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Pharmacokinetics and bioavailability of pembrolizumab with berahyaluronidase alfa for subcutaneous administration in participants with advanced or metastatic solid tumors: The phase 1 study 3475A-C18

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ABSTRACT

Background: MK-3475A is pembrolizumab with berahyaluronidase alfa for subcutaneous administration (pembrolizumab SC). The phase 1 study 3475A-C18 (NCT05017012) assessed the pharmacokinetic and safety profiles of pembrolizumab SC.

Methods: The study had 4 arms that enrolled participants with unresectable or advanced melanoma (arms 1, 2, and 4), metastatic NSCLC (arms 1–3), or advanced or metastatic RCC (arms 1 and 2). Participants received pembrolizumab SC 650 mg Q6W at solution strengths of 165 mg/mL (arms 1 and 3), 130 mg/mL (arm 2), or pembrolizumab SC 395 mg Q3W at 165 mg/mL (arm 4). Key endpoints included pembrolizumab SC bioavailability, pharmacokinetics, immunogenicity, and safety and tolerability.

Results: 140 participants received study treatment. Across all arms, mean bioavailability of pembrolizumab SC was 61 % (95 % CI, 58 %—64 %; CV%, 22.4 %) and absorption rate was 0.30/day (95 % CI, 0.28–0.32/day; CV%, 43.7 %). Pharmacokinetic exposure, bioavailability, and absorption rate did not differ meaningfully with

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pembrolizumab SC by solution strength. Treatment-emergent anti-drug antibodies against pembrolizumab and berahyaluronidase occurred in 1 % and 2 % of participants, respectively. Injection site AEs with pembrolizumab SC occurred in 16 % of participants; all were grade 1/2 in severity. Immune-mediated AEs occurred in 41 % of participants in arms 1–3 and 18 % of participants in arm 4.
Conclusion: Results from study 3475A-C18 informed selection of pembrolizumab SC 790 mg Q6W at 165 mg/mL for further clinical development to ensure that all patients have the appropriate pembrolizumab exposure to derive expected clinical benefit. Arm 4 results provided key clinical data supporting the pembrolizumab SC 395 mg Q3W dosing regimen.
Trial registration: ClinicalTrials.gov, NCT05017012

1. Introduction

Pembrolizumab is a humanized monoclonal antibody that binds with high affinity to the PD-1 receptor on the surface of immune cells and blocks the receptor's interaction with its ligands, PD-L1 and PD-L2[1,2]. As a result, immune system inhibition is alleviated, and T-cell—mediated antitumor activities, including T-cell proliferation and cytokine secretion, are enabled[3,4]. Pembrolizumab was initially approved at a dose of 2 mg/kg administered by intravenous (IV) infusion once every 3 weeks (Q3W)[5,6]. Using model-based analyses to evaluate pharmacokinetic exposures and bridge safety and clinical efficacy across dosing regimens, and support clinical trial design, pembrolizumab was later approved for use across all adult indications at doses of 200 mg Q3W IV and 400 mg every 6 weeks (Q6W) IV[7,8].

For cancer therapies that are available for dosing by more than 1 route of administration, both patients and providers express a preference for subcutaneous (SC) over IV treatment options due to shorter time spent in the clinic, greater satisfaction, lower anxiety and stress among patients, improved patient convenience, and reduced healthcare resource utilization [9–18]. The availability of pembrolizumab for SC administration would represent a new, more convenient treatment option.

MK-3475A (hereafter pembrolizumab SC) is pembrolizumab with berahyaluronidase alfa for SC administration. Berahyaluronidase alfa is a human hyaluronidase variant developed and manufactured by Alteogen Inc. that acts as a permeation enhancer by temporarily degrading the extracellular matrix at the injection site and increasing drug dispersion. We evaluated the pharmacokinetics, including bioavailability, and the safety and tolerability of pembrolizumab SC.

2. Materials and methods

2.1. Study design and treatments

The phase 1, open-label study 3475A-C18 (NCT05017012) comprised 4 arms with participants from 20 global sites enrolled to arms 1, 2, and 4 and participants from 4 Japanese sites enrolled to arm 3 (Supplementary Table S1 and Supplementary Figure S1). Participants were allocated sequentially to arms 1 and 2 and received pembrolizumab SC (pembrolizumab 650 mg with berahyaluronidase alfa 2000 U/mL) at solution strengths of 165 and 130 mg/mL, respectively. Treatment alternated between pembrolizumab SC 650 mg Q6W and pembrolizumab IV 400 mg Q6W for cycles 1–4, followed by up to 14 additional cycles of pembrolizumab IV 400 mg Q6W. As appropriate, participants also received standard-of-care therapy with platinum-doublet chemotherapy for non-small cell lung cancer (NSCLC) or axitinib for renal cell carcinoma (RCC) (see Supplementary Methods for additional details). In arm 3, participants from Japan received pembrolizumab SC at a solution strength of 165 mg/mL in cycle 1 and pembrolizumab IV 400 mg Q6W in cycles 2–18, in combination with standard-of-care platinum-doublet chemotherapy. Each treatment cycle in arms 1–3 was 6 weeks. In arm 4, pembrolizumab SC monotherapy (pembrolizumab 395 mg with berahyaluronidase alfa 2000 U/mL) at a solution strength of 165 mg/mL was administered Q3W for up to 35 cycles. Each treatment cycle in arm 4 was 3 weeks.

