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ORIGINAL ARTICLE

Pembrolizumab for locally advanced and recurrent/metastatic cutaneous squamous cell carcinoma (KEYNOTE-629 study): an open-label, nonrandomized, multicenter, phase II trial

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Background: Pembrolizumab demonstrated clinically meaningful and durable antitumor activity with a manageable safety profile in recurrent/metastatic (R/M) cutaneous squamous cell carcinoma (cSCC).

Patients and methods: KEYNOTE-629 was a global, open-label, nonrandomized, phase II trial of patients with locally advanced (LA) or R/M cSCC conducted at 59 centers. Eligible patients received intravenous pembrolizumab 200 mg every 3 weeks for up to 35 cycles. Primary endpoint was objective response rate (ORR), defined as the percentage of patients with a complete (CR) or partial response (PR), by blinded independent central review as per Response Evaluation Criteria in Solid Tumors 1.1. Secondary endpoints included duration of response (DOR), disease control rate, progression-free survival, overall survival, and safety and tolerability. Efficacy and safety were analyzed in patients who were treated with at least one dose of pembrolizumab.

Results: Between 29 November 2017 and 25 September 2019, 159 patients were enrolled and treated with pembrolizumab (LA cohort, $n = 54$; R/M cohort, $n = 105$). The median time from the first dose to data cut-off date (29 July 2020) was 14.9 [interquartile range (IQR), 12.6-17.2] months for the LA cohort and 27.2 (IQR, 25.6-29.2) months for the R/M cohort. In the LA cohort, ORR was 50.0% [95% confidence interval (CI), 36.1% to 63.9%], including 16.7% of patients with a CR and 33.3% with a PR. In the R/M cohort, ORR was 35.2% (95% CI, 26.2% to 45.2%), including 10.5% of patients with a CR and 24.8% with a PR. Median DOR was not reached in either cohort. Grade 3-5 treatment-related adverse events occurred in 11.9% of patients.

Conclusions: The robust antitumor activity of pembrolizumab in both LA and R/M cSCC was confirmed and demonstrated to be durable without unexpected safety signals. Our findings establish pembrolizumab as a promising treatment option for cSCC.

Key words: cutaneous squamous cell carcinoma, programmed cell death protein 1 (PD-1), immunotherapy, pembrolizumab

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common non-melanoma skin cancer (NMSC), representing ~20% of all NMSCs and 20% of all skin cancer-related mortalities.[1,2] Risk factors for cSCC include exposure to ultraviolet (UV) radiation, ionizing radiation, and chemical carcinogens; the presence of chronic wounds

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or scars; fair skin; genetic conditions; and human papillomavirus infections.[3]

Although most patients with cSCC can be treated with surgical resection of the primary site, incurable and recurrent disease tends to metastasize,[4] involving regional lymph nodes in ~85% of cases and distant sites in the remaining 15% of cases.[5] Long-term prognosis of metastatic disease is extremely poor, with 10-year survival rates <20% for patients having regional lymph node metastasis and <10% for those having distant metastases.[5]

High tumor mutational burden (TMB) is a predictive biomarker for immunotherapy efficacy, and pembrolizumab was approved by the USA Food and Drug Administration (FDA) for treating unresectable or metastatic TMB-high solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.[6-8] NMSC, including basal cell carcinoma (BCC) and cSCC, has high TMB resultant from UV radiation-induced DNA damage. Because of their high TMB, NMSCs may be responsive to immunotherapy.[9,10] In a phase II study, an objective response rate (ORR) of 31% was observed with the anti-programmed cell death protein 1 (PD-1) agent cemiplimab in patients with locally advanced (LA) BCC who were previously treated with a hedgehog pathway inhibitor.[11] Cemiplimab also demonstrated antitumor activity and acceptable safety in patients with metastatic cSCC with an ORR of 47%[12] and in LA cSCC with an ORR of 44%[13] in a phase II study and is approved for patients with metastatic or LA cSCC who are not candidates for curative surgery or curative radiation by both the USA FDA and European Medicines Agency (EMA). These findings demonstrate that targeting the PD-1 pathway is an effective option for recurrent/metastatic (R/M) or unresectable LA cSCC. In KEYNOTE-629, pembrolizumab demonstrated clinically meaningful and durable antitumor activity with a manageable safety profile in patients with R/M cSCC based on the first interim analysis (IA).[14] Thus, pembrolizumab was approved for R/M cSCC that is not curable by surgery or radiation by the USA FDA.[8] In the ongoing multicenter, phase II study of pembrolizumab in patients with unresectable squamous cell CARcinoma of the SKIN (CARSKIN), pembrolizumab showed robust and durable antitumor activity as first-line therapy in patients with chemotherapy-naïve unresectable cSCC (locally or regionally advanced or metastatic).[15] Additionally, pembrolizumab is approved for Merkel cell carcinoma, another type of aggressive NMSC also associated with UV exposure and viral etiology, by the USA FDA.[16] Pembrolizumab is also approved as monotherapy or in combination with chemotherapy as first-line therapy for metastatic or unresectable, recurrent head and neck squamous cell carcinoma by the USA FDA and EMA.[17]

Here, we report results of the second IA of KEYNOTE-629, including initial data for the LA cohort, which led to the July 2021 USA FDA approval of pembrolizumab for LA sCC that is not curable by surgery or radiation,[8] and updated data for the R/M cohort.

PATIENTS AND METHODS

Study design and patients

KEYNOTE-629 is a phase II, multicenter, nonrandomized, single-arm, open-label trial conducted at 59 centers in 10 countries (USA, Canada, Mexico, Australia, Israel, Norway, France, Spain, Germany, and the UK), including an LA cohort and an R/M cohort. Eligible patients were ≥18 years old and had histologically confirmed LA or R/M cSCC with measurable disease by blinded independent central review (BICR) as per Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), and an Eastern Cooperative Oncology Group performance status score of 0 or 1. Patients in the LA cohort were required to be ineligible for surgical resection, must have undergone prior radiation therapy (to the index site), or were deemed ineligible for radiation therapy. Patients in the R/M cohort had locoregionally recurrent disease not curable by surgery/radiation or distant metastatic disease. In March 2018, the protocol was amended to include first-line patients in the R/M cohort.

