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ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Subcutaneous versus intravenous nivolumab for renal cell carcinoma☆

L. Albiges[1]*, M. T. Bourlon[2], M. Chacón[3], H. J. Cutuli[4], Y. A. L. Chuken[5], B. Żurawski[6], J. M. Mota[7], I. Magri[8], M. Burotto[9], M. Luz[10], J. de Menezes[11], E. P. Y. Ruiz[12], S. Fu[13,14], M. Richardet[15], B. P. Valderrama[16], M. Maruzzo[17], S. Bracarda[18], M. Breckenridge[19], H. E. Vezina[19], D. Rathod[19], Z. Yu[19], Y. Zhao[19], M. Dixon[19], D. Perumal[19] & S. George[20]

[1]Department of Oncology, Institut Gustave Roussy, Villejuif, France; [2]Urologic Oncology Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [3]Department of Oncology, Instituto Medico Especializado Alexander Fleming, Buenos Aires; [4]Uro-Oncology Research Unit, Hospital Sirio Libanês, Buenos Aires, Argentina; [5]iCan Oncology Center, Monterrey, Mexico; [6]Department of Outpatient Chemotherapy, Prof. Franciszek Łukaszczyk Oncology Centre, Bydgoszcz, Poland; [7]Instituto do Cancer do Estado de São Paulo, University of São Paulo, São Paulo, Brazil; [8]Centro Privado de RMI Rio Cuarto SA II, Rio Cuarto, Argentina; [9]Medical Oncology Department, Centro de Investigación Clínica Bradford Hill, Santiago de Chile, Chile; [10]IOP Instituto de Oncologia do Paraná, Curitiba; [11]Department of Oncology, Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; [12]School of Medicine, Department of Oncology, Universidad de la Frontera, Temuco, Chile; [13]Auckland City Hospital, Auckland; [14]Department of Oncology, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand; [15]Fundacion Richardet Longo, Instituto Oncologico de Cordoba, Cordoba, Argentina; [16]Hospital Universitario Virgen del Rocio, Department of Medical Oncology, Sevilla, Spain; [17]Oncology 1 Unit, Department of Oncology, Istituto Oncologico Veneto, IOV-IRCCS, Padova; [18]Medical Oncology Department, Azienda Ospedaliera Santa Maria, Terni, Italy; [19]Bristol Myers Squibb, Princeton; [20]Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, USA

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Background: The evolving oncology treatment paradigm has created an unmet need for administration options that improve patient experiences and health care efficiencies.

Patients and methods: CheckMate 67T (NCT04810078) was a phase III, open-label, multicenter, noninferiority trial in which patients with advanced/metastatic clear cell renal cell carcinoma were randomized to subcutaneous nivolumab (1200 mg every 4 weeks; coformulated with recombinant human hyaluronidase PH20 20 000 units) or intravenous nivolumab (3 mg/kg every 2 weeks). The primary objective was to assess the noninferiority of subcutaneous versus intravenous nivolumab by coprimary endpoints determined from a population pharmacokinetics analysis [time-averaged serum concentration over the first 28 days (C_{avgd28}), and minimum steady-state serum concentration (C_{minss}); noninferiority threshold: lower boundary of 90% confidence interval (CI) of the geometric mean ratios (GMR) $\geq$0.8]. Objective response rate (ORR) was a key secondary endpoint powered for noninferiority [noninferiority threshold: lower boundary of 95% CI of relative risk of ORR (subcutaneous versus intravenous nivolumab) $\geq$0.60].

Results: Overall, 495 patients were randomized. Relative exposure in the subcutaneous versus intravenous arm reported by the GMR of C_{avgd28} and C_{minss} was 2.098 (90% CI 2.001-2.200) and 1.774 (90% CI 1.633-1.927), respectively. After 8 months of minimum follow-up, ORR was 24.2% with subcutaneous nivolumab (95% CI 19.0%-30.0%) versus 18.2% with intravenous nivolumab [95% CI 13.6%-23.6%; relative risk: 1.33 (95% CI 0.94-1.87)]. Coprimary endpoints and ORR met noninferiority thresholds. Additional efficacy and safety measures were similar.

Conclusions: Subcutaneous nivolumab was noninferior to intravenous nivolumab based on pharmacokinetics and ORR. No new safety signals were observed.

Key words: nivolumab, subcutaneous, intravenous, noninferiority, renal cell carcinoma

INTRODUCTION

Nivolumab is approved for the treatment of multiple tumors and is associated with improved patient outcomes.[1-8] Intravenous (i.v.) administration of immune checkpoint inhibitors such as nivolumab carries a level of burden for both patients and health care systems due to the chronicity of treatment, long periods of time spent in the clinic for administration, the need for venous access, and, frequently, the use of a permanent access port, which is commonly associated with several complications.[9-12]

Evolving treatment paradigms require delivery options that reduce the treatment burden for patients while improving the efficiency of health care systems. Subcutaneous (s.c.) delivery of antibodies for various cancer indications has previously been shown to be effective and well tolerated.[13-16] Subcutaneous administration is typically preferred by patients over i.v. infusion[17-19] and has a shorter

*Correspondence to: Prof. Laurence Albiges, Medical Oncology Department, Gustave Roussy, Université Paris-Saclay, 114 Rue Edouard Vaillant, Villejuif, F-94805, France. Tel: +33-1-42-11-66-90

E-mail: Laurence.ALBIGES@gustaveroussy.fr (L. Albiges).

