Nivolumab subcutaneous versus nivolumab intravenous in patients with previously treated advanced or metastatic clear cell renal cell carcinoma (ccRCC): updated efficacy and safety results from CheckMate 67T*

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Objectives

- To compare the efficacy and safety of NIVO subcutaneous (SC) with NIVO intravenous (IV) in patients with advanced or metastatic ccRCC after extended 15 months' minimum follow-up

Conclusions

- CheckMate 67T met its co-primary endpoints and key powered secondary endpoint at the primary analysis, demonstrating pharmacokinetic and efficacy (objective response rate [ORR] by blinded independent central review [BICR]) noninferiority of NIVO SC to NIVO IV[5]
- ORR with extended 15 months' minimum follow-up (NIVO SC, 26.6%; NIVO IV, 20.6%) was consistent with the primary analysis (NIVO SC, 24.2%; NIVO IV, 18.2%),[5] with additional responses observed in each arm
- Disease control rate, time to response, progression-free survival (PFS), and overall survival (OS) rates were similar between arms
- The safety profile of NIVO SC was consistent with that of NIVO IV, with no new safety concerns or signals identified after extended 15 months' minimum follow-up
  - Local injection-site reactions in the SC arm were low-grade (mostly grade 1), transient, and most resolved without treatment
- The incidence of anti-NIVO antibodies remained higher with NIVO SC vs NIVO IV after extended 15 months' minimum follow-up and was consistent with observations from the primary analysis
  - The incidence of anti-NIVO antibodies in the SC arm was within historical rates seen across NIVO IV monotherapy studies, and had no apparent clinically meaningful impact on pharmacokinetics, efficacy, or safety
- These data further support the use of NIVO SC as a potential new option to improve patient treatment experience and healthcare efficiency

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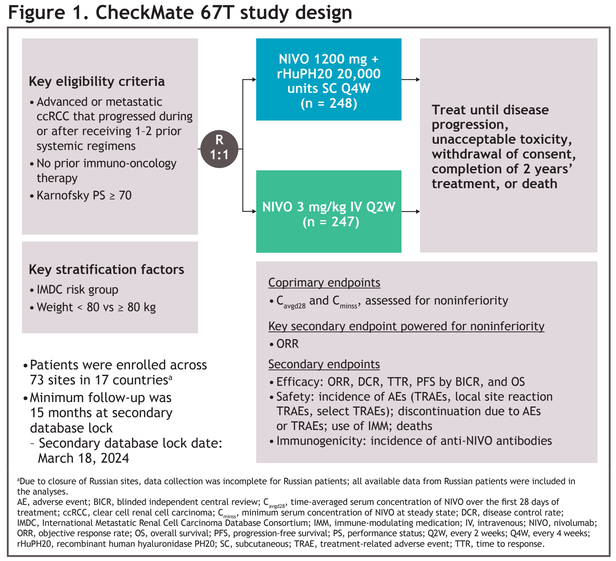
Background

- The evolving treatment paradigm in oncology has created an unmet need for administration options to improve patients' treatment experience and reduce healthcare inefficiencies
- SC delivery may address these challenges and is typically preferred by patients over IV delivery[1,2]
- NIVO SC is co-formulated with recombinant human hyaluronidase PH20 (rHuPH20), which degrades hyaluronan in the extracellular matrix around the SC injection area, enabling administration of large volumes[3]
  - Preclinical studies have shown that rHuPH20 transiently increases the dispersion of injected molecules; 24 hours after rHuPH20 administration, dispersion of injected molecules returned to baseline[4]
- CheckMate 67T (NCT04810078) is a phase 3 trial comparing NIVO SC with NIVO IV in advanced or metastatic ccRCC
  - After 8 months' minimum follow-up, coprimary pharmacokinetic and key secondary efficacy (ORR) endpoints, all powered for noninferiority analysis, were noninferior with NIVO SC compared to NIVO IV[5]
  - The overall safety profile of NIVO SC was consistent with that of NIVO IV, with no new safety concerns identified[6]
- Here, we report updated efficacy, safety, and immunogenicity data after extended 15 months' minimum follow-up

