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ORIGINAL REPORT

Evaluation of Immune-Related Response Criteria and RECIST v1.1 in Patients With Advanced Melanoma Treated With Pembrolizumab

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ABSTRACT

Purpose

We evaluated atypical response patterns and the relationship between overall survival and best overall response measured per immune-related response criteria (irRC) and Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) in patients with advanced melanoma treated with pembrolizumab in the phase Ib KEYNOTE-001 study (clinical trial information: NCT01295827).

Patients and Methods

Patients received pembrolizumab 2 or 10 mg/kg every 2 weeks or every 3 weeks. Atypical responses were identified by using centrally assessed irRC data in patients with ≥ 28 weeks of imaging. Pseudoprogression was defined as ≥ 25% increase in tumor burden at week 12 (early) or any assessment after week 12 (delayed) that was not confirmed as progressive disease at next assessment. Response was assessed centrally per irRC and RECIST v1.1.

Results

Of the 655 patients with melanoma enrolled, 327 had ≥ 28 weeks of imaging follow-up. Twenty-four (7%) of these 327 patients had atypical responses (15 [5%] with early pseudoprogression and nine [3%] with delayed pseudoprogression). Of the 592 patients who survived ≥ 12 weeks, 84 (14%) experienced progressive disease per RECIST v1.1 but nonprogressive disease per irRC. Two-year overall survival rates were 77.6% in patients with nonprogressive disease per both criteria (n = 331), 37.5% in patients with progressive disease per RECIST v1.1 but nonprogressive disease per irRC (n = 84), and 17.3% in patients with progressive disease per both criteria (n = 177).

Conclusion

Atypical responses were observed in patients with melanoma treated with pembrolizumab. Based on survival analysis, conventional RECIST might underestimate the benefit of pembrolizumab in approximately 15% of patients; modified criteria that permit treatment beyond initial progression per RECIST v1.1 might prevent premature cessation of treatment.

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INTRODUCTION

Immune checkpoint blockade has emerged as a principal therapeutic modality for the treatment of many cancers. Ipilimumab, a fully human monoclonal antibody that blocks cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), was the first immune checkpoint inhibitor approved by regulatory authorities and prolongs overall survival (OS) in metastatic melanoma.[1-3] Conventional response criteria might underestimate the therapeutic benefit of immune checkpoint blockade because objective response and prolonged disease stabilization can occur after an initial increase in tumor burden or appearance of new lesions.[1,4,5] Whereas conventional criteria, such as Response Evaluation Criteria in Solid Tumors (RECIST), were developed based on data from clinical trials of cytotoxic chemotherapy agents for advanced malignancies,[6] immune-related response criteria (irRC) were developed to provide more rigorous characterization of the atypical response patterns observed in the phase II development program for ipilimumab in melanoma.[1] Key differences between irRC[1] and RECIST

version 1.1 (v1.1)[7] are summarized in Table 1. Initial evidence of disease progression is handled differently with irRC compared with conventional response criteria. For example, irRC require confirmation of initial evidence of progressive disease, whereas RECIST do not. Similarly, appearance of new lesions would define progression of disease by RECIST v1.1, whereas new lesions may be added to the sum of the products of the two largest perpendicular diameters of all index lesions at any time point and will only result in progressive disease if the sum is ≥ 25% compared with nadir. Retrospective evaluations of phase II clinical trials of ipilimumab that included patients with imaging data available beyond initial progression demonstrated that patients who experienced a response or stable disease per irRC had survival rates similar to those of patients who experienced response or stable disease per RECIST.[1,8,9]

Inhibitors of programmed death receptor 1 (PD-1) and one of its ligands, PD-L1, represent the next generation of checkpoint inhibitors that have demonstrated significant anticancer activity. PD-1 is a surface marker induced on activated T cells[10]; elevated PD-1 expression is a marker for T-cell exhaustion.[11] Its ligands PD-L1 and PD-L2, normally expressed on antigen-presenting cells and endothelia, can be upregulated on various tumor cells.[12] Engagement of PD-1 with its ligands leads to inhibition of T-cell receptor signaling[13] and a lowering of the T-cell apoptotic threshold.[14] Therefore, tumor cell expression of PD-1 is a clear example of immune surveillance evasion. The PD-1/PD-L1 pathway is likely dominant for tumor escape from effective host immune responses.

