First-line nivolumab plus ipilimumab versus sunitinib in patients with long-term survival of ≥ 5 years in the CheckMate 214 trial

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Background

- First-line nivolumab plus ipilimumab (NIVO+IPI), a current standard of care, has demonstrated superior long-term survival (LTS) and response benefits over sunitinib (SUN) in patients with advanced renal cell carcinoma (aRCC) along with improved safety after 5 years minimum follow-up in the CheckMate 214 trial[1-5]
  - Data on LTS among patients with aRCC receiving immunotherapy are limited
  - Characterizing clinical measures associated with LTS may inform treatment approaches and guide future immune checkpoint blockade–based clinical trial design[6]
- Here, we report an exploratory analysis in a subgroup of patients from CheckMate 214 with aRCC and LTS ≥ 5 years

Methods

- Patients with previously untreated clear cell aRCC were randomized 1:1 to receive intravenous NIVO 3 mg/kg + IPI 1 mg/kg every 3 weeks for 4 doses then NIVO 3 mg/kg every 2 weeks, or SUN 50 mg orally once daily (4 weeks on, 2 weeks off; 6-week cycle)[1,2]
  - Patients were stratified by geographic region and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk status (favorable, intermediate, or poor)
- Overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) outcomes were assessed in intent-to-treat (ITT), intermediate/poor-risk (I/P), and favorable-risk (FAV) populations, with a median follow-up of 67.7 months
  - Response outcomes were confirmed and reported by an independent radiology review committee (IRRC) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- In this post hoc exploratory analysis, patients with LTS, defined as those alive at 5 years, were assessed in the ITT population and by IMDC risk (I/P and FAV)
  - Non-prespecified outcomes included characterization of baseline demographic and clinical characteristics, subsequent systemic therapy, depth and duration of response, treatment-free interval, treatment exposure, and treatment-related adverse events (TRAEs) leading to discontinuation
  - Data in the total CheckMate 214 ITT trial population have been included for reference
- Treatment-free interval, defined as the time from end of therapy until last known date alive, was assessed post hoc and included treated patients with a confirmed objective response per IRRC who were off study treatment and never received subsequent therapy
- Safety was assessed in all treated patients per the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0[7]

Results

Patients with LTS ≥ 5 years

- Of the 1096 patients randomized to NIVO+IPI or SUN, LTS was reported in 236 of 550 (43%) total patients, 163 of 425 (38%) I/P-risk patients, and 73 of 125 (58%) FAV-risk patients in the NIVO+IPI arm, and in 171 of 546 (31%) total patients, 112 of 422 (27%) I/P-risk patients, and 59 of 124 (48%) FAV-risk patients in the SUN arm

Table 1. Select baseline characteristics

Characteristic[a]	ITT patients[1]		All patients with LTS	
	NIVO+IPI (N = 550)	SUN (N = 546)	NIVO+IPI (n = 236)	SUN (n = 171)
Median age (range), years	62 (26-85)	62 (21-85)	61 (34-81)	61 (32-85)
Sex, n (%)				
Male	413 (75)	395 (72)	172 (73)	126 (74)
Female	137 (25)	151 (28)	64 (27)	45 (26)
IMDC prognostic score, n (%)[a]				
Favorable (0)	125 (23)	124 (23)	68 (29)	53 (31)
Intermediate (1-2)	334 (61)	333 (61)	143 (61)	108 (63)
Poor (3-6)	91 (17)	89 (16)	25 (11)	9 (5)
Not reported	0	0	0	1 (< 1)
Region, n (%)				
United States	154 (28)	153 (28)	71 (30)	49 (29)
Canada/Europe	201 (37)	199 (36)	91 (39)	74 (43)
Rest of the world	195 (35)	194 (36)	74 (31)	48 (28)
Prior radiotherapy, n (%)	63 (11)	70 (13)	20 (8)	15 (9)
Prior nephrectomy, n (%)	453 (82)	437 (80)	200 (85)	155 (91)
No. of sites with target/ nontarget lesions, n (%)[b]				
1	123 (22)	118 (22)	71 (30)	52 (30)
≥ 2	427 (78)	427 (78)	165 (70)	118 (69)
Median sum of reference diameters of target lesion (range), mm	65.5 (10-357)	63.0 (10-359)	50.5 (10-276)	48.0 (10-283)
Sites of metastasis, n (%)[c,d]				
Lung	381 (69)	373 (68)	164 (69)	106 (62)
Lymph node	246 (45)	268 (49)	96 (41)	77 (45)
Bone[e]	112 (20)	119 (22)	25 (11)	18 (11)
Liver	99 (18)	107 (20)	31 (13)	27 (16)
Quantifiable tumor PD-L1 expression, n (%)	**n = 499**	**n = 503**	**n = 223**	**n = 158**
< 1%	386 (77)	376 (75)	170 (76)	123 (78)
≥ 1%	113 (23)	127 (25)	53 (24)	35 (22)

