and Sanofi; and support for attending meetings and/or travel from BMS, MSD, Pierre Fabre, Sun Pharma, and Sanofi. JW reports grants and contracts to their institution for clinical studies from MSD, Leo, Philogen, and Almirall and research funding to their institution from BMBF (the German federal ministry of education and research); consulting fees from Boehringer Ingelheim and Almirall; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie, Almirall, Leo, MSD, BMS, Novartis, and Lilly; support for attending meetings and/or travel from AbbVie and Janssen; and leadership or fiduciary role in other board, society, committee, or advocacy group, paid or unpaid: President of the German Society of Dermatology. JCS reports the payment of fees for study conduct to institution by Philogen; consulting fees from Philogen, Novartis, BMS, Pfizer, Pierre Fabre, Regeneron, and Sanofi; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Novartis; and participation on a data safety monitoring board or advisory board from Dr. August Wolff. TŚ reports support for attending meetings and/or travel from MSD. MG reports payment or honoraria for lectures, presentations, or educational events from BMS, MSD, Sanofi, Novartis, Roche, Amgen, Pierre Fabre, and Sun Pharma; and support for attending meetings and/or travel from Novartis, Roche, BMS, MSD, Pierre Fabre, Amgen, and Sanofi. TA reports the payment of fees for study conduct to institution by Philogen, for clinical trials to institution from Agenus, AstraZeneca, BioNTech, BMS, Huyabio, iFIT, Immunocore, IO Biotech, Medical Nutritional Institute (MNI), MSD, NeraCare, Novartis, Pascoe, Pfizer, Philogen, Regeneron, Roche, Sanofi, SkylineDx, and Unicancer; consulting fees from Delcath, Pierre Fabre, Philogen, BMS, Novartis, and CeCaVa; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Pierre Fabre; support for attending meetings and/or travel from NeraCare; patents planned, issued or pending: 18/386 708; and leadership or fiduciary role in other board, society, committee, or advocacy group, unpaid: Chair of the ESMO Leadership Development Committee. EL reports the payment of fees for study conduct to institution by Philogen; consulting fees from MSD, Novartis, BMS, Pierre Fabre, Sun Pharma, Takeda, and Sanofi; payment or honoraria for lectures, presentations, speakers

bureaus, manuscript writing, or educational events from Novartis, Pierre Fabre, and Sun Pharma; and support for attending meetings and/or travel from Pierre Fabre and Sun Pharma. DN reports patents planned, issued and pending with Philogen; leadership or fiduciary role in other board, society, committee, or advocacy group, paid: Chief Executive Officer of Philogen; and stock or stock option ownership from Philogen. PAA reports grants and contracts to their institution from BMS, Roche-Genentech, Pfizer, and Sanofi; consulting fees from BMS, Roche-Genentech, MSD, Novartis, Merck Serono, Pierre Fabre, Sun Pharma, Sanofi, Sandoz, Italfarmaco, Pfizer, Lunaphore, Medicenna, Bio-Al Health, ValoTx, Replimmune, Bayer, Philogen, and BioNTech; support for attending meetings and/or travel from Pfizer, Bio-Al Health, Replimmune, MSD, Pierre Fabre, Philogen; and participation on a data safety monitoring board or advisory board from BMS, Roche-Genentech, MSD, Novartis, Boehringer Ingelheim, Regeneron, Nouscom, Erasca, and Anaveon. CG reports payment for advisory board from Philogen; consulting fees from CeCaVa, MSD, NeraCare, and Philogen; and leadership or fiduciary role in other board, society, committee, or advocacy group, unpaid: President of the European Association of Dermatooncology. CRob reports consulting fees from BMS, Roche, Pierre Fabre, Novartis, Sanofi, Pfizer, MSD, Merck, Sun Pharma, Ultimovacs, Regeneron, Egle, Philogen, Maat Pharma, and IO Biotech; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Pierre Fabre, Sanofi, BMS, MSD, and Novartis; support for attending meetings and/or travel from Pierre Fabre; and participation on a data safety monitoring board or advisory board from BMS, Roche, Pierre Fabre, Novartis, Sanofi, Pfizer, MSD, Merck, Sun Pharma, Ultimovacs, Regeneron, Egle, Philogen, and Maat Pharma. DS reports the payment of fees for study conduct to institution by Philogen, for clinical trials to institution from Amgen, BMS, MSD, and Pfizer; consulting fees from Philogen, InflaRx, NeraCare, MSD, Novartis, BMS, Pfizer, Pierre Fabre, Replimmune, Sun Pharma, Daiichi Sankyo, AstraZeneca, IQVIA, LabCorp, UltimoVacs, Seagen, Immunocore, Immatics, BioNTech, PamGene, BioAlta, Regeneron, Agenus, Erasca, Formycon, NoviGenix, CureVac, and Sanofi; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from NeraCare, MSD, Novartis, BMS, Pierre Fabre, Replimmune, Sun Pharma, and Sanofi; support for attending meetings and/or travel from Pierre Fabre; participation on a data safety monitoring board or advisory board from Immunocore, AstraZeneca, BioAlta, Daiichi Sankyo, InflaRx, and Replimmune; and leadership or fiduciary role in other board, society, committee, or advocacy group, unpaid: European Organisation for. Research and Treatment of Cancer-Melanoma Group steering board, DeCOG steering board, Nationale Versorgungskonferenz Hautkrebs chair, and Comprehensive Cancer Center chair. AH reports grants and personal fees from Amgen, BMS, MerckPfizer, MSD/Merck, Philogen, Pierre Fabre, Regeneron, Sanofi-Genzyme, Novartis Pharma, Replimmune, and NeraCare; grants from Huyabio; and personal fees from Roche, Eisai, Immunocore, Seagen, IO Biotech, Dermagnostix, Incyte, Kyowa Kirin, Highlight Therapeutics, Iovance, CureVac, Xenthera, Agenus, Almirall, and Sun Pharma, outside the submitted work.

