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ORIGINAL RESEARCH

A Time and Motion Study Comparing Subcutaneous Pembrolizumab Versus Intravenous Pembrolizumab in Combination with Chemotherapy for the Treatment of Metastatic Non-small Cell Lung Cancer

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ABSTRACT

***Introduction*:** Subcutaneous (SC) formulations of oncology therapies could provide time-saving benefits for both patients and healthcare professionals (HCPs) compared with intravenous (IV) delivery. This prospective observational study, conducted alongside the MK-3475A-D77 phase 3, open-label randomized clinical trial, quantifies HCP and patient time with pembrolizumab SC versus pembrolizumab IV among patients with metastatic non-small cell lung cancer.

***Methods*:** Seventeen sites across eight countries in Europe ($n=4$), South America ($n=3$), and Asia ($n=1$) were enrolled. Primary endpoints were active HCP time; patient time in the treatment chair, treatment room, and healthcare facility; and consumables usage. Descriptive statistics included weighted mean (WM), and a linear mixed model (LMM) was employed to explore differences in time measures between pembrolizumab SC and pembrolizumab IV per visit.

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***Results*:** Overall, 212 observations were analyzed (153 SC and 59 IV). Total active HCP time was reduced by 45.6% with SC versus IV (WM, 14.0 vs 25.8 min); HCPs spent 44.3% less time on the drug preparation process with SC versus IV (WM, 5.1 vs 9.1 min) and 46.3% less time on the drug administration process with SC versus IV (WM, 8.9 vs 16.7 min). Patient chair time was reduced by 49.6% with SC versus IV (WM, 59.0 vs 117.2 min). Patients receiving SC spent less time in the treatment room than those receiving IV (WM, 66.7 vs 126.9 min; difference – 47.4%). Exploratory LMM showed considerable between-group differences for active HCP time and patient time in the treatment chair and treatment room.
***Conclusion*:** Pembrolizumab SC substantially reduces active HCP time and patient chair time versus pembrolizumab IV. Time liberated for HCPs could be reallocated toward additional patient care activities, while optimized chair utilization could improve overall healthcare efficiency.

Keywords: Clinic workflow; Healthcare professional time; Operational efficiency; Non-small cell lung cancer; Patient chair time; Pembrolizumab; Subcutaneous administration; Time and motion study; Time savings; Treatment efficiency

Key Summary Points

Why carry out this study?

Intravenous (IV) pembrolizumab is prepared and administered in a multistep process at the clinic, which is known to be time consuming for healthcare professionals (HCPs) and patients

Pembrolizumab administered via subcutaneous (SC) route is expected to be time efficient for both HCPs and patients

This time and motion (T&M) study was designed to quantify and compare HCP time, patient time, and consumables usage associated with pembrolizumab SC compared with pembrolizumab IV in patients with metastatic non-small cell lung cancer (mNSCLC)

What was learned from the study?

This study showed substantial reductions in HCP time and patient time related to pembrolizumab SC compared with pembrolizumab IV

The findings show that pembrolizumab SC may lead to important time and resource efficiencies from the healthcare facility perspective, where time liberated for HCPs could be reallocated toward additional patient care activities

INTRODUCTION

Pembrolizumab administered by intravenous (IV) infusion was first approved in 2014 for treatment of advanced melanoma and has since gained regulatory approval in many countries for multiple tumor types and disease stages, including metastatic non-small cell lung cancer (mNSCLC) [1, 2]. Pembrolizumab has significantly improved overall survival across a wide range of early-stage and metastatic cancers [3]. Currently, for all approved indications, pembrolizumab is administered intravenously for 30 min [2]. Administering anticancer treatments via IV infusion is a time- and resource-intensive process. Multiple healthcare professionals (HCPs) are required to prepare and administer infusions and monitor patients during and after drug administration as part of a multistep process in the clinic [4, 5].

Because of these challenges, there is increasing interest in alternative routes of administration, such as subcutaneous (SC), for oncology therapies that are approved globally, including by the European Medicines Agency and the US Food and Drug Administration [6–13]. Compared with IV use, SC administration generally reduces the time for drug preparation and administration processes [4, 5]. These time savings alleviate pressure on pharmacy and hospital staff, optimize resource availability, and increase overall practice efficiency, which enables HCPs to treat more patients without compromising quality of care [4, 5]. From the patient's perspective, a recent systematic literature review of studies comparing SC to IV administrations of approved cancer biologics found a higher proportion of patients who expressed preference for and had greater satisfaction with the SC route compared with the IV route of administration [5]. Reasons associated with the preference for SC administration were shorter administration time, less injection-site pain, more comfort, and less anxiety [5].