Pembrolizumab (MK-3475) is a humanized monoclonal antibody against PD-1 that has been approved in several countries for the treatment of advanced melanoma. US Food and Drug Administration approval of pembrolizumab was based on data obtained from 411 patients enrolled in multiple expansion cohorts of the large KEYNOTE-001 phase I clinical trial.[15-17] As assessed per RECIST v1.1 by independent central review, the response rate was 39% in patients with ipilimumab-naive melanoma and 29% in patients with ipilimumab-treated melanoma.[17] After an 18-month median follow-up, 81% of responders did not experience progressive disease, and the median OS was 25.9 months.[17]

Anecdotal evidence of immune-related response patterns was observed with pembrolizumab during its early clinical development. On the basis of the pembrolizumab mechanism of action and the atypical response patterns observed with ipilimumab, we hypothesized that atypical response patterns would be observed with pembrolizumab and that assessing response per RECIST v1.1 would not provide a comprehensive assessment of the pembrolizumab antitumor effect. By using the larger KEYNOTE-001 655-patient melanoma data set,[18] we aimed to identify and describe atypical response patterns with pembrolizumab and to assess the relationship between OS and response measured through RECIST v1.1 and irRC.

PATIENTS AND METHODS

Study Design and Patients

KEYNOTE-001 (clinical trial information: NCT01295827) was an international, multicenter, open-label, phase Ib study of pembrolizumab for patients with advanced solid tumors, which included multiple melanoma expansion cohorts. Detailed eligibility criteria were published previously.[15-18] Briefly, adults age 18 years and older with confirmed, unresectable melanoma, an Eastern Cooperative Oncology Group performance status of 0 or 1, no active infection, no active autoimmune disease or history thereof, no ongoing systemic corticosteroid therapy, and no previous treatment that targeted the PD-1 pathway were included. Both ipilimumab-naive and ipilimumab-treated patients enrolled. The number of previous therapies was unlimited for patients previously treated with ipilimumab and was two or fewer for patients naive to ipilimumab. Patients with active brain metastases or carcinomatous meningitis were excluded.

The study was performed in accordance with protocol, good clinical practice standards, and the Declaration of Helsinki, and protocols and all amendments were approved by the appropriate institutional review board or ethics body at each institution. All patients provided written informed consent.

Treatment and Assessments

Patients received pembrolizumab intravenously over 30 min at doses of 2 mg/kg or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks. Treatment was continued until confirmed disease progression, intolerable

Table 1. Comparison of Key Differences in RECIST v1.1 and irRC

Category	RECIST v1.1	irRC
Measurement of tumor burden	Unidimensional	Bidimensional
Target lesions	Maximum, 5*	Maximum, 15 index lesions
New lesion	Results in progressive disease at first appearance	Up to 10 new visceral lesions and 5 cutaneous lesions may be added to the sum of the products of the two largest perpendicular diameters of all index lesions at any time point
Complete response	Disappearance of all target and nontarget lesions Nodes must regress to < 10 mm short axis No new lesions Confirmation required	
Partial response	≥ 30% decrease in tumor burden compared with baseline Confirmation required	≥ 50% decrease in tumor burden compared with baseline† Confirmation required
Progressive disease	≥ 20% + 5-mm absolute increase in tumor burden compared with nadir Appearance of new lesions or progression of nontarget lesions	≥ 25% increase in tumor burden compared with baseline, nadir, or reset baseline† New lesions added to tumor burden Confirmation required
Stable disease	Neither partial response nor progressive disease	

Abbreviations: irRC, immune-related response criteria; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.
*For the present analyses, the maximum number of target lesions was 10.
†If an increase in tumor burden is observed at the first scheduled assessment, the baseline is reset to the value observed at the first assessment.

toxicity, consent withdrawal, physician decision, or any other reason. Radiologic tumor measurements were performed every 12 weeks. Treatment decisions were based on investigator assessment of response per irRC. Per protocol, patients with evidence of radiographic progression could remain on therapy until progression was confirmed on the next imaging assessment performed ≥ 4 weeks later. Retrospectively, an independent core laboratory (PAREXEL International, Waltham, MA) assessed response per RECIST v1.1 and per irRC. A maximum of 10 target lesions per RECIST v1.1 and 15 index lesions per irRC were assessed per patient. Primary end point assessment was based on RECIST v1.1 by central review.

Analyses

Atypical responses were identified by using centrally assessed irRC data among patients with measurable disease per irRC and RECIST v1.1 by central review at baseline who were followed by imaging for ≥ 28 weeks as of the analysis cutoff date of April 18, 2014. The rationale for requiring patients to have ≥ 28 weeks of follow-up was to allow for two time points after baseline (ie, three total time points by week 28) to identify atypical responses and subsequently to confirm disease progression or response. Early pseudoprogression was defined as ≥ 25% increase in tumor burden at imaging assessment 1 (week 12) not confirmed as progressive disease per irRC at assessment 2. Delayed pseudoprogression was defined as ≥ 25% increase in tumor burden at any imaging assessment after the week 12 assessment that was not confirmed as progressive disease per irRC at the next imaging assessment. Patients were excluded from tumor size analysis if they underwent resection or metastasectomy, received subsequent radiation or other therapy, or experienced inflammation at tumor sites. Qualitative assessment of the metastatic sites was performed for patients with atypical responses.