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preparation and chair occupancy time, which may improve health care resource utilization and reduce administrative workload.[17-22]

Recombinant human hyaluronidase (rHuPH20), with which nivolumab s.c. is coformulated, reversibly depolymerizes hyaluronan around the s.c. injection site. This allows the administration of large volumes (e.g. 10-15 ml), with fewer injections, reduced pain, and higher flow rates, than with s.c. administration without rHuPH20.[15] Various doses of nivolumab s.c. ± rHuPH20 were previously assessed in the multi-tumor dose-finding phase I/II study CheckMate 8KX (NCT03656718); population pharmacokinetic analysis including data from CheckMate 8KX and historical nivolumab i.v. data were used to determine a flat dose of 1200 mg nivolumab s.c. + rHuPH20 for further investigation.[23] This dose provides nivolumab exposure within the known safe and efficacious therapeutic window, and accounts for a range of patient body weights while mitigating potentially low bioavailability when administered to a broad patient population.

CheckMate 67T (NCT04810078) evaluated the noninferiority of nivolumab s.c. versus i.v. by pharmacokinetic and efficacy endpoints in patients with locally advanced or metastatic clear cell renal cell carcinoma (ccRCC) treated in the second- or third-line setting. A Supplementary Material of this article is available at https://doi.org/10.1016/j.annonc.2024.09.002.

PATIENTS AND METHODS

Patients

Eligible patients were aged at least 18 years with advanced (not amenable to curative surgery or radiation therapy) or metastatic, histologically confirmed ccRCC with or without sarcomatoid features. The Karnofsky performance status had to be 70 or more at screening. Patients were required to have evidence of intolerance or progression on or after the prior treatment regimen and within 6 months of randomization. Patients had a maximum of two prior systemic regimens with no prior immune checkpoint inhibitor therapy.

Trial design and treatments

CheckMate 67T was a phase III, open-label, multicenter, randomized, noninferiority trial. Patients were randomized 1 : 1 using interactive response technology, and stratified by baseline body weight (<80 kg versus ≥80 kg) and International Metastatic RCC Database Consortium (IMDC) risk score (favorable versus intermediate versus poor risk), to receive nivolumab monotherapy administered either subcutaneously at a flat dose of 1200 mg coformulated with rHuPH20 20 000 units every 4 weeks or intravenously at a dose of 3 mg/kg every 2 weeks per dosing guidelines at the time of study initiation. Treatment continued until progression, unacceptable toxicity, withdrawal of consent, completion of 2 years' treatment, or death.

This trial was conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and all applicable country and local regulations. The protocol was approved by the institutional review board or independent ethics committee at each site and is available online. All patients provided written informed consent.

Assessments

The schedules for collecting blood/plasma samples for pharmacokinetic and immunogenicity analysis are described in the protocol (available at https://doi.org/10.1016/j.annonc.2024.09.002). Nivolumab quantification and population pharmacokinetic analysis were carried out as previously described.[23]

Tumor response was assessed using computed tomography and/or magnetic resonance imaging carried out every 8 weeks (±7 days) from randomization for the first year, then every 12 weeks (±7 days) for the second year, and then every 24 weeks until investigator-assessed disease progression or treatment discontinuation, whichever occurred later. Safety analyses were summarized using worst grade per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Patient-reported outcomes (PROs) were assessed using the Functional Assessment of Cancer Therapy—Kidney Symptom Index-19 (FKSI-19) and the EuroQol 5 dimensions, 5 levels (EQ-5D-5L). PRO assessments were conducted within 14 days before randomization and before dosing and clinical assessments at each treatment visit in the s.c. arm or at every other treatment visit in the i.v. arm. Additional details are provided in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2024.09.002.

Study endpoints

The coprimary endpoints were time-averaged serum concentration of nivolumab over the first 28 days (C_{avgd28}) and the minimum serum concentration of nivolumab at steady state (C_{minss}), both assessed for noninferiority. These endpoints were derived from all pharmacokinetic-assessable participants using a population pharmacokinetic analysis where the structural, covariate, and residual components were prespecified, and the population and individual parameters were estimated using the study data. Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.09.002, illustrates these two parameters.

The objective response rate (ORR) was evaluated on an ongoing basis and defined as the rate of confirmed complete response (CR) or partial response (PR) in patients with at least 6 months' follow-up divided by the number of randomized participants, and was a key secondary endpoint powered for noninferiority. Tumor response to treatment was assessed per Response Evaluation Criteria in Solid Tumors version 1.1 by blinded independent central review (BICR), and confirmation of response was required at least 4 weeks after the initial response was recorded.

Other secondary efficacy endpoints included disease control rate (DCR), time to objective response (TTR), and progression-free survival (PFS; defined as the time from randomization to the date of the first documented tumor progression or death due to any cause), all assessed by BICR; OS was also assessed. Participants who died without a reported prior progression were considered to have progressed on the date of their death; those who did not die or progress were censored on the date of their last evaluable tumor assessment, and those without any on-study tumor assessment (who did not die) were censored on the date of randomization. Two censoring definitions were used regarding subsequent treatment: the primary definition censored patients who received subsequent anticancer therapy, including on-treatment palliative therapy, before or without documented progression on the date of the last evaluable tumor assessment conducted before or on the date of initiation of the subsequent anticancer therapy; the secondary definition did not censor patients who received subsequent therapy.