The study protocol (Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2021.07.008) and amendments were approved by the appropriate institutional review boards and ethics review committees. The study was conducted in accordance with the protocol, Good Clinical Practice guidelines, and the Declaration of Helsinki. All patients provided written informed consent.

Treatment and masking

This is a single-arm, open-label trial. All enrolled patients were allocated to receive pembrolizumab 200 mg intravenously over 30 minutes every 3 weeks.

Procedures

Patients received pembrolizumab for up to 35 cycles (~2 years) or until disease progression, unacceptable toxicity, consent withdrawal, investigator decision, or other discontinuation criteria were met. Treatment could continue until disease progression was confirmed ≥4 weeks after the first tumor imaging indicating progressive disease in clinically stable patients. Patients who attained complete response (CR) and discontinued treatment or who discontinued treatment after 24 months for reasons other than progression or intolerability could be eligible for up to 17 cycles of pembrolizumab (second course) after progression at the discretion of the investigator. Response was assessed every 6 weeks for the first 12 months and then every 9 weeks afterward with radiologic/photographic imaging by BICR as per RECIST version 1.1 until disease progression, the start of new anticancer treatment, consent withdrawal, death, or notification by the sponsor, whichever occurred first. Survival status was assessed every 12 weeks and at any time upon the sponsor's request.

Adverse events (AEs) were assessed throughout treatment and for 30 days thereafter (90 days for serious AEs; 30 days if a new anticancer therapy started, whichever was

earlier). Treatment-related serious AEs were reported at any time throughout or after the study.

Programmed death-ligand 1 (PD-L1) expression was assessed by immunohistochemistry (IHC) of newly obtained or archival tumor samples with the PD-L1 IHC 22C3 pharmDx kit (Agilent Technologies, Inc., Carpinteria, CA). PD-L1 expression was measured by the combined positive score (CPS) and tumor proportion score (TPS). The full protocol is provided in the Supplementary Appendices, available at https://doi.org/10.1016/j.annonc.2021.07.008.

Outcomes

The primary endpoint was ORR, defined as the proportion of patients with a confirmed CR or partial response (PR) (as per RECIST 1.1 by BICR). Secondary endpoints included duration of response (DOR) (i.e. time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurred first), disease control rate (DCR) (i.e. the proportion of patients with a CR or PR or stable disease for ≥12 weeks), and progression-free survival (PFS) (i.e. time from the first day of study treatment to first documented disease progression or death, whichever occurred first), all as per RECIST 1.1 by BICR; overall survival (OS) (i.e. time from the first day of study treatment to death from any cause); and safety and tolerability.

Statistical analysis

The planned sample size was up to ∼50 patients with LA unresectable cSCC and 100 patients with R/M cSCC. Based on calculations as per the exact binomial method by Clopper and Pearson, the study has >95% power to have the lower bound of the 95% confidence interval (CI) >15%, assuming an expected ORR of ≥30% for the R/M cohort, and >84% power to have the lower bound of the 95% CI >20%, assuming an expected ORR of ≥40% for the LA cohort (Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2021.07.008).

IAs were prespecified to be carried out periodically to assess efficacy and safety. The first IA was conducted ∼18 months after the start of the study, and results were reported for the R/M cohort.[14] The results reported here were based on the second IA, which included new data from the LA cohort (∼21 months after the start of the cohort) and updated data from the R/M cohort (∼33 months after study initiation, representing ∼15 months of additional follow-up since the first IA).

Efficacy and safety were assessed in patients who received ≥1 dose of study treatment. DOR was assessed in responders. Because this was an open-label, single-arm study, there was no hypothesis testing or multiplicity adjustment. The estimate and 95% CI of the ORR and DCR were based on the Clopper—Pearson method. The Kaplan—Meier method was used to estimate DOR, PFS, and OS. Prespecified subgroup analyses for ORR by age category (<65 versus ≥65 years), sex (female versus male), race (white versus all others), and region (North America versus European Union versus rest of the world) were conducted. Post hoc analyses of efficacy by the line of therapy for pembrolizumab (first line versus second line or beyond) were carried out for the R/M cohort; post hoc analyses of ORR by PD-L1 status (CPS <1, CPS ≥1; TPS <50%, TPS ≥50%) were carried out for both the LA and R/M cohorts.

This study is registered with ClinicalTrials.gov, NCT03284424. The data cut-off date was 29 July 2020; the study is ongoing for follow-up but is no longer enrolling patients.

RESULTS

Patients

Between 29 November 2017 and 25 September 2019, 159 patients met the eligibility criteria and were enrolled (LA, $n = 54$; R/M, $n = 105$) after 238 patients were screened. The median time from the first dose to data cut-off date was 14.9 [interquartile range (IQR), 12.6-17.2] months for the LA cohort and 27.2 (IQR, 25.6-29.2) months for the R/M cohort. All patients received ≥1 dose of pembrolizumab. In the LA cohort, 20 (37.0%) patients were still receiving pembrolizumab, and 34 (63.0%) had discontinued. In the R/M cohort, 20 (19.0%) patients completed pembrolizumab, 2 (1.9%) were still receiving treatment, and 83 (79.0%) had discontinued (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.07.008). The most common reason for discontinuation in both cohorts was disease progression. Baseline demographics and disease characteristics are shown in Table 1. No patients received pembrolizumab as a second course as of the data cut-off date.

