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INTRODUCTION

Helen Gogas

Chair

Professor in Medical Oncology
National and Kapodistrian University of Athens
Director of the First Department of Internal Medicine
Greece

ESMO WEBINAR SERIES

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LEARNING OBJECTIVES

- To discuss and critically evaluate notable recent publications.
- To enhance the understanding and application of the latest research in the field.
- To assess the study's robustness, its significance to oncology practice, limitations, and its place within existing research.
- To identify and highlight any unclear aspects or unmet needs.

PROGRAMME AND SPEAKERS

22 January 2025

5 min	**Welcome and introduction** Helen Gogas
20 min	**HIMALAYA Study - Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma** Su Pin Choo
20 min	**Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma.** Helen Gogas
10 min	**Live Q&A and Discussion** All speakers

Helen J. Gogas

Speaker

1st Department of Internal Medicine University of Athens

Su Pin Choo

Speaker

Curie Oncology Singapore National Cancer Centre Singapore and Duke-NUS Graduate Medical School

PUBLICATIONS

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma

B. Sangro[1]*, S. L. Chan[2], R. K. Kelley[3], G. Lau[4], M. Kudo[5], W. Sukeepaisarnjaroen[6], M. Yarchoan[7], E. N. De Toni[8], J. Furuse[9], Y. K. Kang[10], P. R. Galle[11], L. Rimassa[12,13], A. Heurgué[14], V. C. Tam[15], T. Van Dao[16], S. C. Thungappa[17], V. Breder[18], Y. Ostapenko[19], M. Reig[20], M. Makowsky[21], M. J. Paskow[22], C. Gupta[23], J. F. Kurland[21], A. Negro[21] & G. K. Abou-Alfa[24,25,26], for the HIMALAYA investigators†

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ORIGINAL ARTICLE

Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma

C.U. Blank, M.W. Lucas, R.A. Scolyer, B.A. van de Wiel, A.M. Menzies, M. Lopez-Yurda, L.L. Hoeijmakers, R.P.M. Saw, J.M. Lijnsvelt, N.G. Maher, S.M. Pulleman, M. Gonzalez, A. Torres Acosta, W.J. van Houdt, S.N. Lo, A.M.J. Kuijpers, A. Spillane, W.M.C. Klop, T.E. Pennington, C.L. Zuur, K.F. Shannon, B.A. Seinstra, R.V. Rawson, J.B.A.G. Haanen, S. Ch'ng, K.A.T. Naipal, J. Stretch, J.V. van Thienen, M.A. Rtshiladze, S. Wilgenhof, R. Kapoor, A. Meerveld-Eggink, L.G. Grijpink-Ongering, A.C.J. van Akkooi, I.L.M. Reijers, D.E. Gyorki, D.J. Grünhagen, F.M. Speetjens, S.B. Vliek, J. Placzke, L. Spain, R.C. Stassen, M. Amini-Adle, C. Lebbé, M.B. Faries, C. Robert, P.A. Ascierto, R. van Rijn, F.W.P.J. van den Berkmortel, D. Piersma, A. van der Westhuizen, G. Vreugdenhil, M.J.B. Aarts, M.A.M. Stevense-den Boer, V. Atkinson, M. Khattak, M.C. Andrews, A.J.M. van den Eertwegh, M.J. Boers-Sonderen, G.A.P. Hospers, M.S. Carlino, J.-W.B. de Groot, E. Kapiteijn, K.P.M. Suijkerbuijk, P. Rutkowski, S. Sandhu, A.A.M. van der Veldt, and G.V. Long

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NEOADJUVANT NIVOLUMAB AND IPILIMUMAB IN RESECTABLE STAGE III MELANOMA

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https://www.nejm.org/doi/full/10.1056/NEJMoa2402604

Background

- The standard management of macroscopic stage III melanoma is currently surgery, which can be followed by adjuvant systemic therapy
- After surgery the 5-year RFS is 30% and OS 50%
- Adjuvant therapy improves relapse-free survival but none of the trials has shown significant overall survival benefit, even after long-term follow-up

Eggermont et al. EJC 2019, Eggermont et al. NEJM 2016, Eggermont et al. NEJM Evid 2022, Ascierto et al. Lancet Oncol 2020, Long et al. NEJM 2024, Blank CU et al. N Engl J Med2024;391:1696-1708

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Background

- 4-year RFS with adjuvant Nivolumab is 52% and 41% with adjuvant Ipilimumab
- 5-year RFS with adjuvant Pembrolizumab is 55% versus 38% with Placebo
- 4-year RFS with adjuvant Dabrafenib + Trametinib is 54% versus 38% with Placebo

