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Axel Hauschild, Jessica C. Hassel, Mirjana Ziemer, Piotr Rutkowski, Friedegund Meier, Lukas Flatz, Caroline Gaudy-Marqueste, Mario Santinami, Francesco Russano, Imke von Wasielewski, Thomas Eigentler, Michele Maio, Iris Zalaudek, Sebastian Haferkamp, Pietro Quaglino, Julia Welzel, Michael Weichenthal, Giuliano Elia, Alfredo Covelli, Katia Lorizzo, Agnese Parca, Dario Neri, Paolo A. Ascierto, Caroline Robert, Dirk Schadendorf, Katharina C. Kaehler

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Neoadjuvant Intralesional Daromun (L19IL2/L19TNF) in Resectable Locally Advanced Melanoma: An Update on the Efficacy and Safety Results of the PIVOTAL Phase III Trial

Axel Hauschild, MD[1]; Jessica Cecile Hassel, MD[2]; Mirjana Ziemer, MD[3]; Piotr Rutkowski, MD[4]; Friedegund Meier, MD[5]; Lukas Flatz, MD[6]; Caroline Gaudy-Marqueste, MD[7]; Mario Santinami, MD[8]; Francesco Russano, MD[9]; Imke von Wasielewski, MD[10]; Thomas Eigentler, MD[11]; Michele Maio, MD[12]; Iris Zalaudek, MD[13,14]; Sebastian Haferkamp, MD[15]; Pietro Quaglino, MD[16]; Julia Welzel, MD[17]; Michael Weichenthal, MD[1]; Giuliano Elia, PhD[18]; Alfredo Covelli, MD[19]; Katia Lorizzo, MD[19]; Agnese Parca, PhD[19]; Dario Neri, PhD[19]; Paolo Antonio Ascierto, MD[20]; Caroline Robert, MD[21]; Dirk Schadendorf, MD[22]; and Katharina Charlotte Kaehler, MD[1]

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ABSTRACT

Daromun (L19IL2/L19TNF) was investigated as a neoadjuvant, intralesional therapy for patients with fully resectable stage III melanoma in the phase III PIVOTAL trial (ClinicalTrials.gov identifier: NCT02938299). The trial enrolled 256 patients in the European Union and met its primary end point, demonstrating a statistically significant improvement in recurrence-free survival (RFS; hazard ratio, 0.59; $P = .005$) for daromun followed by surgery versus up-front surgery, at a median follow-up (FU) of 21 months from random assignment. PIVOTAL included two clinically distinct subgroups, namely, patients with de novo diagnosed metastatic disease (n = 34; 13%) and patients with recurrence(s) after surgery with or without radiotherapy and/or adjuvant systemic therapies (n = 222; 87%). Here, we present an updated analysis of the primary and secondary end points, including safety data, at a median FU of 36.8 months from random assignment (database cutoff: November 28, 2025), alongside new sensitivity analyses of event-free survival (EFS). The updated analysis confirms the clinically and statistically meaningful improvements in RFS and distant metastasis-free survival recorded in the neoadjuvant daromun versus control arm. The EFS post hoc analysis, conducted in both the overall population and the recurrent patient subgroups (with or without prior systemic therapies), provides consistency and robustness to the benefit of neoadjuvant daromun observed for the primary efficacy end point. No new safety signals of concern were recorded.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Data Supplement
- Protocol

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INTRODUCTION

The landmark NADINA and SWOG S1801 trials established neoadjuvant immune checkpoint inhibitors (ICIs) as the emerging standard of care for resectable stage III melanoma.[1,2] Importantly, both trials enrolled patients without prior exposure to ICI. A consistent proportion of these patients, however, experience relapse after prior (neo)adjuvant treatment with ICIs and their combinations and have never been thoroughly investigated in previous trials.[1,2]

Intralesional therapies offer a localized approach to immune modulation, allowing high intratumoral drug exposure with limited systemic toxicity.[3] Daromun, a novel intralesional immunocytokine,[4,5] promotes robust local tumor regression and induction of systemic antitumor immune responses by combining the T-cell–stimulating properties of IL-2 with the proinflammatory and vascular-disrupting effects of TNF. Early clinical studies have demonstrated the promising activity of daromun in patients with injectable melanoma lesions, including regression of both injected and non-injected tumors.[4]

The phase III PIVOTAL trial (ClinicalTrials.gov identifier: NCT02938299) is a randomized study evaluating neoadjuvant intralesional daromun in patients with fully resectable, locally advanced melanoma, who were mostly pretreated. The trial enrolled 256 patients in the European Union and met its primary end point, showing statistically significant improvement in recurrence-free survival (RFS; hazard ratio [HR], 0.59; $P = .005$) of daromun versus up-front surgery, with a mild and manageable safety profile.[5] The PIVOTAL trial included patients newly diagnosed and patients with recurrent disease, that is, at first or further relapse after surgery with or without radiotherapy (RT) or systemic therapies, representing 13% and 87% of the overall population, respectively.