All other authors (MS, FR, SH, CRöc, AE, NM, GE, AC, KL, SM, AP, BP) have declared no conflicts of interest.

REFERENCES

1. Patel SP, Othus M, Chen Y, et al. Neoadjuvant-adjuvant or adjuvant-only pembrolizumab in advanced melanoma. *N Engl J Med*. 2023;388:813-823.
2. Blank CU, Lucas MW, Scolyer RA, et al. Neoadjuvant nivolumab and ipilimumab in resectable stage III melanoma. *N Engl J Med*. 2024;391:1696-1708.
3. Amaral T, Ottaviano M, Arance A, et al. Cutaneous melanoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2025;36(1):10-30.
4. Sondak VK, Atkins MB, Messersmith H, et al. Systemic therapy for melanoma: ASCO Guideline Update Q and A. *JCO Oncol Pract*. 2024;20:173-177.
5. Dummer R, Gyorki DE, Hyngstrom JR, Ning M, Lawrence T, Ross MI. Final 5-year follow-up results evaluating neoadjuvant talimogene laherparepvec plus surgery in advanced melanoma: a randomized clinical trial. *JAMA Oncol*. 2023;9:1457-1459.
6. Zardi L, Carnemolla B, Siri A, et al. Transformed human cells produce a new fibronectin isoform by preferential alternative splicing of a previously unobserved exon. *EMBO J*. 1987;6:2337-2342.
7. Carnemolla B, Balza E, Siri A, et al. A tumor-associated fibronectin isoform generated by alternative splicing of messenger RNA precursors. *J Cell Biol*. 1989;108:1139-1148.
8. Castellani P, Viale G, Dorcaratto A, et al. The fibronectin isoform containing the ED-B oncofetal domain: a marker of angiogenesis. *Int J Cancer*. 1994;59:612-618.
9. Frey K, Fiechter M, Schwager K, et al. Different patterns of fibronectin and tenascin-C splice variants expression in primary and metastatic melanoma lesions. *Exp Dermatol*. 2011;20:685-688.
10. Eigentler TK, Weide B, de Braud F, et al. A dose-escalation and signal-generating study of the immunocytokine L19-IL2 in combination with dacarbazine for the therapy of patients with metastatic melanoma. *Clin Cancer Res*. 2011;17:7732-7742.
11. Pretto F, Elia G, Castioni N, Neri D. Preclinical evaluation of IL2-based immunocytokines supports their use in combination with dacarbazine, paclitaxel and TNF-based immunotherapy. *Cancer Immunol Immunother*. 2014;63:901-910.
12. Danielli R, Patuzzo R, Di Giacomo AM, et al. Intralesional administration of L19-IL2/L19-TNF in stage III or stage IVM1a melanoma patients: results of a phase II study. *Cancer Immunol Immunother*. 2015;64:999-1009.
13. Gilboa S, Pras Y, Mataraso A, Bomze D, Markel G, Meirson T. Informative censoring of surrogate end-point data in phase 3 oncology trials. *Eur J Cancer*. 2021;153:190-202.
14. Long GV, Menzies AM, Scolyer RA. Neoadjuvant checkpoint immunotherapy and melanoma: the time is now. *J Clin Oncol*. 2023;41:3236-3248.
15. Garbe C, Dummer R, Amaral T, et al. Neoadjuvant immunotherapy for melanoma is now ready for clinical practice. *Nat Med*. 2023;29:1310-1312.
16. Long GV, Hauschild A, Santinami M, et al. Final results for adjuvant dabrafenib plus trametinib in stage III melanoma. *N Engl J Med*. 2024;391:1709-1720.
17. Eggermont AM, Kicinski M, Blank CU, et al. Seven-year analysis of adjuvant pembrolizumab versus placebo in stage III melanoma in the EORTC1325/KEYNOTE-054 trial. *Eur J Cancer*. 2024;211:114327.
18. Amaria RN, Menzies AM, Burton EM, et al. Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium. *Lancet Oncol*. 2019;20:e378-e389.
19. Hieken TJ, Kreidieh F, Aedo-Lopez V, Block MS, McArthur GA, Amaria RN. Neoadjuvant immunotherapy in melanoma: the paradigm shift. *Am Soc Clin Oncol Educ Book*. 2023;43:e390614.