We also evaluated OS in patients with best overall response of stable disease or better per RECIST v1.1 and irRC (first group), versus progressive disease per RECIST v1.1 but nonprogressive disease per irRC (second group), versus progressive disease per RECIST v1.1 and irRC (third group). For all three groups, Kaplan-Meier estimates of OS were assessed. Only patients who survived beyond 12 weeks (ie, the time of the first tumor assessment) were included in this landmark analysis because at least one postbaseline disease assessment was required for patients to qualify for inclusion in the first group.

RESULTS

Pseudoprogression Analysis

Of the 655 patients enrolled in the KEYNOTE-001 melanoma expansion cohorts, 327 had ≥ 28 weeks of imaging follow-up as of April 18, 2014, and were eligible for atypical response analysis. Atypical responses were observed in 24 (7.3%) of 327 patients (15 [4.6%] with early pseudoprogression and nine [2.8%] with delayed pseudoprogression; Fig 1). Patterns of atypical response included regression of tumor burden and stable disease per irRC despite the development of new lesions, which would be classified as progressive disease per RECIST, as well as initial increases in the size of target lesions followed by decreases without evidence of new lesions. Atypical responses were observed in both visceral organs and lymph nodes (Fig 2; Appendix Table A1, online only). Among atypical responders, 19 (79%) were ipilimumab naive (13 early pseudoprogression, six delayed pseudoprogression), four (17%) were ipilimumab refractory (two each for early and delayed pseudoprogression), and one (4%) was ipilimumab treated (delayed pseudoprogression). Seven (29%) had PD-L1–positive tumors, and median baseline tumor size was 52.6 mm (range, 10.6 to 242.0). These characteristics were similar between patients with early and delayed pseudoprogression (Appendix Table A2, online only). At the time of analysis, all 24 patients who experienced pseudoprogression were alive, with a survival duration ranging from 7.6+ to 26.4+ months.

Two examples of early pseudoprogression are shown in Figure 3. In the first, a 56-year-old female with advanced melanoma treated with pembrolizumab 2 mg/kg every 3 weeks experienced disease progression per RECIST v1.1 and irRC in a skin lesion and liver metastasis at week 12 (Fig 3A). The patient continued pembrolizumab, and at week 24, both the skin and the liver lesions regressed. By week 24, response per irRC was partial response. Complete response was achieved at week 96 and was ongoing 28 months after enrollment. In the second example, a 72-year-old female with ipilimumab-naive advanced melanoma was treated with pembrolizumab 10 mg/kg every 2 weeks for two cycles (4 weeks). Due to development of grade 2 rash, the patient was switched to a dosage of 10 mg/kg every 3 weeks and continued therapy with no further dose modification. At the first assessment (week 12), there was a 35.7% increase in the total tumor burden, but at the follow-up scan performed at week 16, tumor burden decreased by 8.9% (Fig 3B). As of the last assessment on January 26, 2015 (week 154), the patient remains in partial response by irRC and continues to be on pembrolizumab beyond 3 years with durable partial response.

Comparison of irRC and RECIST v1.1

The best overall response per irRC by central review for the 15 patients with early pseudoprogression was complete response in three patients, partial response in eight patients, and stable disease in four patients. Per RECIST v1.1, best overall response after initial progression was complete response in three patients, partial response in four patients, stable disease in one patient, and progressive disease in seven patients. The best overall response per irRC by central review for the nine patients with delayed pseudoprogression was complete response in one patient, partial response in two patients, stable disease in five patients, and progressive disease in one patient; per RECIST v1.1, best response was complete response in one patient, partial response in two patients, stable disease in three patients, and progressive disease in three patients. Discrepancies in best overall response were noted for eight patients with early pseudoprogression and two patients with delayed pseudoprogression. Possible factors that contributed to these differences are that irRC uses bidimensional measurements, includes new lesions in the overall tumor burden, and allows for the ability to reset baseline.

As of the analysis cutoff date of April 18, 2014, median follow-up duration for all 655 patients was 15 months (range, 8 to 29 months). There were 584 patients who had one or more irRC assessments, including 307 (52.6%) with one or more assessments of progressive disease. For the 92 (30.0%) patients with confirmed progressive disease per irRC after the first progressive disease assessments, median time to the confirmatory measurement was 47 days (range, 20 to 98 days).