Eggermont et al. EJC 2019, Eggermont et al. NEJM 2016, Eggermont et al. NEJM Evid 2022, Ascierto et al. Lancet Oncol 2020, Long et al. NEJM 2024, Blank CU et al. N Engl J Med2024;391:1696-1708

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Scientific Rationale

- On the basis of preclinical and phase I data, neoadjuvant administration of immune checkpoint inhibitors is hypothesized to yield efficacy superior to that of adjuvant administration
- A recent randomized phase II study (SWOG S1801) showed that event free survival was longer amongst patients who received 3 neoadjuvant cycles of Pembrolizumab
- 2-year event free survival 72% versus 49%
- Another phase II trial showed in 2 independent cohorts that a neoadjuvant combination of 2 cycles of Ipilimumab plus Nivolumab resulted in an event free survival of 77%-80% at 2 years

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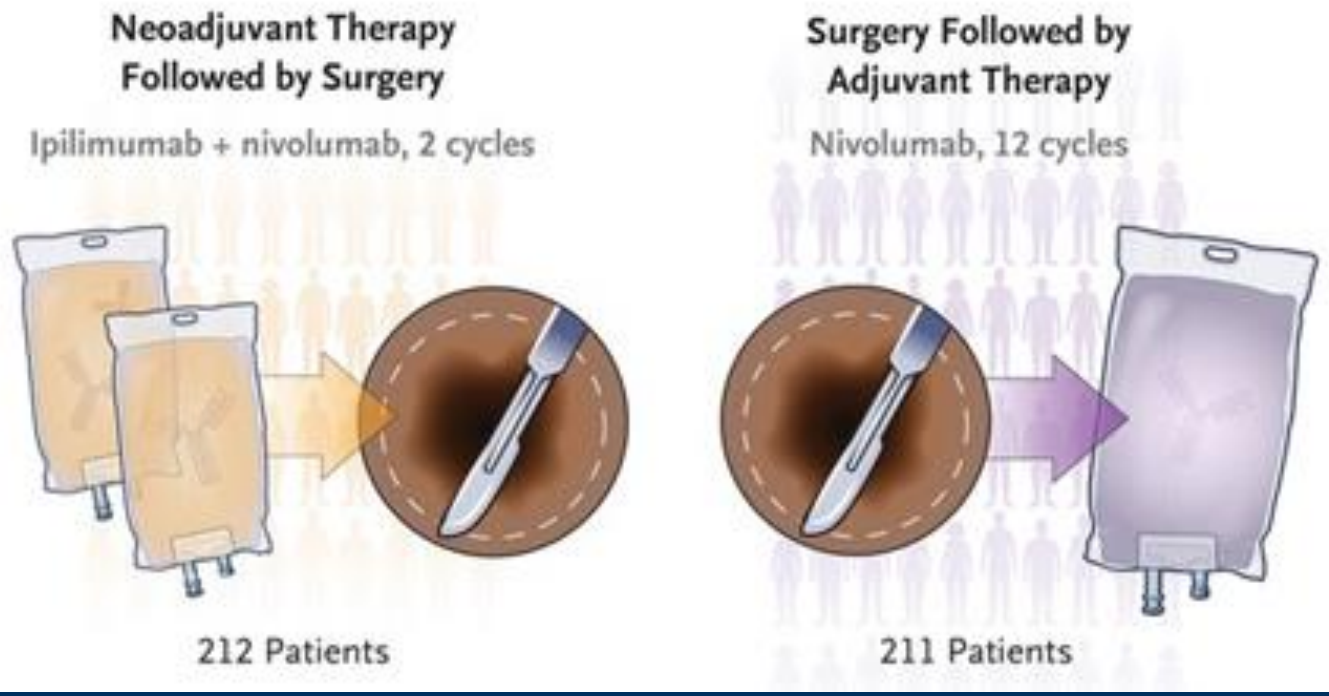
HOW WAS THE TRIAL CONDUCTED?

Patients 16 years of age or older with resectable, macroscopic stage III melanoma were randomly assigned to receive either two cycles of neoadjuvant ipilimumab (80 mg each) plus nivolumab (240 mg each), followed by therapeutic lymph-node dissection, or lymph-node dissection followed by 12 cycles of adjuvant nivolumab. Patients in the neoadjuvant group who had a pathological partial response or nonresponse also received adjuvant therapy. The primary end point was event-free survival.