Secondary pharmacokinetic endpoints included minimum serum concentration at day 28 (C_{mind28}), maximum serum concentration after the first dose (C_{max1}), maximum serum concentration at steady state (C_{maxss}) and time-averaged serum concentration at steady state (C_{avgss}), all derived from a population pharmacokinetic analysis, and the observed trough concentration (C_{trough}) at week 17.

Safety endpoints included incidence rates of adverse events (AEs), treatment-related adverse events (TRAEs), AEs/TRAEs leading to discontinuation, serious adverse events (SAEs), and treatment-related SAEs (TRSAEs). The incidence rates of hypersensitivity/infusion-related reactions and local site reactions were also assessed. Immunogenicity assessments included the incidence of anti-nivolumab antibodies and neutralizing antibodies.

Key exploratory objectives included PROs to assess health-related quality of life (HRQoL) for each route of nivolumab administration.

Study populations

Pharmacokinetic endpoints were assessed in all patients with adequate dosing and nivolumab serum concentration—time data to estimate at least one pharmacokinetic endpoint. Patient baseline characteristics, efficacy, biomarkers, and PROs were assessed in all randomized patients, and safety and exposure were assessed in all patients who received at least one dose of nivolumab.

Statistical analysis

The study sample size was based on power calculation for ORR. The assumed noninferiority margin for the key secondary endpoint was defined using a 60% retention of ORR (nivolumab s.c. versus nivolumab i.v.). At least 454 randomized participants (randomized 1 : 1) were needed to demonstrate ORR by BICR noninferiority of nivolumab s.c. compared with nivolumab i.v. with 80% power and a one-sided overall significance level (alpha) of 0.025, assuming an ORR of 21% in both groups. For the pharmacokinetic coprimary endpoints, 46 pharmacokinetic-assessable participants per arm were needed to provide >99% and 90% power (one-sided alpha 0.05) for C_{avgd28} and C_{minss}, respectively. The overall power for the pharmacokinetic coprimary endpoints was >99% with 454 randomized patients.

The ORR risk ratio was estimated by the Mantel—Haenszel method stratified by weight category (<80 kg versus ≥80 kg) and IMDC risk group (favorable versus intermediate versus poor). To declare noninferiority, the lower boundary of the 95% confidence interval (CI) of the relative risk of ORR had to be 0.60 or greater, as used in previous s.c. versus i.v. noninferiority studies.[24] We assumed the true ORR point estimate to be within 3% of 21.5%, which was the ORR reported in CheckMate 025.[25]

Efficacy noninferiority determined by assessment of ORR by BICR was tested in a hierarchical fashion to preserve the overall experiment-wise type I error rate. The noninferiority needed to be met for both pharmacokinetic coprimary endpoints before the key secondary endpoint of ORR by BICR could be assessed.

Individual pharmacokinetic exposure measures were derived using the individual pharmacokinetic model parameters estimated by a population pharmacokinetic model. A linear fixed effects model (treatment and stratification factors as fixed effects) fitted to the log-transformed C_{avgd28} and C_{minss} was used to estimate effects and construct CIs. The noninferiority of s.c. nivolumab versus i.v. nivolumab was assessed using the two one-sided tests method, and noninferiority was concluded if the lower limit of the two-sided 90% CIs was 0.8 or greater for both geometric mean ratios (GMRs; C_{avgd28} and C_{minss}). Additional details are provided in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2024.09.002.

Noninferiority testing was carried out after the primary database lock on 21 August 2023, after 8.0 months' minimum follow-up.

PFS was estimated using the Kaplan—Meier product-limit method with associated two-sided 95% CIs calculated using Greenwood's formula via the log(-log) transformation method.

RESULTS

Study population and demographics

Patients were enrolled across 73 sites in 17 countries. Among randomized patients, 248 and 247 were assigned to the nivolumab s.c. and i.v. arms, respectively (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2024.09.002). The median age (range) was 64.0 years (35-93 years) in the s.c. arm and 66.0 years (20-87 years) in the i.v. arm (Table 1).

Results are reported from two study database locks, both occurring after enrollment and randomization were complete. Pharmacokinetic and efficacy (ORR) noninferiority endpoints, secondary pharmacokinetic endpoints, and the effect of antidrug antibodies on the pharmacokinetics of