Of the 63 patients with < 12 weeks of observation, 55 died and eight were censored. In the 592 patients who survived ≥ 12 weeks and as assessed by central review, 331 (56%) had nonprogressive disease and 177 (30%) had progressive disease per RECIST v1.1

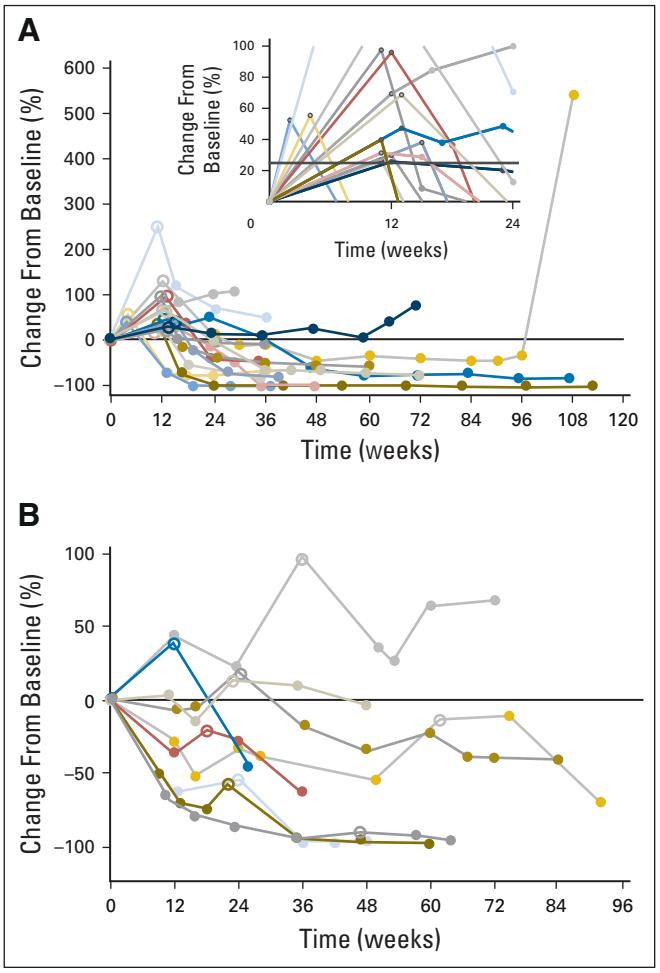

Fig 1. Percent change from baseline in target lesions per immune-related response criteria by central review in patients with early (A) and delayed (B) pseudoprogression. Circles represent times of radiologic assessment. Open circles represent times at which the 25% threshold was crossed. Colors represent individual patients. The inset in (A) is an enlargement of the change from a baseline of 0% to 100% from weeks 0 to 24, with the 25% threshold indicated by the horizontal line. In (B), the patient represented by the top gray line did not have a best overall response of progressive disease because progressive disease was not confirmed at the second assessment (change from baseline, 22.1%). The patient represented by the dark blue line is considered to have delayed pseudoprogression because a return to nonprogressive disease could not be confirmed at the time of the data cutoff date.

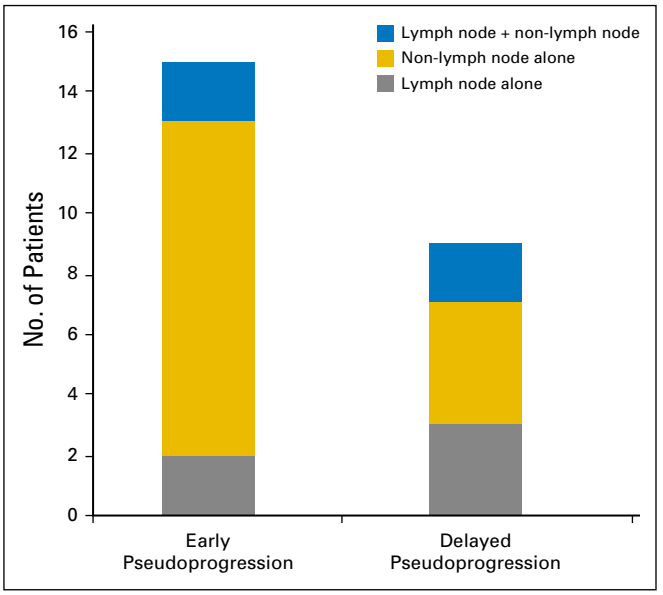

Fig 2. Distribution of target lesions in patients with atypical response patterns.

and irRC. A discrepancy in best overall response by central review was observed for the remaining 84 (14%) patients such that best overall response was progressive disease per RECIST v1.1 but nonprogressive disease by irRC. Of these patients, progressive disease per RECIST v1.1 was declared because of a single factor in 59 (70.2%) patients (Appendix Table A3, online only). In comparison, 88 (49.7%) patients with progressive disease per both criteria had more than one progressive disease factor, including 25 (14.1%) who had > 20% growth in target lesions, unequivocal growth of nontarget lesions, and appearance of new lesions (Appendix Table A3, online only).