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Characteristics of the Patients at Baseline

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Neoadjuvant Group (N=212)	Adjuvant Group (N=211)
Sex — no. (%)		
Female	71 (33.5)	76 (36.0)
Male	141 (66.5)	135 (64.0)
Median age (range) — yr	60 (22–84)	59 (19–87)
Continent — no. (%)		
Australia	71 (33.5)	71 (33.6)
Europe	141 (66.5)	139 (65.9)
North America	0	1 (0.5)
Median weight (range) — kg†	85.1 (52.0–144.0)	83.1 (49.0–151.0)
Median body-mass index (range)†	27.6 (19.1–52.3)	26.9 (19.1–42.0)
WHO performance-status score — no. (%)‡		
0	192 (90.6)	192 (91.0)
1	20 (9.4)	19 (9.0)
Tumor stage — no. (%)§		
T1	25 (11.8)	36 (17.1)
T2	41 (19.3)	39 (18.5)
T3	41 (19.3)	49 (23.2)
T4	52 (24.5)	46 (21.8)
Tx	7 (3.3)	6 (2.8)
Melanoma of unknown primary origin	46 (21.7)	35 (16.6)
Ulceration — no. (%)		
Yes	71 (33.5)	57 (27.0)
No	85 (40.1)	102 (48.3)
Melanoma of unknown primary origin	46 (21.7)	35 (16.6)
Unknown	10 (4.7)	17 (8.1)
In-transit metastases — no. (%)		
Yes	22 (10.4)	25 (11.8)
No	190 (89.6)	186 (88.2)
Short-axis diameter of largest lymph node — no. (%)¶		
<15 mm	67 (31.6)	74 (35.1)
15–30 mm	115 (54.2)	102 (48.3)
31–50 mm	24 (11.3)	29 (13.7)
>50 mm	4 (1.9)	4 (1.9)
No lymph node reported on CT scan	2 (0.9)	2 (0.9)
Median sum of diameters of lymph nodes (range) — mm²	25 (15–74)	25 (15–82)
Location or locations of affected lymph nodes — no./total no. (%)‖		
Neck	55/211 (26.1)	57/211 (27.0)
Axilla	86/211 (40.8)	86/211 (40.8)
Groin	66/211 (31.3)	66/211 (31.3)
Axilla and neck	3/211 (1.4)	0
Other	1/211 (0.5)	2/211 (0.9)
No. of lymph nodes positive for disease on PET — no./total no. (%)**		
1	126/200 (63.0)	122/205 (59.5)
2 or 3	52/200 (26.0)	64/205 (31.2)
>3	17/200 (8.5)	12/205 (5.9)
0	5/200 (2.5)	7/205 (3.4)
BRAF mutation status — no. (%)		
V600E	95 (44.8)	87 (41.2)
V600K	17 (8.0)	25 (11.8)
Other *BRAF* mutation	5 (2.4)	4 (1.9)
Wild type	95 (44.8)	95 (45.0)
LDH level — no. (%)		
<ULN	196 (92.5)	192 (91.0)
1–1.5×ULN	16 (7.5)	19 (9.0)
Previous surgical treatment to nodal basin — no. (%)		
Sentinel-node procedure	75 (35.4)	78 (37.0)
Lymph-node dissection	1 (0.5)	1 (0.5)
Both procedures	0	3 (1.4)
None	136 (64.2)	129 (61.1)