Study design

- Patients were stratified by their International Metastatic Renal Cell Carcinoma Database Consortium risk grouping and baseline weight, and randomized 1:1 to either NIVO 1200 mg + rHuPH20 20,000 units SC every 4 weeks (n = 248) or NIVO 3 mg/kg IV every 2 weeks (n = 247) (**Figure 1**)
- Baseline characteristics and efficacy were assessed in all randomized patients; safety was assessed in all patients who received ≥ 1 dose of NIVO; immunogenicity was assessed in all treated patients with baseline and ≥ 1 post-baseline assessment for immunogenicity data

Figure 1. CheckMate 67T study design



[a]Due to closure of Russian sites, data collection was incomplete for Russian patients; all available data from Russian patients were included in the analyses.
AE, adverse event; BICR, blinded independent central review; C_{avg28}, time-averaged serum concentration of NIVO over the first 28 days of treatment; ccRCC, clear cell renal cell carcinoma; C_{minss}, minimum serum concentration of NIVO at steady state; DCR, disease control rate; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IMM, immune-modulating medication; IV, intravenous; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q2W, every 2 weeks; Q4W, every 4 weeks; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; TRAE, treatment-related adverse event; TTR, time to response.

Results

Baseline demographics and disease characteristics

- Baseline demographics and disease characteristics were balanced between the arms (**Table 1**)

Efficacy

- Responses by BICR were comparable between NIVO SC and NIVO IV (**Table 2**)
- Median PFS by BICR and OS rates were similar between the NIVO SC and NIVO IV arms (**Table 2**, **Figure 2**)

Safety

- The safety profile of NIVO SC was consistent with that of NIVO IV, with no new safety concerns or signals identified (**Table 3**)
  - One additional death due to study drug toxicity (vanishing bile duct syndrome) was reported in the NIVO IV arm after 15 months' minimum follow-up vs the primary analysis after 8 months' minimum follow-up
  - Study drug toxicity led to 3 deaths in the NIVO SC arm (myocarditis [n = 1], myasthenia [n = 1], colitis complications [n = 1]) and 2 deaths in the NIVO IV arm (immune-mediated pneumonitis/pneumocystis jirovecii bronchopneumonia/disease progression [n = 1] and vanishing bile duct syndrome [n = 1])

Immunogenicity

- Incidence of anti-NIVO antibodies was higher with NIVO SC (24.0%) than NIVO IV (6.9%), which is consistent with the findings from the primary analysis[5]; no additional patients in either arm developed anti-NIVO neutralizing antibodies
- Across the NIVO IV monotherapy clinical program, significant variation with anti-NIVO antibodies has been observed; the incidence in the NIVO SC study was within the overall range of anti-NIVO antibodies previously seen across other studies[7]
- There was no apparent clinically meaningful impact of development of anti-NIVO antibodies on efficacy and safety, which is consistent with findings from the primary analysis[7]

Table 1. Baseline demographics and disease characteristics

Patient characteristics	NIVO + rHuPH20 SC (n = 248)	NIVO IV (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)	76.7 (47.5-157.4)
Weight category, n (%)		
< 80 kg	140 (56.5)	141 (57.1)
≥ 80 kg	108 (43.5)	106 (42.9)
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 (%)		
Yes	203 (81.9)	205 (83.0)
No	45 (18.1)	42 (17.0)
CNS metastasis, n (%)		
Yes	34 (13.7)	23 (9.3)
No	214 (86.3)	224 (90.7)

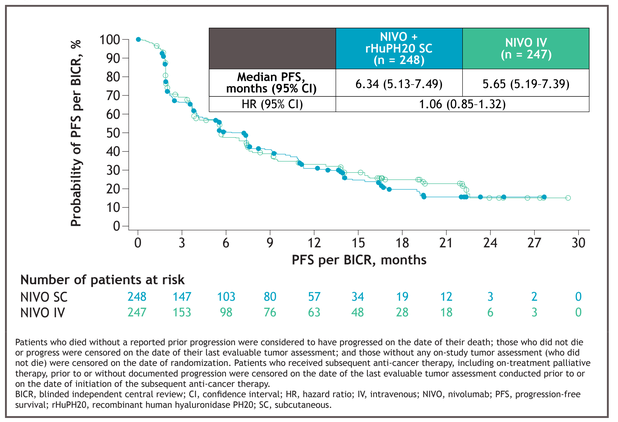
CNS, central nervous system; EU, European Union; IMDC, International Metastatic renal cell carcinoma Database Consortium; IV, intravenous; NIVO, nivolumab; PS, performance status; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; US, United States.