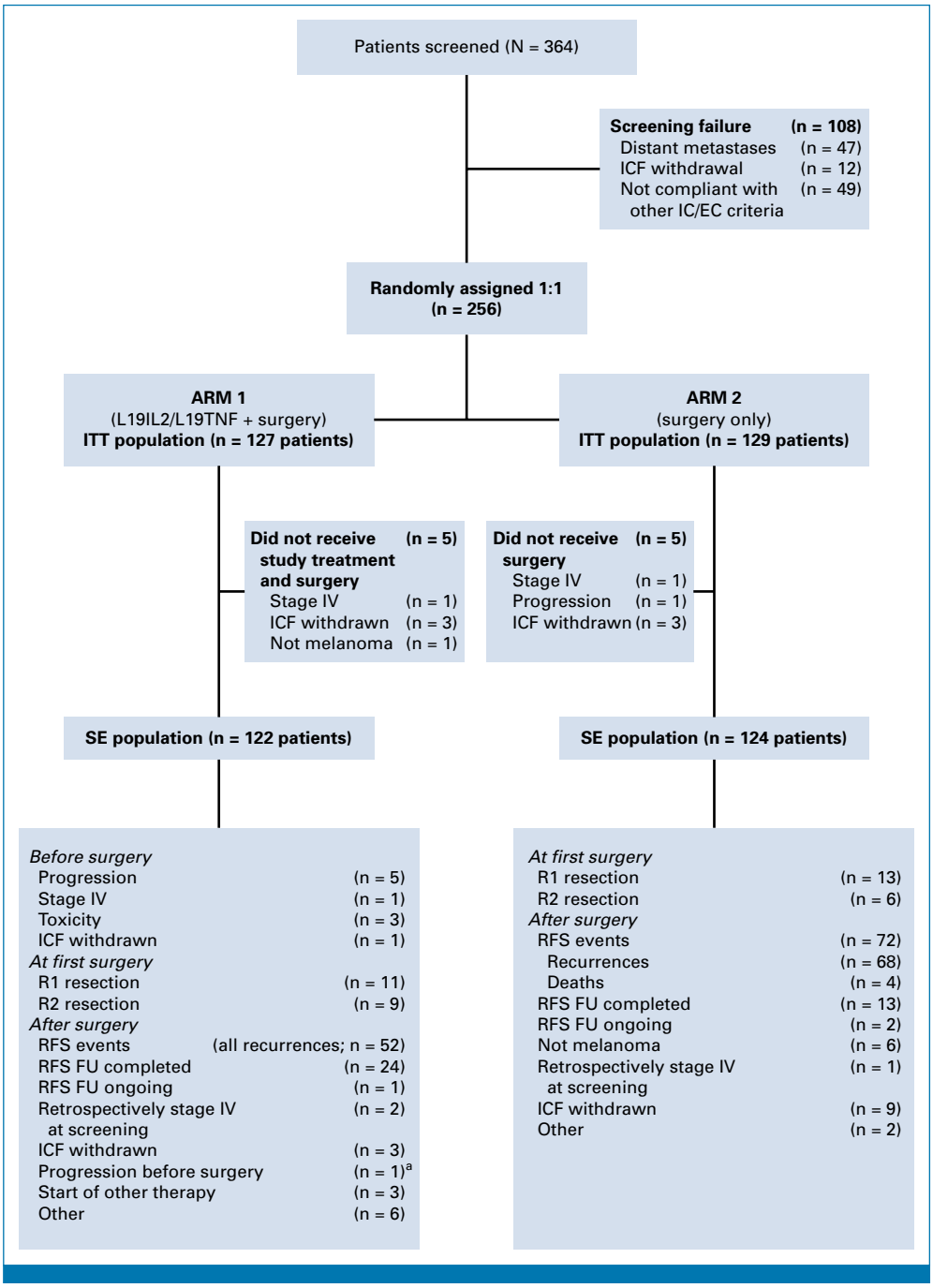


FIG 1. CONSORT diagram of patients' disposition and random assignment. [a]Retrospectively detected. FU, follow-up; ICF, informed consent; IC/EC, inclusion/exclusion criteria; ITT, intention to-treat; RFS, recurrence-free survival; SE, safety-evaluable.

Here, we present an updated analysis of primary and secondary end points at a median follow-up (FU) period of 36.8 months from random assignment. We also present a post hoc analysis of event-free survival (EFS) in the overall population. Exploratory EFS analyses were also conducted in the subgroup of patients with recurrent disease, either as a whole or stratified based on prior therapies (systemic *v* surgery/RT).

METHODS

A total 256 adult patients with locally advanced melanoma and at least one injectable skin or nodal lesion, eligible for complete surgical resection, were randomly assigned 1:1 to two study arms to receive either (1) intralesional neoadjuvant daromun (n = 127, Arm 1; 13 million IU of L19IL2 and 400 μg of L19TNF, once weekly for up to 4 weeks)

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TABLE 1. Baseline Demographic and Clinical Characteristics of the ITT Population and the Recurrent Patient Subgroup

	Overall (N = 256)		Recurrent (n = 222)	
Characteristic	Arm 1 (n = 127)	Arm 2 (n = 129)	Arm 1 (n = 108)	Arm 2 (n = 114)
Age, years, No. (%)				
<65	65 (51.2)	68 (52.7)	53 (49.1)	57 (50.0)
≥65	62 (48.8)	61 (47.3)	55 (50.9)	57 (50.0)
Age, years, median (min-max)	64.0 (23.0-88.0)	63.0 (22.0-91.0)	65.0 (24.0-88.0)	64.5 (22.0-87.0)
Sex, No. (%)				
Female	54 (42.5)	55 (42.6)	47 (43.5)	51 (44.7)
Male	73 (57.5)	74 (57.4)	61 (56.5)	63 (55.3)
ECOG, No. (%)				
0	118 (92.9)	125 (96.9)	102 (94.4)	110 (96.5)
1	9 (7.1)	4 (3.1)	6 (5.6)	4 (3.5)
LDH level, No. (%)				
Normal	110 (86.6)	106 (82.2)	97 (89.8)	95 (83.3)
Elevated	17 (13.4)	23 (17.8)	11 (10.2)	19 (16.7)
Time from first diagnosis of melanoma to random assignment, months, median (95% CI)	25.0 (19.0-36.0)	25.0 (19.0-33.0)	35.0 (25.0-44.0)	29.5 (23.0-37.0)
Disease stage (AJCC 7th version), No. (%)				
IIIB	39 (30.7)	38 (29.5)	35 (32.4)	36 (31.6)
IIIC	70 (55.1)	71 (55.0)	58 (53.7)	63 (55.3)
III unspecified	9 (7.1)	16 (12.4)	7 (6.5)	11 (9.6)
IV	7 (5.5)	2 (1.6)	6 (5.6)	2 (1.8)
Unknown	2 (1.6)	2 (1.6)	2 (1.9)	2 (1.8)
Disease stage (AJCC 8th version), No. (%)				
IIIB	20 (15.7)	23 (17.8)	17 (15.7)	22 (19.3)
IIIC	86 (67.7)	87 (67.4)	76 (70.4)	76 (66.7)
IIID	10 (7.9)	4 (3.1)	7 (6.5)	3 (2.6)
III unspecified	4 (3.1)	13 (10.1)	2 (1.9)	11 (9.6)
IV	7 (5.5)	2 (1.6)	6 (5.6)	2 (1.8)
BRAF mutation status, No. (%)				
Mutated	49 (38.6)	43 (33.3)	41 (38.0)	34 (29.8)
Wild-type	43 (33.9)	51 (39.5)	36 (33.3)	47 (41.2)
Unknown	35 (27.6)	35 (27.1)	31 (28.7)	33 (28.9)
Melanoma metastases at study entry, No. (%)				
1	70 (55.1)	76 (58.9)	63 (58.3)	68 (59.6)
2	22 (17.3)	24 (18.6)	17 (15.7)	19 (16.7)
≥3	35 (27.6)	29 (22.5)	28 (25.9)	27 (23.7)
Location of melanoma metastases, No. (%)[a]	n = 145 (100)	n = 136 (100)	n = 122 (100)	n = 119 (100)
Skin (cutaneous and subcutaneous)	76 (52.4)	66 (48.5)	71 (58.2)	60 (50.4)
Lymph nodes	66 (45.5)	67 (49.3)	48 (39.3)	56 (47.1)
Soft tissue	1 (0.7)	1 (0.7)	1 (0.8)	1 (0.8)
Other	2 (1.4)	2 (1.5)	2 (1.6)	2 (1.7)
Sum of diameters of melanoma lesions, mm, median (95% CI)	26.5 (21.0-30.0)	26.0 (23.0-30.0)	24.8 (20.1-29.0)	26.0 (22.0-30.0)
Prior systemic therapy, No. (%)				
No	83 (65.4)	87 (67.4)	64 (59.3)	72 (63.2)
Yes	44 (34.6)	42 (32.6)	44 (40.7)	42 (36.8)