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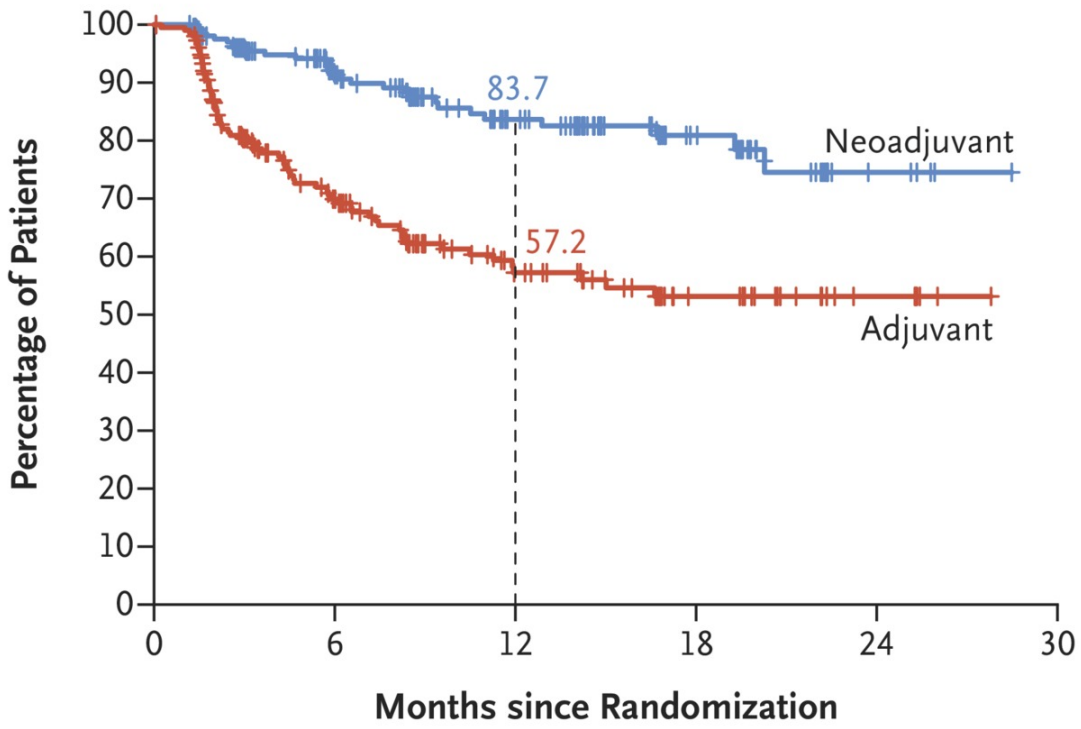
Event-free Survival in the Intention-to-Treat Population



	No. of Events/ Total No. of Patients
Neoadjuvant	28/212
Adjuvant	72/211

Adjusted difference in restricted mean survival time, 8.00 mo (99.9% CI, 4.94–11.05); P<0.001

Hazard ratio for progression, recurrence, or death, 0.32 (99.9% CI, 0.15–0.66)

No. at Risk (no. censored)

Neoadjuvant	212 (0)	126 (71)	77 (111)	34 (152)	5 (179)
Adjuvant	211 (0)	100 (57)	53 (89)	23 (116)	6 (133)

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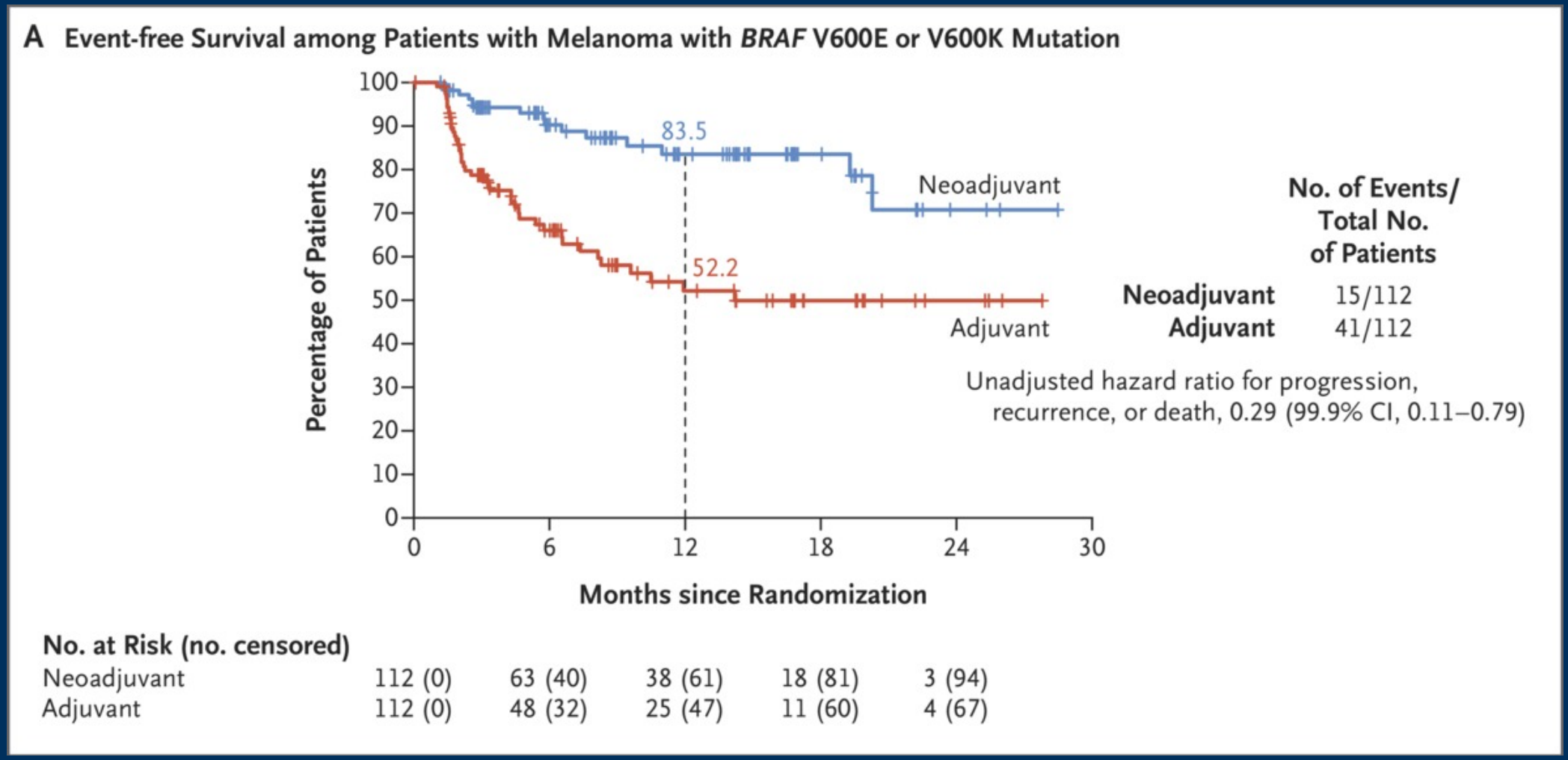
Event-free Survival According to BRAF Mutation Status and Recurrence-free Survival.



