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Long-Term Follow-Up of Standard-Dose Pembrolizumab Plus Reduced-Dose Ipilimumab in Patients With Advanced Melanoma: KEYNOTE-029 Part 1B

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Running head: Long-Term Follow-Up KEYNOTE-029 1B

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TRANSLATIONAL RELEVANCE

As programmed death 1 and cytotoxic T-lymphocyte–associated antigen 4 inhibitors act through distinct mechanisms, it is expected that their use in combination would be more effective than either agent alone; however, increased toxicity with such combination therapy has been reported. This report describes the long-term results of part 1B of the KEYNOTE-029 trial, which assessed the safety and efficacy of standard-dose pembrolizumab plus

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reduced-dose ipilimumab in patients with advanced melanoma. The results demonstrated robust antitumor activity, durable response, and favorable long-term survival with manageable toxicity with the combination of standard-dose pembrolizumab and reduced-dose ipilimumab. These findings support further exploration of alternative dosing strategies of checkpoint inhibitors in order to determine whether efficacy can be maintained while further reducing toxicity in patients with advanced melanoma.

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ABSTRACT

Purpose: Combination therapy with reduced-dose programmed death 1 inhibitor plus standard-dose cytotoxic T-lymphocyte–associated antigen 4 inhibitor demonstrated efficacy, but substantial toxicity, in melanoma. We present long-term results of part 1B of KEYNOTE-029, which assessed safety and efficacy of standard-dose pembrolizumab plus reduced-dose ipilimumab in advanced melanoma.

Experimental Design: Part 1B was an expansion cohort of the open-label, phase Ib portion of KEYNOTE-029. Eligible patients had advanced melanoma and no previous immune checkpoint inhibitor therapy. Patients received pembrolizumab 2 mg/kg (amended to 200 mg) every 3 weeks plus ipilimumab 1 mg/kg every 3 weeks (four cycles), then pembrolizumab alone for up to 2 years. Primary end point was safety; secondary end points included objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), and overall survival (OS).

Results: A total of 153 patients received at least one dose of pembrolizumab plus ipilimumab. At a median follow-up of 36.8 months, 71.9% had received four doses of ipilimumab and 30.7% had completed 2 years of pembrolizumab; 26.1% completed both treatments. Treatment-related adverse events occurred in 96.1% (47.1% grade 3/4; no deaths), leading to discontinuation of one or both study drugs in 35.9%. ORR was 62.1% with 42 (27.5%) complete and 53 (34.6%) partial responses. Median DOR was not reached; 36-month ongoing response rate was 84.2%. Median PFS and OS were not reached; 36-month rates were 59.1% and 73.4%, respectively.

Conclusions: Standard-dose pembrolizumab plus reduced-dose ipilimumab demonstrated robust antitumor activity, durable response, and favorable long-term survival with manageable toxicity.

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The anti–programmed death 1 (PDCD1; PD-1) agents pembrolizumab and nivolumab are standard treatments for advanced melanoma and have demonstrated prolonged survival and decreased toxicity compared with cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor ipilimumab in phase III trials (1,2). Because PD-1 and CTLA-4 receptors attenuate T-cell activation through distinct mechanisms, therapy with PD-1 plus ipilimumab is expected to be more effective than monotherapy (3). Standard-dose ipilimumab (3 mg/kg) plus reduced-dose nivolumab (1 mg/kg) has shown superior efficacy but substantially higher toxicity compared with ipilimumab alone (4). Recently, reduced-dose ipilimumab (1 mg/kg) plus standard-dose nivolumab (3 mg/kg) was associated with significantly reduced grade 3 or higher treatment-related adverse events (TRAEs) compared with standard-dose ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg); furthermore, no clinically meaningful differences in efficacy were observed between the regimens per descriptive analyses (5).