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TABLE 1. Baseline Demographic and Clinical Characteristics of the ITT Population and the Recurrent Patient Subgroup (continued)

	Overall (N = 256)		Recurrent (n = 222)	
Characteristic	Arm 1 (n = 127)	Arm 2 (n = 129)	Arm 1 (n = 108)	Arm 2 (n = 114)
Prior systemic therapy type, No. (%)				
ICI	27 (21.3)	20 (15.5)	27 (25.0)	20 (17.5)
ICI only	20 (45.5)	15 (35.7)	20 (45.5)	15 (35.7)
ICI + BRAFi/MEKi	2 (4.5)	2 (4.8)	2 (4.5)	2 (4.8)
ICI + other	5 (11.4)	3 (7.1)	5 (11.4)	3 (7.1)
BRAFi/MEKi	3 (6.8)	6 (14.3)	3 (6.8)	6 (14.3)
Other	14 (31.8)	16 (38.1)	14 (31.8)	16 (38.1)

NOTE. The data shown are for the ITT population. 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. Percentages might not total 100 because of rounding.
Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; ITT, intention to-treat; LDH, lactate dehydrogenase.
[a]Patient can have multiple lesions (double counting).

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followed by surgery or (2) up-front surgery (n = 129, Arm 2).

Prior antitumor treatment, including surgery, RT, and approved systemic therapies, was allowed, as well as adjuvant treatment after surgery with approved therapies at physician's discretion.

The primary outcome was RFS in a blinded independent central review (BICR) analysis. Secondary end points included distant metastasis-free survival (DMFS), overall survival (OS), and safety. A post hoc analysis of EFS was also performed. Safety was assessed by capturing adverse event (AE) data using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03).

HR for comparison of survival curves was estimated using univariate Cox regression analyses. The proportional hazards assumption was verified using Schoenfeld residuals.

Additional information of trial design, patient population, study objectives, and definitions of primary and secondary end points and details of the statistical methods used are given in the Data Supplement (online only).

RESULTS

Patients

A total 364 patients were screened between June 2016 and May 2023, and 256 of these were randomly assigned and included in the intention to-treat analysis (127 in arm 1 and 129 in arm 2). At random assignment, 34 patients were newly diagnosed with stage III melanoma, whereas 222 patients had already experienced relapse(s) after surgery + RT with or without systemic treatments, including prior adjuvant therapies (the median time from prior systemic therapy was 16.5 months [arm 1] and 25.5 months [arm 2]).

Overall, postsurgery adjuvant treatment was conducted on 32.3% (41 of 127) and 41.8% (54 of 129) of patients in the treatment and control arm, respectively. Among recurrent patients, these proportions were 28.7% (31 of 108) and 37.7% (43 of 114), respectively.

Patient disposition (CONSORT diagram) is shown in Figure 1, and demographic, clinical, and tumor characteristics of the patients are reported in Table 1. Details of postsurgery adjuvant treatment modalities are provided in Appendix Table A1 (online only).

The original protocol and all amendments were approved by the institutional review board or the 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.

Efficacy

The updated primary outcome analysis in the BICR assessment at a median FU of 36.8 months from random assignment (database cutoff November 28, 2025) confirmed a clinically relevant improvement in RFS (HR, 0.55 [95% CI, 0.38 to 0.78]; P = <.001) for daromun versus up-front surgery (Fig 2A) as well as for DMFS (HR, 0.53 [95%