Recently, the pharmacokinetics, efficacy, and safety of a SC formulation of pembrolizumab with berahyaluronidase alfa (hereafter referred to as pembrolizumab SC) were evaluated among patients with mNSCLC in a phase 3 open-label, active-controlled, randomized clinical trial, MK-3475A-D77 [14]. Pembrolizumab SC, a human hyaluronidase variant (developed and manufactured by Alteogen Inc.), is a permeation enhancer that temporarily degrades hyaluronan in the extracellular matrix surrounding the injection area, increasing dispersion and enabling SC administration of pembrolizumab [14]. In the MK-3475A-D77 clinical trial, the dual primary pharmacokinetic endpoints were met; pembrolizumab SC compared with pembrolizumab IV, both administered every 6 weeks in combination with chemotherapy, demonstrated noninferiority for area under the curve during the first dosing cycle and for trough concentration of pembrolizumab measured at steady state (cycle 3) [14]. Additional pharmacokinetic, efficacy, and safety measures assessed as secondary endpoints were consistent between treatment groups [14]. These data indicate that pembrolizumab SC is a treatment option for all indications where pembrolizumab IV can be used [14].

In contrast to the 30-min infusion of pembrolizumab IV, the median administration time for pembrolizumab SC was 2 min in the MK-3475A-D77 clinical trial [14]. A comprehensive characterization of the drug preparation and administration processes between pembrolizumab IV and SC, along with their impact on time and consumables usage, would be valuable to better understand differences in efficiency between these two forms of administration. To this end, this study evaluated these processes using time and motion (T&M) methodology, which deconstructs a process into individual tasks and measures time for each task through multiple observations to estimate the average time to complete the individual task [15]. This methodology has been widely used to quantify HCP time for workflows involving either SC injection or IV infusion of monoclonal antibodies in clinical trial settings and to measure efficiencies associated with the SC route of administration [16, 17]. The aim of this T&M study was to quantify and compare active HCP time, patient time, and consumables usage associated with pembrolizumab SC and pembrolizumab IV workflows for the treatment of patients with mNSCLC enrolled in the MK-3475A-D77 clinical trial. This descriptive study was not

hypothesis-driven but designed to comprehensively characterize workflow efficiencies and resource utilization, providing valuable insights to inform optimization of treatment delivery and patient care.

METHODS

Study Design

This prospective, observational, multicountry T&M study was conducted alongside the MK-3475A-D77 clinical trial (NCT05722015) [14]. There were 61 global sites in MK-3475A-D77, and some study sites were invited to participate; a total of 17 sites across 8 countries in Europe ($n=4$), South America ($n=3$), and Asia ($n=1$) contributed data to this T&M study. Most sites were in an urban area (94.1%) and were academic medical centers (58.8%).

Regulatory and Ethics Approval

Ethics approval for this T&M study was obtained for each site in accordance with local regulations, where applicable. The study was conducted in compliance with the approved protocol, the applicable principles outlined in Good Pharmacoepidemiology Practice guidelines, and the Declaration of Helsinki (1964 and its later amendments).

The Western Institutional Review Board-Copernicus Group Institutional Review Board (WCG IRB) served as the master ethics committee for this study. WCG IRB approval was received on 13 September 2023 (WCG IRB tracking no. 20234046). Additional institutional review boards (IRBs) overseeing site-specific approvals are listed in the Supplementary Material Table S1, along with their respective reference identifiers.

All HCPs provided written agreements prior to observation. Patients under passive observation verbally consented after reviewing the study's patient information leaflet. All HCPs and study sites participated voluntarily and retained the right to withdraw from the study at any time and for any reason.

Study Population

Study participants consisted of HCPs performing pembrolizumab-related tasks at MK-3475A-D77 trial sites enrolled in the T&M study and who agreed to be observed. Patients who were enrolled in MK-3475A-D77 were not considered study participants in this T&M study. De-identified patient-related data recorded in the T&M study were limited to the time points at entry and exit of treatment chair/bed (hereafter referred to as chair), treatment room, and healthcare facility.

Drug Preparation and Administration Process Mapping

Prespecified tasks within the drug preparation and administration processes of pembrolizumab SC and pembrolizumab IV were defined based on published literature [16, 17], the MK-3475A-D77 clinical trial protocol, and MK-3475A-D77 clinical trial pharmacy manual. Active HCP task time was bounded by clear start and stop points, with corroboration obtained during a pre-study semi-structured interview at each site. Tasks associated with preparation and administration processes of concomitant chemotherapy were excluded from both workflows.

The preparation of pembrolizumab SC varied by site, occurred either in a centralized pharmacy under sterile conditions or directly in the clinic.

Generic workflows for preparation and administration processes of pembrolizumab SC and pembrolizumab IV are illustrated in Fig. 1.

Data Collection

The generic paper case report form (CRF) was adapted to reflect site-specific practices, ensuring accurate measurements. However, the site-specific CRF adaptations aimed to maintain consistent task definitions of prespecified tasks to ensure homogeneity across sites. Each site selected at least one staff member familiar with the pembrolizumab SC and pembrolizumab IV workflows (e.g., nurses) to serve as an observer, who then underwent training to record data