KEYNOTE-029 explored the combination of standard-dose pembrolizumab (2 mg/kg) with reduced-dose ipilimumab (1 mg/kg). In an expansion cohort (part 1B) involving 153 patients with advanced melanoma, the toxicity profile of the combination compared favorably with that of standard-dose ipilimumab and reduced-dose nivolumab and showed promising antitumor activity (6). Long-term results are presented.

Methods

Study Design

The KEYNOTE-029 (ClinicalTrials.gov, NCT02089685) study design is reported elsewhere (6). Adults with histologically confirmed, unresectable stage III-IV melanoma (excluding uveal or ocular melanoma), Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, measurable disease according to RECIST v1.1 (7), and no previous CTLA-4, programmed death 1 (PD-1), or programmed death ligand 1 (PD-L1) inhibition were

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included. Each patient provided an archival or newly obtained melanoma tissue sample for PD-L1 immunohistochemistry.

Patients received pembrolizumab 2 mg/kg intravenously once every 3 weeks (Q3W) with ipilimumab 1 mg/kg intravenously Q3W for four doses, followed by pembrolizumab 2 mg/kg Q3W for up to 2 years or until disease progression, intolerable toxicity, withdrawal of consent, or investigator decision to withdraw the patient.

The primary end point was safety and tolerability; secondary end points were objective response rate (ORR) by RECIST v1.1 (7) per independent central review, duration of response (DOR), progression-free survival (PFS), and overall survival (OS) in all patients.

Statistical Analysis

Safety was assessed in all patients who received at least one dose of combination therapy. DOR was assessed in patients with confirmed complete response (CR) or partial response (PR). ORR is presented as a percentage with exact 95% confidence intervals (CIs). PFS, OS, and DOR were estimated using the Kaplan-Meier method.

Procedures

Patients who had radiologically confirmed progressive disease (PD) and whose conditions were clinically stable were able to continue treatment until confirmatory imaging was performed at least 4 weeks later (Table S1 in Supplement). Patients with confirmed PD could continue treatment if repeat imaging showed a reduction in tumor burden compared to the initial scan demonstrating PD. Patients who achieved complete response (CR) could discontinue pembrolizumab after receiving at least 24 weeks of treatment, provided they had maintained CR for at least 2 scans and received at least 2 doses of pembrolizumab after the first confirmation of CR. Patients who had to discontinue ipilimumab because of toxicity

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were allowed to continue pembrolizumab treatment. Details of patient discontinuation, dose interruptions, and dose reductions can be found in the study protocol.

Assessments

Tumor imaging was conducted at baseline, week 12, then every 6 weeks until week 30, and every 12 weeks thereafter. ORR, PFS, and DOR assessments involved target lesions per RECIST v1.1 (7) by independent central review; the sponsor allowed a maximum of 10 target lesions in total and five per organ, if clinically relevant, to enable broader sampling of tumor burden. Cutaneous lesions and other superficial lesions that were detectable only by physical examination were considered nonmeasurable and therefore were classified as nontarget lesions. PFS was defined as the time from randomization to first documented disease progression based on independent central review or death due to any cause, whichever occurred first. Treatment decisions were informed by applying a modified version of RECIST (by investigator review) that accounts for the atypical response patterns observed with immunotherapeutic agents (see the "Modified RECIST" section). Adverse events (AEs) were evaluated throughout treatment and for 30 days thereafter (90 days for serious AEs) and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. PD-L1 expression was assessed using an immunohistochemistry assay (Agilent Technologies, Carpinteria, CA, USA) and the 22C3 antibody (Merck & Co., Inc, Kenilworth, NJ, USA). PD-L1 positivity was defined as staining of at least 1% of tumor cells or mononuclear inflammatory cells intercalated within or contiguous to tumor nests.