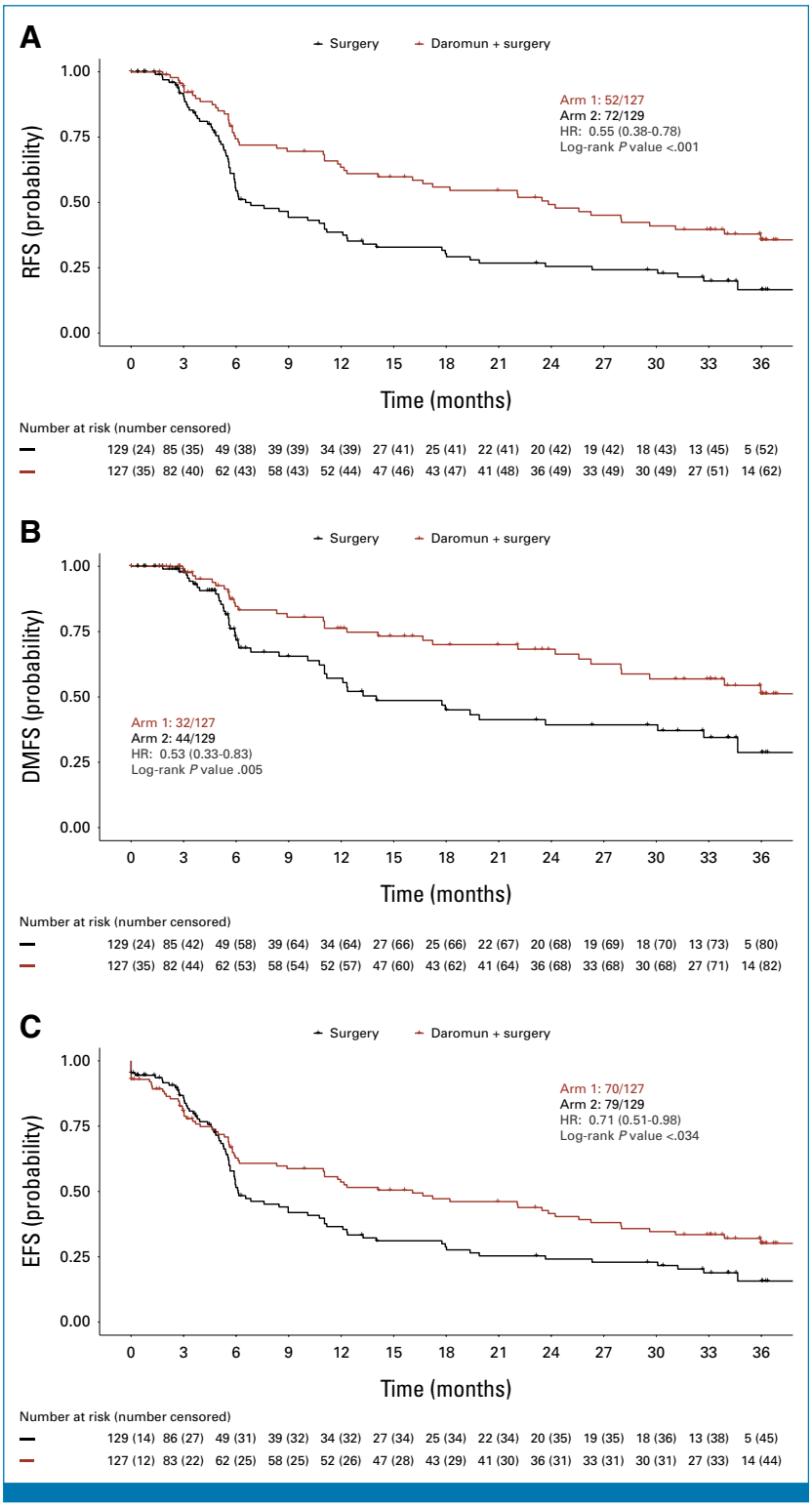


FIG 2. (A) Kaplan-Meier estimates of RFS in the ITT population. Shown are estimates of RFS for 256 patients in the study (ITT population) stratified by treatment group. The median RFS was 6.5 months in the surgery arm and 23.8 months in the daromun + surgery arm. The 1-year, 2-year, and 3-year RFS rates were 38.6%, 25.5%, and 16.6% in the surgery arm and 63.5%, 49.2%, and 35.7% in the daromun + surgery arm, respectively. (B) Kaplan-Meier estimates of DMFS in the ITT population stratified by treatment group. The median (continued on following page)

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FIG 2. (Continued). DMFS was 14.0 months in the surgery arm and 38.7 months in the daromun + surgery arm. The 1-year, 2-year, and 3-year DMFS rates were 57.2%, 39.3%, and 28.7% in the surgery arm and 76.3%, 68.3%, and 51.2% in the daromun + surgery arm, respectively. (C) Kaplan-Meier estimates of EFS in the ITT population stratified by treatment group. The median EFS was 6.1 months in the surgery arm and 16.1 months in the daromun + surgery arm. The 1-year, 2-year, and 3-year EFS rates were 36.6%, 24.1%, and 15.7% in the surgery arm and 53.6%, 41.6%, and 30.1% in the daromun + surgery arm, respectively. The results were assessed by retrospective BICR. Tick marks show data censored at the time of last disease assessment. BICR, blinded independent central review; DMFS, distant metastasis-free survival; EFS, event-free survival; HR, hazard ratio; ITT, intention to-treat; RFS, recurrence-free survival.

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CI, 0.33 to 0.83]; P = .005; Fig 2B). The EFS sensitivity analysis performed in the overall population was consistent with the RFS results (HR, 0.71 [95% CI, 0.51 to 0.98]; P = .034; Fig 2C).

A per-protocol subgroup analysis of recurrent patients also showed that in this subpopulation, daromun significantly improved RFS (HR, 0.50 [95% CI, 0.34 to 0.75; Fig 3A) and DMFS (HR, 0.43 [95% CI, 0.26 to 0.72]; not shown) compared with the control. Further subgroup analyses of recurrent patients, according to their treatment history, showed comparable RFS benefit for those patients who had received and failed prior surgery accompanied by systemic therapies (HR, 0.53 [95% CI, 0.29 to 0.95]; Fig 3C) and for those who had only received surgery with or without RT (HR, 0.46 [95% CI, 0.27 to 0.78]; Fig 3E).

Exploratory EFS in the recurrent population favored neoadjuvant therapy (HR, 0.68 [95% CI, 0.48 to 0.97]; Fig 3B). Further analyses of the recurrent patient group were also performed according to the systemic treatment history. The EFS benefit showed a strong trend in recurrent patients who had received and failed prior surgery accompanied by systemic therapies (HR, 0.68 [95% CI, 0.40 to 1.15]; Fig 3D) and in those who had only received surgery with or without RT (HR, 0.65 [95% CI, 0.40 to 1.05]; Fig 3F). However, these results demonstrate only a strong trend without reaching statistical significance.

OS data were still immature at the time of data cutoff (37 of 104 events recorded).

Safety

The updated safety profile of daromun remained manageable in the overall population, with no new concerning signals recorded.[5] By the database cutoff date, AEs of NCI CTCAE grade ≥3 were reported in 33.6% (41 of 122) of safety-evaluable (SE) patients in the neoadjuvant arm and in 11.3% (14 of 124) of SE patients in the control arm. Grade 3 treatment-related AEs (TRAEs) occurred in 28.7% (35 of 122) of SE patients in the daromun arm and in 7.3% (9 of 124) of patients in the control arm. The most frequently reported grade 3 TRAE in patients treated with daromun was injection site reaction occurring in 12.3% (15 of 122) of SE patients. There were no CTC grade >3 TRAEs and no treatment-related deaths.

DISCUSSION

The updated analysis confirms that neoadjuvant intralesional daromun provides clinically and statistically meaningful improvements in RFS and DMFS in patients with locally advanced recurrent melanoma. Exploratory EFS analyses, which were designed to capture preoperative events that could prevent definitive surgery, produced consistent results with RFS and DMFS analyses. A post hoc analysis of EFS confirms the benefit of neoadjuvant daromun observed with the primary efficacy end point (RFS).

