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ORIGINAL ARTICLE

Survival update of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma in the OpACIN and OpACIN-neo trials☆

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Background: Neoadjuvant ipilimumab plus nivolumab has yielded high response rates in patients with macroscopic stage III melanoma. These response rates translated to high short-term survival rates. However, data on long-term survival and disease recurrence are lacking.

Patients and methods: In OpACIN, 20 patients with macroscopic stage III melanoma were randomized to ipilimumab 3 mg/kg plus nivolumab 1 mg/kg q3w four cycles of adjuvant or split two cycles of neoadjuvant and two adjuvant. In OpACIN-neo, 86 patients with macroscopic stage III melanoma were randomized to arm A (2× ipilimumab 3 mg/kg plus nivolumab 1 mg/kg q3w; $n = 30$), arm B (2× ipilimumab 1 mg/kg plus nivolumab 3 mg/kg q3w; $n = 30$), or arm C (2× ipilimumab 3 mg/kg q3w plus 2× nivolumab 3 mg/kg q2w; $n = 26$) followed by surgery.

Results: The median recurrence-free survival (RFS) and overall survival (OS) were not reached in either trial. After a median follow-up of 69 months for OpACIN, 1/7 patients with a pathologic response to neoadjuvant therapy had disease recurrence. The estimated 5-year RFS and OS rates for the neoadjuvant arm were 70% and 90% versus 60% and 70% for the adjuvant arm. After a median follow-up of 47 months for OpACIN-neo, the estimated 3-year RFS and OS rates were 82% and 92%, respectively. The estimated 3-year RFS rate for OpACIN-neo was 95% for patients with a pathologic response versus 37% for patients without a pathologic response ($P < 0.001$). In multiple regression analyses, pathologic response was the strongest predictor of disease recurrence. Of the 12 patients with distant disease recurrence after neoadjuvant therapy, 5 responded to subsequent anti-PD-1 and 8 to targeted therapy, although 7 patients showed progression after the initial response.

Conclusions: Updated data confirm the high survival rates after neoadjuvant combination checkpoint inhibition in macroscopic stage III melanoma, especially for patients with a pathologic response. Pathologic response is the strongest surrogate marker for long-term outcome.

Key words: neoadjuvant therapy, adjuvant therapy, immune checkpoint inhibition, immunotherapy, melanoma

INTRODUCTION

The outcome of patients with macroscopic stage III melanoma treated with surgery only is poor with a 5-year overall survival (OS) rate of <50%.[1-3] Adjuvant immune checkpoint inhibition (ICI) and targeted therapies reduce the risk of recurrence.[4-6] Despite this improvement, disease recurrence is still observed in >30% of these patients with

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high-risk melanoma within 2 years after surgery.[4,7-9] In addition, ∼15%-25% of patients were not included in the phase III adjuvant drug trials due to progression in the screening phase, after surgery and prior to randomization, suggesting an event-free survival (EFS) of <50% in the intention-to-treat population.[7,10] Indeed, in the recently presented randomized phase II S1801 trial comparing neoadjuvant versus adjuvant pembrolizumab, the estimated 2-year EFS in the adjuvant arm was 49%.[11]

Neoadjuvant therapy bears several advantages over adjuvant therapy.[12,13] It can reduce tumor burden, thereby facilitating surgery, and enables response evaluation within the individual patient, which can guide the extent of surgery and the matter of adjuvant therapy. Because of the presence of the tumor at start of the therapy, neoadjuvant ICI can induce a deeper and broader immune response, as shown in preclinical models and the pilot OpACIN trial.[14,15] The S1801 trial showed a superior EFS for the neoadjuvant arm, confirming the earlier postulated hypotheses.[11] Neoadjuvant anti-PD-1 (anti-programmed cell death protein 1) with or without anti-CTLA-4 (anti-cytotoxic T-lymphocyte-associated protein 4) has not only shown promising activity in melanoma,[15-18] but also in other malignancies, such as bladder cancer, colorectal carcinoma, head and neck cancer, lung cancer, and triple-negative breast cancer.[19-23]

Pathologic response to ICI might be considered to be an accurate surrogate marker for long-term outcome,[24] but long-term data on the durability of high survival rates after pathologic response are lacking. Here, we report the 5- and 3-year recurrence-free survival (RFS), EFS, and OS data from the OpACIN and OpACIN-neo trials, including characteristics of patients with disease recurrence and its management.

METHODS

Inclusion and exclusion criteria and the methods of response assessment for both trials have been described previously.[15,16] Radiologic response on computed tomography (CT) scan was assessed according to RECIST 1.1 methods.[25] Pathologic response assessment was carried out according to the International Neoadjuvant Melanoma Consortium (INMC) criteria,[26] classifying the following subcategories: major pathologic response [MPR; ≤10% residual viable tumor, which included patients with a complete pathologic response (pCR, 0% residual viable tumor) and those with a near-complete pathologic response (>0%-≤10% residual viable tumor)], pathologic partial response (pPR; >10%-≤50% residual viable tumor), and pathologic nonresponse (pNR; >50% residual viable tumor). Pathologic response is classified as either MPR or pPR.

Protocols of both trials were reviewed by the review boards and medical ethics committee of the Netherlands Cancer Institute (NKI) for OpACIN (NCT02437279) and of each of the participating centers for OpACIN-neo (NCT02977052). The trials were carried out in accordance with Good Clinical Practice guidelines and all patients provided written informed consent before enrollment. Both investigator-initiated trials were funded by Bristol-Myers Squibb, with NKI as sponsor. Data were collected by the clinical research department of the sponsor and independently monitored.