Modified RECIST

For treatment decision-making purposes, RECIST v1.1 was adapted to adjust for the atypical response patterns observed with immunotherapeutic agents. As feasible, patients were not to discontinue treatment until confirmation of PD to allow for the observation that some patients

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can have a transient tumor flare in the first few months after the start of immunotherapy but can have subsequent disease response. If radiologic imaging showed PD, tumor assessment was repeated at least 4 weeks later to confirm PD, with the option of continuing treatment at the treating physician's discretion (considering performance status, clinical symptoms, laboratory values, and tumor site) while awaiting radiologic confirmation of progression. If repeat imaging revealed a reduction in the tumor burden compared with the initial scan demonstrating PD, treatment could be continued per the treatment calendar. Confirmation of PD on repeat imaging led to discontinuation from the trial therapy. All target and nontarget lesions were considered when determining whether the tumor burden had increased or decreased. Patients deemed clinically unstable or who had biopsy-proven new metastatic lesions did not require repeat imaging for confirmation of PD.

Ethics

The study protocol and all amendments were approved by the institutional review board or ethics committee at each center. The study was conducted in compliance with local and national regulations and in accordance with the Declaration of Helsinki and standards of Good Clinical Practice. All patients provided written informed consent.

Results

Patient baseline characteristics (n = 153) have been previously reported (6). Median age was 60 years; most patients were male (66.0%), had programmed death ligand 1 (PD-L1)–positive disease (83.0%), and Eastern Cooperative Oncology Group performance status (ECOG PS) 0 (73.2%) (Table S2 in Supplement). As of July 17, 2018, median follow-up was 36.8 months (range, 0.8–42.1). One hundred ten patients (71.9%) received all four doses of ipilimumab; 47 (30.7%) completed 2 years of pembrolizumab; and 40 (26.1%) received all four doses of

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ipilimumab and completed 2 years of pembrolizumab. Ten patients (6.5%), 11 (7.2%), and 22 (14.4%) received one, two, and three ipilimumab doses, respectively. One hundred six patients (69.3%) discontinued treatment for the following primary reasons: 46 (30.1%), adverse events (AEs); 41 (26.8%) clinical or radiologic progression; 13 (8.5%) CR; four (2.6%) consent withdrawal; one (0.7%) nonadherence; and one (0.7%) use of anticancer therapy (letrozole).

Any-grade and grade 3/4 TRAEs occurred in 147 patients (96.1%) and 72 patients (47.1%), respectively (Table 1). A total of 55 patients (35.9%) had a TRAE that led to treatment discontinuation (Table S3 in Supplement). The most common any-grade TRAEs (incidence ≥20%) were fatigue, rash, pruritus, diarrhea, increased lipase level, and vitiligo (Table 1). Grade 3/4 TRAEs (incidence ≥5%) were increased lipase level, hepatitis, and colitis. No treatment-related deaths occurred.

Immune-mediated AEs and infusion reactions occurred in 94 patients (61.4%) and were predominantly mild or moderate (Table 2). Immune-mediated AEs with incidence ≥10% were hypothyroidism, hyperthyroidism, hypophysitis, pneumonitis, and hepatitis. The most common grade 3/4 immune-mediated AEs (incidence ≥5%) were colitis, hepatitis, and severe skin reactions. Sixty-five (69.1%) patients with immune-mediated AEs were treated with systemic corticosteroids.

ORR was 62.1% (95% CI, 53.9%–69.8%); 42 (27.5%) and 53 (34.6%) patients achieved CR and PR, respectively (Table S4 in Supplement). Of 127 patients with PD-L1–positive tumors, 34 (26.8%) had CR and 49 (38.6%) had PR. Of 24 patients with PD-L1–negative tumors, eight (33.3%) had CR and four (16.7%) had PR. Twenty-eight patients (18.3%) experienced PD as best overall response, including three (33.3%) with brain metastasis at baseline (Table S4 in Supplement). Of 140 patients with at least one evaluable postbaseline imaging assessment, 116 (82.8%) experienced reduction in target lesion size from baseline, with a

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median change of –72.0% (Fig. S1 in Supplement). Median time to response was 2.8 months (range, 1.0-12.4). Median DOR, median PFS, and median OS were not reached (Fig. 1). Three-year PFS and OS rates were 59.1% and 73.4%, respectively.