Table 1. Baseline demographics and disease characteristics

Patient characteristics	Nivolumab + rHuPH20 s.c. (*n* = 248)	Nivolumab i.v. (*n* =247)
Age, years		
Mean	63.6	64.1
Median (range)	64.0 (35-93)	66.0 (20-87)
Sex, *n* (%)		
Female	84 (33.9)	76 (30.8)
Male	164 (66.1)	171 (69.2)
Weight (kg)		
Mean	77.8	77.8
Median (range)	76.8 (35.0-152.6)	76.70 (47.5-157.4)
Region, *n* (%)		
US and EU	67 (27.0)	76 (30.8)
Mexico and South America	159 (64.1)	148 (59.9)
Rest of the world	22 (8.9)	23 (9.3)
Ethnicity, *n* (%)		
Hispanic or Latino	93 (37.5)	84 (34.0)
Not Hispanic or Latino	80 (32.3)	83 (33.6)
Not reported	75 (30.2)	80 (32.4)
Prior lines of therapy, *n* (%)		
One	220 (88.7)	234 (94.7)
Two	28 (11.3)	13 (5.3)
Karnofsky PS, *n* (%)		
70	17 (6.9)	19 (7.7)
80	52 (21.0)	49 (19.8)
90	78 (31.5)	88 (35.6)
100	101 (40.7)	91 (36.8)
IMDC risk group, *n* (%)		
Favorable	48 (19.4)	57 (23.1)
Intermediate	158 (63.7)	147 (59.5)
Poor	42 (16.9)	43 (17.4)
Prior nephrectomy, *n* (%)		
No	45 (18.1)	42 (17.0)
Yes	203 (81.9)	205 (83.0)
CNS metastasis, *n* (%)		
No	214 (86.3)	224 (90.7)
Yes	34 (13.7)	23 (9.3)

CNS, central nervous system; IMDC, International Metastatic RCC Database Consortium; i.v., intravenous; PS, performance status; rHuPH20, recombinant human hyaluronidase PH20; s.c., subcutaneous.

nivolumab as well as biomarkers and the PRO results are from the primary database lock on 21 August 2023, after 8.0 months' minimum follow-up. Secondary efficacy endpoints (including updated ORR), safety, and the effect of antidrug antibodies on efficacy and safety are reported from a secondary database lock on 18 March 2024, after 15 months' minimum follow-up (median follow-up was 21.2 months for all randomized patients). At the secondary database lock, patients who received nivolumab s.c. every 4 weeks versus nivolumab i.v. every 2 weeks had received a median of 8.0 versus 17.0 doses, respectively, corresponding to similar treatment durations (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.09.002).

Coprimary pharmacokinetic endpoints

In the noninferiority analysis of C_{avgd28} and C_{minss} pharmacokinetic endpoints (illustrated in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.09.002), the geometric mean of C_{avgd28} was 77.373 μg/ml (90% CI 74.555-80.297 μg/ml) in the s.c. arm (n = 242) and 36.875 μg/ml (90% CI 35.565-38.235 μg/ml) in the i.v. arm (n = 245), with a GMR of 2.098 (90% CI 2.001-2.200) (Figure 1). Likewise, the geometric mean of C_{minss} was 122.227 μg/ml (90% CI 114.552-130.416 μg/ml) in the s.c. arm and 68.901 μg/ml (90% CI 64.676-73.402 μg/ml) in the i.v. arm, with a GMR of 1.774 (90% CI 1.633-1.927 μg/ml) (Figure 1). For both C_{avgd28} and C_{minss}, the lower boundary of the 90% CI for the GMR was 0.8 or greater, the prespecified cut-off for noninferiority, indicating that these pharmacokinetic endpoints for nivolumab s.c. were noninferior to those for nivolumab i.v.

Secondary efficacy endpoints

At the primary database lock, ORR was 24.2% (95% CI 19.0%-30.0%) in the s.c. arm and 18.2% (95% CI 13.6%-23.6%) in the i.v. arm, with a risk ratio of 1.33 (95% CI 0.94%-1.87%). The lower boundary of the 95% CI for the risk ratio was 0.6 or greater, indicating noninferiority of ORR of s.c. versus i.v. (Table 2). After the longer follow-up at the second database lock, ORR was 26.6% (95% CI 21.2%-32.6%) in the s.c. arm and 20.6% (95% CI 15.8%-26.2%) in the i.v. arm, with a risk ratio of 1.28 (95% CI 0.93-1.77), and DCR, TTR, PFS, and OS were numerically similar between the two arms (Table 2, Figure 2, Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2024.09.002).

Secondary pharmacokinetic endpoints

Secondary pharmacokinetic endpoints showed that exposures were higher with s.c. than with i.v. (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.09.002).

Safety

Overall, the safety profile was consistent between the s.c. and i.v. arms (Table 3, Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.09.002). Rates of all-causality AEs, TRAEs, and all-causality AEs and TRAEs leading to discontinuation were similar or lower for the s.c. arm than the i.v. arm. In the nivolumab i.v. and s.c. arms, 38.1% and 59.2% of patients had at least one dose delayed, and 0% and 4.9% of patients had at least one infusion/injection interrupted, respectively (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.09.002). Study drug toxicity led to three deaths in the s.c. arm due to myocarditis (one patient), myasthenia (one patient), and colitis complications (one patient) and two deaths in the i.v. arm due to immune-mediated pneumonitis/*Pneumocystis jirovecii* bronchopneumonia and disease progression (one patient) and vanishing bile duct syndrome (one patient). A summary of deaths and all-causality AEs leading to death is shown in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.09.002. Local injection-site reactions in the s.c. arm were low grade (mostly grade 1) and most resolved without treatment. Data from the