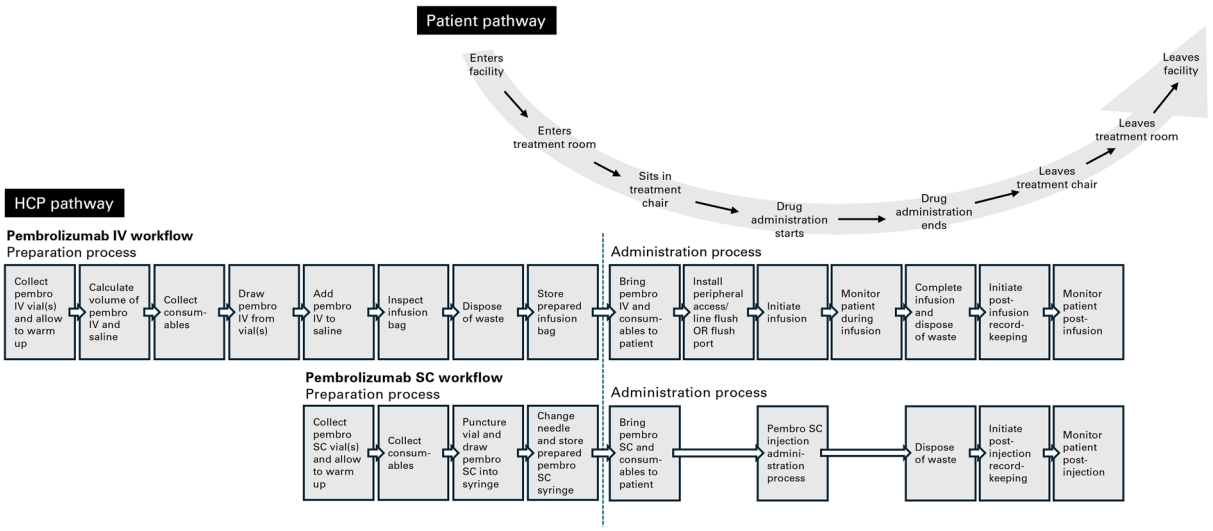

Fig. 1 Patient pathway during clinic visit and HCP pathway showing generic workflows for pembrolizumab IV and pembrolizumab SC preparation and administration processes. Workflow variations may have occurred between study sites and were captured by site-specific case report forms. Boxes do not represent duration of time. *HCP* healthcare professional, *IV* intravenous, *pembro* pembrolizumab, *SC* subcutaneous

for the T&M study. Eligible visits for observation were those occurring on day 1 of any cycle of the MK-3475A-D77 clinical trial. Any preparation and administration processes for pembrolizumab IV performed outside the MK-3475A-D77 clinical trial were not eligible for observation.

Observers measured active HCP time for each task using a stopwatch, recording the time (in minutes and seconds) on the site-specific CRF. Observers documented treatment group (pembrolizumab SC or pembrolizumab IV), mNSCLC histology (squamous or nonsquamous), treatment phase (platinum-doublet or post–platinum-doublet), title of the observed HCP (HCP type), concomitant chemotherapy (type and duration), patient time in the treatment chair, treatment room and healthcare facility, and consumables usage (item and quantity per item).

Data collection overlapped with the conduct of the MK-3475A-D77 clinical trial, with observations occurring from December 2023 to October 2024.

Additional details regarding data collection and quality control are included in the Supplementary Material; *Data collection*.

Study Endpoints

Prespecified study endpoints were as follows: active HCP time, defined as the time that an HCP was actively engaged in performing each prespecified task; total active HCP time, calculated as the sum of active times for all tasks; patient time in treatment chair, treatment room, and healthcare facility, each measured based on the time of day when a patient entered and exited the specific locations; and consumables usage, measured based on number of items used per visit related to pembrolizumab SC and/or pembrolizumab IV treatment.

Statistical Analysis

In this descriptive study, the target sample was 180 observations (120 pembrolizumab SC, 60 pembrolizumab IV), guided by the MK-3475A-D77 clinical trial, which had a 2:1 (SC:IV) randomization scheme and competitive recruitment. All endpoints were analyzed using descriptive statistics, including number (percentage) for discrete variables, mean (standard

deviation), median (minimum, maximum), 95% confidence intervals for time-based variables, and mean and median for consumables. These statistics were calculated per site, per country, and for all countries combined. To address variability across sites and countries, weighted mean (WM) was calculated for all time-based endpoints and for consumables. For each country, this involved summing the site means and dividing by the number of sites in the country. The overall WM across countries combined was then calculated similarly by summing the country means and dividing by the number of countries in the study.

Reported duration of chemotherapy administration was subtracted from patient time endpoints to avoid potential confounding when comparing time between pembrolizumab SC and pembrolizumab IV.

For time-based endpoints (active HCP time and patient time), extreme outliers were identified using Tukey's method with an outer fence formula: lower bound = quartile 1 – quartile 3 * (quartile 3 – quartile 1) and upper bound = quartile 3 + quartile 3 * (quartile 3 – quartile 1) [18, 19]. Those outliers were removed from the analysis because they were deemed clinically implausible or atypical, potentially distorting the summary statistics.

Since time data are hierarchical with observations organized at multiple levels (sites and countries), this violates the assumption of independent observations. Therefore, to explore any difference between SC and IV for time-based endpoints, a linear mixed model (LMM) was employed as an alternative to the WM approach. The LMM modeled random effects (site and country) to account for within-group correlation and fixed effect (route of administration) to explore statistical differences between groups. Data were analyzed using SAS© version 9.4 (SAS Institute).

