Conditional survival and 5-year follow-up in CheckMate 214: first-line nivolumab plus ipilimumab versus sunitinib in advanced renal cell carcinoma

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Background

- Nivolumab plus ipilimumab (NIVO+IPI) has demonstrated durable survival and response benefits versus sunitinib (SUN), providing the opportunity to conduct long-term conditional survival analyses in CheckMate 214[1-4]
  - Conditional survival analyses estimate the probability of remaining event free (ie, remaining alive, or progression free, or in response) for a defined period of time beyond reaching a landmark study milestone[5]
- With a minimum follow-up of 5 years, we present the longest phase 3 follow-up reported for a checkpoint inhibitor combination therapy in advanced renal cell carcinoma (aRCC), with updated efficacy and safety outcomes and the first long-term conditional survival analyses of patients in the CheckMate 214 trial

Methods

- Patients with previously untreated aRCC with a clear cell component were randomized 1:1 to receive intravenous NIVO 3 mg/kg + IPI 1 mg/kg every 3 weeks for 4 doses followed by NIVO 3 mg/kg every 2 weeks, or SUN 50 mg orally once daily for 4 weeks on, 2 weeks off (6-week cycles)[1,2]
- Overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) outcomes were assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[6] in intent-to-treat (ITT), International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor-risk (I/P), and favorable-risk (FAV) populations with a median follow-up of 67.7 months
- Conditional survival outcomes were defined as the probability of a patient remaining alive, progression free, or in response for an additional 2 years beyond annual landmark timepoints, and were analyzed post hoc in the ITT, I/P, and FAV populations
  - Conditional OS, conditional PFS (time zero was date of randomization for both), and conditional response (time zero was date of first confirmed response) were assessed until death or censored at the date of last follow-up. Data from patients who died before the landmark timepoint or whose follow-up interval was less than the landmark time were excluded
- Conditional OS was also estimated in subgroups of ITT patients in the NIVO+IPI arm based on best overall response (BOR) of complete response (CR) or by baseline clinical features (tumor programmed death ligand [PD-L1] expression [< 1% or ≥ 1%], grade ≥ 3 immune-mediated adverse event [IMAE] experience [with or without], body mass index [BMI; < 30 or ≥ 30], and age [< 65 years, 65 to < 75 years, or ≥ 75 years])
- Safety was assessed in all treated patients

Results

Patients

- In total, 1096 patients were randomized to NIVO+IPI (ITT, 550; I/P, 425; FAV, 125) or SUN (ITT, 546; I/P, 422; FAV, 124)
- Key baseline characteristics were generally similar between treatment arms in ITT patients, as previously reported[1-4]
- Thirty-four (6%) of 547 treated patients in the NIVO+IPI arm and 9 (2%) of 535 treated patients in the SUN arm continued therapy at 5 years follow-up
- Median duration of therapy (quartile [Q] Q1-Q3) was 7.9 (2.1-21.8) months in the NIVO+IPI arm and 7.8 (3.5-19.6) months in the SUN arm
- Subsequent systemic therapy was received by 55% (305/550) of ITT patients in the NIVO+IPI arm and 68% (372/546) in the SUN arm