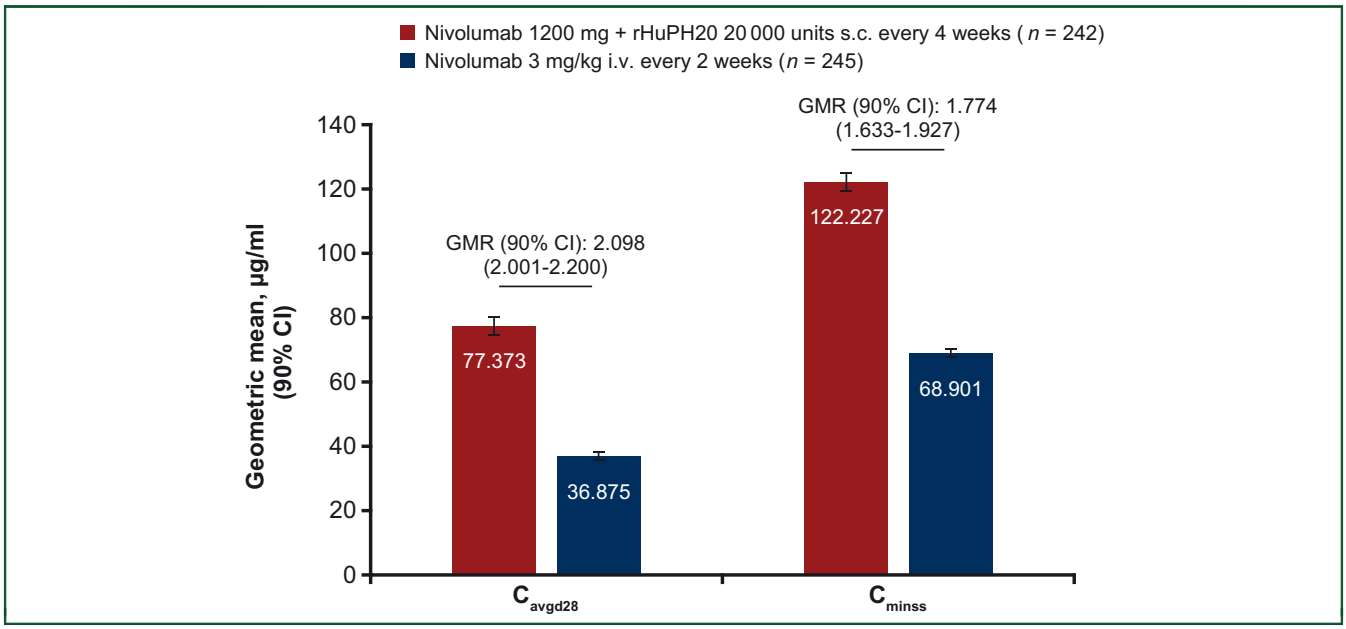

Figure 1. Geometric means of the coprimary pharmacokinetic endpoints. Data from primary database lock (21 August 2023); minimum 8 months' follow-up. C_{avgd28}, time-averaged serum concentration over the first 28 days; CI, confidence interval; C_{minss}, minimum steady-state serum concentration; GMR, geometric mean ratio; i.v., intravenous; rHuPH20, recombinant human hyaluronidase PH20; s.c., subcutaneous.

primary database lock indicated that local site reactions were transient (mean duration 3.02 days). The most common local site reaction was injection-site erythema. No anaphylactic reactions were observed in either arm.

Table 2. Secondary efficacy endpoints

	Nivolumab + rHuPH20 s.c. (*n* = 248)	Nivolumab i.v. (*n* = 247)
Primary database lock (minimum 8 months' follow-up)		
ORR, *n*	60	45
% (95% CI)	24.2 (19.0-30.0)	18.2 (13.6-23.6)
RR (95% CI)	1.33 (0.94-1.87)	
BOR		
CR, *n* (%)	5 (2.0)	4 (1.6)
PR, *n* (%)	55 (22.2)	41 (16.6)
SD, *n* (%)	96 (38.7)	110 (44.5)
PD, *n* (%)	62 (25.0)	66 (26.7)
UTD, *n* (%)	30 (12.1)	26 (10.5)
Secondary database lock (minimum 15 months' follow-up)		
ORR, *n*	66	51
% (95% CI)	26.6 (21.2-32.6)	20.6 (15.8-26.2)
RR (95% CI)	1.28 (0.93-1.77)	
BOR		
CR, *n* (%)	5 (2.0)	7 (2.8)
PR, *n* (%)	61 (24.6)	44 (17.8)
SD, *n* (%)	89 (35.9)	104 (42.1)
PD, *n* (%)	63 (25.4)	66 (26.7)
UTD, *n* (%)	30 (12.1)	26 (10.5)
DCR, *n* (%)	155 (62.5)	155 (62.8)
95% CI	56.2-68.5	56.4-68.8
RR (95% CI)	1.00 (0.88-1.15)	
Median TTR, months (range)	3.71 (1.7-11.3)	3.68 (1.6-13.8)
6-month OS rate, % (95% CI)	83.8 (78.5-87.9)	86.4 (81.3-90.2)
12-month OS rate, % (95% CI)	72.4 (66.2-77.6)	72.9 (66.7-78.2)

BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; i.v., intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; rHuPH20, recombinant human hyaluronidase PH20; RR, risk ratio; s.c., subcutaneous; SD, stable disease; TTR, time to objective response; UTD, unable to determine.