This trial was conducted in compliance with global standards, local and/or national regulations of each study site, and International Council for Harmonisation Good Clinical Practice guidelines and in accordance with the ethical principles originating from the Declaration of Helsinki.

2.2. Study participants

Adults aged $\geq$ 18 years diagnosed with histologically or cytologically confirmed unresectable stage III/IV melanoma (arms 1, 2, and 4), stage IV squamous or nonsquamous NSCLC with no *EGFR*, *ALK*, or *ROS1* genomic tumor alterations (arms 1–3), or stage IV RCC with a clear cell component (arms 1 and 2) were eligible. In arms 1, 2, and 4, participants with previously treated or untreated disease were enrolled, whereas in arm 3, previously untreated participants with metastatic NSCLC were enrolled in Japan. All participants were required to provide an archival or newly obtained tumor tissue biopsy sample. All participants had measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) [19] and an Eastern Cooperative Oncology Group performance status $\leq$ 1. Participants provided informed consent. Full eligibility criteria are listed in the Supplementary Methods.

2.3. Endpoints

The primary endpoints of arms 1 and 2 were cycle 1 trough concentration (C_{trough}), peak concentration (C_{max}), time to peak concentration (T_{max}), area under the curve from week 0 to week 6 ($AUC_{0–6wk}$), and bioavailability of pembrolizumab SC administered at solution strengths of 165 mg/mL (arm 1) and 130 mg/mL (arm 2). Secondary endpoints were the detection of antidrug antibodies (ADAs) against pembrolizumab and safety and tolerability of pembrolizumab SC (including the incidence of adverse events [AEs] and AE-related study treatment discontinuations). The primary endpoints of arm 3 were cycle 1 C_{trough}, C_{max}, T_{max}, $AUC_{0–6wk}$, and safety and tolerability of pembrolizumab SC administration in cycle 1, including the incidence of dose-limiting toxicities (DLTs). Secondary endpoints were the detection of ADAs against pembrolizumab and the bioavailability of pembrolizumab SC administered at a solution strength of 165 mg/mL. The primary endpoints of arm 4 were cycle 1 and steady-state (cycle 6) C_{trough}, C_{max}, and $AUC_{0–3wk}$. Secondary endpoints were the detection of ADAs against pembrolizumab and the safety and tolerability of pembrolizumab SC.

For all arms, tertiary endpoints included objective response rate (ORR; defined as the rate of complete and partial responses [CR + PR]), duration of response (defined for participants who demonstrate CR or PR as the time from first documented CR or PR until disease progression or death due to any cause, whichever occurs first), and progression-free survival (defined as the time from first dose of study treatment to first documented disease progression or death, whichever comes first), all per RECIST v1.1 as assessed by the investigator (all arms) and by blinded independent central review (arm 4 only); overall survival (OS; defined as the time from first day of study treatment to death due to any cause [arm 4 only]); detection of ADAs against berahyaluronidase alfa (all arms); and systemic concentrations of berahyaluronidase alfa following

pembrolizumab SC (all arms).

Details on pharmacokinetic, immunogenicity, safety, and efficacy assessments are provided in the Supplementary Methods.

2.4. Statistical analysis

With the assumption of pharmacokinetic absorption variability of 80 %, enrollment of 60 participants to arms 1 and 2 (30 per arm) and 40 participants to arm 4 was expected to provide > 80 % probability to estimate pharmacokinetic parameters with sufficient precision (ie, 95 % CI within 60 %—140 % of the mean parameter estimate). The planned sample size was approximately 36 participants each for arms 1 and 2 (sequential allocation), 6 participants from Japan for arm 3, and 50 participants for arm 4.

The pharmacokinetic analysis population included all participants who had evidence of treatment exposure, availability of pharmacokinetic measurements, and absence of major protocol violations, ensuring that their data could be used to characterize their pharmacokinetic profile. A population pharmacokinetic analysis approach with nonlinear mixed-effects modeling was used to characterize the pharmacokinetics of pembrolizumab following administration of pembrolizumab SC using concentration data from subjects in arms 1–4 (Supplementary Methods). The absorption phase parameters, including bioavailability and absorption rate, were estimated for both the 165- and 130-mg/mL solution strengths of pembrolizumab SC.