Study design and patient allocation have been previously published for both trials.[15,16] In brief, 20 patients with clinical stage III melanoma were randomized to four cycles of ipilimumab 3 mg/kg plus nivolumab 1 mg/kg q3w (every 3 weeks) adjuvant ($n = 10$) or two cycles of neoadjuvant, therapeutic lymph node dissection at week 6 and subsequent two cycles of adjuvant ($n = 10$) in the single-center OpACIN trial. In the multicenter OpACIN-neo trial, 86 patients were randomized to arm A ($n = 30$), two cycles of ipilimumab 3 mg/kg plus nivolumab 1 mg/kg q3w; arm B ($n = 30$), two cycles of ipilimumab 1 mg/kg plus nivolumab 3 mg/kg q3w; and arm C ($n = 26$), two cycles of ipilimumab 3 mg/kg q3w, directly followed by two cycles of nivolumab 3 mg/kg q2w. Therapeutic lymph node dissection was planned at week 6 and no adjuvant therapy was administered.

Patients were evaluated for disease recurrence in both trials according to the institutional standards: for the first 3 years at NKI a CT scan was carried out every 3 months for patients without a pathologic response and every 6 months for patients with a pathologic response; at Melanoma Institute Australia a CT scan and magnetic resonance imaging of the brain were carried out every 3 months and a positron emission tomography—CT every year, and at Karolinska Institute a CT scan was carried out every 6 months. Subsequent follow-up was according to institutional standards, which was in general six monthly scans for years 4 and 5. The database locks for the presented analyses took place on 7 February 2022 for OpACIN and 14 February 2022 for OpACIN-neo.

Statistical considerations

In both trials, data on disease recurrence and survival were censored at the last date of contact without evidence of disease or death. The median follow-up was calculated using the inverted Kaplan—Meier approach; the estimated survival rates were calculated using the Kaplan—Meier method. RFS was defined as the time from surgery and EFS as the time from randomization until the date of first recurrence (local, regional, or distant metastasis) and/or death from any cause. Distant metastasis-free survival (DMFS) was defined as the time from surgery until the date of first presentation of distant disease and/or death from any cause, and OS as the time from randomization until death from any cause.

As the OpACIN trial had clinical feasibility as the primary endpoint and was not powered for comparison of the two arms, all efficacy endpoints are descriptive. To compare differences between treatment arms and between patient response groups in OpACIN-neo, the log-rank test was used.

Regression analyses were carried out using IBM SPSS Statistics, version 27 (IBM Inc., New York, NY). Chi-square and Mann—Whitney *U* test were used for comparison of

baseline characteristics. For multivariable analyses, variables with a *P* value of <0.100 in univariable analyses were taken along. Cox regression was used to determine risk factors for disease recurrence and distant metastases. To identify risk factors for regional and distant metastases as first progressive event, ordinal logistic regression analyses were carried out.

RESULTS

OpACIN trial

At data cut-off, the median follow-up was 69 months for patients included in OpACIN, with a minimum follow-up of 60 months for all patients alive. As reported previously, the demographic and other baseline characteristics were comparable in both arms (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.01.004) and radiologic response underestimated pathologic response.[15] The median RFS, EFS, DMFS, and OS have not been reached for both arms.

The estimated 5-year RFS rate was 70% [95% confidence interval (CI) 47% to >99%] for the neoadjuvant arm and 60% (95% CI 36% to >99%) for the adjuvant arm (Figure 1A). The estimated 5-year EFS rate was identical to the 5-year RFS rate in both arms, as none of the patients had an event prior to surgery (Figure 1B). In both arms four patients developed disease recurrence. In the adjuvant arm three patients had distant metastases and one patient had an initial regional recurrence but developed distant metastases >1 year later. In the neoadjuvant arm, 1/7 patients with a pathologic response recurred (distant disease) versus 2/2 with pNR (one regional and one distant), and 1 patient who was not evaluable for a pathologic response developed distant metastases. The patient with a pCR who recurred had a solitary metastasis in the ileum after 5.5 years, underwent surgery, and received adjuvant nivolumab.

Similar to the RFS, the estimated DMFS rate at 5 years was numerically higher for the neoadjuvant arm (80%; 95% CI 59% to >99%) compared with the adjuvant (60%; 95% CI 36% to >99%; Figure 1C). Except for one patient, all patients with a DMFS event ($n = 7$) presented with distant metastases as the first recurrent event.

The estimated 5-year OS rate was 90% (95% CI 73% to >99%) in the neoadjuvant arm and 70% (95% CI 47% to >99%) in the adjuvant arm (Figure 1D). All patients who died had developed distant metastases and died from metastatic melanoma, except for one patient in the neoadjuvant arm. This patient died after >6 years, due to cardiac failure from severe aortic valve stenosis,