Efficacy

In the LA cohort, 27 of 54 patients achieved a confirmed response, with an ORR of 50.0% (95% CI, 36.1% to 63.9%); 9 patients had CR (16.7%) and 18 had PR (33.3%). Stable disease was observed in 13 patients, including 8 patients who achieved stable disease for ≥12 weeks. DCR was 64.8% ($n = 35$; 95% CI, 50.6% to 77.3%; Table 2). ORR was generally consistent across subgroups analyzed (Supplementary Figure S2A, available at https://doi.org/10.1016/j.annonc.2021.07.008). Of the 48 patients with evaluable baseline and post-baseline imaging assessments, 40 (83.3%) had a reduction in target lesion size from baseline, including 32 (66.7%) patients who had a ≥30% reduction (Figure 1A). Median time to response was 2.6 (IQR, 1.4-3.6) months, with the initial response observed by week 6 for 14 of the 27 confirmed responses (Figure 1B). Median DOR was not reached (NR) (95% CI, NR-NR) (Supplementary Figure S3A, available at https://doi.org/10.1016/j.annonc.2021.07.008). Of the 27 responders with a confirmed response, 77.8% had ongoing responses as of the data cut-off date. As per Kaplan—Meier estimates, 88.1% and 84.1% of responders had responses that lasted ≥6 months and ≥12 months, respectively (Table 2). Some patients experienced rapid tumor reduction after 6 weeks of pembrolizumab treatment (Figure 2A and Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2021.07.008).

Table 1. Baseline demographics and disease characteristics

Characteristic, *n* (%)	LA cSCC (*n* = 54)	R/M cSCC (*n* = 105)	Total (*n* = 159)
Median age (IQR), years	75.5 (67-83)	72.0 (61-81)	74.0 (62-82)
Male	39 (72.2)	80 (76.2)	119 (74.8)
Region			
North America	13 (24.1)	25 (23.8)	38 (23.9)
European Union	30 (55.6)	50 (47.6)	80 (50.3)
Rest of the world	11 (20.4)	30 (28.6)	41 (25.8)
ECOG performance status			
0	22 (40.7)	36 (34.3)	58 (36.5)
1	32 (59.3)	69 (65.7)	101 (63.5)
PD-L1[a]			
CPS ≥1	46 (85.2)	69 (65.7)	115 (72.3)
CPS <1	5 (9.3)	10 (9.5)	15 (9.4)
TPS ≥50%	10 (18.5)	23 (21.9)	33 (20.8)
TPS <50%	41 (75.9)	56 (53.3)	97 (61.0)
Overall cancer staging			
I	1 (1.9)	0	1 (0.6)
II	7 (13.0)	5 (4.8)	12 (7.5)
III	25 (46.3)	14 (13.3)	39 (24.5)
IV	21 (38.9)	86 (81.9)	107 (67.3)
Primary tumor staging			
T1	3 (5.6)	16 (15.2)	19 (11.9)
T2	12 (22.2)	13 (12.4)	25 (15.7)
T3	27 (50.0)	24 (22.9)	51 (32.1)
T4	11 (20.4)	29 (27.6)	40 (25.2)
TX	1 (1.9)	23 (21.9)	24 (15.1)
Nodal involvement staging			
N0	37 (68.5)	38 (36.2)	75 (47.2)
N1	4 (7.4)	18 (17.1)	22 (13.8)
N2a	1 (1.9)	7 (6.7)	8 (5.0)
N2b	4 (7.4)	13 (12.4)	17 (10.7)
N2c	1 (1.9)	5 (4.8)	6 (3.8)
N3	6 (11.1)	14 (13.3)	20 (12.6)
NX	1 (1.9)	10 (9.5)	11 (6.9)
Metastasis staging			
M0	54 (100.0)	47 (44.8)	101 (63.5)
M1	0	58 (55.2)	58 (36.5)
Disease status			
LA	54 (100.0)	0	54 (34.0)
Locally recurrent only	0	47 (44.8)	47 (29.6)
Metastatic only	0	25 (23.8)	25 (15.7)
Locally recurrent and metastatic	0	33 (31.4)	33 (20.8)
Presence of ulceration	27 (50.0)	47 (44.8)	74 (46.5)
Presence of synchronous primary lesion	10 (18.5)	13 (12.4)	23 (14.5)
Prior systemic therapy for curative intent for LA cSCC	12 (22.2)[b]	NA	12 (7.5)
≥1 prior systemic therapy for R/M cSCC	NA	91 (86.7)[c]	91 (57.2)

CPS, combined positive score; cSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; LA, locally advanced; NA, not applicable; PD-L1, programmed death-ligand 1; R/M, recurrent/metastatic; TPS, tumor proportion score.

[a] Current laboratory standards for tumor samples collected for biomarker analysis state that the stability of a cut slide is 6 months for PD-L1 staining. In the LA cohort, three samples did not have PD-L1 results due to staining/assay errors. In the R/M cohort, samples from 26 patients were analyzed outside the defined 6-month PD-L1 stability period and thus were not available for the baseline biomarker analysis. CPS was defined as the number of PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. TPS was defined as the percentage of viable tumor cells that showed partial or complete membrane staining of PD-L1 relative to all viable tumor cells in the sample.

[b] Three of the 12 patients received concurrent chemoradiotherapy.

[c] Thirty-five of the 91 patients received prior systemic therapy with curative intent, and 17 of the 35 patients had concurrent chemoradiotherapy; among the remaining 56 of the 91 patients, 27 had prior chemotherapy for recurrent incurable disease and 29 had prior systemic therapy for metastatic incurable disease. Across both cohorts, the most frequently reported (incidence ≥15%) prior systemic oncologic therapies were carboplatin (32.7%), cetuximab (26.4%), cisplatin (23.3%), and fluorouracil (19.5%).