The safety analysis population included all participants who received ≥ 1 dose of study treatment. Safety findings were reported using descriptive statistics. The DLT-evaluable population in arm 3 included participants who received ≥ 1 dose of study treatment, received ≥ 75 % of the total pembrolizumab SC treatment and/or chemotherapy during the DLT evaluation period (cycle 1 days 1–21), completed safety evaluations on study, and experienced a DLT. Counts and frequencies of AEs were summarized by treatment. Injection site reaction AEs occurring in arms 1 and 2 (cycles 1 and 3), arm 3 (cycle 1), and arm 4 (any cycle) were summarized. Participant responses to the *Subcutaneous Injection Site Signs and Symptoms* questionnaire were summarized by treatment arm.

The efficacy analysis population consisted of all participants with baseline imaging that showed measurable disease by investigator assessment and who received ≥ 1 dose of study treatment. Statistical methods for efficacy analysis are described in the Supplementary Methods.

3. Results

3.1. Participants

A total of 186 participants were screened for eligibility, of whom 141 were enrolled between September 21, 2021, and February 16, 2024: 46 to arm 1, 44 to arm 2, 6 to arm 3, and 44 to arm 4 (Fig. 1). Of those enrolled, all but 1 participant in arm 4 received ≥ 1 dose of study treatment. Baseline characteristics were as expected for a population with unresectable or advanced melanoma, metastatic NSCLC, and

Table 1
Participant Demographics and Baseline Clinical Characteristics.

	Arm 1 (n = 46)	Arm 2 (n = 44)	Arm 3 (n = 6)	Arm 4 (n = 44)
Age, y				
Median (range)	61.0 (37–81)	66.5 (40–84)	68.0 (41–79)	60.0 (30–89)
< 65	26 (57)	17 (39)	2 (33)	30 (68)
≥ 65	20 (43)	27 (61)	4 (67)	14 (32)
Sex				
Male	33 (72)	26 (59)	6 (100)	22 (50)
Female	13 (28)	18 (41)	0 (0)	22 (50)
Race				
American Indian or Alaska Native	1 (2)	0 (0)	0 (0)	0 (0)
Asian	1 (2)	12 (27)	6 (100)	0 (0)
Black or African American	3 (7)	1 (2)	0 (0)	4 (9)
Multiple	0 (0)	2 (5)	0 (0)	1 (2)
White	36 (78)	27 (61)	0 (0)	39 (89)
Missing	5 (11)	2 (5)	0 (0)	0 (0)
Geographic region				
European Union	22 (48)	6 (14)	0 (0)	0 (0)
Rest of the world	24 (52)	38 (86)	6 (100)	44 (100)
Primary diagnosis				
Melanoma	19 (41)	13 (30)	0 (0)	44 (100)
Renal cell carcinoma	18 (39)	13 (30)	0 (0)	0 (0)
Non–small-cell lung cancer	9 (20)	18 (41)	6 (100)	0 (0)
ECOG performance status				
0	18 (39)	18 (41)	1 (17)	24 (55)
1	28 (61)	26 (59)	5 (83)	20 (45)

Data are n (%) unless noted otherwise.
ECOG, Eastern Cooperative Oncology Group.