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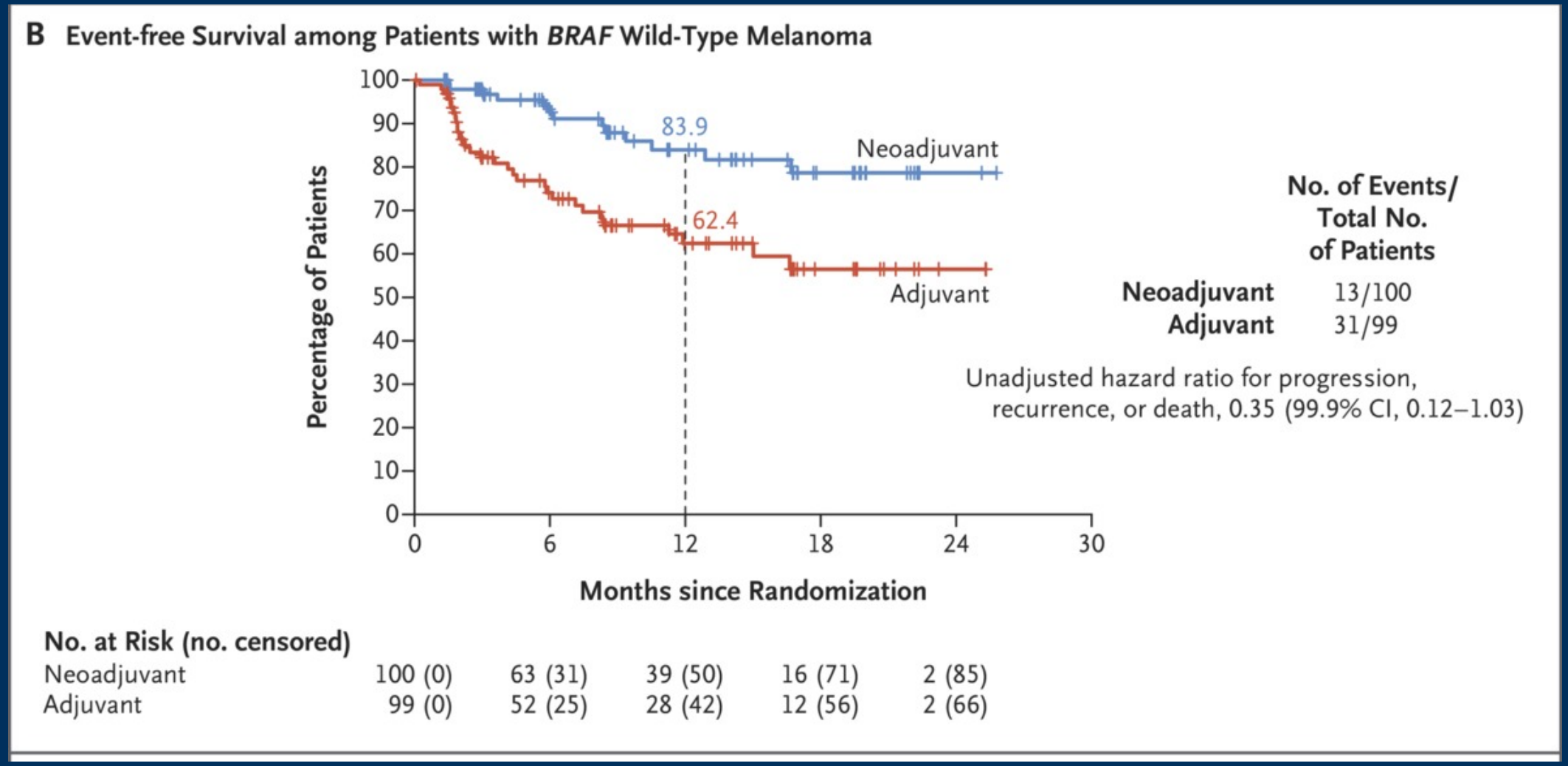