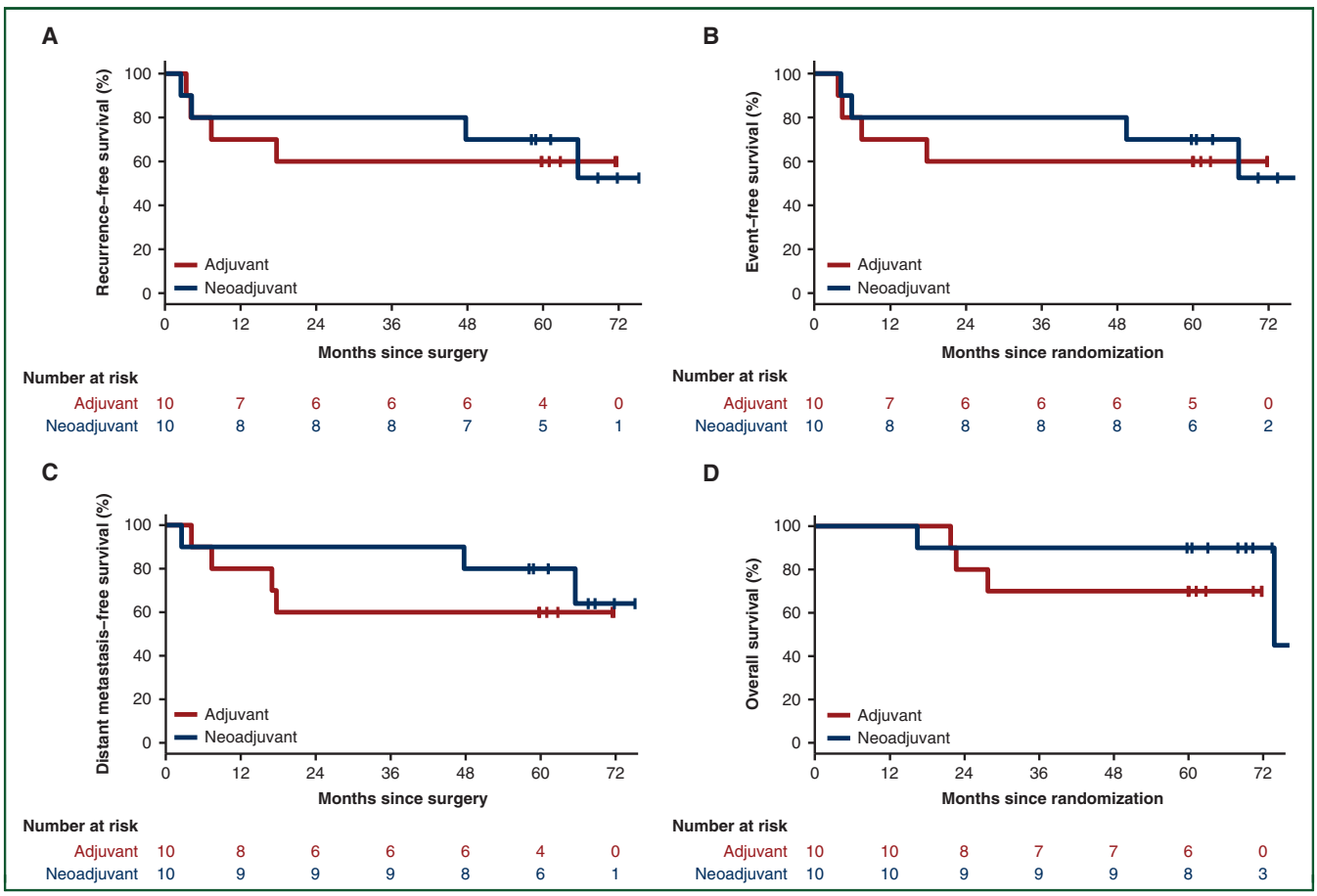

Figure 1. Survival curves of the OpACIN trial. (A) Recurrence-free survival, reported for the adjuvant and neoadjuvant arms. (B) Event-free survival of OpACIN, reported for the adjuvant and neoadjuvant arms. (C) Distant metastases-free survival of OpACIN, reported for the adjuvant and neoadjuvant arms. (D) Overall survival of OpACIN, reported for the adjuvant and neoadjuvant arms.