[a]Data collected with an interactive voice-response system. [b]The number of target/nontarget lesions at baseline was not reported for 1 ITT patient in the SUN arm. [c]Includes target/nontarget lesions. [d]Patients may have lesions at more than 1 site. [e]Bone with/without soft-tissue component.
PD-L1, programmed death ligand 1.

- Among all patients with LTS, 32 (14%) patients in the NIVO+IPI arm and 8 (5%) patients in the SUN arm remained on treatment at 5 years follow-up
- Baseline characteristics generally did not distinguish all patients with LTS from the general study population in the NIVO+IPI arm, except that all patients with LTS had a lower target lesion burden at baseline and a smaller proportion of all patients with LTS had ≥ 2 sites of target/nontarget lesions or bone metastases versus the ITT population as a whole (**Table 1**)
  - Similarly, I/P patients with LTS in the NIVO+IPI arm had a lower target lesion burden at baseline versus all I/P patients (56.0 vs 72.0 mm), and a smaller proportion of I/P patients with LTS in the NIVO+IPI arm had ≥ 2 sites of target/nontarget lesions (70% vs 79%) or sites of bone metastases (11% vs 22%), respectively
- Fewer patients with LTS required subsequent systemic therapy with NIVO+IPI versus SUN (**Table 2**)
  - Most patients in the SUN arm who received subsequent systemic therapy received NIVO monotherapy regardless of risk (ITT, 57%; I/P, 53%; FAV, 66%)
- Among I/P patients in the NIVO+IPI arm, 47% of patients with LTS received subsequent systemic therapy versus 67% of those without LTS
  - In FAV patients with LTS in the NIVO+IPI arm, 71% received subsequent systemic therapy compared with 62% of FAV patients without LTS

Table 2. Subsequent therapy in all patients with LTS and by IMDC intermediate/poor and favorable risk

	All patients with LTS		I/P patients with LTS		FAV patients with LTS	
	NIVO+IPI (n = 236)	SUN (n = 171)	NIVO+IPI (n = 163)	SUN (n = 112)	NIVO+IPI (n = 73)	SUN (n = 59)
Any subsequent systemic therapy, n (%)[a,b]	114 (48)	133 (78)	64 (39)	84 (75)	50 (68)	49 (83)
NIVO	33 (14)	98 (57)	17 (10)	59 (53)	16 (22)	39 (66)
Axitinib	36 (15)	42 (25)	22 (13)	28 (25)	14 (19)	14 (24)
Cabozantinib	45 (19)	43 (25)	27 (17)	26 (23)	18 (25)	17 (29)
Pazopanib	37 (16)	9 (5)	19 (12)	6 (5)	18 (25)	3 (5)
SUN	40 (17)	27 (16)	24 (15)	15 (13)	16 (22)	12 (20)

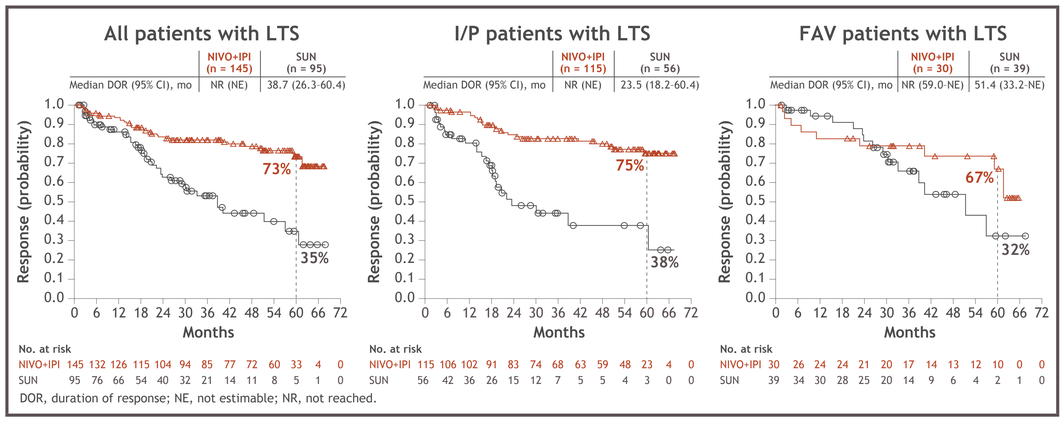
[a]Patients may have received more than 1 type of subsequent therapy, defined as therapy started on or after first dosing date (randomization date if patient never treated).
[b]Listed therapies include the most common subsequent systemic therapies received.