RESULTS

Observations

In total, 220 observations were collected, of which 212 valid observations were analyzed (pembrolizumab SC, $n = 153$; pembrolizumab IV, $n = 59$). Due to missing data and the removal of some outliers, sample sizes varied slightly for the patient time endpoints. Documented characteristics of the observed processes by treatment group are presented in Table 1. Variations in workflows between sites are described in the Supplementary Material; *Differences in workflows between sites*. No medical adverse events occurred during this T&M study.

Active HCP Time

Total active HCP time (preparation and administration processes combined) was 45.6% lower for pembrolizumab SC compared with pembrolizumab IV (WM, 14.0 versus 25.8 min; see Supplementary Figure S1). HCPs dedicated 44.3% less time to the drug preparation process (WM, 5.1 versus 9.1 min) and 46.3% less time to the drug administration process (WM, 8.9 versus 16.7 min) with pembrolizumab SC compared with pembrolizumab IV (Fig. 2; for total active HCP time in each treatment group per country, see Supplementary Figure S2).

When exploring results in the subgroup of ten sites that collected observations for both treatment groups, the difference per site in total active HCP time between pembrolizumab SC and IV ranged between – 28.6 min (difference – 80.7%) and 0.3 min (difference 1.9%), with an average reduction of – 10.3 min (difference – 37.6%) (Supplementary Figure S3).

Patient Time

Patients who received pembrolizumab SC spent less time in the chair (– 58.2 min [difference – 49.6%]), treatment room (– 60.2 min [difference – 47.4%]), and healthcare facility (– 31.3 min [difference – 13.1%]) than patients who received pembrolizumab IV (Fig. 3). The

Table 1 Number of observations and characteristics of observed processes, overall and by country

		Argentina	Chile	Guatemala	Hungary	Romania	Spain[b]	Taiwan[b]	Turkey	Overall
Total number of valid observations[a]		65	35	23	12	11	11	3	52	212
Pembro IV		18	15	5	4	4	0	0	13	59
Pembro SC		47	20	18	8	7	11	3	39	153
Concomitant Chemotherapy, *n* (%)										
Pembro IV	No	4 (22.2)	4 (26.7)	0	0	2 (50.0)	N/A	N/A	6 (46.2)	16 (27.1)
	Yes	14 (77.8)	11 (73.3)	5 (100.0)	4 (100.0)	2 (50.0)	N/A	N/A	7 (53.8)	43 (72.9)
Pembro SC	No	31 (66.0)	5 (25.0)	3 (16.7)	1 (12.5)	1 (14.3)	9 (81.8)	0	18 (46.2)	68 (44.4)
	Yes	16 (34.0)	15 (75.0)	15 (83.3)	7 (87.5)	6 (85.7)	2 (18.2)	3 (100.0)	21 (53.8)	85 (55.6)
Chemotherapy Administered, *n* (%)										
Pembro IV	Pemetrexed	14 (100.0)	11 (100.0)	4 (80.0)	4 (100.0)	2 (100.0)	N/A	N/A	7 (100.0)	42 (97.7)
	Pemetrexed, carboplatin	0	0	1 (20.0)	0	0	N/A	N/A	0	1 (2.3)
Pembro SC	Paclitaxel	0	0	0	1 (14.3)	0	0	0	0	1 (1.2)
	Pemetrexed	16 (100.0)	15 (100.0)	14 (93.3)	6 (85.7)	6 (100.0)	2 (100.0)	3 (100.0)	21 (100.0)	83 (97.6)
	Pemetrexed, carboplatin	0	0	1 (6.7)	0	0	0	0	0	1 (1.2)
Type of IV Access, *n* (%)										
Peripheral access		44 (67.7)	22 (62.9)	13 (56.5)	12 (100.0)	10 (90.9)	7 (63.6)	0	49 (94.2)	157 (74.1)
Permanent access		0	4 (11.4)	0	0	0	0	3 (100.0)	0	7 (3.3)
Missing data, *n* (%)		21 (32.3)	9 (25.7)	10 (43.5)	0	1 (9.1)	4 (36.4)	0	3 (5.8)	48 (22.6)

HCP healthcare professional, *N/A* not applicable (site did not collect observations for respective treatment arm), *pembro IV* pembrolizumab intravenous, *pembro SC* pembrolizumab subcutaneous

[a]Data for active HCP time were complete ($N = 212$). Missing data and outlier removal occurred for patient time endpoints (chair: 2 pembrolizumab SC missing, 5 pembrolizumab SC outliers; treatment room: 2 pembrolizumab SC missing, 11 pembrolizumab SC outliers; healthcare facility: 2 pembrolizumab SC missing, no outliers)

[b]Observations were not collected for the pembrolizumab IV treatment group because it was not dispensed at this study site