Discussion

With more than 36 months of median follow-up in KEYNOTE-029, standard-dose pembrolizumab plus reduced-dose ipilimumab had manageable toxicity with substantial efficacy and high 3-year PFS and OS rates. Safety of the combination remained consistent, but the proportion of patients with CR increased (27.5% vs 15%) compared to that reported previously (6).

Only ipilimumab plus an anti–PD-1 agent have suggested improved efficacy compared with anti–PD-1 monotherapy (2,4,8). However, alternative combinations are being explored because of substantial toxicity of ipilimumab plus nivolumab. The incidence of grade ≥3 TRAEs with standard-dose pembrolizumab plus low-dose ipilimumab in the current study was comparable to that observed with standard-dose ipilimumab plus low-dose nivolumab in CheckMate-511 (47% vs 48%) but was higher than that with low-dose ipilimumab and standard-dose nivolumab (47% vs 34%) (5) and lower versus standard-dose ipilimumab plus nivolumab (47% vs 59%) in a study with a similar follow-up duration (2). Toxicity rates typically associated with anti–PD-1 treatment (e.g., elevations in lipase levels and hypothyroidism) seemed generally comparable, although the rates of pneumonitis (11% vs 7%) and diabetes (3% vs not reported) appeared to be higher in this analysis than has been previously reported for patients receiving ipilimumab plus nivolumab (2,5).

The 62.1% ORR in the current study compares favorably with that of single-agent anti–PD-1 therapy (36%–42%) (1,2) and is comparable with those of standard-dose ipilimumab plus

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nivolumab (58%) (2) or nivolumab 3 mg/kg plus reduced-dose ipilimumab at 1 mg/kg (45.6%) (5). Despite similar ORRs, the 3-year PFS and OS rates in KEYNOTE-029 (59.1% and 73.4%, respectively) are higher than rates with standard-dose ipilimumab/nivolumab (39% and 58%, respectively) (2).

Cross-trial comparisons should be interpreted carefully given differences in study design and patient populations. In KEYNOTE-029, compared with CheckMate-067, a lower proportion of patients had the poor prognostic feature of elevated lactate dehydrogenase levels (25% vs 36%), although similar proportions had M1c disease (56% vs 58%), ECOG PS 0 (73.2% vs 73.2%), and *BRAF*-mutant disease (36.6% vs 31.5%) (8). However, in KEYNOTE-029, 13.1% of patients had previously received therapy, most commonly BRAF and/or MEK inhibitors, a factor associated with reduced response to checkpoint inhibition (9), whereas in CheckMate-067 all patients were treatment naive (8). The proportion of patients with PD-L1–positive disease also has the potential to complicate comparison of efficacy between studies. In KEYNOTE-029, 83% of patients had PD-L1 expression of ≥1% compared with 171 of 314 (54.5%) patients in the nivolumab arm and 171 of 316 (54.1%) patients in the nivolumab plus ipilimumab arm of CheckMate-067 (2,6). However, PD-L1 status alone may not be a definitive biomarker of outcome in patients treated with the combination of nivolumab and ipilimumab (2).

Another plausible explanation for the improved PFS and OS seen in KEYNOTE-029 may be toxicity management. In response to significant toxicity, initial ipilimumab/nivolumab studies mandated cessation of both agents. In KEYNOTE-029, ipilimumab could be ceased until resolution of toxicity grade 1 or less, whereas pembrolizumab could be continued at the investigator's discretion. The ability to continue pembrolizumab may be responsible for the favorable DOR seen in KEYNOTE-029 (3-year ongoing response rate, 84.2%; median DOR,

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50.1 months in CheckMate-067). Interestingly, the use of systemic corticosteroids to manage immune-mediated AEs were also different in KEYNOTE-029 and CheckMate-067 (69.1% in KEYNOTE-029; 83.4% in CheckMate-067) (8). The impact of corticosteroid use on survival outcomes of patients receiving pembrolizumab or nivolumab in combination with ipilimumab remains to be determined.