In the R/M cohort, 37 of 105 patients achieved a response, with an ORR of 35.2% (95% CI, 26.2% to 45.2%); 11 patients had CR (10.5%) and 26 had PR (24.8%). Stable disease was observed in 30 patients, including 18 patients who achieved stable disease for ≥12 weeks. DCR was 52.4% (*n* = 55; 95% CI, 42.4% to 62.2%; Table 2). ORR was generally consistent across subgroups analyzed (Supplementary Figure S2B, available at https://doi.org/10.1016/j.annonc.2021.07.008). In patients who received pembrolizumab as first-line therapy (*n* = 14) versus those who received pembrolizumab as second-line therapy or beyond (*n* = 91), median time to response was 1.4 versus 2.1 months, and the ORR was higher (50.0% versus 33.0%) (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.07.008). Of the 95 patients with evaluable baseline and post-baseline imaging assessments for the sum of the longest diameters of target lesions, 74 (77.9%) had a reduction in target lesion size from baseline, including 56 (58.9%) patients who had a ≥30% reduction (Supplementary Figure S5A, available at https://doi.org/

Table 2. Summary of best overall response as per RECIST v1.1 by BICR

	LA cSCC (n = 54)	R/M cSCC (n = 105)	Total (n = 159)
ORR,[a] % (95% CI)	50.0 (36.1-63.9)	35.2 (26.2-45.2)	40.3 (32.6-48.3)
DCR,[b] % (95% CI)	64.8 (50.6-77.3)	52.4 (42.4-62.2)	56.6 (48.5-64.4)
Best overall response, n (%)			
CR	9 (16.7)	11 (10.5)	20 (12.6)
PR	18 (33.3)	26 (24.8)	44 (27.7)
Stable disease	13 (24.1)	30 (28.6)	43 (27.0)
Stable disease ≥12 weeks	8 (14.8)	18 (17.1)	26 (16.4)
Progressive disease	9 (16.7)	28 (26.7)	37 (23.3)
Not evaluable[c]	1 (1.9)	2 (1.9)	3 (1.9)
No assessment[d]	4 (7.4)	8 (7.6)	12 (7.5)
Time to response,[a] median (IQR), months	2.6 (1.4-3.6)	1.6 (1.4-3.1)	2.0 (1.4-3.3)
DOR,[a] median (95% CI), months	NR (NR-NR)	NR (22.4-NR)	NR (23.3-NR)
Patients with extended response duration (as per Kaplan–Meier estimates; %)			
≥6 months	88.1	80.7	83.7
≥12 months	84.1	77.8	80.3

BICR, blinded independent central review; CI, confidence interval; CR, complete response; cSCC, cutaneous squamous cell carcinoma; DCR, disease control rate; DOR, duration of response; IQR, interquartile range; LA, locally advanced; NR, not reached; ORR, objective response rate; PR, partial response; R/M, recurrent/metastatic.
[a] Includes patients with CRs and PRs.
[b] Includes stable disease ≥12 weeks, PRs, and CRs.
[c] Post-baseline assessment available but not evaluable for response.
[d] No post-baseline assessment available for response evaluation.

10.1016/j.annonc.2021.07.008). Median time to response was 1.6 (IQR, 1.4-3.1) months, with the initial response observed by week 6 for 20 of the 37 confirmed responses (Supplementary Figure S5B, available at https://doi.org/10.1016/j.annonc.2021.07.008). Median DOR was NR (95% CI, 22.4 months-NR) (Supplementary Figure S3B, available at https://doi.org/10.1016/j.annonc.2021.07.008). Of the 37 responders with a confirmed response, 48.6% had ongoing responses as of the data cut-off date. As per Kaplan–Meier estimates, 80.7% and 77.8% of responders had extended responses that lasted ≥6 months and ≥12 months, respectively (Table 2). Rapid tumor reduction was observed after 6 weeks of pembrolizumab treatment in some patients (Figure 2B and Supplementary Figure S6, available at https://doi.org/10.1016/j.annonc.2021.07.008).

In the total population, 64 of 159 patients achieved a response, with an ORR of 40.3% (95% CI, 32.6% to 48.3%); 20 patients had CR and 44 had PR. Stable disease was observed in 43 patients, including 26 patients who achieved stable disease for ≥12 weeks. DCR was 56.6% (n = 90; 95% CI, 48.5% to 64.4%; Table 2). ORR was generally consistent across subgroups analyzed. Although responses were observed regardless of PD-L1 expression level, an increase in ORR was observed in patients with CPS ≥1 or TPS ≥50% (Supplementary Table S4 and Figure S2C, available at https://doi.org/10.1016/j.annonc.2021.07.008). Of the 143 patients with evaluable baseline and post-baseline imaging assessments for the sum of the longest diameters of target lesions, 114 (79.7%) had a reduction in target lesion size from baseline, including 88 (61.5%) patients who had a ≥30% reduction. Median time to response was 2.0 (IQR, 1.4-3.3) months, with the initial response observed by week 6 for 30 of the 64 confirmed responses. Median DOR was NR (95% CI, 23.3 months-NR). Of the 64 responders with a confirmed response, 60.9% had ongoing responses as of the data cut-off date. As per Kaplan–Meier estimates, 83.7% and 80.3% of responders had extended responses that lasted ≥6 months and ≥12 months, respectively (Table 2).

In the LA cohort, 24 of 54 patients (44.4%) had experienced disease progression or died. Median PFS was NR (95% CI, 5.5 months-NR), and estimated PFS rates at 6 and 12 months were 60.9% (95% CI, 46.2% to 72.8%) and 54.4% (95% CI, 39.6% to 67.0%), respectively (Figure 3A). Of the 54 patients, 14 (25.9%) had died. Median OS was NR (95% CI, NR-NR), and the estimated OS rate at both 12 and 18 months was 73.6% (95% CI, 59.5% to 83.4%) (Figure 3B).

In the R/M cohort, 69 of 105 patients (65.7%) had experienced disease progression or died. Median PFS was 5.7 (95% CI, 3.1-8.5) months, and estimated PFS rates at 6 and 12 months were 49.4% (95% CI, 39.3% to 58.7%) and 36.4% (95% CI, 27.0% to 45.9%), respectively (Figure 3C). Of the 105 patients, 59 patients (56.2%) had died. Median OS was 23.8 (95% CI, 13.4-29.8) months, and the OS rates at 12 and 24 months were 61.0% (95% CI, 50.9% to 69.5%) and 48.4% (95% CI, 38.5% to 57.6%), respectively (Figure 3D).