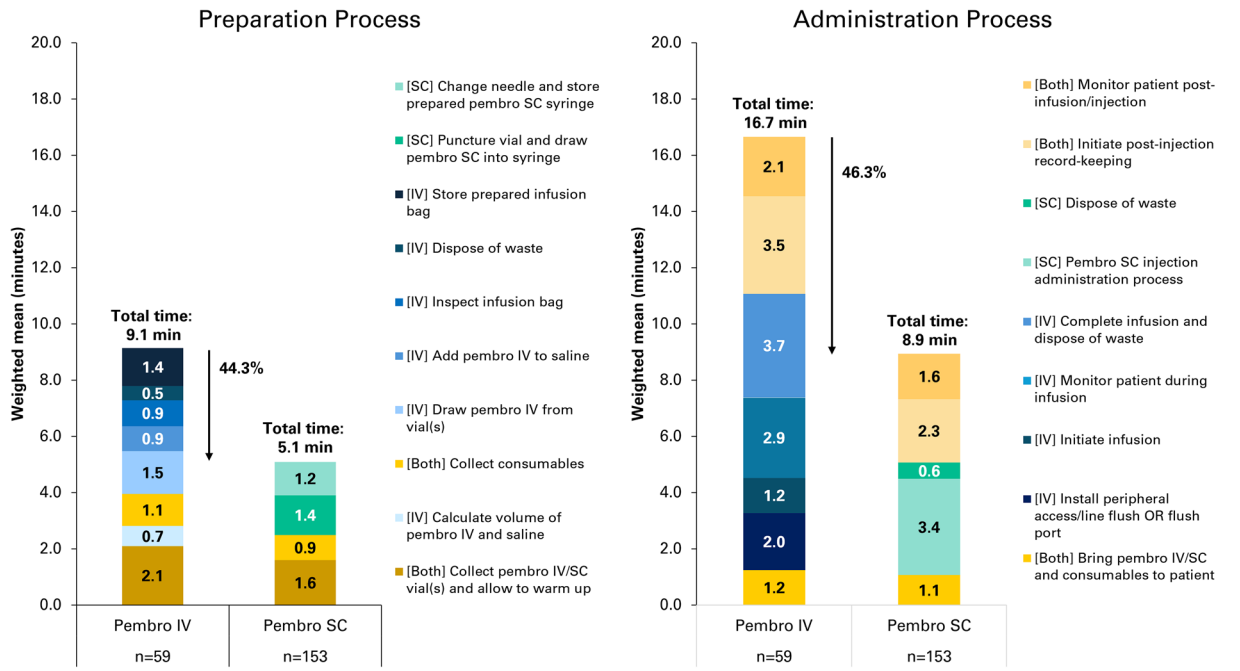

Fig. 2 Overall average active HCP time for preparation and administration processes by treatment group. Values are in weighted mean time (minutes). *HCP* healthcare professional, *IV* intravenous, *pembro* pembrolizumab, *SC* subcutaneous

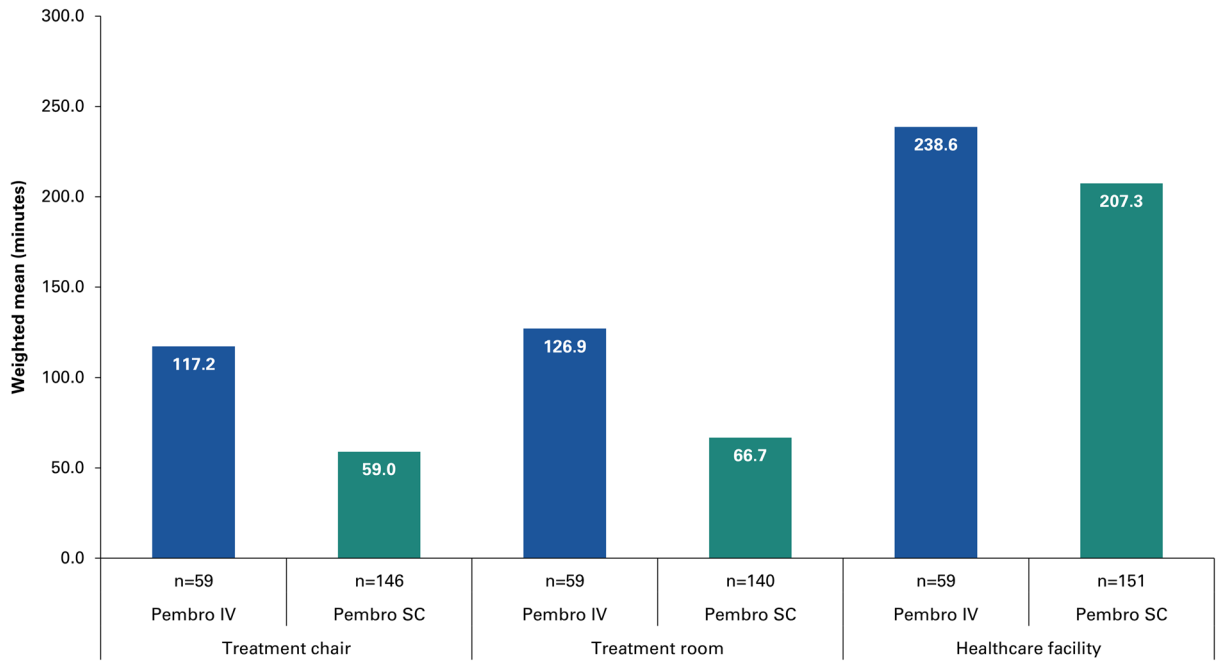

Fig. 3 Overall average patient time spent in the treatment chair, treatment room, and healthcare facility, by treatment group[a]. Values are in weighted mean time (minutes). [a]For observations including concomitant chemotherapy [43/59 (72.9%) for pembrolizumab IV and 85/153 (55.6%) for pembrolizumab SC; 98% pemetrexed for both treatment groups], any time associated with chemotherapy administration (on average 12.7 min) was removed from patient time endpoints (see Statistical analysis). *IV* intravenous, *pembro* pembrolizumab, *SC* subcutaneous