Immunogenicity

The incidence of nivolumab immunogenicity was as expected for the s.c. route of administration (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2024.09.002), which was within historical rates seen across nivolumab i.v. monotherapy studies (1.4%-23.7%). The presence versus absence of anti-nivolumab antibodies did not have any apparent clinically meaningful impact on pharmacokinetics, efficacy, or safety findings (Supplementary Tables S6 and S7; Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2024.09.002).

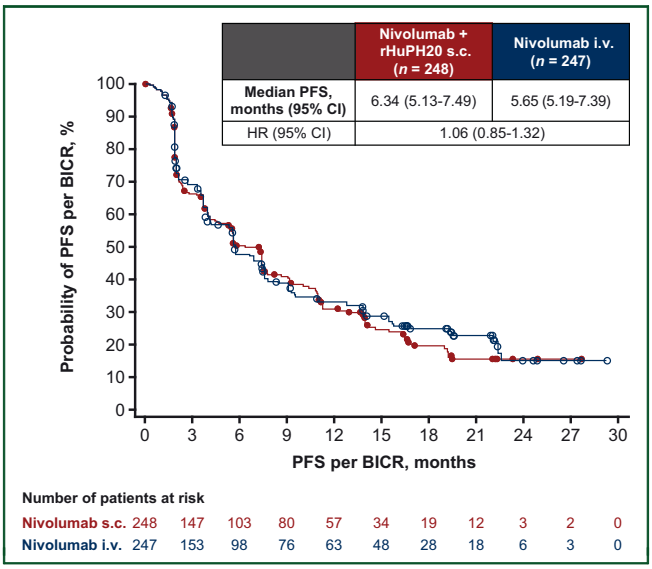

Figure 2. Progression-free survival by blinded independent central review with censoring upon receipt of subsequent therapy. Data from secondary database lock (18 March 2024); minimum 15 months' follow-up.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; i.v., intravenous; PFS, progression-free survival; rHuPH20, recombinant human hyaluronidase PH20; s.c., subcutaneous.

Table 3. Safety summary

n (%)	Nivolumab + rHuPH20 s.c. (*n* = 247)		Nivolumab i.v. (*n* = 245)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
All-causality AE[a,b]	230 (93.1)	99 (40.1)	231 (94.3)	114 (46.5)
Anemia	66 (26.7)	16 (6.5)	66 (26.9)	25 (10.2)
Pruritus	44 (17.8)	1 (0.4)	53 (21.6)	0
Arthralgia	35 (14.2)	1 (0.4)	54 (22.0)	3 (1.2)
Elevated creatinine	32 (13.0)	1 (0.4)	47 (19.2)	2 (0.8)
Cough	31 (12.6)	0	33 (13.5)	0
Diarrhea	28 (11.3)	1 (0.4)	43 (17.6)	1 (0.4)
Hyperglycemia	28 (11.3)	6 (2.4)	35 (14.3)	4 (1.6)
Hypothyroidism	25 (10.1)	0	32 (13.1)	1 (0.4)
Decreased appetite	24 (9.7)	0	32 (13.1)	3 (1.2)
Fatigue	22 (8.9)	2 (0.8)	41 (16.7)	8 (3.3)
TRAE[a]	152 (61.5)	29 (11.7)	161 (65.7)	42 (17.1)
All-causality AE leading to discontinuation[a]	31 (12.6)	23 (9.3)	34 (13.9)	24 (9.8)
TRAE leading to discontinuation[a]	11 (4.5)	7 (2.8)	13 (5.3)	9 (3.7)
All-causality AEs that required IMM[a]	94 (38.1)	34 (13.8)	106 (43.3)	39 (15.9)
Hypersensitivity/infusion-related reaction TRAEs[a]	1 (0.4)	1 (0.4)	7 (2.9)	0
Local site reaction TRAEs[c]	18 (7.3)	0	5 (2.0)	0
All-causality endocrine IMAEs[c]				
Hypothyroidism/thyroiditis	24 (9.7)	0	27 (11.0)	1 (0.4)
Adrenal insufficiency	6 (2.4)	2 (0.8)	3 (1.2)	0
Hyperthyroidism	3 (1.2)	0	11 (4.5)	0
Hypophysitis	0	0	3 (1.2)	2 (0.8)
All-causality nonendocrine IMAEs[c]				
Rash	18 (7.3)	2 (0.8)	15 (6.1)	3 (1.2)
Hepatitis	9 (3.6)	7 (2.8)	18 (7.3)	12 (4.9)
Diarrhea/colitis	8 (3.2)	1 (0.4)	7 (2.9)	0
Pneumonitis	7 (2.8)	3 (1.2)	7 (2.9)	2 (0.8)
Nephritis/renal dysfunction	4 (1.6)	0	2 (0.8)	0

Data from secondary database lock (18 March 2024); minimum 15 months' follow-up.
AE, adverse event; IMAE, immune-mediated adverse event; IMM, immune-modulating medication; i.v., intravenous; rHuPH20, recombinant human hyaluronidase PH20; s.c., subcutaneous; TRAE, treatment-related adverse event.
[a]Within 30 days of the last dose.
[b]The 10 most frequent all-causality AEs are presented here.
[c]Within 100 days of the last dose.