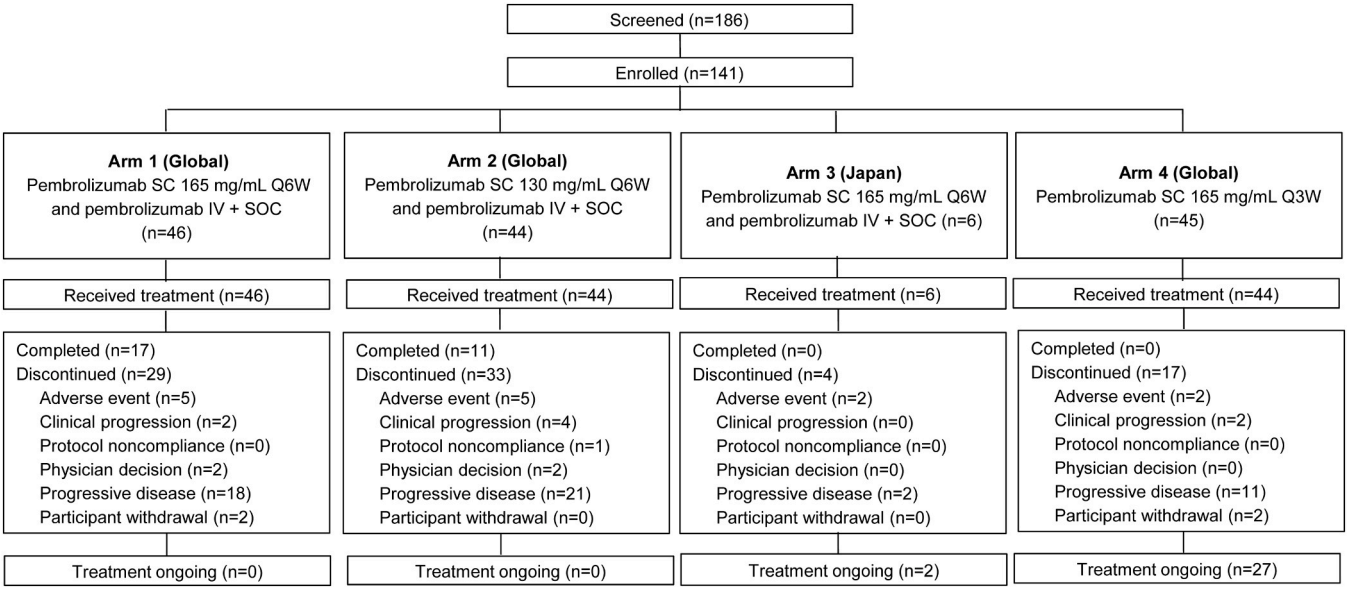

Fig. 1. CONSORT diagram. IV, intravenous; Q3W, every 3 weeks; Q6W, every 6 weeks; SC, subcutaneous; SOC, standard of care.

Table 2
Analysis of Pharmacokinetic Exposure Measures.

Arm (Treatment)	Cycle	N		C_{max}, μg/mL	C_{trough}, μg/mL	$AUC_{0–6wk}$, μg·d/mL	T_{max}, d
1 (pembrolizumab SC 650 mg at 165 mg/mL Q6W)	1	46	Mean (SD)	47.8 (15.5)	15.4 (6.84)	1249 (397)	5.91 (2.04)
			Median (range)	44.5 (19.4–79.6)	15.1 (3.76–36.1)	1280 (562–2382)	6.00 (3.00–10.0)
			Geometric mean (CV%)	45.2 (36.5)	13.9 (51.0)	1185 (34.9)	5.59 (35.1)
2 (pembrolizumab SC 650 mg at 130 mg/mL Q6W)	1	44	Mean (SD)	52.4 (16.8)	17.0 (8.72)	1355 (479)	5.50 (1.92)
			Median (range)	51.2 (23.5–112)	16.0 (0.595–44.4)	1287 (529–2648)	5.00 (2.0–10.0)
			Geometric mean (CV%)	49.9 (32.7)	14.4 (80.0)	1277 (36.4)	5.20 (35.0)
3 (pembrolizumab SC 650 mg at 165 mg/mL Q6W)	1	6	Mean (SD)	67.0 (19.7)	18.7 (4.51)	1600 (381)	4.50 (1.05)
			Median (range)	73.8 (35.7–86.1)	19.0 (11.7–25.5)	1681 (962–2055)	4.50 (3.00–6.00)
			Geometric mean (CV%)	64.1 (35.4)	18.2 (26.2)	1556 (27.4)	4.39 (24.6)
Arm (Treatment)	**Cycle**	**N**		**C_{max}, μg/mL**	**C_{trough}, μg/mL**	**$AUC_{0–3wk}$, μg·d/mL**	**T_{max}, d**
	1	44	Mean (SD)	35.3 (12.3)	21.4 (6.75)	578 (186)	5.48 (2.14)
			Median (range)	34.1 (10.6–63.7)	21.2 (9.73–40.5)	567 (192–979)	5.00 (2.0–10.0)
			Geometric mean (CV%)	33.0 (40.6)	20.3 (34.2)	546 (36.7)	5.11 (38.9)
4 (pembrolizumab SC 395 mg at 165 mg/mL Q3W)	6 (steady state)	44	Mean (SD)	81.7 (28.8)	53.6 (22.2)	1439 (528)	4.18 (1.21)
			Median (range)	80.7 (30.9–162)	54.6 (21.7–123)	1446 (604–3050)	4.00 (2.0–8.0)
			Geometric mean (CV%)	76.5 (39.0)	49.0 (45.8)	1343 (39.9)	4.02 (28.6)

$AUC_{0–3wk}$ area under the curve from week 0 to week 3; $AUC_{0–6wk}$, area under the curve from week 0 to week 6; C_{max}, peak concentration; C_{trough}, trough concentration; CV%, coefficient of variation; Q3W, every 3 weeks; Q6W, every 6 weeks; SC, subcutaneous; T_{max}, time to peak concentration.

advanced or metastatic RCC (Table 1). At data cutoff (June 24, 2024), the median time on study treatment was 15.1, 11.6, 4.3, and 4.9 months in arms 1–4, respectively. Across arms, at least half of the study population received ≥ 4 cycles of treatment (Supplementary Table S2).