Longitudinal analysis of the change from baseline over time in the sum of target lesions demonstrated that the 84 patients with progressive disease per RECIST v1.1 but nonprogressive disease per irRC were able to gain control of their disease through either stabilization of or a decrease in tumor burden with additional time (Fig 4). OS was longer in the 84 patients with progressive disease by RECIST v1.1 but nonprogressive disease by irRC compared with that in the 177 patients with progressive disease by both RECIST v1.1 and irRC (Fig 5). Median OS was not reached (95% CI, 25.9 months to not reached) for patients with nonprogressive disease per both criteria, 22.5 months (95% CI, 16.5 months to not reached) for patients with progressive disease per RECIST v1.1 but nonprogressive disease per irRC, and 8.4 months (95% CI, 6.6 to 9.9 months) for patients with progressive disease per both criteria. The 2-year OS rates were 77.6%, 37.5%, and 17.3%, respectively. A general correlation between shorter OS and a higher number of progressive disease criteria was observed, particularly in patients who had progressive disease per RECIST v1.1 and irRC (Appendix Table A3, online only).

DISCUSSION

Immunotherapeutic agents are being tested as anticancer therapy for many advanced solid tumors and hematologic malignancies. On the basis of the efficacy observed to date, these agents are likely to play a major role in cancer treatment in the near future. Pembrolizumab alone is in clinical development for > 30 tumor types, including hematologic malignancies, and is approved in several countries for the treatment of advanced melanoma and in the United States, for the treatment of patients with metastatic non–small-cell lung cancer whose tumors express PD-L1 as determined by a Food and Drug Administration–approved test, with disease progression on or after platinum-containing chemotherapy. On the basis of the novel mechanism of action, the likely widespread use of this agent, and the desire to accurately and practically assess clinical benefit, an urgent need exists for new standards for assessing response to pembrolizumab and other novel immunotherapies.

RECIST v1.1, the conventional criteria for tumor measurement, provide a simple, standardized method for defining the therapeutic effect of chemotherapeutic agents. The use of unidimensional tumor