Table 2. Efficacy summary

	NIVO + rHuPH20 SC (n = 248)	NIVO IV (n = 247)
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)
ORR by BICR, % (95% CI)	26.6 (21.2-32.6)	20.6 (15.8-26.2)
Risk ratio (95% CI)	1.28 (0.93-1.77)	
DCR, % (95% CI)	62.5 (56.2-68.5)	62.8 (56.4-68.8)
Risk ratio (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)

BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; IV, intravenous; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SD, stable disease; TTR, time to response; UTD, unable to determine.

Figure 2. PFS by BICR



Patients 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. Patients who received subsequent anti-cancer therapy, including on-treatment palliative therapy, prior to or without documented progression were censored on the date of the last evaluable tumor assessment conducted prior to or on the date of initiation of the subsequent anti-cancer therapy.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; IV, intravenous; NIVO, nivolumab; PFS, progression-free survival; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

Table 3. Safety summary

n (%)	NIVO + rHuPH20 SC (n = 247)		NIVO IV (n = 245)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
AEs	230 (93.1)	99 (40.1)	231 (94.3)	114 (46.5)
TRAEs	152 (61.5)	29 (11.7)	161 (65.7)	42 (17.1)
Discontinuation due to AEs	31 (12.6)	23 (9.3)	34 (13.9)	24 (9.8)
Discontinuation due to TRAEs	11 (4.5)	7 (2.8)	13 (5.3)	9 (3.7)
Local site reaction TRAEs occurring in ≥ 2 patients[a]	18 (7.3)	0	5 (2.0)	0
Injection site erythema	6 (2.4)	0	0	0
Application site pain	2 (0.8)	0	0	0
Injection site edema	2 (0.8)	0	0	0
Injection site reaction	2 (0.8)	0	0	0
Infusion related reaction	0	0	5 (2.0)	0
Patients who received IMM[b]	46 (71.9)[c]	11 (91.7)[d]	46 (70.8)[e]	15 (93.8)[f]
Patients who received corticosteroids (≥ 40 mg prednisone or equivalent)[b]	21 (32.8)[c]	6 (50.0)[d]	32 (49.2)[e]	13 (81.3)[f]
Select TRAEs				
Endocrine	31 (12.6)	2 (0.8)	44 (18.0)	3 (1.2)
Gastrointestinal	15 (6.1)	0	17 (6.9)	1 (0.4)
Hepatic	23 (9.3)	8 (3.2)	31 (12.7)	10 (4.1)
Pulmonary	12 (4.9)	4 (1.6)	8 (3.3)	2 (0.8)
Renal	8 (3.2)	1 (0.4)	14 (5.7)	0
Skin	60 (24.3)	4 (1.6)	67 (27.3)	3 (1.2)
Hypersensitivity/infusion reaction	1 (0.4)	1 (0.4)	7 (2.9)	0

[a]The following events occurred at grade 1/2 in 1 patient each in the NIVO + rHuPH20 SC arm: administration site pain, application site erythema, application site rash, injection site discoloration, injection site inflammation, injection site pain, injection site pruritus, puncture site erythema; [b]These data are from the primary database lock (August 21, 2023), minimum 8 months' follow-up for subjects who experienced at least one immune-mediated AE; [c]n = 64; [d]n = 12; [e]n = 65; [f]n = 16.
AE, adverse event; IMM, immune-modulating medication; IV, intravenous; NIVO, nivolumab; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; TRAE, treatment-related adverse event.

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Declaration of interests

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