3.2. Pharmacokinetics

In arms 1 and 2, median C_{max} (44.5 and 51.2 μg/mL), C_{trough} (15.1 and 16.0 μg/mL), $AUC_{0–6wk}$ (1280 and 1287 μg·d/mL), and T_{max} (6.0 and 5.0 days) for pembrolizumab SC 650 mg Q6W were largely consistent between the 165 and 130 mg/mL solution strengths, with overlapping ranges in the global population (Table 2). In arm 3, which evaluated pembrolizumab SC 650 mg Q6W at the 165 mg/mL solution strength in the Japanese population, median cycle 1 C_{max} was 73.8 μg/mL, C_{trough} was 19.0 μg/mL, $AUC_{0–6wk}$ was 1681 μg·d/mL, and T_{max} was 4.5 days; ranges overlapped with those observed in arms 1 and 2 (Table 2). In arm 4, which evaluated pembrolizumab SC 395 mg Q3W at the 165 mg/mL solution strength, median cycle 1 C_{max} was 34.1 μg/mL, C_{trough} was 21.2 μg/mL, $AUC_{0–3wk}$ was 567 μg·d/mL, and T_{max} was 5 days. The observed mean concentration-time profiles of pembrolizumab SC 650 mg Q6W and pembrolizumab IV 400 mg Q6W are illustrated in Fig. 2.

Using a pharmacokinetic model-based analysis across all arms, the estimated mean bioavailability of pembrolizumab SC was 61 % (95 % CI, 58 %—64 %; CV%, 22.4 %) and the absorption rate was 0.30/day (95 % CI, 0.28–0.32/day; CV%, 43.7 %). No meaningful differences in bioavailability or absorption rate were found between the pembrolizumab SC 165 and 130 mg/mL solution strengths.

Systemic absorption of berahyaluronidase alfa was negligible. There were no participants with postdose samples containing measurable concentrations of berahyaluronidase alfa following pembrolizumab SC administration in the absence of positive predose samples.

3.3. Immunogenicity

Across all arms, 1 of 127 evaluable participants (1 %) had treatment-emergent ADAs against pembrolizumab. No neutralizing positive antibodies were detected (Supplementary Table S3) and there was no evidence of a clinically meaningful impact of ADAs on pembrolizumab exposure. In addition, across all arms, 3 of 129 evaluable participants (2 %) had treatment-emergent ADAs against berahyaluronidase alfa (Supplementary Table S3).

3.4. Safety

Across arms 1–3 (n = 96), 57 participants (59 %) experienced a treatment-related AE in cycle 1, most frequently fatigue (9 %) and nausea (9 %), and hypertension (7 %; Table 3; Supplementary Table S4). Most treatment-related AEs were grade 1 or 2. No participants in arm 3 experienced a DLT. In arm 4 (n = 44), 24 participants (55 %) had a treatment-related AE, most frequently pruritus (14 %; Table 3; Supplementary Table S4). All treatment-related AEs in arm 4 were grade 1 or 2. Immune-mediated AEs and infusion reactions occurred in 39 participants (41 %) across arms 1–3 and in 8 (18 %) in arm 4; the most frequently reported immune-mediated AEs included hypothyroidism and pneumonitis (Supplementary Table S5).

Across arms 1–3, 2 participants (2 %) experienced fatal AEs during cycle 1 (febrile neutropenia and respiratory failure, n = 1 each). Three additional fatal AEs occurred after cycle 1 (congestive cardiac failure, septic shock, and pneumonitis, n = 1 each; Supplementary Table S6). These fatal AEs all occurred in participants with NSCLC receiving pembrolizumab in combination with chemotherapy; the grade 5 febrile neutropenia and pneumonitis events were considered treatment-related by the investigator. In arm 4 across all cycles, 2 participants (5 %) experienced fatal AEs (sepsis and death, n = 1 each; Supplementary Table S6); neither was considered treatment-related.

Across arms 1–4 (n = 140), 22 patients (16 %) experienced

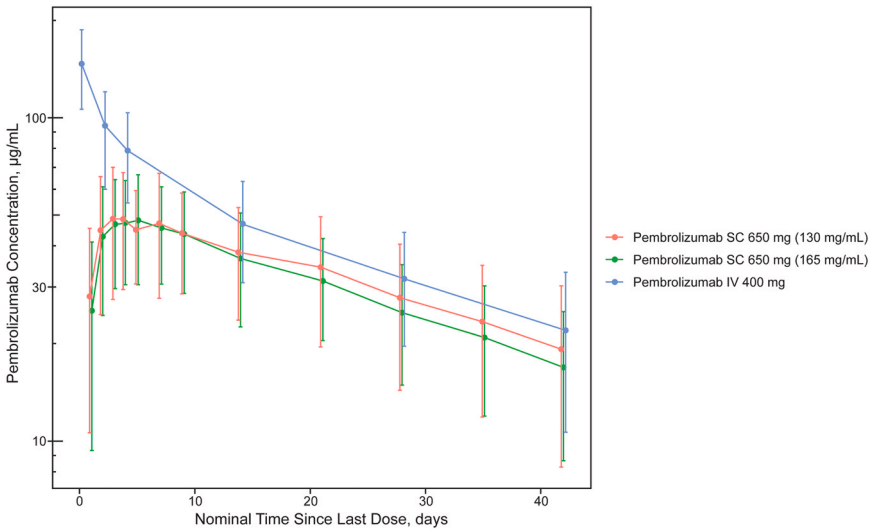

Fig. 2. Observed mean concentration-time profiles in cycles 1 and 2 for arms 1–3. Data and error bars represent mean ± SD for pembrolizumab SC 650 mg at 130 mg/mL (red; arms 1 and 3) or 165 mg/mL (green; arm 2) solution strengths in cycle 1 and pembrolizumab IV 400 mg (blue; arms 1–3) in cycle 2. IV, intravenous; SC, subcutaneous.