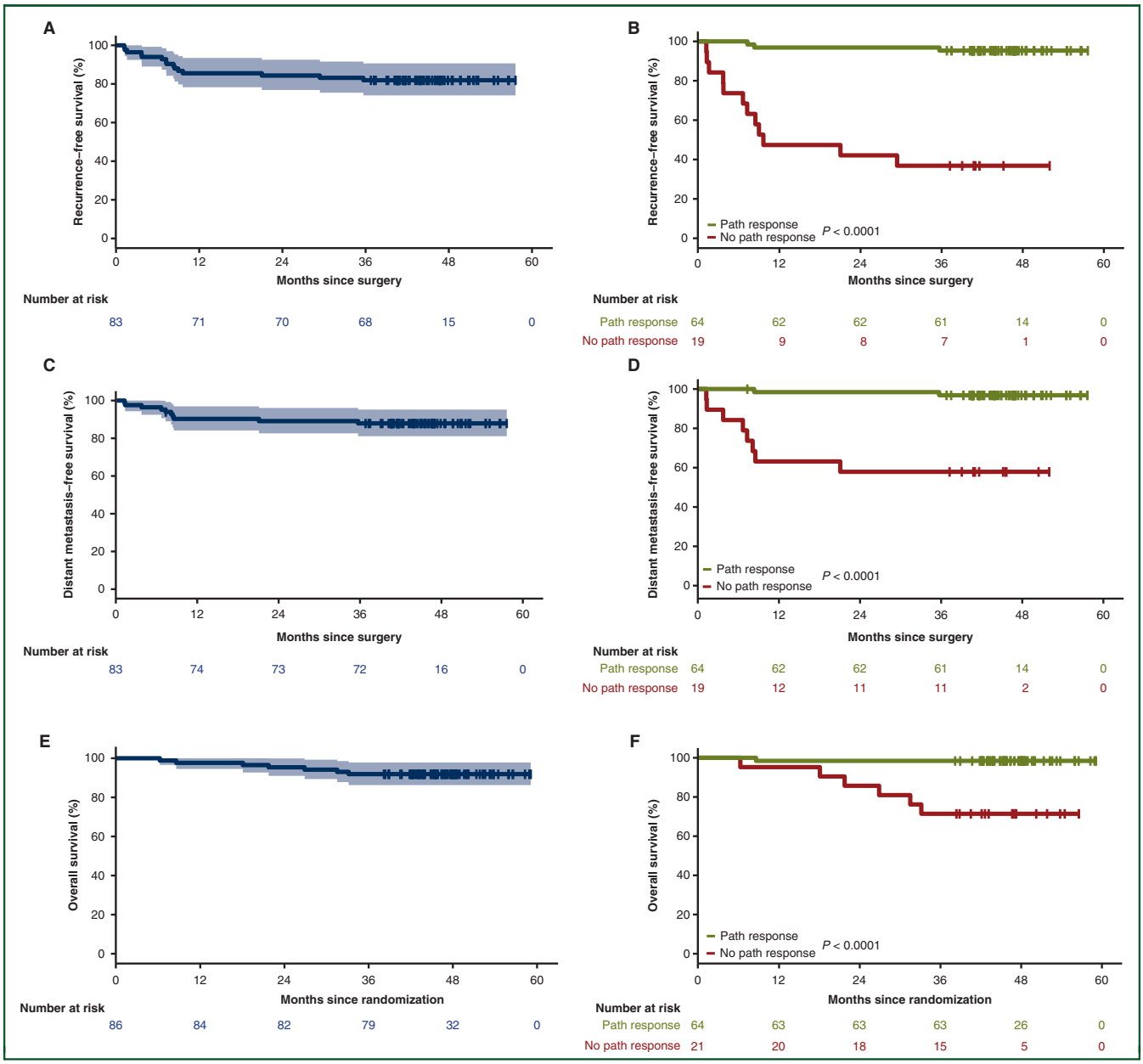

Figure 2. Survival curves of the OpACIN-neo trial. (A) Recurrence-free survival of OpACIN-neo. (B) Recurrence-free survival of OpACIN-neo, reported for patients with and without a pathologic response. (C) Distant metastases-free survival of OpACIN-neo. (D) Distant metastases-free survival of OpACIN-neo, reported for patients with and without a pathologic response. (E) Overall survival of OpACIN-neo. (F) Overall survival of OpACIN-neo, reported for patients with and without a pathologic response. No path response, pathologic nonresponse, >50% residual viable tumor; path response: pathologic response, ≤50% residual viable tumor.

with limited treatment options because of his history of melanoma.

OpACIN-neo trial

We also report the updated data of OpACIN-neo ($n = 86$), in which all patients were treated with neoadjuvant ipilimumab plus nivolumab in different treatment schemes. At data cut-off, the median follow-up for OpACIN-neo patients was 47 months, with a minimum follow-up of 38 months for all patients alive. Demographic and other baseline characteristics were comparable in the three arms, as reported previously (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.01.004), and radiologic response underestimated pathologic response.[16] The median RFS, EFS, DMFS, and OS have not been reached.

The estimated 3-year RFS rate was 82% (95% CI 74% to 91%) for the total cohort (Figure 2A), and 87% (95% CI 75% to >99%), 79% (95% CI 66% to 96%), and 79% (95% CI 65% to 97%; $P = 0.720$) for arms A, B, and C, respectively (Supplementary Figure S1A, available at https://doi.org/10.1016/j.annonc.2023.01.004). At 3 years, the RFS rate of 95% (95% CI 90% to >99%) for patients with a pathologic response was superior ($P < 0.001$) to the 37% (95% CI 20% to 66%) observed for patients with pNR (Figure 2B). In the group of patients with a pathologic response, three events occurred: one patient with a pCR died due to toxicity (immune-related encephalitis) without disease recurrence, and

two patients (one pCR and one pPR) had melanoma recurrence (in the brain and distant lymph nodes, respectively). Treatment for this first presentation of disease was combined surgery and stereotactic radiotherapy for the former patient, whereas the latter patient received radiotherapy followed by nivolumab monotherapy.

The EFS rates at 3 years were similar to the RFS rates; however, two patients progressed to stage IV prior to surgery (2%; one in arm B and one in arm C), resulting in the EFS rates being slightly lower for these arms [EFS arm A 87% (95% CI 75% to >99%), arm B 77% (95% CI 63% to 93%), and arm C 81% (95% CI 67% to 97%); Supplementary Figure S1B and C, available at https://doi.org/10.1016/j.annonc.2023.01.004].

The estimated 3-year DMFS rate for the whole cohort was 88% (95% CI 81% to 95%; Figure 2C), and in arms A, B, and C it was 93% (95% CI 85% to >99%), 86% (95% CI 75% to >99%), and 83% (95% CI 70% to >99%; $P = 0.540$) respectively (Supplementary Figure S1D, available at https://doi.org/10.1016/j.annonc.2023.01.004). The 3-year DMFS rate was superior in patients with any pathologic response (97%; 95% CI 93% to >99%) compared with those with pNR (58%; 95% CI 40% to 85%; $P < 0.001$; Figure 2D). Nine patients presented with distant metastasis as the first recurrence event in the whole cohort; one patient with pNR had first regional and then subsequent distant disease.

At 3 years, the estimated OS rate for the whole cohort was 92% (95% CI 86% to 98%; Figure 2E), and similar in arms A, B, and C with 90% (95% CI 80% to >99%), 93% (95% CI 85% to >99%), and 92% (95% CI 83% to >99%; $P = 0.880$), respectively (Supplementary Figure S1E, available at https://doi.org/10.1016/j.annonc.2023.01.004). The 3-year OS rate of 98% (95% CI 96% to >99%) was also significantly higher for patients with any pathologic response, compared with 71% (95% CI 55% to 94%) for patients with pNR ($P < 0.001$; Figure 2F).

The 3-year RFS, EFS, DMFS, and OS rates for patients with MPR were higher compared with non-MPR patients (96% versus 58%, 96% versus 58%, 98% versus 71%, and 98% versus 82%, respectively; Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.01.004). For both patients with MPR and pPR the 3-year RFS (96% versus 92%), EFS (96% versus 100%), DMFS (98% versus 92%), and OS (98% versus 100%) rates were comparable (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2023.01.004).