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Pathological Responses in the Neoadjuvant Group.

Table 2. Pathological Responses in the Neoadjuvant Group.*

Type of Response	Local Assessment (N=212)	Central Review (N=212)
	number (percent)	
Major pathological response	120 (56.6)	125 (59.0)
Pathological complete response†	97 (45.8)	100 (47.2)
Pathological near-complete response	23 (10.8)	25 (11.8)
Pathological partial response	20 (9.4)	17 (8.0)
Pathological nonresponse	53 (25.0)	56 (26.4)
Progression before surgery	5 (2.4)	5 (2.4)
Not reported	5 (2.4)	0
Not available‡	9 (4.2)	9 (4.2)

* Patients in the neoadjuvant group who received at least one dose of neoadjuvant treatment were assessed for pathological response. The pathological response was determined according to the International Neoadjuvant Melanoma Consortium criteria. A pathological complete response was defined as 0% residual viable tumor in the surgical resection specimen, pathological near-complete response as 0 to 10% residual viable tumor, pathological partial response as 11 to 50% residual viable tumor, and pathological nonresponse as more than 50% residual viable tumor. Major pathological response included pathological complete response and pathological near-complete response.

† As confirmed by central review, the material from surgical resection in 9 of 100 patients who had a complete pathological response did not show any signs of viable or regressed tumor, nor were there clinical indications that the tumor was still in situ.

‡ At the time of the data cutoff, no material from surgical resection was available for 9 patients (5 patients underwent surgery after the data-cutoff date, 3 patients had not undergone surgery because of toxic effects, and 1 patient had not undergone surgery for an unknown reason).

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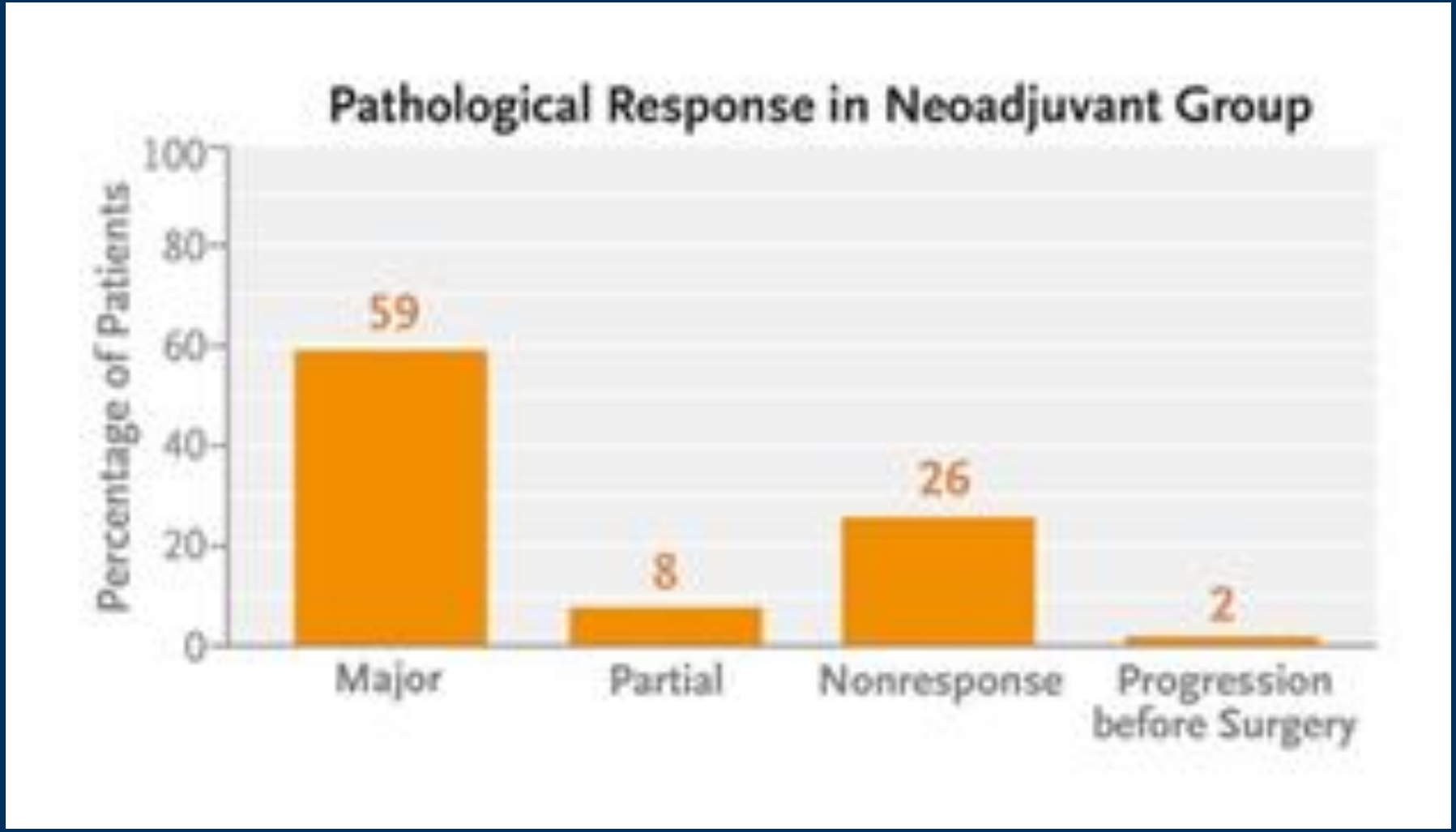