Table 2 Estimated difference in total active HCP time and patient time between the workflows for pembrolizumab SC and pembrolizumab IV by linear mixed model

Study endpoint	Estimated time difference, pembro SC vs pembro IV[a]		*P* value[c]
	Difference, minutes	95% CI	
Total active HCP time (preparation process)	− 3.6	− 4.4, −2.8	< 0.0001
Total active HCP time (administration process)	− 6.3	− 7.6, −5.0	< 0.0001
Total active HCP time (preparation and administration processes)	− 9.9	− 11.4, −8.4	< 0.0001
Patient time in the treatment chair[b]	− 35.6	− 47.8, −23.4	< 0.0001
Patient time in the treatment room[b]	− 34.9	− 46.6, −23.1	< 0.0001
Patient time in the healthcare facility[b]	− 22.3	− 44.8, 0.1	0.0515

HCP healthcare professional, *pembro SC* pembrolizumab subcutaneous, *pembro IV* pembrolizumab intravenous

[a]Pembro IV = reference group

[b]Adjusted by subtracting time associated with chemotherapy and removal of outliers

[c]*P*-values are for informational purposes only and do not confirm the existence of a difference between the two groups

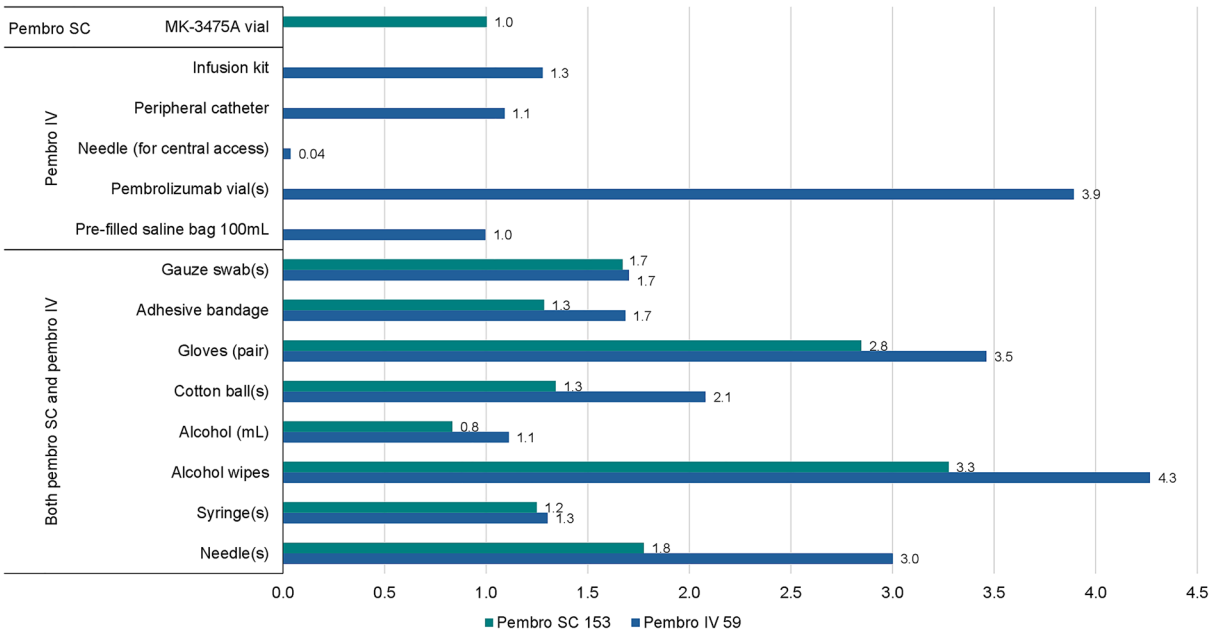

Fig. 4 Consumables usage for pembrolizumab SC and pembrolizumab IV. Values are weighted mean units. IV, intravenous; pembro, pembrolizumab; SC, subcutaneous

reductions in treatment room and chair time were driven by simpler and shorter drug administration with pembrolizumab SC (– 30.1 min). The reduction in facility time with pembrolizumab SC was less marked, likely attributable to variability in institutional workflows and patient pathways (e.g., clinic check-in and check-out times and various tests and procedures conducted during the entire visit; information not collected). Patient time endpoints by country demonstrated a high level of heterogeneity in measured chair time, treatment room time, and healthcare facility time (Supplementary Figure S5). For patient time results in the ten study sites with observations for both pembrolizumab IV and pembrolizumab SC, see Supplementary Figure S6.

Exploratory Results from LMM

An exploratory analysis using the LMM method was performed to account for within-group correlation (sites and countries) and to explore differences in time between workflows for pembrolizumab SC and pembrolizumab IV. The LMM showed substantial reductions in total active HCP time and patient time endpoints (except healthcare facility time) between pembrolizumab SC and pembrolizumab IV workflows (Table 2).