Patients with disease recurrence after neoadjuvant therapy

Combining both trials, 18 out of the 96 patients (19%) had disease recurrence and 2 patients (2%) progressed to stage IV disease during the neoadjuvant phase before surgery. Excluding the two with early progression, as these were considered to have progression of disease rather than disease recurrence, the 18 patients with disease recurrence were younger, more likely to have BRAF V600 E/K-mutant melanoma, and less frequently had a radiologic or pathologic response than the patients without disease recurrence ($n = 76$; Table 1).

A total of 6 patients had regional recurrence (33%), while 12 patients presented with distant metastases (67%). Distant metastases were located at seven sites: lymph nodes ($n = 5$, 2 patients had lymph node only disease), lung ($n = 3$), bowel ($n = 2$), brain ($n = 2$), bone ($n = 2$), subcutaneous ($n = 2$), and muscle ($n = 1$). Baseline characteristics were comparable for patients with regional versus distant recurrence (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.01.004). All six patients with regional recurrence were pathologic non-responders, as were the majority (67%) of patients with distant metastases. All three patients with a pathologic response (two MPR and one pPR) who developed disease recurrence had distant metastases. One of the patients with initial regional recurrence developed distant metastases.

The median time to recurrence from randomization date was 9 months, ranging from 3 to 67 months [interquartile range (IQR) 5-25 months; Figure 3A]. The median time to recurrence was similar for patients with regional recurrence [8 months (range 3-31, IQR 5-16 months)] and for those with distant metastases [9 months (range 6-67, IQR 6-34 months); $P = 0.904$], but significantly longer for patients with a pathologic response compared with patients with pNR (38 months versus 7 months; $P = 0.047$). Across both trials, only four (4%) patients had a recurrence >2 year following surgery.

Risk factors for disease recurrence. To determine risk factors for disease recurrence, Cox regression analyses were carried out. In univariable analyses lower age, BRAF V600 mutation, absence of radiologic response, and absence of a pathologic response were associated with risk of disease recurrence (Table 2). Only pathologic response remained significant in the multivariable analysis (hazard ratio 0.04, 95% CI 0.01-0.21; $P < 0.001$).

To assess whether there was a difference in patients who had no disease recurrence ($n = 76$), regional disease recurrence ($n = 6$), and distant metastases ($n = 12$), ordinal logistic regression analyses were carried out. The factors of importance in univariable analyses were lower age, presence of BRAF V600 mutation, radiologic response, and pathologic response (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2023.01.004). In the multivariable model only pathologic response (odds ratio 0.03, 95% CI 0.00-0.15; $P < 0.001$) remained significant, indicating that patients with a pathologic response have a statistically lower risk of developing distant metastases.

Subsequent treatment. We evaluated the subsequent treatment of all 18 patients with disease recurrence. Of the six patients with regional recurrence, four patients underwent surgery. This was followed by adjuvant radiotherapy for two patients; the other two received subsequent adjuvant systemic therapy (one received dabrafenib plus trametinib, and the other initially anti-PD-1 but then switched to dabrafenib plus trametinib). The remaining two patients

Table 1. Baseline characteristics of neoadjuvant patients with and without recurrence

	All patients (n = 96)	Patients without recurrence (n = 76)	Patients with recurrence (n = 18)	P value
Sex				0.215
Female	41 (43)	30 (39)	10 (56)	
Male	55 (57)	46 (61)	8 (44)	
Age at randomization, median (IQR), years	57 (45-66)	59 (47-67)	47 (36-61)	**0.028**
BRAF V600 mutation				**0.005**
Mutated	43 (45)	28 (37)	14 (78)	
Not mutated	40 (42)	36 (47)	3 (17)	
Unknown	13 (14)	12 (16)	1 (6)	
Location of affected lymph node				0.621
Axilla	49 (51)	39 (51)	8 (44)	
Axilla + neck	3 (3)	3 (4)	0 (0)	
Epitrochlear	1 (1)	1 (1)	0 (0)	
Groin	29 (30)	21 (28)	8 (44)	
Neck	14 (15)	12 (16)	2 (11)	
Sum of diameter target lesions in millimeter, median (IQR)	24 (18-37)	23 (18-37)	25 (16-38)	0.770
PDL-1 expression on tumor cells				0.877
<1%	45 (47)	35 (46)	9 (50)	
1%-50%	24 (25)	20 (26)	4 (22)	
>50%	7 (7)	5 (7)	2 (11)	
Unknown	20 (21)	16 (21)	3 (17)	
Neoadjuvant treatment regimen				0.214
2× IPI 3 mg/kg + NIVO 1 mg/kg q3w (2× adjuvant)	10 (10)	6 (8)	4 (22)	
2× IPI 3 mg/kg + NIVO 1 mg/kg q3w	30 (31)	27 (36)	3 (17)	
2× IPI 1 mg/kg + NIVO 3 mg/kg q3w	30 (31)	23 (30)	6 (33)	
2× IPI 3 mg/kg q3w + 2× NIVO 3 mg/kg q2w	26 (27)	20 (26)	5 (28)	
Radiologic response on neoadjuvant treatment				**0.001**
Complete response	6 (6)	6 (8)	0 (0)	
Partial response	43 (45)	40 (53)	3 (17)	
Stable disease	33 (34)	25 (33)	8 (44)	
Progression	11 (12)	4 (5)	5 (28)	
Nonevaluable	3 (3)	1 (1)	2 (11)	
Pathologic response on neoadjuvant treatment				**<0.001**
Major pathologic response	58 (60)	56 (74)	2 (11)	
Partial response	13 (14)	12 (16)	1 (6)	
No response	23 (24)	7 (9)	14 (78)	
Nonevaluable	2 (2)	1 (1)	1 (6)	
Immune-related grade ≥3 adverse events	44 (46)	34 (45)	9 (50)	0.687
Prednisone usage	47 (49)	41 (54)	6 (33)	0.116
Prednisone usage before TLND	31 (32)	26 (34)	5 (28)	0.578
Second-line immunosuppressives	14 (15)	10 (13)	4 (22)	0.331

Data are reported as n (%) unless indicated otherwise; due to rounding, number percentages may not add up to 100.
IPI, ipilimumab; IQR, interquartile range; NIVO, nivolumab; q2w, every 2 weeks; q3w, every 3 weeks; TLND, therapeutic lymph node dissection.

with regional recurrence received and responded to systemic therapy without local treatment, receiving anti-PD-1 and BRAF-targeted therapy, respectively (Figure 3B). These six patients were alive at data cut-off.