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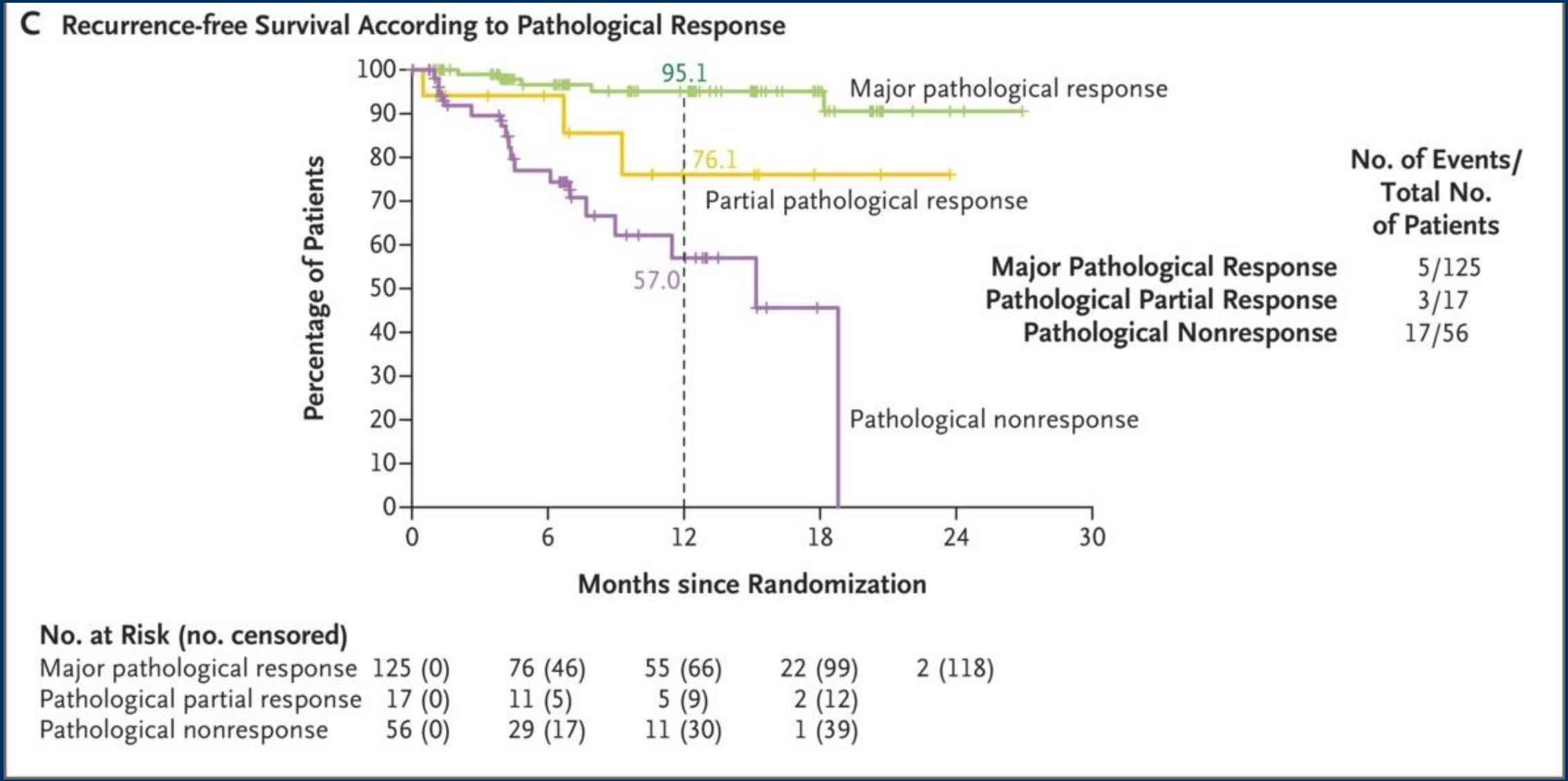
Recurrence-free Survival According to Pathologic Response