injection site AEs following pembrolizumab SC administration. The most frequent injection site AEs were injection site erythema (n = 12, 9 %), swelling (n = 7, 5 %), and pruritus (n = 5, 4 %; Table 3). All injection site AEs reported were grade 1, except for 2 grade 2 events in arm 2 (injection site erythema and injection site pruritus). Approximately half of the participants self-reported ≥ 1 sign or symptom immediately following pembrolizumab SC administration on the *Subcutaneous Injection Site Signs and Symptoms* questionnaire, with redness the most frequently reported (n = 54, 42 %; Table 4). Most signs and symptoms were reported by the participant as mild, except in 4 instances that were reported as moderate (itching, n = 1; redness, n = 2; swelling, n = 1).

Table 3
Summary of Treatment-Related[a] AEs With Incidence ≥ 5 % and Injection Site AEs.

	Arms 1–3, Cycle 1 (n = 96)		**Arm 4, All Cycles (n = 44)**	
Treatment-related AEs occurring in ≥ 5 % of participants in any treatment arm	**Any Grade**	**Grade 3–5**	**Any Grade**	**Grade 3–5**
Fatigue	9 (9)	0 (0)	3 (7)	0 (0)
Nausea	9 (9)	0 (0)	2 (5)	0 (0)
Hypertension	7 (7)	3 (3)	0 (0)	0 (0)
Alopecia	6 (6)	0 (0)	0 (0)	0 (0)
Anemia	6 (6)	3 (3)	0 (0)	0 (0)
Injection site erythema	6 (6)	0 (0)	3 (7)	0 (0)
Mucosal inflammation	6 (6)	0 (0)	0 (0)	0 (0)
Pruritus	6 (6)	0 (0)	6 (14)	0 (0)
ALT increase	5 (5)	1 (1)	2 (5)	0 (0)
Asthenia	5 (5)	0 (0)	1 (2)	0 (0)
Constipation	5 (5)	1 (1)	0 (0)	0 (0)
Injection site pruritus	5 (5)	0 (0)	0 (0)	0 (0)
Rash	4 (4)	0 (0)	3 (7)	0 (0)
Hypothyroidism	0 (0)	0 (0)	3 (7)	0 (0)
	Arm 1, Cycles 1 and 3 (n = 46)	**Arm 2, Cycles 1 and 3 (n = 44)**	**Arm 3, Cycle 1 (n = 6)**	**Arm 4, Cycle 1 (n = 44)**
Injection site AEs[b]	7 (15)	5 (11)	1 (17)	9 (20)
Erythema	4 (9)	4 (9)	0 (0)	4 (9)
Swelling	4 (9)	2 (5)	0 (0)	1 (2)
Pruritus	2 (4)	2 (5)	1 (17)	0 (0)
Pain	1 (2)	1 (2)	0 (0)	0 (0)
Discoloration	1 (2)	0 (0)	0 (0)	0 (0)
Site reaction	1 (2)	0 (0)	0 (0)	2 (5)
Edema	0 (0)	1 (2)	0 (0)	0 (0)
Inflammation	0 (0)	0 (0)	0 (0)	1 (2)
Irritation	0 (0)	0 (0)	0 (0)	1 (2)
Rash	0 (0)	0 (0)	0 (0)	1 (2)

All data are n (%).
AE, adverse event; ALT, alanine aminotransferase.
[a] Determined by the investigator to be related to treatment.
[b] Participants are counted a single time for each applicable row. Nonserious AEs up to 30 days after the last dose and serious AEs up to 90 days after the last dose are included.

Table 4
Summary of Responses to the Subcutaneous Injection Site Signs and Symptoms Questionnaire.

Participants with ≥ 1 injection site sign/symptom[a]	Arm 1, Cycles 1 and 3 (n = 46)		Arm 2, Cycles 1 and 3 (n = 44)		Arm 3, Cycle 1 (n = 6)		Arm 4, Cycle 1 (n = 44)	
	26 (57)		21 (48)		1 (17)		18 (41)	
	Mild	Moderate	Mild	Moderate	Mild	Moderate	Mild	Moderate
Itching	9 (20)	1 (2)	4 (9)	0 (0)	1 (17)	0 (0)	3 (7)	0 (0)
Pain	6 (13)	0 (0)	5 (11)	0 (0)	0 (0)	0 (0)	3 (7)	0 (0)
Redness	21 (46)	1 (2)	17 (39)	1 (2)	1 (17)	0 (0)	13 (30)	0 (0)
Swelling	12 (26)	1 (2)	9 (20)	0 (0)	1 (17)	0 (0)	5 (11)	0 (0)

All data are n (%).
[a] Participants are counted a single time for each applicable row.