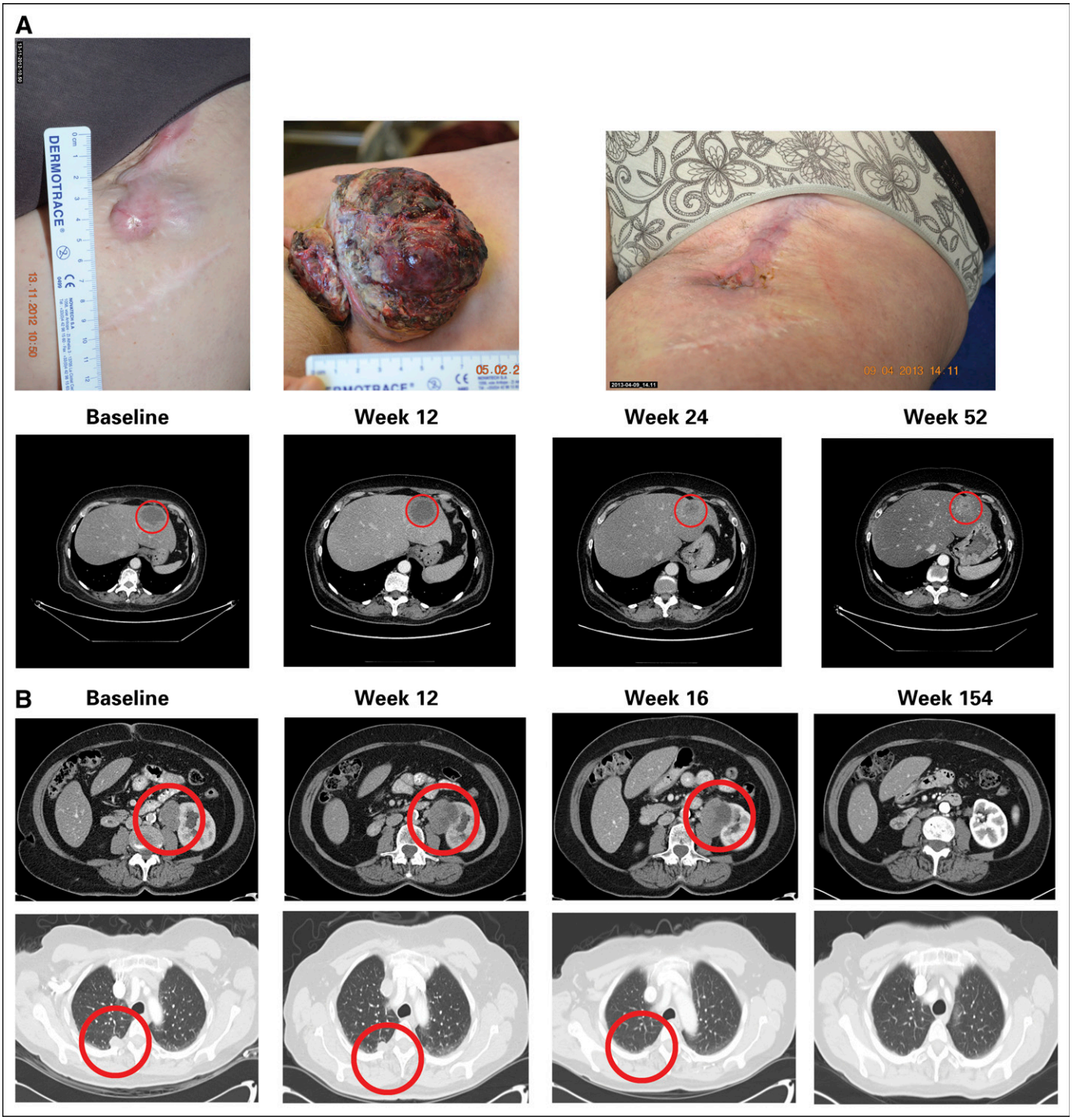

Fig 3. Case studies of patients with early progression. (A) Scans at baseline and 12, 24, and 52 weeks in a 56-year-old woman with advanced melanoma. Per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) and immune-related response criteria (irRC), the patient experienced progressive disease at week 12. At week 24, response was partial response by irRC. Complete response was obtained at week 96 and has been ongoing for 28 months. (B) Scans at baseline and 12, 16, and 154 weeks in a 72-year-old woman with advanced melanoma. RECIST v1.1 identified stable disease at an earlier time point than irRC. At week 12, response was unconfirmed progressive disease by irRC but stable disease by RECIST v1.1. At week 16, response was stable disease by both criteria. As of the last assessment (treatment ongoing), patient remains with partial response.

measurements facilitates their application while minimizing variability, but they are unable to capture responses that occur after disease progression, which might limit their usefulness when assessing response to immunotherapeutic agents.[4] The irRC were developed to provide standardization for assessing response to immunotherapeutic agents.[1] Their original conception was based on the modified World Health Organization criteria, which use bidimensional tumor measurements. The irRC incorporate