In the PIVOTAL trial, most patients (87%) had locally advanced recurrent melanoma after prior surgery with or without RT, with or without prior systemic adjuvant therapy. Both RFS and EFS analyses demonstrate a clinically significant advantage for the experimental arm in this higher-risk group. The safety profile was consistent with that observed in the overall trial, with no new safety concerns emerging.

Recent perioperative immunotherapy trials[1,2] have established the role of neoadjuvant therapy in de novo stage III melanoma. The findings of the present study extend the scope of neoadjuvant strategies to include recurrent patients, whether they have received prior systemic treatment. The results also support tumor-targeted intralesional cytokine delivery as a means of boosting local immune modulation while minimizing systemic exposure.[4,5] However, the study has several limitations, including its open-label design, the exploratory nature of the subgroup analyses, and the immaturity of the OS data. A longer FU period is required to clarify the potential impact on survival, and further prospective investigation in nodal-positive patients is necessary. A parallel, Phase 3 neoadjuvant study in stage III resectable melanoma is

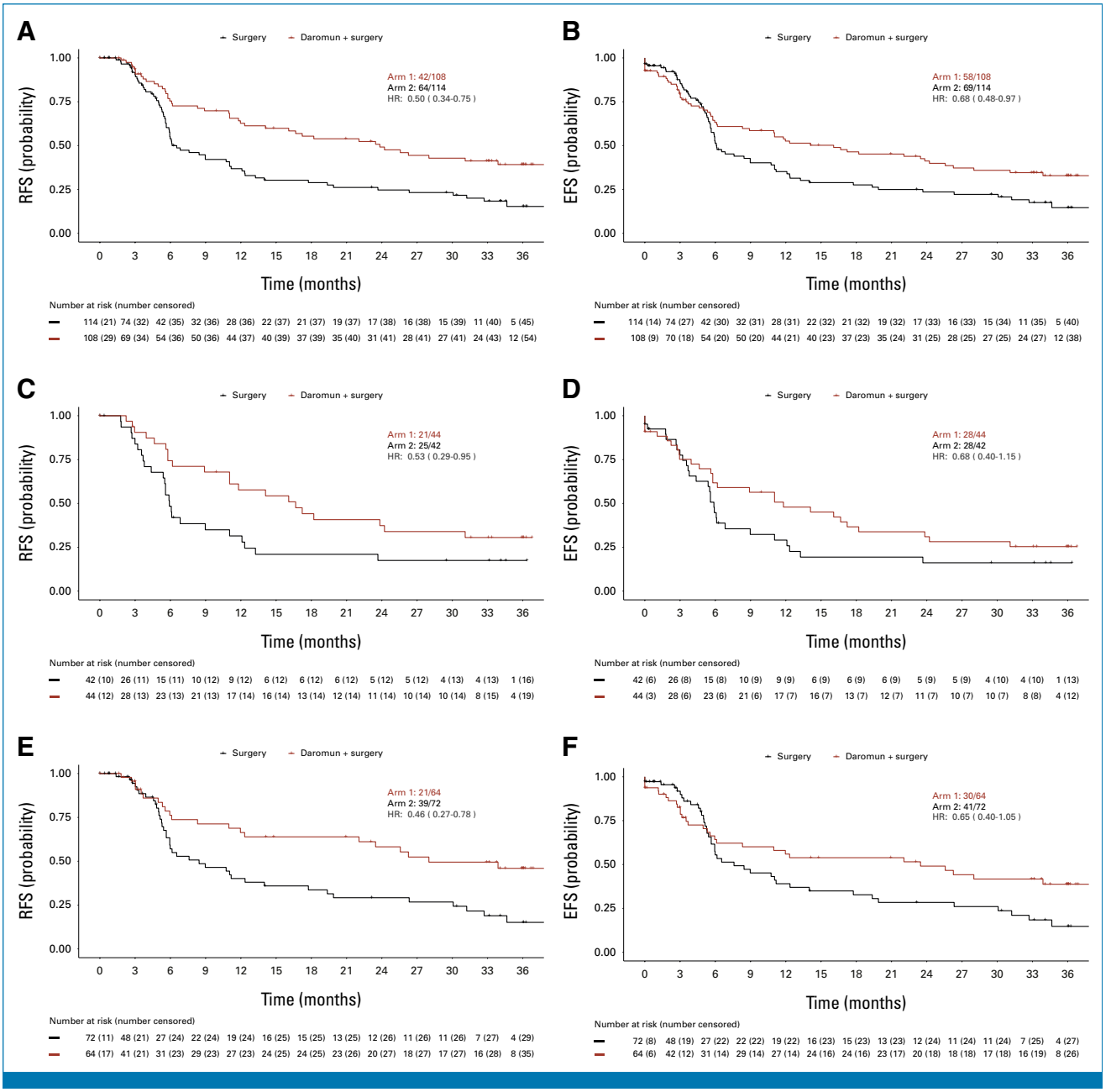


FIG 3. (A) Kaplan-Meier estimates of RFS in the subgroup of recurrent patients (n = 222), stratified by treatment group. The median RFS was 6.1 months in the surgery arm and 23.8 months in the daromun + surgery arm. The 1-year, 2-year, and 3-year RFS rates were 36.8%, 24.7%, and 15.3% in the surgery arm and 62.7%, 49.2%, and 39.2% in the daromun + surgery arm, respectively. (B) Kaplan-Meier estimates of EFS in the subgroup of recurrent patients (n = 222), stratified by treatment group. The median EFS was 6.1 months in the surgery arm and 16.1 months in the daromun + surgery arm. The 1-year, 2-year, and 3-year EFS rates were 35.2%, 23.6%, and 14.6% in the surgery arm and 52.6%, 41.2%, and 32.8% in the daromun + surgery arm, respectively. (C) Kaplan-Meier estimates of RFS in the subgroup of recurrent patients who had received and failed prior surgery accompanied by systemic therapies (n = 86). The median RFS was 5.9 months in the surgery arm and 16.7 months in the daromun + surgery arm. The 1-year, 2-year, and 3-year RFS rates were 31.5%, 17.5%, and 17.5% in the surgery arm and 57.7%, 37.3%, and 30.5% in the daromun + surgery arm, respectively. (D) Kaplan-Meier estimates of EFS in the subgroup of recurrent patients who had received and failed prior surgery accompanied by systemic therapies (n = 86). The median EFS was 5.9 months in the surgery arm and 11.8 months in the daromun + surgery arm. The 1-year, 2-year, and 3-year EFS rates were 29.1%, 16.2%, and 16.2% in the surgery arm and 47.9%, 31.0%, and 25.4% in the daromun + surgery arm, respectively. (E) Kaplan-Meier estimates of RFS in the subgroup of recurrent patients who had received prior surgery(ies), with or without RT (n = 136). The median RFS was 8.4 months in the surgery arm and 28.0 months in the daromun + surgery arm. The 1-year, 2-year, and 3-year RFS rates were 40.1%, 29.2%, and 15.1% in the surgery arm and 66.4%, 58.2%, and 45.9% in the daromun + surgery arm, respectively. (F) Kaplan-Meier estimates of EFS in the subgroup of recurrent patients who had received prior surgery(ies), with or without RT (n = 136). The median EFS was 7.6 months in the surgery arm and 23.5 months in the daromun + surgery arm. The 1-year, 2-year, and 3-year EFS rates were 39.0%, 28.4%, and 14.7% in the surgery arm and 55.9%, 49.1%, and 38.7% in the daromun + surgery arm, respectively. The results were assessed by retrospective BICR. Tick marks (continued on following page)