3.5. Efficacy

Efficacy outcomes were generally consistent across the arms. Investigator-assessed ORR in arms 1–3 was 50 % in participants with melanoma (n = 32), 42 % in NSCLC (n = 33), and 52 % in RCC (n = 31; Supplementary Table S7). In arm 4, investigator-assessed ORR was 27 % in participants with melanoma (n = 44; Supplementary Table S7). Most participants had a reduction in target lesion dimensions from baseline (Supplementary Figure S2). Across all arms, the majority of responding participants in the 3 tumor types demonstrated durable responses of ≥ 6 months (Supplementary Figures S3A and S4A), and > 40 % of participants were progression-free at 6 months (Supplementary Figures S3B and S4B). Kaplan-Meier estimates of OS in arm 4 are shown in Supplementary Figure S4C.

4. Discussion

The phase 1 study 3475A-C18 sought to characterize the bioavailability and pharmacokinetic characteristics of pembrolizumab SC administration in participants with advanced melanoma, NSCLC, or RCC. The analysis demonstrated that the pharmacokinetic exposure, bioavailability, and absorption rate of pembrolizumab SC 650 mg Q6W were generally comparable between the 2 solution strengths (165 vs 130 mg/mL) and across populations (global vs Japan). Our analyses also indicated that systemic absorption of berahyaluronidase alfa after pembrolizumab SC administration was negligible. No evidence of increased immunogenicity or new safety signals were identified with pembrolizumab SC.

Based on the totality of available pembrolizumab SC pharmacokinetic data, including bioavailability and inter-participant variability, pembrolizumab SC 790 mg Q6W at 165 mg/mL was selected as the optimal dose for further clinical development. This dose is expected to achieve exposures consistent with pembrolizumab IV 400 mg Q6W and allows for the smallest possible injection volume. The selected dose of pembrolizumab SC 790 mg Q6W was compared with the approved dose of pembrolizumab IV 400 mg in the phase 3 study 3475A-D77 in participants with metastatic NSCLC[20]. In that study, cycle 1 $AUC_{0–6wk}$ and steady-state (cycle 3) C_{trough} of pembrolizumab SC 790 mg Q6W were noninferior to pembrolizumab IV 400 mg Q6W when coadministered with chemotherapy[20], confirming pharmacokinetic similarity of pembrolizumab SC with pembrolizumab IV[20]. Furthermore, using the combined SC and IV population pharmacokinetic model, model-based pharmacokinetic exposures of pembrolizumab SC 790 mg Q6W were generally consistent with those of the approved doses of pembrolizumab IV 400 mg Q6W and 200 mg Q3W[21].

Arm 4 of this study evaluated the pharmacokinetic characteristics of pembrolizumab SC 395 mg Q3W[21]. Observed pharmacokinetic concentrations for pembrolizumab SC 395 mg Q3W were consistent with model-based predictions at this dose, thereby validating the model used to predict pharmacokinetic exposures of pembrolizumab SC 395 mg Q3W[21]. Moreover, model-based pharmacokinetic exposures for pembrolizumab SC 395 mg Q3W were consistent with pembrolizumab SC 790 mg Q6W and pembrolizumab IV 200 mg Q3W[21], supporting this dosing regimen for pembrolizumab SC as well.

The immunogenicity of pembrolizumab SC was low. Treatment-emergent ADAs against pembrolizumab and berahyaluronidase alfa were detected in 1 (1 %) and 3 participants (2 %), respectively. Moreover, none of the ADAs against pembrolizumab were neutralizing antibodies, and they had no impact on pembrolizumab exposure. The limited immunogenicity of pembrolizumab SC was consistent with the findings of an immunogenicity analysis of pembrolizumab IV (n = 2000), which found ADAs detectable in 1.8 % of participants and neutralizing antibodies in 0.5 % of participants[22]. Furthermore, the immunogenicity of pembrolizumab SC in study 3475A-C18 was similar to that in the phase 3 study 3475A-D77 in participants with previously untreated metastatic NSCLC, which reported ADAs against pembrolizumab detected in 1.4 % of participants in the pembrolizumab SC arm[20]. However, the immunogenicity of pembrolizumab SC in study 3475A-C18 was lower than that of other SC cancer immunotherapies. For example, in the phase 3 IMscin001 study, 43 of 221 (19.5 %) and 12 of 224 participants (5.4 %) treated with SC atezolizumab were ADA-positive to atezolizumab and recombinant human hyaluronidase PH20 (rHuPH20; a type of hyaluronidase used for SC administration), respectively[23]. Similarly, in the phase 3 CheckMate 67T study, 50 of 208 participants (24.0 %) treated with SC nivolumab were ADA-positive to nivolumab[24]. Neither study found any clinical effect of the ADAs [23,24]. Additionally, consistent with the minimal systemic absorption of berahyaluronidase alfa observed in this study, the systemic absorption of rHuPH20 showed no measurable systemic exposure after SC administration[23,25,26].