As many as 12 of the 96 patients (13%) had distant metastases at the moment of disease recurrence, of which 6 patients (6%) have died so far. One patient did not receive systemic therapy, as the best supportive care was given due to high tumor burden (lung, bone, and lymph nodes). This patient died 4 months after the diagnosis of recurrent disease.

Of the 11 patients who received systemic therapy, 5 received anti-PD-1 monotherapy as first-line therapy for stage IV disease. Three patients had prior pathologic response: two patients responded and one patient had no sign of disease during adjuvant therapy for resectable distant disease. The two remaining pNR patients who received anti-PD-1 therapy had initial response but progressed afterward (Figure 3B).

Nine patients received BRAF-targeted therapy for distant disease, of which most patients were treated with dabrafenib plus trametinib (Figure 3B). Two patients achieved a complete response, and one patient had response on dabrafenib plus trametinib combined with surgical resection of disease at other sites. Five patients had initial response to dabrafenib plus trametinib, but developed resistant progressive disease. The ninth patient received vemurafenib plus cobimetinib, switched to dabrafenib plus trametinib due to toxicity but had progressive disease as the best overall response.

The two patients with progression to stage IV disease during the neoadjuvant phase prior to surgery received systemic therapy as well. One was treated with targeted therapy (both dabrafenib plus trametinib and vemurafenib plus cobimetinib), and obtained partial response as the best overall response. The other patient received nivolumab and treatment with anti-ICOS (inducible T-cell costimulator) and enapotamab vedotin in two different trials. Both patients died from melanoma, 22 and 27 months after randomization, respectively.

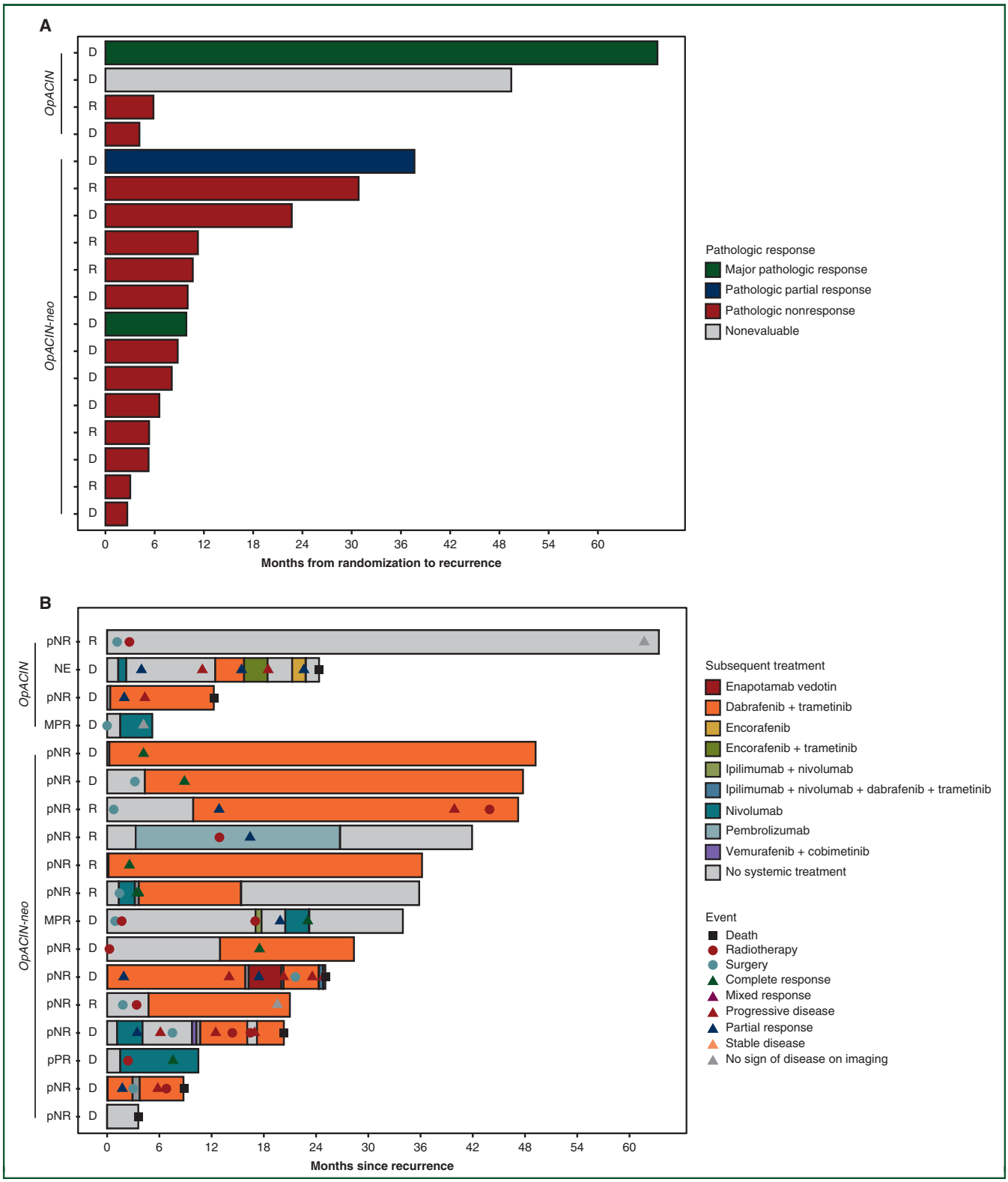

Figure 3. Swimmer plots. (A) Swimmer plot of time to recurrence from the date of randomization. (B) Swimmer plot of subsequent treatments after the date of disease recurrence.