In the total population, 93 of 159 patients (58.5%) had experienced disease progression or died. Median PFS was 7.8 (95% CI, 5.3-12.3) months, and estimated PFS rates at 6 and 12 months were 53.3% (95% CI, 45.0% to 60.9%) and 42.4% (95% CI, 34.3% to 50.2%), respectively. Of the 159 patients, 73 patients (45.9%) had died. Median OS was 26.4 months (95% CI, 19.5 months-NR), and the OS rates at 12 and 24 months were 65.1% (95% CI, 57.1% to 72.0%) and 52.7% (95% CI, 43.8% to 60.9%), respectively.

Safety

In the total population, 110 (69.2%) experienced one or more treatment-related AE (grade 3-5, 11.9%). There were 14 (8.8%) patients who discontinued pembrolizumab because of treatment-related AEs. Two patients experienced a treatment-related fatal AE, including cranial nerve disorder reported in the first IA[14] and immune-mediated colitis

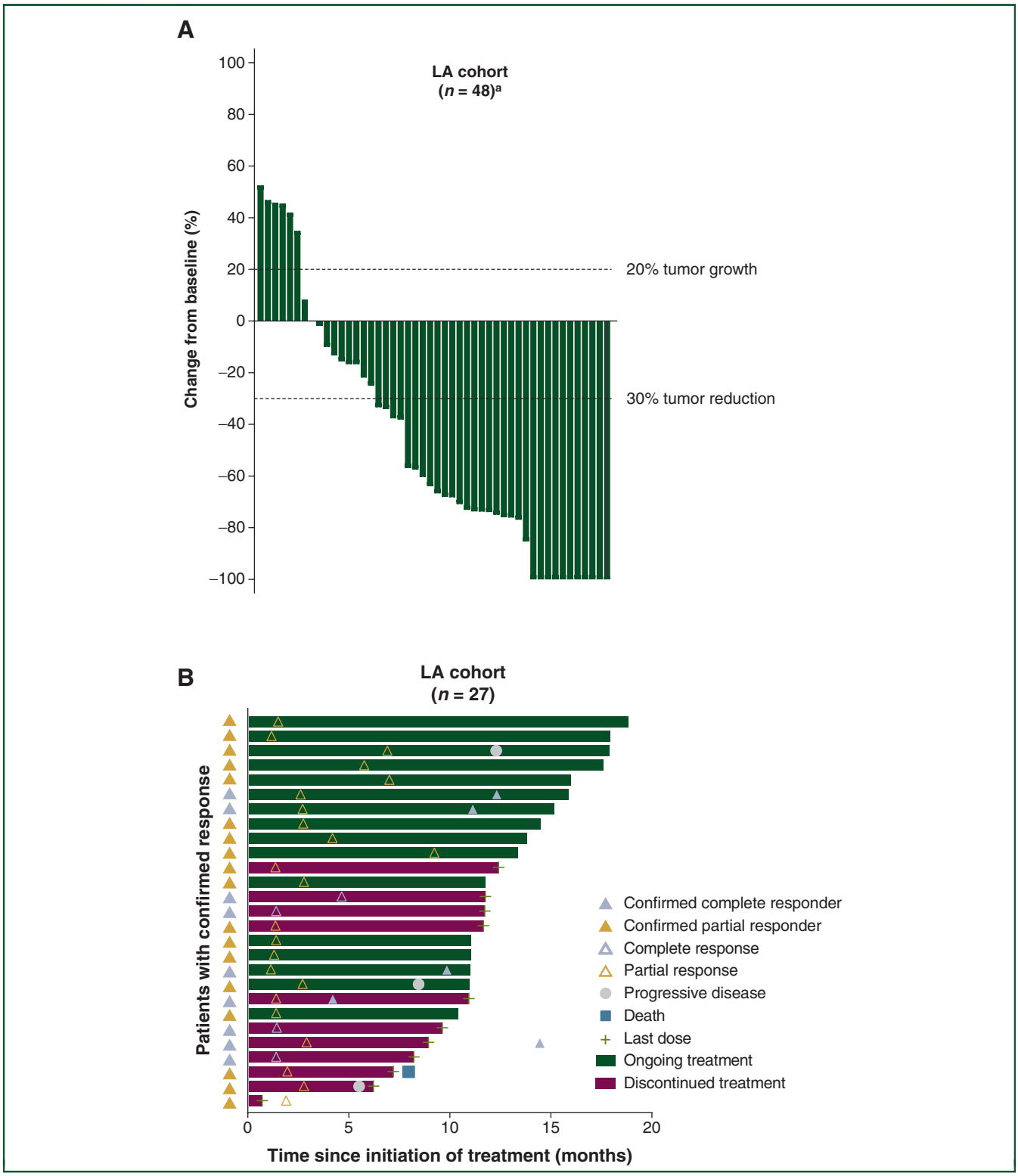

Figure 1. Characteristics of tumor response to pembrolizumab in patients with LA cSCC.
(A) Best percentage change from baseline in target lesion. A total of 48 patients had baseline and post-baseline imaging assessments for the sum of the longest diameters of target lesions. (B) Duration of study treatment and response in responders ($n = 27$). Each horizontal bar represents one patient. Open triangles within each bar indicate the first observed response and time point; solid blue triangles on the *y*-axis indicate confirmed response by BICR. For patients with confirmed CR after an initial PR, solid triangles within the bar indicate when the CR was confirmed.
BICR, blinded independent central review; CR, complete response; cSCC, cutaneous squamous cell carcinoma; LA, locally advanced; PR, partial response.
[a] Included patients who had ≥1 evaluable post-baseline tumor assessment.