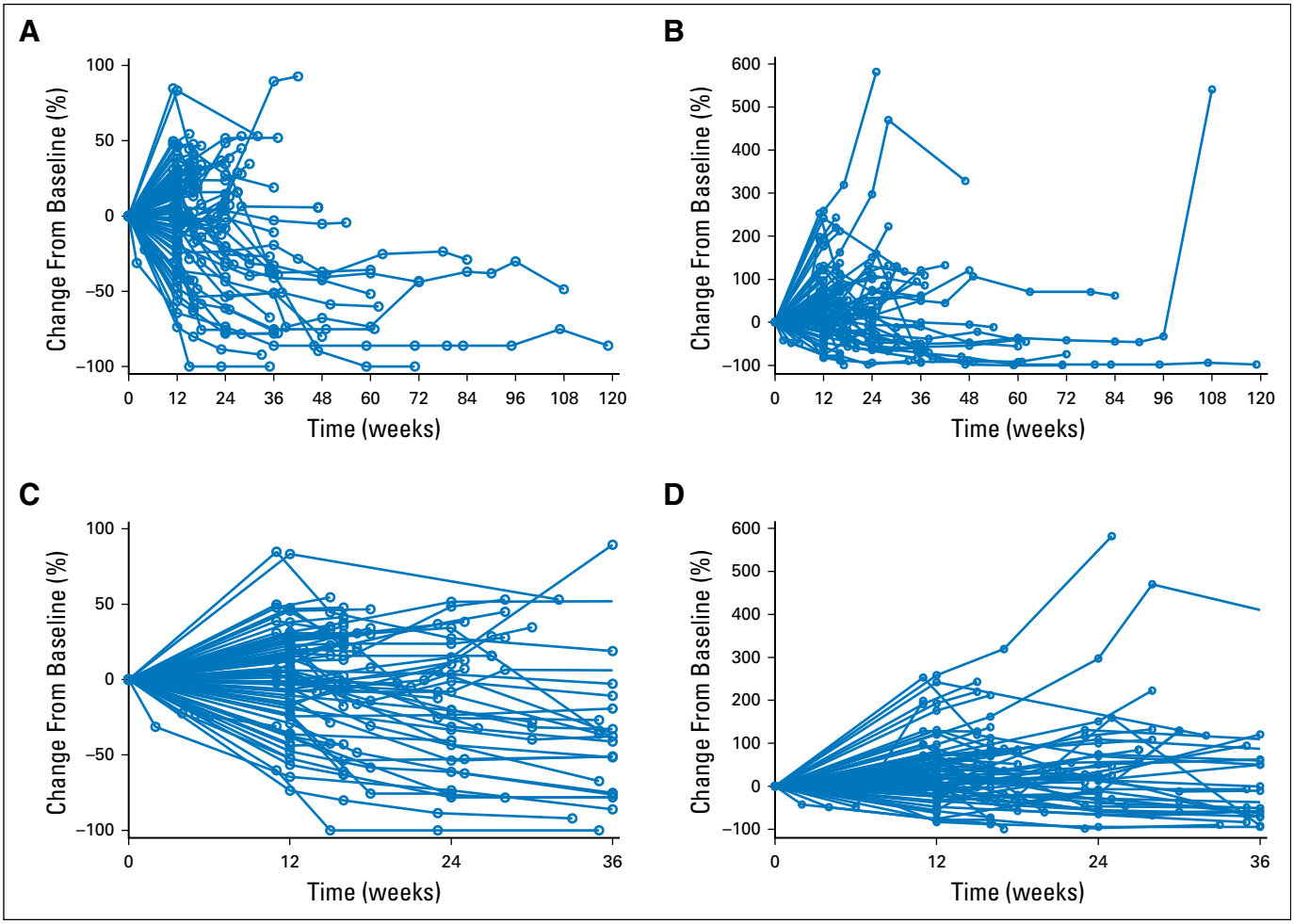

Fig 4. Percent change from baseline in target lesions in patients with best overall response of progressive disease per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) but nonprogressive disease by immune-related response criteria (irRC). Only patients with measurable disease at baseline and at least one postbaseline measurable scan are included (n = 73). Open circles represent times of radiologic assessment. (A) Unidimensional tumor measurements. (B) Bidimensional tumor measurements. (C) Unidimensional tumor measurements that show weeks 0 to 36 only. (D) Bidimensional tumor measurements that show weeks 0 to 36 only.

measurable new lesions into the total tumor burden and describe additional patterns of tumor response that can occur after initial increases in tumor burden.[4] However, greater variability might exist with bidimensional measurements than with unidimensional measurements,[5] and irRC may not fully capture all patterns of clinical responses. Given the rapid development of effective immuno-oncology agents in multiple cancers, there is a growing effort to develop new standard response criteria for patients treated with immunotherapy to provide for robust clinical end points in evaluating these new treatments.[19]

Similar to observations made with ipilimumab,[1] we found unique response patterns in certain patients with advanced melanoma treated with the anti–PD-1 antibody pembrolizumab. In the current analysis of patients with melanoma enrolled in KEYNOTE-001, 7% of evaluable patients experienced early or delayed tumor pseudoprogression. For comparison, in the first report of atypical responses in patients treated with ipilimumab by Wolchok et al,[1] the incidence was 10%. No clear relationship between PD-L1 expression or prior ipilimumab treatment with pseudoprogression was found. Although relatively infrequent, these unique response patterns have important potential implications for patient management, which is particularly true given observed differences in survival by RECIST v1.1 and irRC per central review. The 84 patients with progressive disease by RECIST v1.1 but nonprogressive disease by irRC had a longer OS than the 177 patients with progressive disease per both criteria, which suggests that RECIST v1.1 might underestimate the benefit of pembrolizumab in approximately 15% of patients. These data suggest that patients may benefit from receiving treatment beyond initial evidence of radiographic progression and thus support the use of modified response criteria on the basis of immune-related response patterns. Furthermore, clinicians alert to these criteria might be able to avoid otherwise premature termination of potentially effective treatment.

Limitations of the current analysis include the retrospective assessment of response by central review, variability in the patient populations evaluated, subjective assessment by investigators to continue treatment, availability of data for patients who continue treatment beyond progression, and stratification of survival on the basis of postbaseline events.

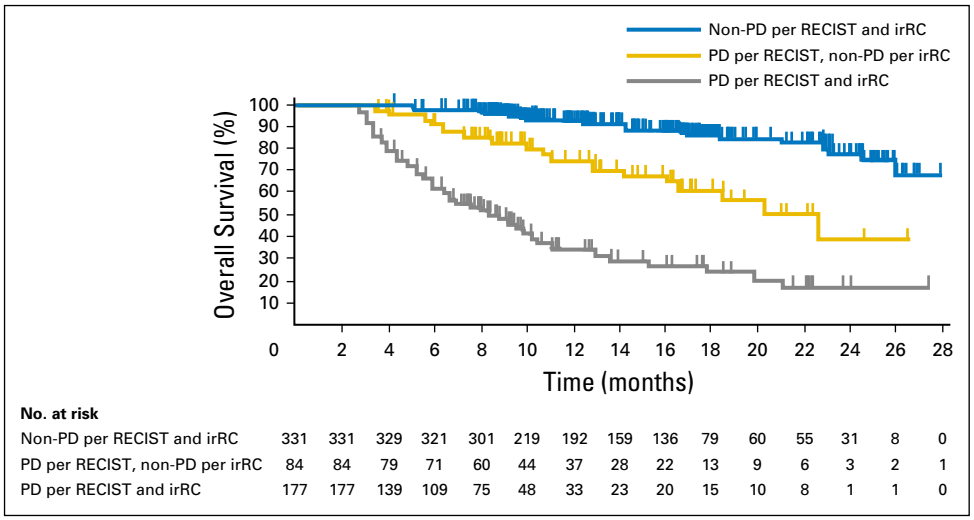

Fig 5. Kaplan-Meier estimates of overall survival on the basis of best overall response per RECIST v1.1 and irRC in patients who survived ≥ 12 weeks (n = 592). irRC, immune-related response criteria; non-PD, non-progressive disease; PD, progressive disease; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