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FIG 3. (Continued). show data censored at the time of last disease assessment. BICR, blinded independent central review; EFS, event-free survival; HR, hazard ratio; RFS, recurrence-free survival; RT, radiotherapy.

ongoing in the United States and various EU countries (NeoDREAM; NCT03567889). Future studies should evaluate predictive biomarkers of response and determine daromun's role in contemporary perioperative treatment sequences, including its optimal integration with checkpoint blockade and/or targeted therapy.

AFFILIATIONS

[1]Department of Dermatology, University Hospital Schleswig-Holstein (UKSH), Campus Kiel, Kiel, Germany
[2]Department of Dermatology and NCT, Heidelberg University, Medical Faculty, University Hospital Heidelberg, Heidelberg, Germany
[3]Skin Cancer Center, University Hospital Leipzig, Leipzig, Germany
[4]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[5]Department of Dermatology, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany
[6]Department of Dermatology, Center for Dermatooncology, Eberhard Karls University of Tübingen, Tübingen, Germany
[7]Dermatology and Skin Cancer Department, Aix-Marseille University, Assistance Publique-Hôpitaux de Marseille, Marseille, France
[8]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[9]IOV—Istituto Oncologico Veneto—IRCCS, Padua, Italy
[10]Department of Dermatology and Allergy, Skin Cancer Center Hannover, Hannover Medical School, Hannover, Germany
[11]Department of Dermatology, Venerology and Allergology, Charité-Universitaetsmedizin Berlin, Berlin, Germany
[12]Center for Immuno-Oncology, University Hospital of Siena, NIBIT Foundation Onlus, University of Siena, Siena, Italy
[13]Department of Dermatology and Venereology of the Medical University of Triest, Trieste, Italy
[14]Department of Dermatology, Medical University of Graz, Graz, Austria
[15]Department of Dermatology, University Hospital of Regensburg, Regensburg, Germany
[16]Department of Medical Sciences, Dermatologic Clinic, University of Turin, Turin, Italy
[17]Department of Dermatology, University Hospital Augsburg, Comprehensive Cancer Center Augsburg, BZKF Bavarian Center for Cancer Research, Augsburg, Germany
[18]Philochem AG, Otelfingen, Switzerland
[19]Philogen S.p.A., Siena, Italy
[20]Università degli Studi di Napoli "Federico II" and Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale", Naples, Italy
[21]Institute Gustave Roussy, Villejuif-Paris, France
[22]Comprehensive Cancer Center (Westdeutsches Tumorzentrum), University Hospital Essen, German Cancer Consortium (DKTK)-Heidelberg, Essen, Germany

CORRESPONDING AUTHOR

Axel Hauschild, MD; e-mail: ahauschild@dermatology.uni-kiel.de.

CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-26-00852.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-26-00852.

AUTHOR CONTRIBUTIONS

Conception and design: Axel Hauschild, Giuliano Elia, Alfredo Covelli, Katia Lorizzo, Dario Neri, Caroline Robert, Katharina Charlotte Kaehler, Dirk Schadendorf
Provision of study materials or patients: Jessica Cecile Hassel, Piotr Rutkowski, Friedegund Meier, Lukas Flatz, Caroline Gaudy-Marqueste, Mario Santinami, Imke von Wasielewski, Thomas Eigentler, Michele Maio, Iris Zalaudek, Julia Welzel, Michael Weichenthal, Katia Lorizzo, Caroline Robert, Dirk Schadendorf, Katharina Charlotte Kaehler
Collection and assembly of data: Axel Hauschild, Jessica Cecile Hassel, Mirjana Ziemer, Piotr Rutkowski, Friedegund Meier, Lukas Flatz, Caroline Gaudy-Marqueste, Mario Santinami, Francesco Russano, Imke von Wasielewski, Thomas Eigentler, Michele Maio, Iris Zalaudek, Sebastian Haferkamp, Pietro Quaglino, Julia Welzel, Michael Weichenthal, Katia Lorizzo, Caroline Robert, Dirk Schadendorf, Katharina Charlotte Kaehler
Data analysis and interpretation: Axel Hauschild, Jessica Cecile Hassel, Mirjana Ziemer, Lukas Flatz, Caroline Gaudy-Marqueste, Mario Santinami, Thomas Eigentler, Michele Maio, Sebastian Haferkamp, Julia Welzel, Michael Weichenthal, Giuliano Elia, Alfredo Covelli, Katia Lorizzo, Agnese Parca, Dario Neri, Paolo Antonio Ascierto, Caroline Robert, Dirk Schadendorf, Katharina Charlotte Kaehler
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Blank CU, Lucas MW, Scolyer RA, et al: Neoadjuvant nivolumab and ipilimumab in resectable stage III melanoma. N Engl J Med 391:1696-1708, 2024
2. Patel SP, Othus M, Chen Y, et al: Neoadjuvant-adjuvant or adjuvant-only pembrolizumab in advanced melanoma. N Engl J Med 388:813-823, 2023
3. Weide B, Neri D, Elia G.: Intralesional treatment of metastatic melanoma: A review of therapeutic options. Cancer Immunol Immunother 66:647-656, 2017
4. 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 64:999-1009, 2015
5. Kahler KC, Hassel JC, Ziemer M, et al: Neoadjuvant intralesional targeted immunocytokines (daromun) in stage III melanoma. Ann Oncol 36:1166-1177, 2025