Consumables Usage

Average consumables usage (WM) is presented in Fig. 4. There was a trend for increased resource use with pembrolizumab IV compared with pembrolizumab SC for consumables that may be used for both modes of administration (e.g., needles, gauze swabs, adhesive bandages). More consumables were required exclusively for pembrolizumab IV, including pembrolizumab vials, prefilled 100-ml saline bags, infusion sets, and peripheral catheters or needles for central access. The only consumable exclusively required for SC administration is the pembrolizumab SC vial.

DISCUSSION

This T&M study, conducted in a subset of sites participating in the phase 3 MK-3475A-D77 clinical trial, demonstrated that pembrolizumab SC simplifies and shortens clinical workflows compared with pembrolizumab IV, providing evidence that pembrolizumab SC may generate substantial time efficiencies for both HCPs and patients. These findings are important to highlight, as oncology care increasingly prioritizes quality, efficiency, and patient-centered delivery. Anti-PD(L)1 inhibitors have transformed the treatment paradigm for numerous malignancies. Pembrolizumab SC offers two dosing regimens that can be administered in 1 min (Q3W) or 2 min (Q6W), and this flexibility, combined with its multiple indications, has the potential to improve patients' lives. Moreover, the choice of administration route for systemic therapies has now become an important factor in enhancing patient outcomes and optimizing healthcare resource utilization [20].

The findings from this T&M study are consistent with previous T&M studies across other monoclonal antibody therapies in various oncology settings that have reported less time dedicated by HCPs, reduced patient chair/treatment unit time, and/or less consumables usage associated with SC versus IV route of administration [4, 5, 16, 17, 21–24]. Our study demonstrated an approximately 46% reduction in total active HCP time and a 50% reduction in patient chair time with pembrolizumab SC compared with pembrolizumab IV. These time savings may be meaningful for practices managing high volumes, facing limited infusion chair availability, or experiencing lean staffing challenges. A key contributor to this efficiency is the streamlined workflow associated with pembrolizumab SC. Unlike IV therapy, SC delivery does not require peripheral or central venous access, line flushing, IV pump programming, or infusion rate checks. This simplified process eliminates multiple steps in both preparation and administration, reducing the potential for delays and allowing for faster patient turnaround. Real-world evidence studies have shown that adoption of SC administration of oncology treatments, in

place of IV-administered forms, led to increases in patient capacity, reduced hospital times, and improved quality of care [25–27].

Our study showed that pembrolizumab SC requires fewer consumable materials compared with pembrolizumab IV. IV delivery requires a saline bag, infusion kit, tubing, pump setup, and flushing supplies, whereas SC only requires the drug vial. This simplified setup lowers not only clinical complexity but also material costs. When scaled across multiple patients and treatment cycles, these reductions can lead to meaningful cost savings for healthcare institutions.

Reducing treatment burden for patients is important for high-quality, patient-centered care. Compared with pembrolizumab IV, pembrolizumab SC reduced patient chair time by nearly 50% and total treatment room time by approximately 47%, offering patients a more efficient, less disruptive clinic experience. Although this study did not assess patient-reported outcomes, prior studies in oncology settings consistently show a strong preference for SC due to shorter administration time, less injection-site pain, more comfort, and less anxiety [5]. These time savings, accumulated over multiple treatment cycles, may improve adherence and patient satisfaction, especially among working adults and those reliant on caregiver transportation.

This study has several notable strengths. First, we applied T&M methodology to identify relevant prespecified tasks and subsequently to adapt task descriptions at a site level to increase measurement accuracy of "active" HCP time. Staff in infusion suites often manage multiple patients simultaneously, therefore avoiding measurement of "nonactive" time —primarily relevant to pembrolizumab IV (e.g., time during IV infusion when HCPs are not actively monitoring the patient or during infusion line flushing). Consequently, our estimate of the efficiencies associated with pembrolizumab SC is likely conservative. This approach has been previously implemented in studies conducted alongside clinical trials [16, 17]. Second, observers were trained to ensure standardized time measurements, and data quality checks occurred in real-time to ensure quick validation to reduce recall bias. Third, in our study, 43 patients (72.9%) in the pembrolizumab IV group and 85 patients (55.6%) in the SC group received concomitant chemotherapy, which could confound patient time endpoints. To mitigate this, we excluded the duration of concomitant chemotherapy from patient time endpoints for a clearer comparison between pembrolizumab SC and IV (see Table 1). Lastly, this study was prospectively conducted across eight countries, capturing data across diverse health systems.

Our study has several limitations. We did not capture a detailed breakdown of the patient treatment pathway (e.g., waiting times, vitals checks, premedication, discharge procedures). Consequently, we lack insight into why patients on average spent 117 min and 59 min in the treatment chair for IV and SC, respectively, or why time in the healthcare facility only showed a 13% difference between the 2 treatment groups. Additionally, since all participants were enrolled in a clinical trial, activities such as monitoring, data collection, and protocol-specific assessments may have extended visit durations beyond what is typical in routine care. Therefore, the reported patient time savings for pembrolizumab SC and pembrolizumab IV may be underestimated relative to real-world practice, since patients were treated within the confines of a clinical trial that involves additional procedures potentially increasing time. This will need further assessment in future real-world studies. Notably, this study is descriptive and non-hypothesis testing in nature, lacking a formal sample size calculation. Therefore, the results from the exploratory LMM analyses should be interpreted as informational only. Lastly, unlike clinical endpoints, workflows and associated time are expected to differ between sites and countries because of local clinical practices, which is a known limitation in prior multicountry T&M studies [12, 13].