Efficacy in ITT, I/P, and FAV populations

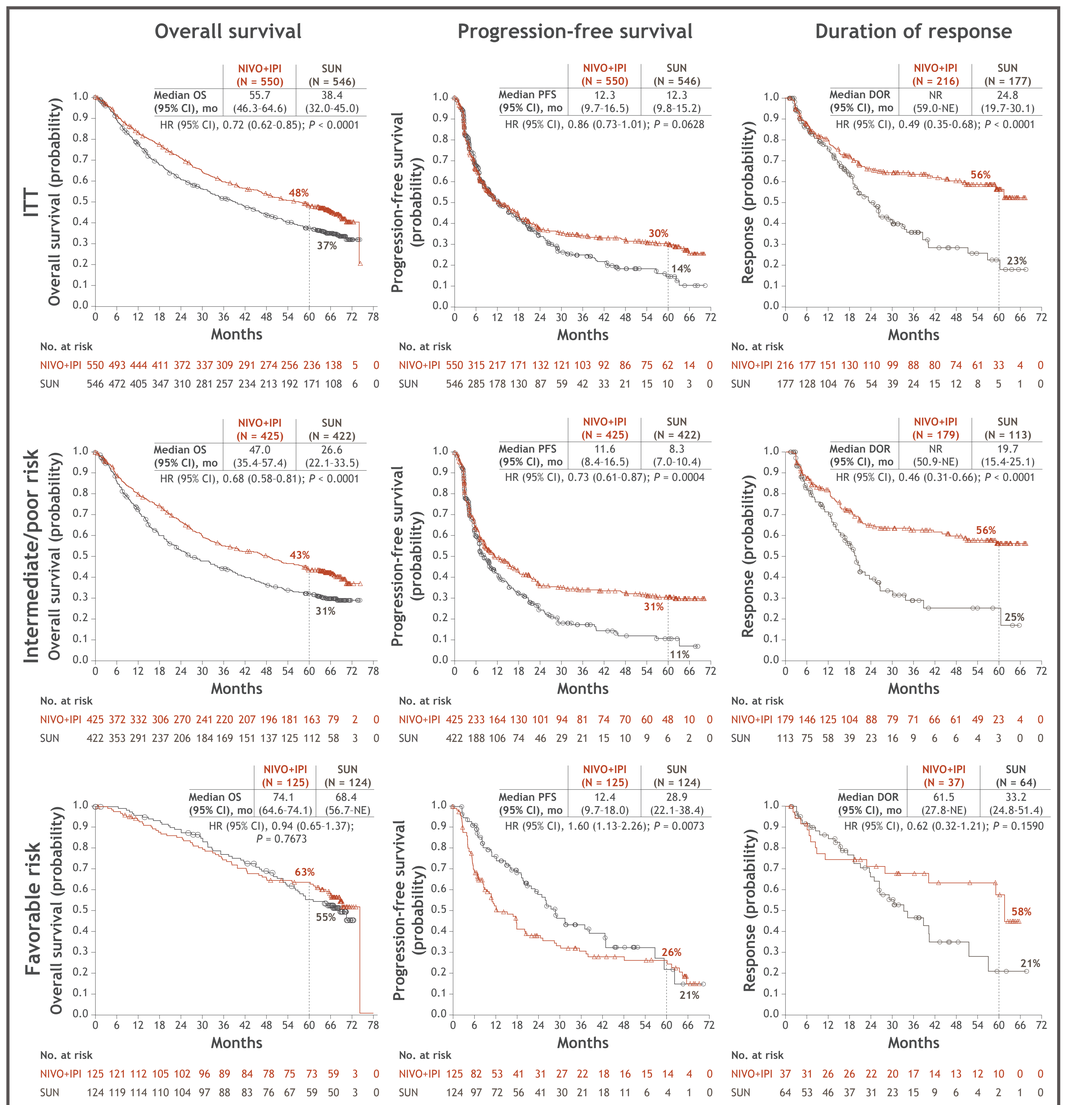
- Median OS, PFS, and duration of response (DOR) with 5-year probabilities are shown in **Figure 1**
- ORR, BOR, and ongoing response are shown in **Table 1**
  - More patients achieved CR and did not subsequently progress with NIVO+IPI (53/550, 9.6%) versus SUN (13/546, 2.4%)