Table 3. ORR, BOR, and depth of response in all patients with LTS and by IMDC intermediate/poor and favorable risk

	All patients with LTS		I/P patients with LTS		FAV patients with LTS	
	NIVO+IPI (n = 236)	SUN (n = 171)	NIVO+IPI (n = 163)	SUN (n = 112)	NIVO+IPI (n = 73)	SUN (n = 59)
Confirmed ORR, % (95% CI)	61 (55-68)	56 (48-63)	71 (63-77)	50 (40-60)	41 (30-53)	66 (53-78)
BOR, n (%)						
Complete response	56 (24)	15 (9)	40 (25)	7 (6)	16 (22)	8 (14)
Partial response	89 (38)	80 (47)	75 (46)	49 (44)	14 (19)	31 (53)
Stable disease	78 (33)	54 (32)	40 (25)	38 (34)	38 (52)	16 (27)
Progressive disease	12 (5)	16 (9)	7 (4)	14 (13)	5 (7)	2 (3)
UTD	1 (< 1)	5 (3)	1 (1)	3 (3)	0	2 (3)
Not reported	0	1 (1)	0	1 (1)	0	0
Median time to response (IQR), months	2.8 (2.6-4.0)	4.0 (2.8-6.7)	2.8 (2.6-3.1)	4.0 (2.8-6.8)	2.8 (2.7-4.2)	4.2 (2.8-6.3)
Ongoing response, n (%)	n = 145 112 (77)	n = 95 56 (59)	n = 115 92 (80)	n = 56 31 (55)	n = 30 20 (67)	n = 39 25 (64)
Best percent tumor reduction from baseline in sum of diameter of target lesions[a]						
	n = 218	**n = 151**	**n = 150**	**n = 99**	**n = 68**	**n = 52**
Any reduction, n (%)	187 (86)	139 (92)	131 (87)	88 (89)	56 (82)	51 (98)
Reduction ≥ 50%, n (%)	134 (61)	64 (42)	107 (71)	37 (37)	27 (40)	27 (52)

[a]Patients with target lesion at baseline and at least 1 on-treatment tumor assessment.
BOR, best overall response; CI, confidence interval; IQR, interquartile range; UTD, unable to determine.

Figure 1. Duration of confirmed response in all patients with LTS and by IMDC intermediate/poor and favorable risk



DOR, duration of response; NE, not estimable; NR, not reached.

Efficacy in patients with LTS

BOR in all patients with LTS and by IMDC I/P, and FAV risk

- ORR (95% CI) was 61% (55-68) with NIVO+IPI versus 56% (48-63) with SUN in all patients with LTS and 71% (63-77) versus 50% (40-60) in I/P patients with LTS, respectively. Among FAV patients with LTS, ORR (95% CI) was 41% (30-53) with NIVO+IPI versus 66% (53-78) with SUN (**Table 3**)
- A higher proportion of patients with LTS achieved complete response (all, 24% vs 9%; I/P, 25% vs 6%; FAV, 22% vs 14%) and had ongoing responses (all, 77% vs 59%; I/P, 80% vs 55%; FAV, 67% vs 64%) with NIVO+IPI versus SUN (**Table 3**)
- Median DOR was notably longer with NIVO+IPI in all 3 LTS populations (all, NR vs 38.7 months; I/P, NR vs 23.5 months; FAV, NR vs 51.4 months; **Figure 1**)

Treatment-free interval in I/P and FAV patients with LTS and confirmed response

- More responders with LTS experienced a treatment-free interval with NIVO+IPI versus SUN
  - I/P, 62 of 115 (54%) versus 8 of 56 (14%); FAV, 13 of 30 (43%) versus 4 of 39 (10%)
- Median treatment-free interval (range) with NIVO+IPI versus SUN was 42 (4-68) months versus 43 (16-60) months in I/P patients, and 59 (7-68) versus 47 (4-62) months in FAV patients