Prospective evaluations of irRC and RECIST v1.1 for patients who receive pembrolizumab and other immunotherapeutic agents are needed. Furthermore, the greater awareness of the response patterns witnessed previously for ipilimumab and now with pembrolizumab and other approved and developmental anti–PD-1 and PD-L1 agents[20,21] has led to growing momentum within the immuno-oncology community to refine imaging criteria. One proposed approach is to modify irRC to follow the same response categories as RECIST and to shift to unidimensional measurements. Alternatively, RECIST could be modified such that after initial evidence of radiologic progression, treatment may be continued until progressive disease is confirmed by imaging performed > 4 weeks later. New lesions could be effectively followed as nontarget lesions instead of as immediate progressive disease. The details of confirmation of progression could be further delineated based on modeling data. To simplify and standardize these assessments, use of unidimensional measurements and adoption of modified RECIST criteria for immune therapy should also be considered. As a community, we must advocate the sharing of clinical data from multiple studies and immunotherapy agents to greatly hasten and provide rigor to this effort.[22]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

Table A1. Distribution of Target Lesions in Patients With Atypical Response Patterns

Patient No.	Lymph Node	Non-Lymph Node
Early pseudoprogression		
1	Inguinal	—
2	—	Peritoneum/omentum
3	—	Kidney, pleura
4	Supraclavicular	—
5	—	Lung
6	—	Liver
7	—	Liver, adnexa
8	—	Lung
9	—	Peritoneum/omentum, adrenal gland
10	—	Breast, abdominal wall, chest wall, liver, skin
11	—	Liver
12	—	Lung
13	Axillary	Adrenal gland, lung, mediastinum, gallbladder, peritoneum/omentum, retroperitoneum
14	—	Lung
15	Cervical	Adrenal gland
Delayed pseudoprogression		
1	Axillary, inguinal	—
2	—	Adrenal gland
3	Pelvic	—
4	—	Liver, peritoneum
5	—	Kidney
6	—	Liver, lung
7	Cervical	—
8	Axillary	Peritoneum/omentum, retroperitoneum, abdominal wall
9	Hilar	Peritoneum/omentum

Table A2. Key Baseline Characteristics for Patients With Atypical Response

	Early Pseudoprogression (n = 15), No. (%)	Delayed Pseudoprogression (n = 9), No. (%)	Total (n = 24), No. (%)
Ipilimumab exposure			
Naive	13 (87)	6 (67)	19 (79)
Refractory	2 (13)	2 (22)	4 (17)
Treated	0 (0)	1 (11)	1 (4)
PD-L1 status			
Positive	4 (27)	3 (33)	7 (29)
Negative	2 (13)	1 (11)	3 (13)
Unknown	9 (60)	5 (56)	14 (58)
Baseline tumor size (mm), median (range)	56.1 (10.6-152.1)	49.1 (19.6-242.0)	52.6 (10.6-242.0)

Abbreviation: PD-L1, programmed death receptor 1 ligand.

Table A3. Overall Survival by Type of Progressive Disease

	PD Per RECIST v1.1/non-PD per irRC (n = 84)		PD Per RECIST v1.1 and irRC (n = 177)	
	Patients, No. (%)	OS (months), Median (95% CI)	Patients, No. (%)	OS (months), Median (95% CI)
Target lesion growth > 20%	10 (11.9)	20.3 (7.0 to NR)	11 (6.2)	10.8 (4.2 to NR)
Unequivocal nontarget lesion growth	13 (15.5)	NR (18.5 to NR)	9 (5.1)	9.6 (4.4 to NR)
Unequivocal new lesion	36 (42.9)	22.5 (14.0 to NR)	30 (16.9)	15.4 (6.7 to NR)
Target lesion growth > 20% + unequivocal nontarget lesion growth	3 (3.6)	NR (NR to NR)	20 (11.3)	9.5 (5.6 to 13.1)
Target lesion growth > 20% + unequivocal new lesion	4 (4.8)	NR (5.8 to NR)	14 (7.9)	9.4 (3.4 to 10.3)
Unequivocal nontarget lesion growth + unequivocal new lesion	10 (11.9)	12.8 (3.4 to NR)	29 (16.4)	9.1 (5.2 to 20.0)
Target lesion growth > 20% + unequivocal nontarget lesion growth + unequivocal new lesion	6 (7.1)	10.6 (6.3 to NR)	25 (14.1)	6.4 (4.9 to 6.8)
Nonevaluable	2 (2.4)	NR (NR to NR)	39 (22.0)	5.8 (3.8 to 19.8)

Abbreviations: irRC, immune-related response criteria; NR, not reached; OS, overall survival; PD, progressive disease; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.