One of the strengths of the current report of KEYNOTE-029 is the length of follow-up. The median follow-up in this analysis was 36.8 months, which provides a robust basis for assessing the long-term impact of pembrolizumab plus reduced-dose ipilimumab in patients with advanced melanoma. In comparison, the only other data currently available investigating PD-1 inhibitors with reduced-dose ipilimumab is from the CheckMate-511 study, which had a median follow-up of only 19 months at the latest data cut (5). The current findings of part 1B of KEYNOTE-029 support exploration of alternative dosing strategies for maintaining efficacy with reduced toxicity. Another cohort of KEYNOTE-029 is exploring alternative ipilimumab dosing (50/100 mg every 6/12 weeks) with standard-dose pembrolizumab to determine whether efficacy can be maintained with further reduction in toxicity in patients with advanced melanoma. A phase I/II study investigating escalating doses of the anti–CTLA-4 antibody MK-1308 plus pembrolizumab in solid tumors including melanoma is also underway (ClinicalTrials.gov, NCT03179436).

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Author Contributions:

AR, MBA, W-JH, NI, BHM, and GVL conceived, designed, or planned the study. MSC, AMM, VA, JSC, MBJ, BMF, CMM, AGH, AR, MBA, JAT, W-JH, FSH, ADG, RK, BHM, and GVL acquired the data. MSC, AMM, VA, AR, W-JH, FSH, HW, NI, BHM, and GVL analyzed the data. MSC, AMM, VA, JSC, MBJ, BMF, AGH, AR, MBA, W-JH, FSH, RK, HW, NI, BHM, and GVL interpreted the results. MSC, MBA, BHM, and GVL drafted the manuscript with contributions from all authors. MSC, AMM, VA, JSC, MBJ, BMF, CMM, AGH, AR, MBA, JAT, W-JH, FSH, ADG, RK, HW, NI, BHM, and GVL critically reviewed or revised the manuscript for important intellectual content. MSC, AMM, CMM, AGH, MBA, JAT, W-JH, RK, contributed to the provision of study materials or patients. HW, provided statistical expertise. All authors reviewed the interim drafts and the final version of the manuscript and agreed with its content and submission. All authors had access to all the relevant study data and related analyses and vouch for the completeness and accuracy of the presented data. All authors agree to be accountable for all aspects of the work and will ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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368 **Table 1. Treatment-related adverse events of any grade occurring in ≥10% of patients**

***n* (%)**	**Any grade**	**Grade 1/2**	**Grade 3**	**Grade 4**
Any	147 (96.1)	75 (49.0)	61 (39.9)	11 (7.2)
Fatigue	75 (49.0)	75 (49.0)	0	0
Rash	67 (43.8)	62 (40.5)	5 (3.3)	0
Pruritus	63 (41.2)	63 (41.2)	0	0
Diarrhea	44 (28.8)	43 (28.1)	1 (0.7)	0
Lipase level increased	34 (22.2)	7 (4.6)	19 (12.4)	8 (5.2)
Vitiligo	31 (20.3)	31 (20.3)	0	0
Dry mouth	27 (17.6)	27 (17.6)	0	0
Nausea	27 (17.6)	27 (17.6)	0	0
Amylase level increased	26 (17.0)	19 (12.4)	6 (3.9)	1 (0.7)
Hypothyroidism	25 (16.3)	25 (16.3)	0	0
Arthralgia	21 (13.7)	20 (13.1)	1 (0.7)	0
Rash maculopapular	19 (12.4)	18 (11.8)	1 (0.7)	0
Pneumonitis	17 (11.1)	14 (9.2)	3 (2.0)	0
ALT level increased	17 (11.1)	15 (9.8)	2 (1.3)	0
Hyperthyroidism	17 (11.1)	15 (9.8)	2 (1.3)	0
Headache	16 (10.5)	15 (9.8)	1 (0.7)	0
AST level increased	16 (10.5)	16 (10.5)	0	0
Autoimmune hepatitis	16 (10.5)	6 (3.9)	10 (6.5)	0