Biomarkers

Nivolumab s.c. and i.v. were associated with similar increases in interferon-gamma, CXCL10, and CXCL9 (Supplementary Figure S5A-C, available at https://doi.org/10.1016/j.annonc.2024.09.002), and programmed cell death protein 1 receptor occupancy on circulating CD3+, CD4+, and CD8+ T cells (Supplementary Figure S5D-F, available at https://doi.org/10.1016/j.annonc.2024.09.002) following treatment administration.

Patient-reported outcomes

FKSI-19 and EQ-5D-5L scores were stable over time and comparable between treatment arms (Supplementary Figures S6 and S7, available at https://doi.org/10.1016/j.annonc.2024.09.002).

DISCUSSION

CheckMate 67T establishes the noninferiority of pharmacokinetic exposures following s.c. versus i.v. administration of nivolumab. As expected with noninferior systemic exposures of s.c. versus i.v. nivolumab (as assessed by pharmacokinetic analysis), the key powered secondary endpoint of ORR by BICR demonstrated noninferiority of s.c. versus i.v. administration, according to a protocol-defined noninferiority cut-off. The ORR was consistent with that reported with nivolumab 3 mg/kg i.v. in CheckMate 025 in patients with previously treated advanced ccRCC; the ORR observed in CheckMate 67T was 24.2%, which is <3% different from that reported in CheckMate 025 (21.5%).[25] The PFS, DCR, and TTR were also similar between the s.c. and i.v. arms. The safety profile of s.c. was consistent with that of i.v., with no new safety signals identified.

Exposures were higher with nivolumab 1200 mg s.c. every 4 weeks than with nivolumab 3 mg/kg i.v. every 2 weeks. This was expected as the s.c. dosing regimen was selected to account for a wide range of body weights and a scenario of potentially low bioavailability with nivolumab s.c. Because body weight has been shown to affect the pharmacokinetics of nivolumab,[26] the flat dosing regimen for nivolumab s.c. was selected using a comprehensive model-based approach, including population pharmacokinetic analysis.[23] This approach identified nivolumab s.c. 1200 mg every 4 weeks as the regimen that would produce exposures similar to or greater than those achieved with a 3 mg/kg i.v. dose every 2 weeks, while remaining below the exposures seen with the

highest studied safe dose of 10 mg/kg i.v. every 2 weeks, taking into account variability in pharmacokinetics primarily due to bioavailability and body weight.

CheckMate 67T was conducted to confirm the dose selection evaluated in CheckMate 8KX, which assessed the s.c. formulation of nivolumab in patients with non-small-cell lung cancer, melanoma, renal cell carcinoma, colorectal cancer, urothelial cancer, gastric cancer, and squamous-cell carcinoma of the head and neck. Results from CheckMate 8KX demonstrated an acceptable tolerability profile for the s.c. formulation of nivolumab and patients' preference for s.c. administration over i.v. infusion.[27]

The proportion of patients with detectable anti-nivolumab antibodies was higher in the s.c. arm than in the i.v. arm. This can happen with s.c. formulations and is proposed to be due to the high antigen-processing efficiency of antigen-presenting cells, such as dendritic cells, in the skin.[28] The rates of anti-nivolumab antibodies have varied greatly across historical nivolumab i.v. monotherapy studies, and the incidence of anti-nivolumab antibodies among patients who received nivolumab s.c. in CheckMate 67T was within these rates. The incidence of neutralizing antibodies was low in both arms. Further assessments did not identify an apparent clinically meaningful impact of the development of antidrug antibodies on nivolumab pharmacokinetics, efficacy, or safety.

Subcutaneous and i.v. administration had a similar impact on patients' HRQoL based on the FKSI-19 total score and EQ-5D-5L over time. An assessment of patient preference for route of administration was conducted in CheckMate 8KX, which found that patients were highly satisfied with nivolumab s.c. and either preferred it to nivolumab i.v. or had no preference.[27]

Administration of s.c. monoclonal antibodies is associated with potential savings on chair/treatment times compared with i.v. administration and could allow for treatment closer to the patient's home. In a simulated cohort of 157 patients with non-Hodgkin lymphoma, a 20% transition from i.v. to s.c. rituximab was estimated to potentially save $150 000 and 270 h of staff time.[20] A phase III study demonstrated the feasibility of home administration of trastuzumab s.c. in patients with early-stage human epidermal growth factor receptor-positive breast cancer, which was preferred by both patients and nurses over i.v. administration and was quicker and less resource-intensive than i.v. administration.[22] In CheckMate 67T, we observed that s.c. administration took on average <5 min; substantially less time than that required for i.v. administration ($\sim$30 min).

The strengths of CheckMate 67T include its noninferiority design, the sample size, the ORR by BICR endpoint powered for statistical analysis, and the ethnic diversity of the patients enrolled, with a large proportion of patients of Latin American ethnicity included. While this dataset was sufficient to assess all the powered endpoints needed to assess noninferiority, one limitation is that some long-term outcomes were immature and require additional follow-up.

Conclusions

This trial demonstrated that nivolumab s.c. was noninferior to nivolumab i.v. The safety profile of nivolumab s.c. was consistent with that of nivolumab i.v., with no new safety concerns emerging. These findings support the potential use of nivolumab s.c. as a new option to reduce patient treatment burden and improve health care efficiency across solid tumors.