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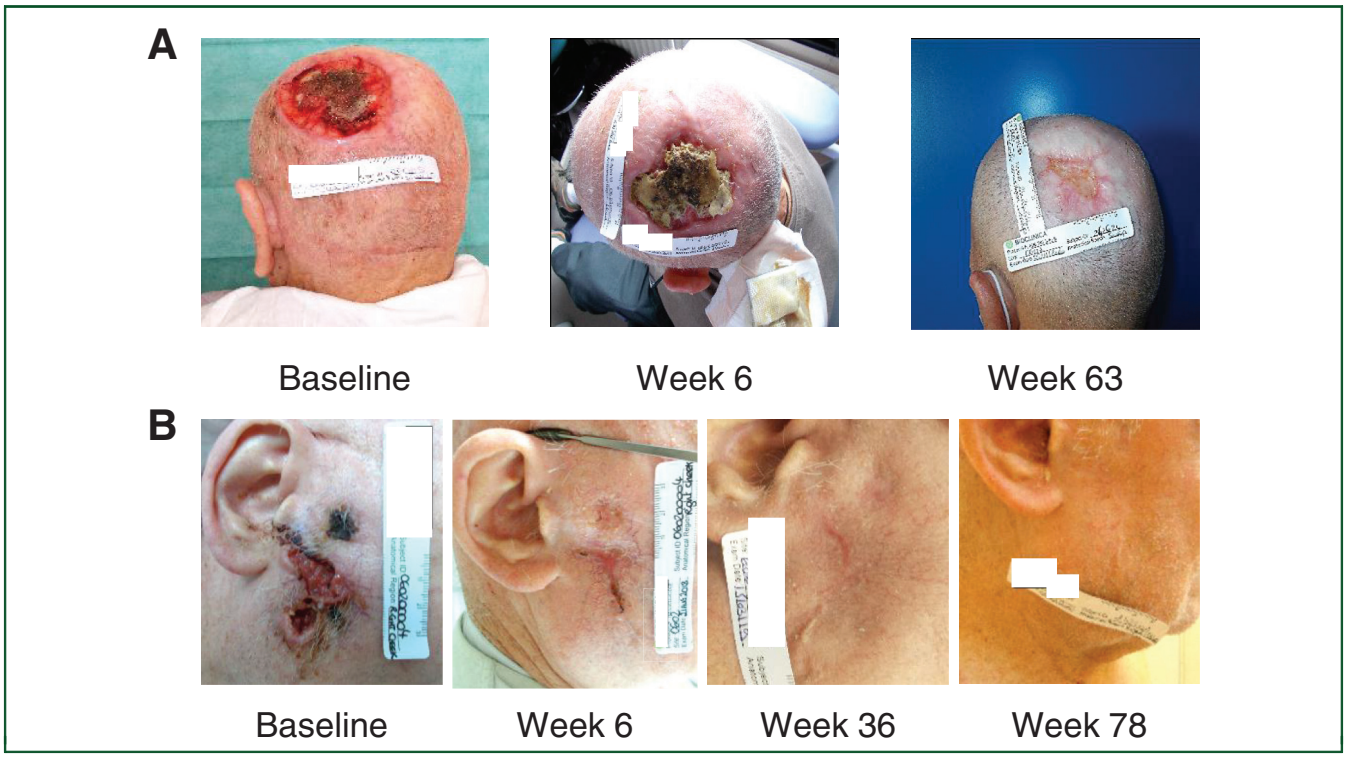

Figure 2. Effects of pembrolizumab monotherapy in patients with LA (A) and R/M (B) cSCC.
(A) A 76-year-old man with unresectable LA cSCC at the left scalp who previously underwent surgery and was not eligible for radiation therapy at baseline (left), after 6 weeks of treatment (middle), and at 63 weeks (right) (best response: CR). (B) A 55-year-old man with R/M cSCC at the preauricular/posterior right cheek who previously received systemic therapy and radiation at baseline (left), after 6 weeks of treatment (left middle), after 36 weeks of treatment (right middle), and after 78 weeks of treatment (right). After week 36, response improved from PR to CR by week 78. Weeks are time since the date of the first dose of pembrolizumab.
CR, complete response; cSCC, cutaneous squamous cell carcinoma; LA, locally advanced; PR, partial response; R/M, recurrent/metastatic.

(both in the R/M cohort). The most common treatment-related AEs are shown in Table 3. Immune-mediated AEs and infusion reactions occurred in 22.6% of patients and were mostly of grade 1-2 severity; grade 3-5 immune-mediated AEs that occurred in more than one patient were severe skin reactions ($n = 4$), colitis ($n = 2$), and hepatitis ($n = 2$). Common treatment-emergent AEs and serious treatment-related AEs are summarized in Supplementary Tables S5 and S6, available at https://doi.org/10.1016/j.annonc.2021.07.008.

DISCUSSION

In this second IA of KEYNOTE-629, with a median follow-up of >1 year in the LA cohort and ~2 years in the R/M cohort, pembrolizumab not only confirmed rapid, robust activity, but also showed durable efficacy and promising survival in cSCC. Safety was manageable in both LA and R/M cSCC. In the LA cohort, ORR was 50.0%, including 16.7% of patients who had a CR, and 84.1% of responses estimated to last ≥12 months. In the R/M cohort, ORR was 35.2%, including 10.5% of patients who had a CR, and 77.8% of responses estimated to last ≥12 months; from the first to second IA, similar ORR and DCR were observed. However, seven more patients achieved CR from PR, representing an increase from 3.8% to 10.5%,[14] indicating that the benefit of immunotherapy can increase over time in responders.

Pembrolizumab treatment resulted in clinical benefit in PFS and OS in both cohorts; in the R/M cohort, survival benefit remained with the longer follow-up and more mature data from the first IA. Subgroup analyses by the line of therapy in the R/M cohort showed evidence of more robust and potentially rapid clinical activity in patients receiving pembrolizumab as first-line versus as second-line therapy or beyond [ORR: 50.0% (CR, 21.4%) versus 33.0% (CR, 8.8%); median time to response, 1.4 versus 2.1 months]; these findings were consistent with the first IA.[14] Although clinical activity was seen in the total population regardless of PD-L1 status, increasing responses were observed over the continuum of increasing PD-L1 expression. Despite the high percentage of elderly patients in our study (≥65 years old, 73.6%), AEs were generally consistent with the established safety profile of pembrolizumab monotherapy. Most treatment-related AEs were mild or moderate, with no new safety concerns identified. Based on these findings, the USA FDA approved pembrolizumab for the treatment of LA cSCC that is not curable by surgery or radiation in July 2021.