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Neoadjuvant Intralesional Daromun (L19IL2/L19TNF) in Resectable Locally Advanced Melanoma: An Update on the Efficacy and Safety Results of the PIVOTAL Phase III Trial

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Axel Hauschild
Honoraria: Bristol Myers Squibb, Merck Serono, Merck Sharp & Dohme, Novartis, Roche, Philogen, Regeneron, Sanofi/Aventis, Immunocore, Replimune, Agenus, Incyte, CureVac, IO Biotech, NeraCare GmbH, Skyline Diagnostics, Pierre Fabre, Almirall Hermal GmbH, Xenthera, Sun Pharma
Consulting or Advisory Role: Amgen, Bristol Myers Squibb, Merck Serono, Merck Sharp & Dohme, Novartis, Roche, Philogen, Regeneron, Sanofi/Aventis, Immunocore, Replimune, IO Biotech
Research Funding: Amgen, Bristol Myers Squibb, Merck Serono, Merck Sharp & Dohme, Novartis, Roche, Regeneron
Travel, Accommodations, Expenses: Amgen, Bristol Myers Squibb, Merck Serono, Merck Sharp & Dohme, Novartis, Roche, Sanofi/Aventis

Jessica Cecile Hassel
Honoraria: MSD, Novartis, Sun Pharma, Bristol Myers Squibb Foundation, Pierre Fabre, Immunocore, Delcath Systems, Amgen, Regeneron
Consulting or Advisory Role: Sun Pharma, MSD (Inst), Pierre Fabre (Inst), BMS GmbH & Co. KG (Inst), Immunocore (Inst), Novartis (Inst), Philogen (Inst), Delcath Systems
Research Funding: Bristol Myers Squibb (Inst), Novartis (Inst), Immunocore (Inst), BioNTech (Inst), Philogen (Inst), Genentech/Roche (Inst), Iovance Biotherapeutics (Inst), Pierre Fabre (Inst), Regeneron (Inst), Sun Pharma (Inst), Genmab (Inst), IO Biotech (Inst), Replimune (Inst), Immatics (Inst), MSD Oncology (Inst), Pfizer (Inst)

Mirjana Ziemer
Employment: Department of Dermatology, University Hospital of Leipzig, Germany
Honoraria: MSD Oncology, Sun Pharma, AstraZeneca, Regeneron, Johnson & Johnson/Janssen, InfectoPharm
Consulting or Advisory Role: Regeneron
Travel, Accommodations, Expenses: Sun Pharma, Pierre Fabre, Recordati

Piotr Rutkowski
Honoraria: Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, Merck, Medison, Genesis Pharma
Consulting or Advisory Role: Novartis, Bristol Myers Squibb, Pierre Fabre, MSD, Amgen, Philogen, AstraZeneca, Immunome, Cogent Medicine
Speakers' Bureau: Pierre Fabre, Medison, Genesis Pharma
Research Funding: Novartis (Inst), Roche (Inst), Bristol Myers Squibb (Inst), Pierre Fabre (Inst)
Travel, Accommodations, Expenses: Orphan Europe, Pierre Fabre

Friedegund Meier
Honoraria: Bristol Myers Squibb, Novartis, MSD, Sanofi, Philogen, Immunocore, Delcath Systems
Consulting or Advisory Role: Bristol Myers Squibb, Novartis, MSD, Sanofi, Pierre Fabre, Immunocore, Regeneron, Philogen
Research Funding: Roche (Inst)
Travel, Accommodations, Expenses: Novartis, Bristol Myers Squibb, MSD, Sanofi, Pierre Fabre, Immunocore

Lukas Flatz
Stock and Other Ownership Interests: Humion AG, Hookipa Pharma, cair.one, Abtherix
Consulting or Advisory Role: Philogen, Sanofi
Research Funding: Hookipa Pharma, Philogen
Patents, Royalties, Other Intellectual Property: Patents relating to the Vaxwave Vaccine Technology currently licensed by Hookipa Pharma

Caroline Gaudy-Marqueste
Honoraria: BMS France, Pierre Fabre, UCB
Consulting or Advisory Role: Pierre Fabre, MSD Oncology, Bristol Meyer Squib, Regeneron, Sun Pharma, Iovance Biotherapeutics
Research Funding: Day One Biopharmaceuticals (Inst), Immunocore (Inst), Merck (Inst), Sairopa (Inst), DOT Therapeutics (Inst), Dragonfly Therapeutics (Inst), Incyte (Inst), Daiichi Sankyo Europe GmbH (Inst), Microbiotica (Inst), Erasca, Inc (Inst), Bristol Myers Squibb (Inst), Pfizer (Inst), Amgen (Inst), GlaxoSmithKline (Inst), Roche (Inst), Novartis (Inst), Pierre Fabre (Inst), Replimune (Inst), MSD (Inst), Janssen (Inst), Kartos Therapeutics (Inst), HUYA Bioscience International (Inst), Regeneron (Inst), IO Biotech (Inst), Philogen (Inst), Sotio (Inst), Kinnate Biopharma (Inst), AstraZeneca (Inst), Cytovation (Inst), InflaRx (Inst)
Travel, Accommodations, Expenses: Pierre Fabre, BMS France, MSD Oncology, Sun Pharma, Janssen, Regeneron, UCB

Imke von Wasielewski
Consulting or Advisory Role: MSD, Sanofi/Regeneron
Travel, Accommodations, Expenses: Pierre Fabre, Kyowa Kirin International

Thomas Eigentler
Stock and Other Ownership Interests: Genmab
Consulting or Advisory Role: Bristol Myers Squibb, Novartis, MSD, Regeneron, Almirall, Philogen, Skyline Diagnostics

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Michele Maio
Stock and Other Ownership Interests: Theravance, Epigen Therapeutics
Honoraria: Bristol Myers Squibb, AstraZeneca, Roche, MSD, Merck, Amgen, Pierre Fabre, Alfasigma, Sanofi, Lilly
Consulting or Advisory Role: Bristol Myers Squibb, Roche, AstraZeneca, MSD, Merck, Pierre Fabre, Alfasigma
Patents, Royalties, Other Intellectual Property: DNA Hypomethylating Agents for Cancer Therapy
Travel, Accommodations, Expenses: Bristol Myers Squibb, AstraZeneca, Roche, MSD, Merck, Amgen, Pierre Fabre, Alfasigma