The overall safety profile of pembrolizumab SC, administered as monotherapy in participants with melanoma or with standard-of-care background therapy in participants with NSCLC or RCC, was consistent with the known safety profile of pembrolizumab IV administered as monotherapy or combination therapy for these indications[27–30]. Injection site AEs associated with pembrolizumab SC administration were infrequent, mostly mild (grade 1), and nonserious, with participant self-assessment of injection site signs and symptoms underscoring that the injection was generally well tolerated with only mild symptoms.

The observed efficacy outcomes in this study, which were assessed as tertiary endpoints in this study, were generally consistent with the established effectiveness of pembrolizumab IV administered for these indications[27–30]. However, given the limited sample size and that participants in arms 1–3 received both pembrolizumab SC and pembrolizumab IV during the study, it is difficult to assess the contribution of pembrolizumab SC to the observed antitumor activity.

In summary, pharmacokinetic exposures of pembrolizumab SC Q6W in this study informed the selection of pembrolizumab SC 790 mg Q6W at a solution strength of 165 mg/mL for further clinical development to ensure that all participants have the appropriate exposure to derive expected clinical benefit. Arm 4 results provided key clinical data supporting the pembrolizumab SC 395 mg Q3W dosing regimen. The immunogenicity of pembrolizumab SC and berahyaluronidase alfa was low, and the overall safety profile of pembrolizumab SC was consistent

with the known safety profile of pembrolizumab IV. Pembrolizumab SC may represent a potential new treatment option for all indications for which pembrolizumab IV is approved.

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CRediT authorship contribution statement

All authors were involved in the drafting and/or writing – review and editing of the manuscript, had access to the study data, and approved the content for submission. **Graham L. Cohen:** Acquisition of the data, reviewing or revising the manuscript for important intellectual content, and provision of study materials/participants; **Corlia Coetzee:** Acquisition of the data, reviewing or revising the manuscript for important intellectual content, and provision of study materials/participants; **Cathryn A. Walton:** Acquisition of the data, reviewing or revising the manuscript for important intellectual content, and provision of study materials/participants; **Òscar Reig Torras:** Acquisition of the data, interpretation of the results, reviewing or revising the manuscript for important intellectual content, and provision of study materials/participants; **Byoung Chul Cho:** Conception, design or planning of the study, analysis of the data, acquisition of the data, drafting of the manuscript and reviewing or revising the manuscript for important intellectual content, and interpretation of the results; **Georgina McAdam:** Acquisition of the data and reviewing or revising the manuscript for important intellectual content; **Carlos I. Rojas:** Acquisition of the data and reviewing or revising the manuscript for important intellectual content; **Laura Medina Rodríguez:** Acquisition of the data, interpretation of the results, and reviewing or revising the manuscript for important intellectual content,; **Zsuzsanna Papai:** Acquisition of the data and reviewing or revising the manuscript for important intellectual content; **Sze W. Chan:** Acquisition of the data, provision of study materials/participants, interpretation of the results, and reviewing or revising the manuscript for important intellectual content; **Bernardo L. Rapoport:** Interpretation of the results, provision of study materials/participants, and reviewing or revising the manuscript for important intellectual content; **Christian Caglevic:** Acquisition of the data, interpretation of the results, provision of study materials/participants, and drafting of the manuscript and reviewing or revising the manuscript for important intellectual content; **Patricio Yañez Weber:** Acquisition of the data and reviewing or revising the manuscript for important intellectual content; **Toshiaki Takahashi:** Acquisition of the data, interpretation of the results, and reviewing or revising the manuscript for important intellectual content; **Takayasu Kurata:** Acquisition of the data, interpretation of the results, provision of study materials/participants, and reviewing or revising the manuscript for important intellectual content; **Gina Song:** Acquisition of the data, analysis of the data, interpretation of the results, and drafting of the manuscript and reviewing or revising the manuscript for important intellectual content; **Julia W. Cohen:** Conception, design or planning of the study, analysis of the data, acquisition of the data, interpretation of the results, and drafting of the manuscript and reviewing or revising the manuscript for important intellectual content; **Omobolaji O. Akala:** Conception, design or planning of the study, analysis of the data, acquisition of the data, interpretation of the results, and drafting of the manuscript and reviewing or revising the manuscript for important intellectual content; **Richard Khanyile:** Acquisition of the data, interpretation of the results, provision of study materials/participants, and reviewing or revising the manuscript for important intellectual content.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115709.

Data availability

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, 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: *https://externaldatasharing-msd.com/*) 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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