369 Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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370 **Table 2. Immune-mediated adverse events and infusion reactions[a]**

	***n* (%)**			
	Any grade	**Grade 1/2**	**Grade 3**	**Grade 4**
Any	94 (61.4)	54 (35.3)	38 (24.8)	2 (1.3)
Hypothyroidism	26 (17.0)	26 (17.0)	0	0
Hyperthyroidism	18 (11.8)	16 (10.5)	2 (1.3)	0
Hypophysitis	17 (11.1)	14 (9.2)	3 (2.0)	0
Pneumonitis	17 (11.1)	14 (9.2)	3 (2.0)	0
Hepatitis	16 (10.5)	6 (3.9)	10 (6.5)	0
Colitis	14 (9.2)	3 (2.0)	11 (7.2)	0
Severe skin reactions[b]	10 (6.5)	1 (0.7)	9 (5.9)	0
Thyroiditis	8 (5.2)	8 (5.2)	0	0
Infusion reactions	3 (2.0)	2 (1.3)	1 (0.7)	0
Adrenal insufficiency	6 (3.9)	4 (2.6)	2 (1.3)	0
Pancreatitis	6 (3.9)	4 (2.6)	1 (0.7)	1 (0.7)
Uveitis	4 (2.6)	4 (2.6)	0	0
Type 1 diabetes mellitus	3 (2.0)	0 (0)	2 (1.3)	1 (0.7)
Nephritis	3 (2.0)	1 (0.7)	2 (1.3)	0
Myositis	1 (0.7)	1 (0.7)	0	0

371 [a]Every patient is counted a single time for each applicable specific adverse event. A patient
372 with multiple adverse events within a system organ class is counted a single time for that
373 system organ class.

374 [b]Includes pemphigoid, rash, rash maculopapular, and rash pruritic.

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Figure Legend

Figure 1. Kaplan-Meier estimates in patients who received standard-dose pembrolizumab plus reduced-dose ipilimumab. A, Duration of response. B, Progression-free survival. C, Overall survival. CI, confidence interval; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival. [a]From Kaplan-Meier method.

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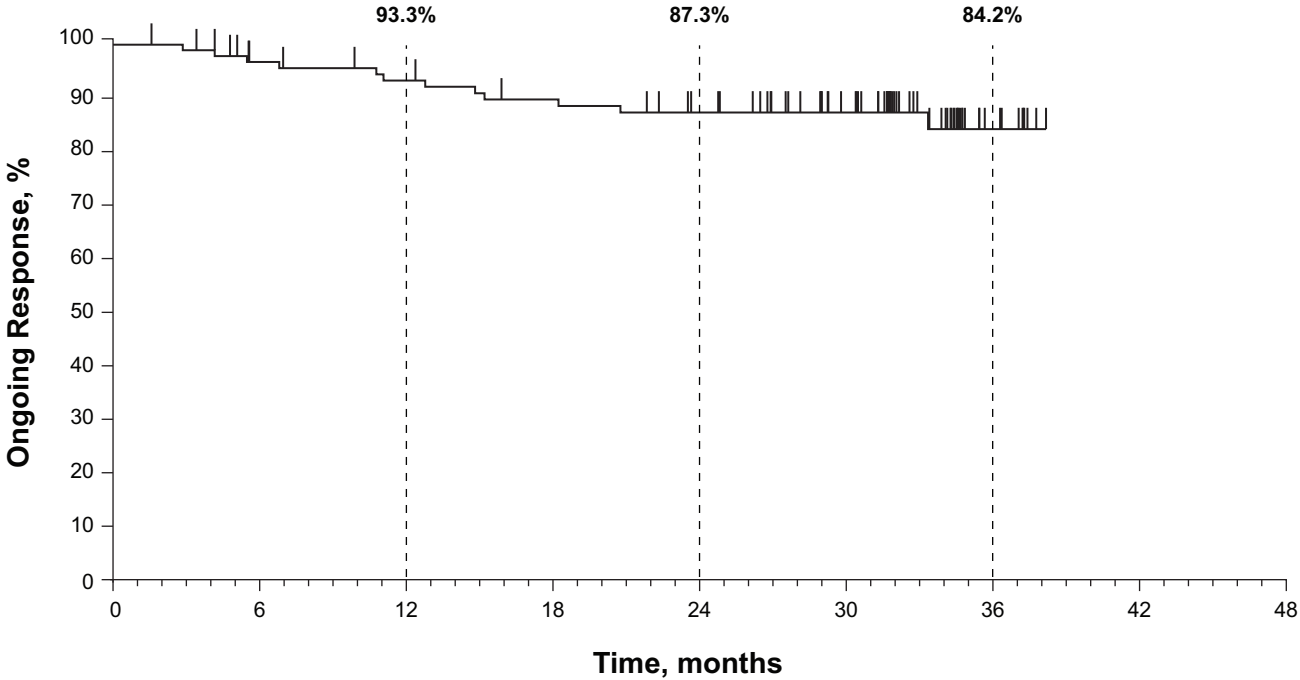
A