Table 1. Objective response

Response assessment	ITT		I/P risk		FAV risk	
	NIVO+IPI (N = 550)	SUN (N = 546)	NIVO+IPI (N = 425)	SUN (N = 422)	NIVO+IPI (N = 125)	SUN (N = 124)
Confirmed ORR, % (95% CI)	39.3 (35.2-43.5)	32.4 (28.5-36.5)	42.1 (37.4-47.0)	26.8 (22.6-31.3)	29.6 (21.8-38.4)	51.6 (42.5-60.7)
P value	0.0055		< 0.0001		0.0002	
BOR, n (%)						
CR	64 (11.6)	17 (3.1)	48 (11.3)	9 (2.1)	16 (12.8)	8 (6.5)
PR	152 (27.6)	160 (29.3)	131 (30.8)	104 (24.6)	21 (16.8)	56 (45.2)
SD	198 (36.0)	230 (42.1)	131 (30.8)	187 (44.3)	67 (53.6)	43 (34.7)
PD	97 (17.6)	77 (14.1)	82 (19.3)	71 (16.8)	15 (12.0)	6 (4.8)
UTD	38 (6.9)	57 (10.4)	32 (7.5)	48 (11.4)	6 (4.8)	9 (7.3)
NR	1 (0.2)	5 (0.9)	1 (0.2)	3 (0.7)	0	2 (1.6)
Ongoing response, n (%)	n = 216 136 (63.0)	n = 177 89 (50.3)	n = 179 114 (63.7)	n = 113 56 (49.6)	n = 37 22 (59.5)	n = 64 33 (51.6)
Ongoing CR, n (%)	n = 64 54 (84.4)	n = 17 15 (88.2)	n = 48 41 (85.4)	n = 9 8 (88.9)	n = 16 13 (81.3)	n = 8 7 (87.5)

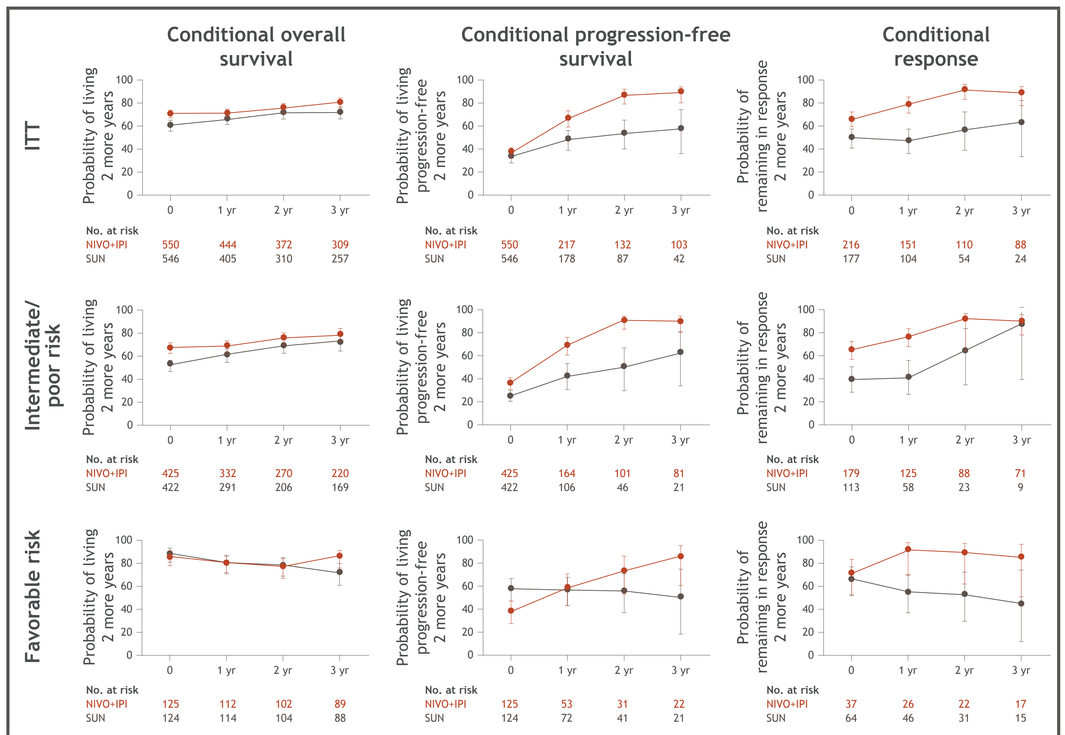
CI, confidence interval; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease; UTD, unable to determine.

Figure 1. OS, PFS, and DOR in ITT patients and by IMDC I/P and FAV risk



HR, hazard ratio; NE, not estimable; NR, not reached.