Several anti-PD-1/PD-L1 agents, including pembrolizumab,[14,15,18] cemiplimab,[12,13,19] nivolumab,[20] and cosibelimab,[21,22] have demonstrated antitumor activity in cSCC. Among these agents, cemiplimab is approved for patients with metastatic or LA cSCC who are not candidates

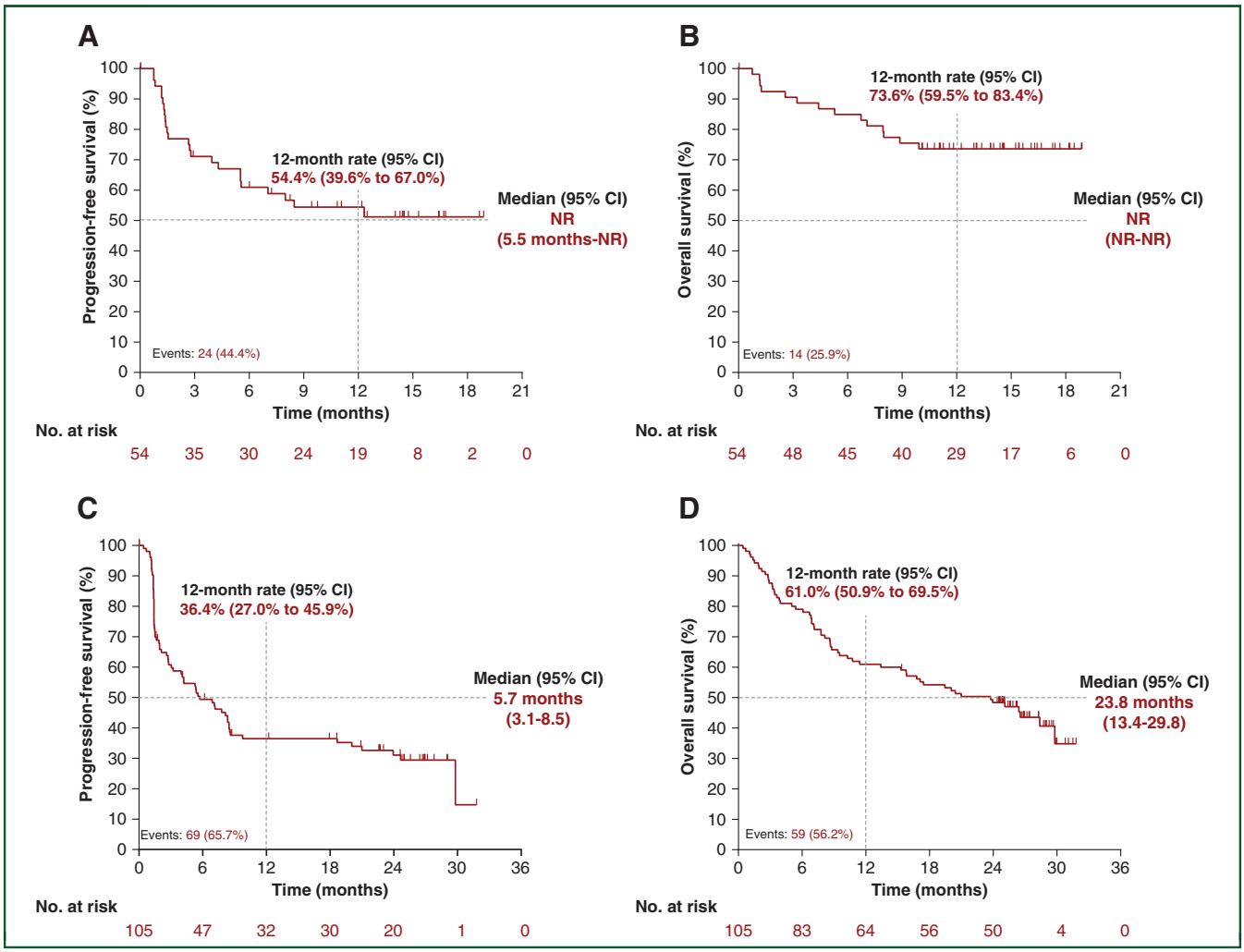

Figure 3. Kaplan–Meier curves for PFS (as per RECIST 1.1 by BICR) and OS.
(A) PFS in the LA cohort. (B) OS in the LA cohort. (C) PFS in the R/M cohort. (D) OS in the R/M cohort.
BICR, blinded independent central review; CI, confidence interval; cSCC, cutaneous squamous cell carcinoma; LA, locally advanced; NR, not reached; OS, overall survival; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumors; R/M, recurrent/metastatic.

for curative surgery or radiation. The European Interdisciplinary Guidelines by multidisciplinary experts from the European Dermatology Forum, the European Association of Dermato-Oncology, and the European Organization for Research and Treatment of Cancer provided the grade A recommendation for patients with LA or metastatic cSCC who are not candidates for curative surgery or curative radiation to receive first-line treatment with a PD-1 antibody.[23] The phase II R2810-ONC-1540 study showed overall response with cemiplimab in 28 (47.4%) of 59 patients (including 4 CRs) with metastatic cSCC[12] and in 34 (44%) of 78 patients (including 13% CR) with unresectable LA cSCC.[13] Notably, 44% of patients with metastatic cSCC received cemiplimab as the first-line treatment.[12] Cross-trial comparisons should always be interpreted with caution, particularly because cSCC cohort definitions were not exactly the same; however, pembrolizumab showed a high ORR and deep responses in LA cSCC that were generally comparable to cemiplimab in R/M cSCC.