It is possible that clinical factors such as Eastern Cooperative Oncology Group performance status (ECOG PS) or difficult venous access could impact patient time-based endpoints, particularly patient chair and treatment room time. For example, patients with difficult venous access may require multiple IV attempts (IV group), and those with higher ECOG PS scores might have moved more slowly or needed assistance;

these factors could potentially extend the chair or treatment room time. However, it is important to note that this study was conducted using the patient population from the MK-3475A-D77 randomized clinical trial, which applied strict inclusion and exclusion criteria (e.g., ECOG PS 0–1) and utilized randomization to ensure balanced baseline clinical characteristics across treatment arms, helping to minimize variability from patient clinical factors that may impact workflow-related endpoints. This study was not designed to collect detailed patient-level data. We hypothesize that any potential clinical confounders would probably affect absolute time values, whereas relative time differences between SC and IV administration may be less sensitive to these confounders, although they could still be influenced if confounders were unevenly distributed.

Site heterogeneity impacts time; therefore when routes of administration are compared, samples are ideally equally balanced, with each country contributing the same number of sites and each site contributing the same number of observations for each treatment group, thereby allowing each site to act as its own control. This design was not feasible because of (1) imbalanced patient numbers across trial sites, (2) randomization timing relative to site activation dates, and (3) patient survival during the trial. Therefore, the study had sample imbalances in both groups. To address this limitation, the WM approach was used, assigning equal weight to each site within a country and to each country in the overall results. Lastly, we acknowledge that variability in time measurements may stem from different observers and staff. To address this bias, we implemented clear task descriptions, limited observers to two per site, and standardized observer training.

Despite its limitations, this T&M study offers valuable insights into time and resource efficiencies associated with pembrolizumab SC compared with pembrolizumab IV. This finding is significant, as pembrolizumab is a key component of the standard of care for multiple tumors.

CONCLUSIONS

This T&M study showed substantial reductions in active HCP time, patient chair time, and patient treatment unit time with the use of pembrolizumab SC compared with pembrolizumab IV. Pembrolizumab SC improves the patient's experience by streamlining the preparation and administration processes and thereby reducing time spent in the chair and treatment room. These findings show that pembrolizumab SC may lead to important time and resource efficiencies from the healthcare facility perspective. Time liberated for HCPs could be reallocated toward additional patient care activities, while optimized chair utilization could improve overall healthcare efficiency.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Erwin De Cock was an employee of Syneos Health at the time of the study. Since the time of the study, Erwin De Cock is no longer affiliated with Syneos Health. Cecilia Lourdudoss is an employee of Syneos Health. Sabine Oskar, Renata Eiras, M. Catherine Pietanza, and Ashwani Arunachalam are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. Gustavo Alves received research support from MSD, grants or contracts from Roche, AstraZeneca, Bristol Myers Squibb, MSD, Merck Serono, Pfizer, BeiGene, Ipsen; consulting fees from AstraZeneca and MSD; payment or honoraria from GlaxoSmithKline, AstraZeneca, MSD; and travel support from Janssen Pharmaceuticals. Gaston Lucas Martinengo reported no conflicts of interest. Enriqueta Felip reported receiving consulting fees from AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daichii, F. Hoffmann–La Roche, Gilead, GlaxoSmithKline, Iteos Therapeutics, Janssen Pharmaceuticals, Johnson & Johnson, MSD, Novartis, Pierre Fabre, Pfizer, Regeneron, Turning Point; payment or honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Daichii Sankyo, Eli Lilly, F. Hoffmann–La Roche, Genentech, Gilead, Janssen Pharmaceuticals, Johnson & Johnson, Medical Trends, Medscape, Merck Serono, MSD, Novartis, Peervoice, Pfizer, Regeneron; travel support from AstraZeneca, Janssen Pharmaceuticals, and Roche; and served as an independent member of the board for Grifols Diagnostic Solutions Inc.

Ethical Approval. Ethics approval for this T&M study was obtained for each site in accordance with local regulations, where applicable. The study was conducted in compliance with the approved protocol, the applicable principles outlined in Good Pharmacoepidemiology Practice guidelines, and the Declaration of Helsinki (1964 and its later amendments). The WCG IRB served as the master ethics committee for this study. WCG IRB approval was received on 13 Sep 2023 (WCG IRB tracking number: 20234046). Additional IRBs overseeing site-specific approvals are listed in Supplementary Material Table S1, along with their respective reference identifiers. All HCPs provided written agreements prior to observation. Patients under passive observation verbally consented after reviewing the study's patient information leaflet. All HCPs and study sites participated voluntarily and retained the right to withdraw from the study at any time and for any reason.

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