Figure 2. Conditional OS, PFS, and response in ITT patients and by IMDC I/P and FAV risk by treatment arm



X-axes show landmark time from randomization (conditional OS and PFS) or landmark time from first confirmed response (conditional response). Error bars are 95% CIs. OS, PFS, and response probabilities were conditioned on time alive, progression free, or in response after time zero.

Conditional survival outcomes with NIVO+IPI versus SUN

- The probability of remaining alive with NIVO+IPI for an additional 2 years increased from time zero (randomization) to landmark year 3 for ITT patients (71% to 81%) and I/P patients (66% to 79%); the probability remained 85% for FAV patients (**Figure 2**)
  - Conditional OS was consistently higher with NIVO+IPI versus SUN beyond the 3-year landmark in all patients and regardless of IMDC risk (ITT, 81% vs 72%; I/P, 79% vs 72%; FAV, 85% vs 72%)
- The probability of remaining progression free for an additional 2 years also increased from time zero to year 3 with NIVO+IPI for ITT patients (37% to 89%), I/P patients (36% to 90%), and FAV patients (38% to 85%; **Figure 2**)
  - At the 3-year landmark, conditional PFS estimates were notably improved with NIVO+IPI versus SUN in all patients and regardless of IMDC risk (ITT, 89% vs 57%; I/P, 90% vs 62%; FAV, 85% vs 50%)
- The probability of remaining in response with NIVO+IPI for an additional 2 years beyond first response also increased from time zero (first confirmed response) to year 3 for ITT patients (66% to 89%), I/P patients (65% to 90%), and FAV patients (71% to 85%; **Figure 2**)
  - Conditional response estimates beyond the 3-year landmark were also higher with NIVO+IPI versus SUN regardless of IMDC risk group (ITT, 89% vs 63%; I/P, 90% vs 88%; FAV, 85% vs 45%)

Conditional survival outcomes with NIVO+IPI by CR and clinical subgroups

- Conditional OS estimates with NIVO+IPI remained consistently high (> 96%) in ITT patients with CR and improved from time zero to year 3 with NIVO+IPI in ITT patients stratified by tumor PD-L1 expression, grade ≥ 3 IMAEs, BMI, and age (data not shown)

Safety

- Comparable rates of treatment-related adverse events (AEs) of any grade occurred with NIVO+IPI (515/547, 94%) versus SUN (522/535, 98%); however, fewer grade 3-4 treatment-related AEs were reported with NIVO+IPI (48%) versus SUN (64%)
  - Treatment-related AEs leading to discontinuation of therapy occurred in 127 (23%) patients in the NIVO+IPI arm and in 70 (13%) patients in the SUN arm
- The overall incidence of any-grade and high-grade treatment-related select (potentially immune-mediated) AEs with NIVO+IPI was similar to previous reports[1-4]

Conclusions

- In the longest phase 3 follow-up for a checkpoint inhibitor combination therapy in aRCC together with the first long-term conditional survival analyses of patients in the CheckMate 214 trial, NIVO+IPI demonstrated durable survival and response benefits versus SUN in all patients
- Patients who were alive, progression free, or in response 3 years after time zero had a greater probability of remaining so at year 5 with NIVO+IPI versus SUN
- Conditional OS, PFS, and response estimates for ITT patients improved from time zero to 3 years for survivors of aRCC in the NIVO+IPI arm, providing meaningful quantitative prognostic information for patients and clinicians
  - Conditional OS estimates remained high with NIVO+IPI in ITT patients with CR and improved over time in ITT patients stratified by PD-L1 expression, IMAE experience, BMI, and age, indicating that none of these clinical features precluded patients from achieving durable survival benefits with NIVO+IPI
- The incidence of grade 3-4 treatment-related AEs remained lower with NIVO+IPI versus SUN with extended follow-up[3-6]
- Taken together, these results highlight the durable clinical benefits observed with NIVO+IPI versus SUN in patients with aRCC after 5 years of follow-up and show that most patients alive or in response at the 3-year landmark will remain alive or in response at 5 years with NIVO+IPI

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