Iris Zalaudek
Honoraria: Sanofi/Regeneron, Sun Pharma, MSD Oncology, Novartis, Philogen, Fotofinder
Consulting or Advisory Role: Philogen, Sun Pharma
Travel, Accommodations, Expenses: Sun Pharma

Sebastian Haferkamp
Honoraria: Novartis, Bristol Myers Squibb, Amgen
Consulting or Advisory Role: Bristol Myers Squibb, Novartis, Pierre Fabre, MSD, Sun Pharma

Pietro Quaglino
Consulting or Advisory Role: Bristol Myers Squibb Foundation, Novartis, Pierre Fabre, Roche, MSD Oncology
Speakers' Bureau: Bristol Myers Squibb Foundation, Roche, Novartis, Pierre Fabre, MSD Oncology

Julia Welzel
Honoraria: Almirall Hermal GmbH, AbbVie, Beiersdorf, Bristol Myers Squibb/Celgene, Johnson & Johnson/Janssen, LEO Pharma, Lilly, Novartis, Sanofi
Consulting or Advisory Role: Almirall, Sanofi, Johnson & Johnson/Janssen, Johnson & Johnson/Janssen, AbbVie
Research Funding: Incyte (Inst), Almirall (Inst)
Travel, Accommodations, Expenses: AbbVie, Almirall, Beiersdorf, Johnson & Johnson/Janssen, LEO Pharma, Lilly, Novartis, Sanofi, Bristol Myers Squibb/Celgene

Michael Weichenthal
Honoraria: Merck Sharp & Dohme, Novartis, Bristol Myers Squibb, Sanofi, Sun Pharma, Regeneron, Immunocore, Pierre Fabre
Consulting or Advisory Role: Merck Sharp & Dohme, Novartis, Bristol Myers Squibb, Sun Pharma, Pierre Fabre
Research Funding: Merck Sharp & Dohme (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Innate Pharma (Inst)

Giuliano Elia
Consulting or Advisory Role: Philochem
Patents, Royalties, Other Intellectual Property: Philogen

Alfredo Covelli
Consulting or Advisory Role: Philogen
Travel, Accommodations, Expenses: Philogen

Katia Lorizzo
Employment: Philogen SpA
Leadership: Philogen SpA

Dario Neri
Employment: Philogen
Leadership: Philogen
Stock and Other Ownership Interests: Philogen
Patents, Royalties, Other Intellectual Property: I am a co-founder, a shareholder, and the CEO of Philogen (www.philogen.com). I am a coinventor in several Philogen patents

Paolo Antonio Ascierto
Consulting or Advisory Role: Bristol Myers Squibb, Roche/Genentech, Merck Sharp & Dohme, Novartis, Pierre Fabre, Sun Pharma, Immunocore, Italfarmaco, Boehringer Ingelheim, Regeneron, Pfizer, Nouscom, Medicenna, ValoTx, Replimune, Bayer, Erasca, Inc, Philogen, BioNTech SE, Anaveon, Genmab, Menarini Silicon Biosystems, ImCheck therapeutics, Incyte, Moderna Therapeutics, Therakos
Research Funding: Bristol Myers Squibb (Inst), Roche/Genentech (Inst), Pfizer (Inst), Regeneron (Inst), Medicenna (Inst)
Travel, Accommodations, Expenses: MSD Oncology, Pierre Fabre, Philogen

Caroline Robert
Honoraria: Pierre Fabre, Bristol Myers Squibb, MSD, Merck, Roche, Pfizer, Sun Pharma, Regeneron, MaaT Pharma, Iovance Biotherapeutics, Moderna Therapeutics, Immatics
Consulting or Advisory Role: Bristol Myers Squibb, Roche, Pierre Fabre, MSD, Pfizer, Sun Pharma, Merck, Regeneron, MaaT Pharma, Iovance Biotherapeutics, Moderna Therapeutics, Immatics, IO Biotech
Travel, Accommodations, Expenses: Pierre Fabre

Dirk Schadendorf
Honoraria: Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Immunocore, Merck Serono, Pierre Fabre, Philogen, Regeneron, NeraCare GmbH, Sun Pharma, Replimune, Immatics, Ipsen, Boehringer Ingelheim, BioNTech SE, IO Biotech, Iovance Biotherapeutics, Skyline Diagnostics, ImCheck therapeutics, EeBeTe, Formycon, Incyte, Moderna Therapeutics, Daiichi Sankyo/Astra Zeneca
Consulting or Advisory Role: Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, AstraZeneca, Daiichi Sankyo, Immatics, Immunocore, NeraCare GmbH, Replimune, BioNTech SE, IO Biotech, Boehringer Ingelheim, Iovance Biotherapeutics, Skyline Diagnostics, Sun Pharma, Philogen, ImCheck Therapeutics, Formycon, EeBeTe, Incyte, Moderna Therapeutics, Ipsen
Speakers' Bureau: Bristol Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, Merck KGaA, Regeneron
Research Funding: Bristol Myers Squibb (Inst), MSD Oncology (Inst), Regeneron (Inst)
Travel, Accommodations, Expenses: Roche/Genentech, Bristol Myers Squibb, Merck Serono, Novartis, Merck Sharp & Dohme, Pierre Fabre, Sanofi/Regeneron

Katharina Charlotte Kaehler
Honoraria: Bristol Myers Squibb, MSD, Novartis, Sanofi, Immunocore, Philogen, Sun Pharma
Consulting or Advisory Role: Bristol Myers Squibb, MSD, Pierre Fabre, Philogen, Sun Pharma
Travel, Accommodations, Expenses: Bristol Myers Squibb, MSD, Novartis, Roche, Pierre Fabre

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APPENDIX

TABLE A1. Postsurgery Adjuvant Treatments (overall population)

Treatment	Arm 1 (n = 41)	Arm 2 (n = 54)	Overall (n = 95)
ICIs	28	38	66
BRAF/MEK inhibitors (TT)	8	12	20
ICI + TT	1	1	2
RT	4	3	7

Abbreviations: ICI, immune checkpoint inhibitor; RT, radiotherapy; TT, targeted therapies.

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