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Adverse Events.

Table 3. Adverse Events.*

Event	Neoadjuvant Group (N = 212)	Adjuvant Group (N = 208)
Any adverse event — no. (%)	204 (96.2)	194 (93.3)
Any grade ≥3 adverse event — no. (%)	100 (47.2)	71 (34.1)
Serious adverse event — no. (%)	77 (36.3)	49 (23.6)
Treatment-related adverse event — no. (%)	196 (92.5)	178 (85.6)
Treatment-related grade ≥3 adverse event — no. (%)	82 (38.7)	50 (24.0)
Surgery-related adverse event — no./total no. (%)	120/198 (60.6)	151/208 (72.6)
Surgery-related grade ≥3 adverse event — no./total no. (%)	28/198 (14.1)	30/208 (14.4)
Adverse event related to systemic treatment — no./total no. (%)	181/212 (85.4)	123/170 (72.4)
Grade ≥3 adverse event related to systemic treatment — no./total no. (%)	63/212 (29.7)	25/170 (14.7)
Discontinuation of treatment due to adverse event — no. (%)	19 (9.0)	30 (14.4)
Death due to treatment-related adverse event — no. (%)	0	1 (0.5)

* Included are adverse events that were reported between randomization and 100 days after the last trial treatment. The safety population included all the patients who started trial treatment. Surgery-related adverse events were assessed in all the patients who underwent surgery. Adverse events related to systemic treatment were assessed in all the patients who received at least one dose of systemic treatment. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

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Conclusions

Among patients with resectable, macroscopic stage III melanoma, neoadjuvant ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy resulted in longer event-free survival than surgery followed by adjuvant nivolumab.

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Conclusions

The estimated event-free survival at 12 months is 83.7% major pathological response is 59%, which is in line with the preceding phase II trial that evaluated neoadjuvant ipilimumab plus nivolumab (Opacin-Neo) and the PRADO trial , in which the event free survival at 12 months was 85-86% and 60-61% of the patients had major pathological response

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Conclusions

- The estimated event-free survival at 12 months in the adjuvant group of 57.2% is lower than the recurrence free survival at 12 months observed in the Checkmate 238 and EORTC 1325 trials (70.5% and 75.4% respectively)
- This difference is most likely due to the inclusion of lower risk patients with microscopic stage III melanoma, as well as the exclusion of patients with early recurrence before the start of adjuvant therapy in the other two trials
- Early disease recurrence before the start of adjuvant therapy is reflected in the reported 10% to 20% of patients in these trials that were excluded at screening because of recurrence, as well as an observation from the SWOG study

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Conclusions

- Event-free survival was similar in the neoadjuvant group regardless of BRAF status
- However, in the adjuvant group event-free survival was shorter among the patients with BRAF-mutated melanoma than among those with BRAF wild-type.
- This finding indicates that the benefit from the addition of ipilimumab as previously observed in stage IV melanoma, and potentially from the class switch for the patients with BRAF mutated melanoma who had a partial response or no response
- Based on the difference in major pathological response and the similarity in event-free survival, it is estimated that this class switch may have accounted for an increase in 12-month event-free survival in the neoadjuvant group

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LIMITATIONS OF THE STUDY

- Too short follow up – Follow up is continued
- Unanswered questions for those with partial response – Heterogeneous group
- Non responders
- Need to evaluate new treatments

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Thank you

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