D, distant recurrence; MPR, major pathologic response, 0% to ≤10% residual viable tumor; NE, nonevaluable; pNR, pathologic nonresponse, >50% residual viable tumor; pPR, pathologic partial response, 10% to ≤50% residual viable tumor; R, regional recurrence.

DISCUSSION

Neoadjuvant ICI in macroscopic stage III melanoma induced high pathologic response rates in early phase I-II trials,[15,16,27] and was superior compared with adjuvant therapy in a randomized phase II trial.[11] However, so far only short-term RFS, EFS, and OS data have been published. Our updated data from the OpACIN and OpACIN-neo trials report for the first time, respectively, 5- and 3-year survival

Table 2. Cox regression analyses of patients with recurrence versus without recurrence

	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Female (*n* = 39)	1.66 (0.65-4.25)	0.289		
Age at randomization (*n* = 93)	**0.97 (0.94-0.995)**	**0.022**	1.02 (0.98-1.06)	0.280
BRAF V600 mutated (*n* = 41)	**4.69 (1.34-16.31)**	**0.016**	2.66 (0.69-10.75)	0.157
Location of affected lymph node				
Axilla (*n* = 47)	0.99 (0.21-4.66)	0.986		
Axilla + neck (*n* = 3)	0 (0-NR)	0.988		
Epitrochlear (*n* = 1)	0 (0-NR)	0.993		
Groin (*n* = 29)	1.65 (0.35-7.86)	0.531		
Neck (*n* = 13)	Reference			
Sum of diameter target lesions in millimeter (*n* = 92)	1.00 (0.96-1.03)	0.879		
Positive PD-L1 expression on tumor cells at baseline (*n* = 31)	0.85 (0.30-2.41)	0.762		
High IPI dose (3 mg/kg; *n* = 64)	0.81 (0.30-2.20)	0.681		
Radiologic response on neoadjuvant treatment				
Complete response (*n* = 5)	0.00 (0.00-0.00)	0.984	0.00 (0.00-0.00)	0.987
Partial response (*n* = 43)	**0.11 (0.03-0.41)**	**0.001**	0.56 (0.09-3.55)	0.536
Stable disease (*n* = 33)	**0.32 (0.10-0.97)**	**0.045**	0.99 (0.32-3.14)	0.992
Progression (*n* = 9)	Reference			
Pathologic response on neoadjuvant treatment (*n* = 71)	**0.03 (0.01-0.12)**	**<0.001**	**0.04 (0.01-0.22)**	**<0.001**
Immune-related grade ≥3 adverse events (*n* = 42)	1.13 (0.44-2.88)	0.799		
Prednisone usage (*n* = 46)	0.53 (0.20-1.42)	0.206		
Prednisone usage before TLND (*n* = 31)	0.84 (0.30-2.38)	0.742		
Second-line immunosuppressives (*n* = 13)	1.79 (0.59-5.46)	0.309		

95% CI, 95% confidence interval; HR, hazard ratio; IPI, ipilimumab; PD-L1, programmed death-ligand 1; TLND, therapeutic lymph node dissection.

data. We show that disease recurrences after >2 years occurred in only 4% of patients, which is in line with the flattening of the RFS and EFS curves of prior reports.[15,16,28] Pathologic response at week 6 remains the strongest predictor for freedom of disease in both trials and is the only significant predictor in multivariable analyses, although our multivariable analyses should be interpreted with caution due to the low number of events and multiple variables analyzed. This observation is in line with a pooled analysis of the INMC of four neoadjuvant checkpoint inhibitor trials (anti-PD-1 with or without anti-CTLA-4), which included an additional 40 patients with melanoma aside from the OpACIN and OpACIN-neo patients, and demonstrated a strong association between pathologic response to neoadjuvant ICI and absence of recurrence at 2 years.[29]

In contrast to the 2-year RFS rate of 100% for patients with pPR in the OpACIN-neo cohort, these same patients in the subsequent PRADO trial had a 2-year RFS rate of only 64%.[27] Although both cohorts contain a low number of patients, these data raise the question as to whether MPR instead of pathologic response would be a better predictor of outcome. Based on the PRADO data, the currently recruiting phase III NADINA trial (NCT04949113)[30] was amended: in patients with MPR adjuvant therapy is omitted and not in all patients with a pathologic response as in the PRADO trial.