Study limitations include the single-arm design and the small number of patients who received pembrolizumab as first-line treatment in the R/M cohort. Additionally, we did not assess the association between TMB and response outcomes in our study. However, other therapeutic options, including chemotherapy and cetuximab, usually provide short-term benefit without well-documented efficacy outcomes in advanced cSCC. In this context, the clinically meaningful and durable efficacy and consistent safety profile with pembrolizumab establish it as an important treatment option for advanced cSCC. The efficacy of anti-PD-1 agents in LA cSCC also suggests their potential benefit in the adjuvant setting following surgery and radiation therapy. This hypothesis is being evaluated in phase III studies including the KEYNOTE-630 study (NCT03833167) of pembrolizumab for LA cSCC and the R2810-ONC-1788 study (NCT03969004) of cemiplimab for high-risk cSCC.

Overall, pembrolizumab demonstrated robust, durable antitumor activity and promising survival in both LA and R/M cSCC. AEs with pembrolizumab were generally consistent with its established safety profile. These data establish pembrolizumab as a treatment option for cSCC.

Table 3. AEs[a] in all treated patients

	Pembrolizumab $n = 159$ n (%)	
Related to treatment[b]		
Any grade	110 (69.2)	
Grade 3-5	19 (11.9)	
Led to discontinuation	14 (8.8)	
Led to death[c]	2 (1.3)	
	Any grade	**Grade 3-5**
Common treatment-related AEs (incidence ≥5%, any grade)		
Pruritus	29 (18.2)	0
Fatigue	23 (14.5)	1 (0.6)
Asthenia	20 (12.6)	0
Rash	17 (10.7)	1 (0.6)
Diarrhea	15 (9.4)	0
Hypothyroidism	14 (8.8)	0
Arthralgia	10 (6.3)	0
Nausea	9 (5.7)	0
Immune-mediated AEs and infusion reactions		
All	36 (22.6)	13 (8.2)
Hypothyroidism	14 (8.8)	0
Pneumonitis	6 (3.8)	1 (0.6)
Hyperthyroidism	5 (3.1)	0
Severe skin reactions	5 (3.1)	4 (2.5)
Adrenal insufficiency	4 (2.5)	1 (0.6)
Infusion reactions	4 (2.5)	1 (0.6)
Colitis	2 (1.3)	2 (1.3)
Hepatitis	2 (1.3)	2 (1.3)
Hypophysitis	2 (1.3)	0
Nephritis	1 (0.6)	1 (0.6)
Type 1 diabetes mellitus	1 (0.6)	1 (0.6)

AE, adverse event.

[a] AEs were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

[b] Determined by the investigator to be related to the treatment.

[c] One 76-year-old patient with multiple underlying comorbidities (e.g. hypothyroidism, chronic kidney disease, hypercholesterolemia, previous prostate cancer, gout, obesity, acute pulmonary embolism, colonic pseudo-obstruction, diabetes mellitus, osteoarthritis of the right knee, systemic inflammatory response syndrome, viral meningitis, multiple basal cell carcinomas, skin ulceration of the scalp) died of treatment-related cranial nerve disorder (diagnosed on day 32) on day 59 after receiving two cycles of treatment (last dose on day 22); one 92-year-old patient with multiple underlying comorbidities (e.g. oral fungal infection, upper abdominal pain, asthenia) died of treatment-related immune-mediated colitis (diagnosed on day 569) on day 610 after receiving 28 cycles of pembrolizumab (last dose on day 566).

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DISCLOSURE

BGMH received grants from Merck Sharp & Dohme during the conduct of the study; was an advisory board member for Merck Sharp & Dohme, Bristol Myers Squibb, Roche, Pfizer, Eisai, Takeda, and AstraZeneca; and received grants from Amgen outside the submitted work. EM-C serves on the advisory board of Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, and Sanofi outside the submitted work and received grant from Merck Sharp & Dohme during the conduct of the study. LM received research grant from Merck Sharp & Dohme during the conduct of the study. ÅB received grant from Merck Sharp & Dohme during the conduct of the study and grants from Merck Sharp & Dome, Bristol Myers Squibb, and Sanofi outside the submitted work. RG received grants from Merck Sharp & Dohme during the conduct of the study; personal fees and non-financial support from Bristol Myers Squibb, Roche Pharma, Merck Serono, Pierre Fabre, Sanofi Regeneron, and Almirall Hermal; grants, personal fees, and non-financial support from Amgen and Novartis; personal fees from Merck Sharp & Dohme, Bayer, Immunocore, Sun Pharma, and 4SC; grants and personal fees from Pfizer; and grants from Johnson & Johnson outside the submitted work. OR, RGM, JS, FG, and AJ received research grant from Merck Sharp & Dohme during the conduct of the study. AA received grants from Merck Sharp & Dohme during the conduct of the study; grants, personal fees, and other from Merck Sharp & Dohme, BMS, Novartis, Roche, and Pierre Fabre; and personal fees from Sanofi and Amgen outside the submitted work. NM received grants from Merck Sharp & Dohme during the conduct of the study; grants and personal fees from BMS and Merck Sharp & Dohme; and personal fees from Novartis, Roche, Pierre Fabre, Sun Pharma, AbbVie, and Sanofi outside the submitted work. SB received grants from Merck Sharp & Dohme during the conduct of the study and personal fees from Merck Sharp & Dohme, BMS, and Merck KGaA outside the submitted work. PZ, BG, and RFS are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, who owns stock in Merck & Co., Inc., Kenilworth, NJ, USA. J-JG received grants from Merck Sharp & Dohme during the conduct of the study and personal fees from Merck Sharp & Dohme, BMS, Novartis, Roche, Sanofi, Pierre Fabre, Merck KGaA, Pfizer, and Sun Pharma outside the submitted work.

DATA SHARING

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company

clinical trial data with qualified external scientific researchers. The MSD data-sharing website (available at http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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Update

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CORRIGENDUM

Corrigendum to 'Pembrolizumab for locally advanced and recurrent/metastatic cutaneous squamous cell carcinoma (KEYNOTE-629 study): an open-label, nonrandomized, multicenter, phase II trial

[Annals of Oncology Volume 32, Issue 10, October 2021, Pages 1276-1285]

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The authors regret that a supplementary file for the protocol of the study was mistakenly missed at the time the article was published, although it was cited. The protocol has now been added to the supplementary files.

The authors would like to apologise for any inconvenience caused.

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