Treatment exposure and safety

- Treated patients in the NIVO+IPI arm of the overall study population received a median (range) of 14.0 doses (1-154) of NIVO and 4.0 doses (1-4) of IPI; patients in the subgroup with LTS received a median (range) of 41.0 (1-154) doses of NIVO and 4.0 doses (1-4) of IPI
- Most treated patients in the overall study population (431/547; 79%) and most patients with LTS (207/236; 88%) received 4 IPI doses
- Twelve percent of patients treated with NIVO+IPI (65/547) in the overall study population received < 4 IPI doses due to TRAEs leading to discontinuation of study treatment (per case report form), and 40% of these patients (26/65) had LTS; this included 12 of 44 (27%) I/P patients and 14 of 21 (67%) FAV patients
- Among patients treated with NIVO+IPI, treatment-related select (potentially immune-mediated) AEs were higher in patients with LTS versus those without LTS (**Table 4**), which was not unexpected given longer duration of treatment and greater exposure to study drug in patients with LTS

Table 4. Treatment-related select AEs in patients with or without LTS

Treatment-related select AEs, n (%)[a,b]	All treated NIVO+IPI patients with LTS (n = 236)		All treated NIVO+IPI patients without LTS (n = 311)		All treated SUN patients with LTS (n = 171)		All treated SUN patients without LTS (n = 364)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Skin	145 (61)	9 (4)	134 (43)	13 (4)	126 (74)	25 (15)	182 (50)	30 (8)
Endocrine	92 (39)	20 (8)	88 (28)	18 (6)	66 (39)	1 (1)	102 (28)	0
GI	84 (36)	13 (6)	79 (25)	15 (5)	110 (64)	13 (8)	175 (48)	18 (5)
Hepatic	51 (22)	25 (11)	57 (18)	23 (7)	30 (18)	7 (4)	50 (14)	13 (4)
Renal	28 (12)	2 (1)	29 (9)	5 (2)	16 (9)	1 (1)	32 (9)	5 (1)
Pulmonary	23 (10)	2 (1)	15 (5)	4 (1)	1 (1)	0	1 (1)	0

[a]Includes events reported between first dose and 30 days after last dose of study therapy.
[b]Treatment-related select AEs were prespecified and defined as events that might be immune-mediated, differ from those caused by non-immunotherapeutic drugs, might require immunosuppression for management, and whose early recognition might mitigate severe toxicity.
GI, gastrointestinal.

- In the overall study population, any-grade TRAEs leading to discontinuation occurred in 127 of 547 (23%) treated patients with NIVO+IPI versus 70 of 535 (13%) treated patients with SUN, and in the subgroup of patients with LTS, 67 of 236 (28%) patients treated with NIVO+IPI versus 28 of 171 (16%) patients treated with SUN

Conclusions

- Analyses in patients with aRCC from CheckMate 214 who had LTS further highlight the greater likelihood of long-term clinical benefits observed with NIVO+IPI versus SUN
- Baseline demographic and clinical characteristics generally did not distinguish patients with LTS in the NIVO+IPI arm from the overall population of NIVO+IPI patients; exceptions were lower target lesion burden and smaller proportions of LTS patients with IMDC poor risk or bone metastases at baseline
- Not having a complete response or a partial response did not prevent some patients from achieving LTS ≥ 5 years with NIVO+IPI
- More than 75% of patients with LTS in the SUN arm received subsequent systemic therapy compared with just under half of LTS patients in the NIVO+IPI arm
- Survival ≥ 5 years was also observed in patients who discontinued due to TRAEs
- These results highlight the long-term clinical benefits observed with NIVO+IPI in patients across a spectrum of baseline characteristics and regardless of IMDC risk

References

1. Motzer RJ, et al. *N Engl J Med* 2018;378:1277-1290.
2. Motzer RJ, et al. *Lancet Oncol* 2019;20:1370-1385.
3. Motzer RJ, et al. *J Immunother Cancer* 2020;8:e000891.
4. Albiges L, et al. *ESMO Open* 2020;5:e001079.
5. Motzer RJ, et al. Poster presentation at the European Society for Medical Oncology (ESMO) Congress; September 16-21, 2021; Virtual. 661P.
6. Topalian SL, et al. *JAMA Oncol* 2019;5:1411-1420.
7. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. June 14, 2010. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40. Accessed August 2, 2021.

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