Although the OpACIN trial was not powered for efficacy data, and the OpACIN-neo trial did not have a direct comparative adjuvant arm, our updated survival data suggest that neoadjuvant therapy could have additional survival benefits compared with the historical data from cohorts of patients with macroscopic stage III melanoma. In the adjuvant trials, the 3-year RFS rates were 58% for nivolumab,[31] 64% for pembrolizumab,[32] and 45% for ipilimumab,[31] whereas in our neoadjuvant trials, the 3-year RFS rates were 80%-82%. The 5-year RFS (55%) and DMFS (61%) rates of adjuvant pembrolizumab are comparable with the adjuvant arm of OpACIN (RFS and DMFS both 60%), but lower than the neoadjuvant arm (RFS 70%, DMFS 80%).[33] Historically, the 5-year RFS rates in macroscopic stage III melanoma after surgery were only 11%-32%.[34]

After a median follow-up of only 14 months, a significantly improved outcome for neoadjuvant pembrolizumab was seen in the randomized S1801 trial, with an estimated 2-year EFS rate of 72% versus 49% for adjuvant pembrolizumab.[11] Although this trial compared the same dosing of 18 cycles of pembrolizumab in both arms, it did not address the need for adjuvant therapy in patients with an MPR. Keeping in mind activation-induced non-responsiveness and activation-induced cell death of repetitive overstimulated T cells,[35] one might postulate that patients with an MPR after neoadjuvant therapy could receive too much treatment when receiving additional adjuvant therapy. Vice versa, one might want to switch pNR patients with BRAFV600E/K mutation-positive melanoma to adjuvant dabrafenib plus trametinib instead, or continue adjuvant anti-PD-1. The PRADO trial addressed this question of treatment de-escalation in patients with a pathologic response while escalating treatment in patient with pNR. This resulted in a 2-year DMFS rate of 98% in MPR patients who received only neoadjuvant therapy, but also in an improved outcome for pNR patients by adding adjuvant therapy (nivolumab in BRAFV600E/K wild-type and adjuvant dabrafenib plus trametinib in BRAFV600E/K-mutant patients). The adjuvant therapy improved the 2-year RFS rate of patients with pNR from 35% observed in OpACIN-neo without adjuvant therapy to 71%.[27,28] This concept of personalized adjuvant therapy is also incorporated in the

ongoing NADINA trial that randomizes patients with stage III melanoma to neoadjuvant ipilimumab plus nivolumab versus adjuvant nivolumab.[30] The promising results of the OpACIN, OpACIN-neo, and the S1801 trials, and the awaited results of the NADINA trial, encourage neoadjuvant ICI to become a standard therapy in populations of patients with macroscopic stage III melanoma.

In both trials, the adverse events and the subsequent use of steroids had no impact on the timely performance of surgery.[15,16] In our current analyses, use of prednisone before surgery was not associated with a higher risk of disease recurrence. In the neoadjuvant trials with anti-PD-1 monotherapy, lower rates of adverse events were seen, but data on use of steroids and long-term outcome have not been reported.[11,17,18] Considering this, one can conclude that combined ipilimumab and nivolumab can safely be administered in the neoadjuvant setting.

Our data illustrate the need to intensify treatment for patients with pNR after neoadjuvant ipilimumab plus nivolumab. In the future, new combinations of neoadjuvant therapy should be investigated to increase the pathologic response rate, or maintain efficacy with lower toxicity. Prior defined biomarkers, such as the interferon-gamma (IFNγ) signature and tumor mutational burden, which were both associated with pathologic response in OpACIN-neo patients,[28] may assist in defining patients who may respond. Considering the fact that in the small DONIMI trial 90% of patients with a high IFNγ signature had a pathologic response to nivolumab alone,[36] one might envision that these patients can be treated with monotherapy, while patients with a low IFNγ signature require combination therapy. Aligning neoadjuvant trial designs, sample collection, and analyses, as proposed by the INMC,[37] will facilitate biomarker analyses for response or resistance and can allow personalized neoadjuvant ICI in the future.

The observed 3-year OS rates after neoadjuvant therapy in OpACIN (90%) and OpACIN-neo (92%) are high compared with the 3-year OS rates after adjuvant treatment in the CheckMate-238 trial (82% for both nivolumab and ipilimumab).[5] Taking into account that the KEYNOTE-054/E1325 trial testing adjuvant pembrolizumab versus placebo is unable to show a significant difference in OS after 5 years of follow-up,[33] we envision that neoadjuvant trials might result in significant OS benefit while for adjuvant therapies the benefit in RFS could be eliminated for OS by the subsequent therapy options for patients with disease recurrence.

Nothing is known so far regarding response to subsequent systemic treatment in case of disease recurrence after neoadjuvant treatment, but there appears to be no signal in our data that those patients will be less responsive to subsequent treatment, or will be disadvantaged by the early use of combination therapy compared with those treated in the adjuvant setting. In our small dataset, half of patients receiving subsequent BRAF plus MEK inhibition had initial benefit, which is consistent with the metastatic setting.[38] Patients responded to subsequent ICI as well, with a favorable bias for patients with an initial pathologic response. Data on rechallenge with anti-PD-1 monotherapy after prior anti-CTLA-4 plus anti-PD-1 in melanoma are scarce. However, rechallenge with anti-PD-1 monotherapy after failure on monotherapy is prospectively investigated in the KEYNOTE-006 trial; of 15 patients with progression after initial response or stable disease, 12 had clinical benefit of rechallenge (3 had a complete response, 4 a partial response, and 5 achieved stable disease).[39]

Whether it is wise to continue adjuvant anti-PD-1 in BRAF-mutated patients with disease recurrence after neoadjuvant ICI or it is better to switch to adjuvant BRAF plus MEK inhibition remains elusive at the moment. It is noteworthy that the presence of BRAF V600E/K mutation and a lower age showed a higher risk of disease recurrence after neoadjuvant therapy in our univariable analyses, arguing possibly for a switch in nonresponding patients with BRAF V600 E/K-mutant melanoma. This should, however, be explored in larger pooled analyses, to understand their prognostic and predictive impact on outcome with neoadjuvant therapy.

In summary, our updated survival data from the OpACIN and OpACIN-neo trials confirm the earlier promising RFS and OS data and show that pathologic response to neoadjuvant combination checkpoint inhibition in high-risk stage III melanoma remains the most significant clinical surrogate marker for long-term RFS, EFS, DMFS, and OS outcomes.

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DISCLOSURE

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