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DATA SHARING

Information on Bristol Myers Squibb's data-sharing policy can be found here: https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

REFERENCES

1. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med*. 2021;384(22):2102-2114.
2. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386(21):1973-1985.
3. Kirkwood JM, Del Vecchio M, Weber J, et al. Adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial. *Nat Med*. 2023;29(11):2835-2843.
4. Robert C, Long GV, Brady B, et al. Five-year outcomes with nivolumab in patients with wild-type *BRAF* advanced melanoma. *J Clin Oncol*. 2020;38(33):3937-3946.
5. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1803-1813.
6. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378(14):1277-1290.
7. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2021;384(9):829-841.
8. OPDIVO® (nivolumab) [package insert]. Bristol Myers Squibb, Princeton, NJ. Published 2024. https://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed June 12, 2024.
9. Drugeon B, Guenezan J, Pichon M, et al. Incidence, complications, and costs of peripheral venous catheter-related bacteraemia: a retrospective, single-centre study. *J Hosp Infect*. 2023;135:67-73.
10. O'Shaughnessy J, Sousa S, Cruz J, et al. Patient (pt) preference for the pertuzumab-trastuzumab fixed-dose combination for subcutaneous use (PH FDC SC) in HER2-positive early breast cancer (EBC): primary analysis of the open-label, randomised crossover PHranceSCa study. *Ann Oncol*. 2020;31:S306-S307.
11. Machat S, Eisenhuber E, Pfarl G, et al. Complications of central venous port systems: a pictorial review. *Insights Imaging*. 2019;10(1):86.
12. Ma LI, Liu Y, Wang J, Chang Y, Yu L, Geng C. Totally implantable venous access port systems and associated complications: a single-institution retrospective analysis of 2,996 breast cancer patients. *Mol Clin Oncol*. 2016;4(3):456-460.
13. Davies M, Duffield EA. Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. *Immunotargets Ther*. 2017;6:51-71.
14. Jackisch C, Stroyakovskiy D, Pivot X, et al. Subcutaneous vs intravenous trastuzumab for patients with ERBB2-positive early breast cancer: final analysis of the HannaH phase 3 randomized clinical trial. *JAMA Oncol*. 2019;5(5):e190339.
15. Locke KW, Maneval DC, LaBarre MJ. ENHANZE® drug delivery technology: a novel approach to subcutaneous administration using

recombinant human hyaluronidase PH20. *Drug Deliv*. 2019;26(1):98-106.
16. Lugtenburg P, Avivi I, Berenschot H, et al. Efficacy and safety of subcutaneous and intravenous rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in first-line diffuse large B-cell lymphoma: the randomized MabEase study. *Haematologica*. 2017;102(11):1913-1922.
17. Rummel M, Kim TM, Aversa F, et al. Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab). *Ann Oncol*. 2017;28(4):836-842.
18. Dent S, Ammendolea C, Christofides A, et al. A multidisciplinary perspective on the subcutaneous administration of trastuzumab in HER2-positive breast cancer. *Curr Oncol*. 2019;26(1):e70-e80.
19. O'Shaughnessy J, Sousa S, Cruz J, et al. Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): a randomised, open-label phase II study. *Eur J Cancer*. 2021;152:223-232.
20. Harvey MJ, Zhong Y, Morris E, et al. Assessing the transition from intravenous to subcutaneous delivery of rituximab: benefits for payers, health care professionals, and patients with lymphoma. *PLoS One*. 2022;17(1):e0261336.
21. Jackisch C, Manevy F, Frank S, Roberts N, Shafrin J. White paper on the value of time savings for patients and healthcare providers of breast cancer therapy: the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection as an example. *Adv Ther*. 2022;39(2):833-844.
22. Denys H, Martinez-Mena CL, Martens MT, et al. Safety and tolerability of subcutaneous trastuzumab at home administration, results of the phase IIIb open-label BELIS study in HER2-positive early breast cancer. *Breast Cancer Res Treat*. 2020;181(1):97-105.
23. Zhao Y, Sanghavi K, Roy A, et al. Model-based dose selection of subcutaneous nivolumab in patients with advanced solid tumors. *Clin Pharmacol Ther*. 2024;115(3):488-497.
24. Mateos MV, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. *Lancet Haematol*. 2020;7(5):e370-e380.
25. Xu JX, Maher VE, Zhang L, et al. FDA approval summary: nivolumab in advanced renal cell carcinoma after anti-angiogenic therapy and exploratory predictive biomarker analysis. *Oncologist*. 2017;22(3):311-317.
26. Bajaj G, Wang X, Agrawal S, et al. Model-based population pharmacokinetic analysis of nivolumab in patients with solid tumors. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(1):58-66.
27. Lonardi S, Ługowska I, O'Donnell A, et al. Pharmacokinetics and safety of a subcutaneous formulation of nivolumab (NIVO SC) monotherapy: updated results from the phase 1/2 CheckMate 8KX study. *J Immunother Cancer*. 2023;11(suppl 1).
28. Jarvi NL, Balu-Iyer SV. Immunogenicity challenges associated with subcutaneous delivery of therapeutic proteins. *BioDrugs*. 2021;35(2):125-146.