	Median (range), months
Duration of response	NR (1.6+-38.2+)



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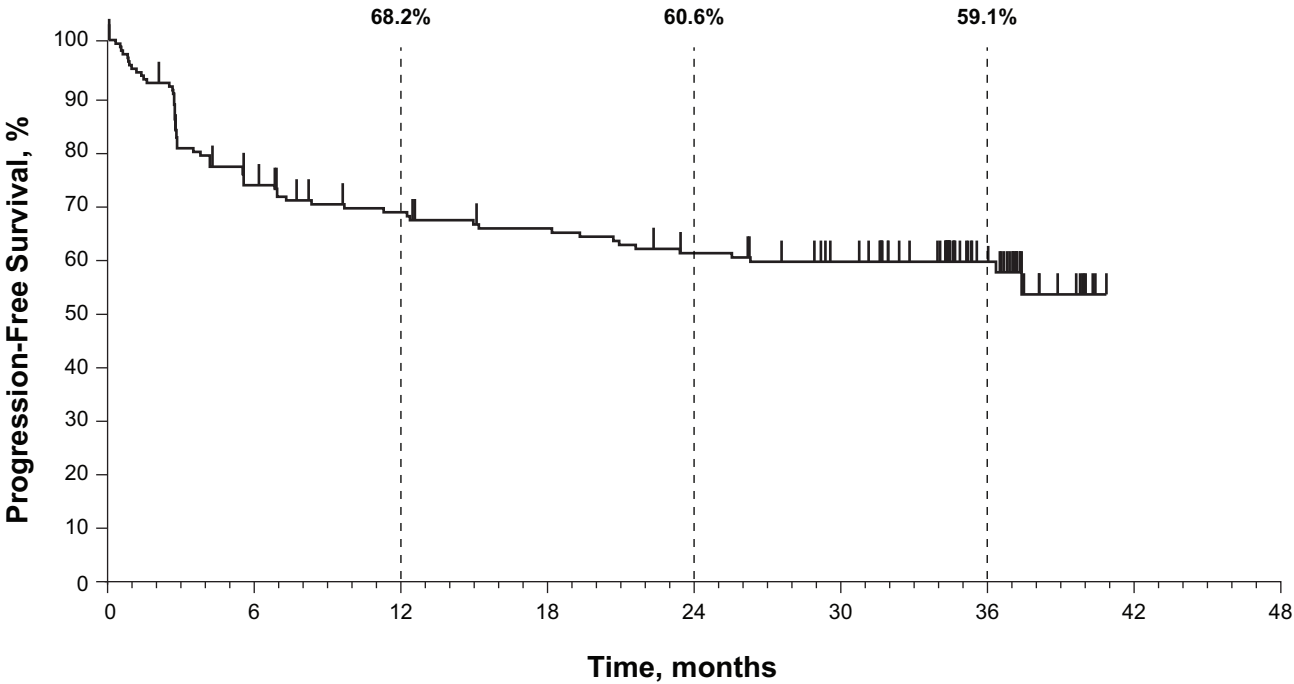
B

	Events, *n* (%)	Median[a] (95% CI), months
Progression-free survival	61 (39.9)	NR (36.4-NE)



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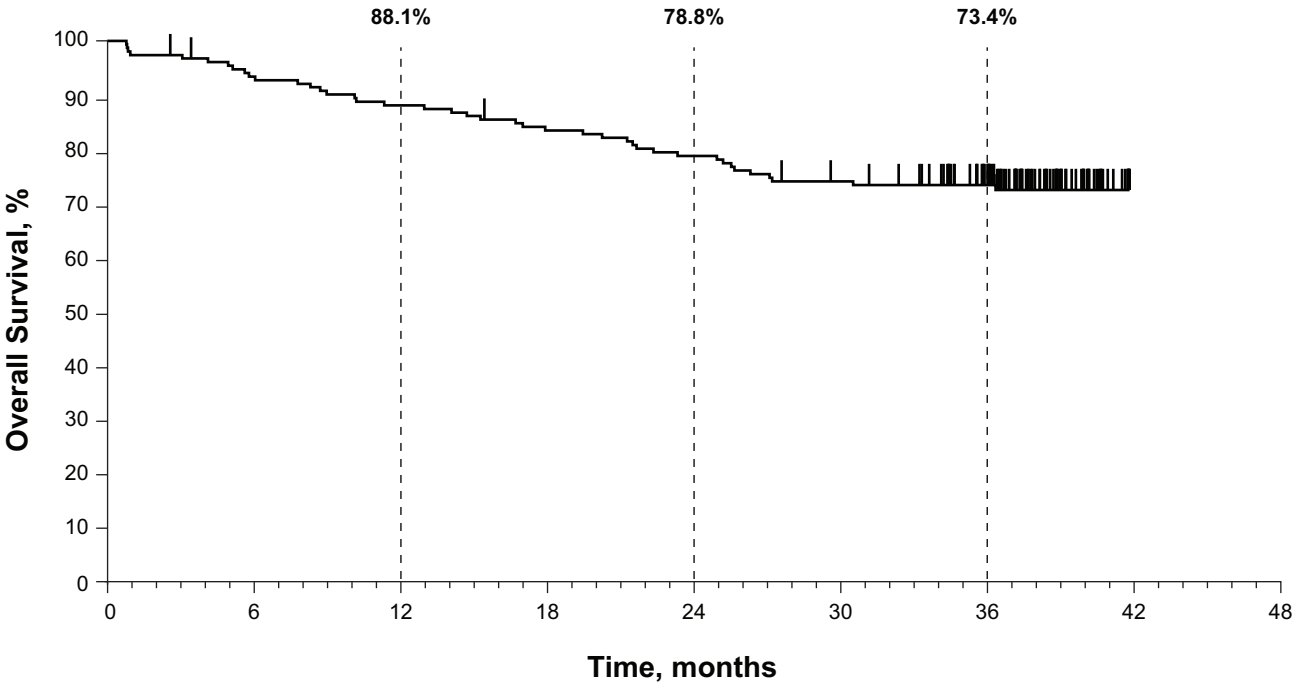
No. at risk	153	106	93	86	78	69	31	0	0

C

	Events, *n* (%)	Median[a] (95% CI), months
Overall survival	41 (26.8)	NR (NE-NE)



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Clinical Cancer Research

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Matteo S. Carlino, Alexander M Menzies, Victoria G Atkinson, et al.

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