Presented at the ESMO Virtual Congress 2021,
September 16-21

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Background

- The combination of nivolumab plus ipilimumab (NIVO+IPI; dual checkpoint inhibition) is approved by the European Commission and the US Food and Drug Administration for first-line treatment of patients with advanced renal cell carcinoma (aRCC) with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor-risk (I/P) disease, based on superior overall survival (OS) and objective response rate (ORR) over sunitinib (SUN) in the randomized, phase 3 CheckMate 214 trial[1-3]
- NIVO+IPI has demonstrated durable survival and response benefits versus SUN, providing the opportunity to conduct long-term conditional survival analyses in CheckMate 214[3-6]
  - 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[7]
  - These emerging analyses are a novel, clinically relevant method to predict continued survival and response benefits as patients reach or exceed annual landmarks, thus providing critical insights for clinicians and patients regarding prognosis and subsequent treatment decisions[7]
- With a minimum follow-up of 5 years, we present the longest phase 3 follow-up reported for a checkpoint inhibitor combination therapy in 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)[3,4]
  - Patients on NIVO monotherapy were permitted to switch from NIVO 3 mg/kg to NIVO 240 mg every 2 weeks, and more recently to NIVO 480 mg every 4 weeks, per protocol amendment
  - Patients were stratified by geographic region and IMDC risk status (favorable, intermediate, or poor)
- OS, progression-free survival (PFS), and ORR outcomes were assessed in intent-to-treat (ITT), 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 using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[8]
- 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 baseline clinical features, including patients with
  - Tumor programmed death ligand 1 (PD-L1) expression (< 1% or ≥ 1%)
  - Grade ≥ 3 immune-mediated adverse event (IMAE) experience (with or without)
  - Body mass index (BMI; < 30 or ≥ 30)
  - Age (< 65 years, 65 to < 75 years, or ≥ 75 years)
- Safety was assessed in all treated patients per the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0,[9] and treatment-related adverse events (AEs) occurring between the first dose and 30 days after last dose of study therapy were reported
- Health-related quality of life (HRQoL) outcomes were reported in ITT and I/P patients using the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19) total scale (scores range from 0-76; higher scores indicate fewer symptoms) and the FKSI disease-related symptoms (DRS) subscale[10]

Results

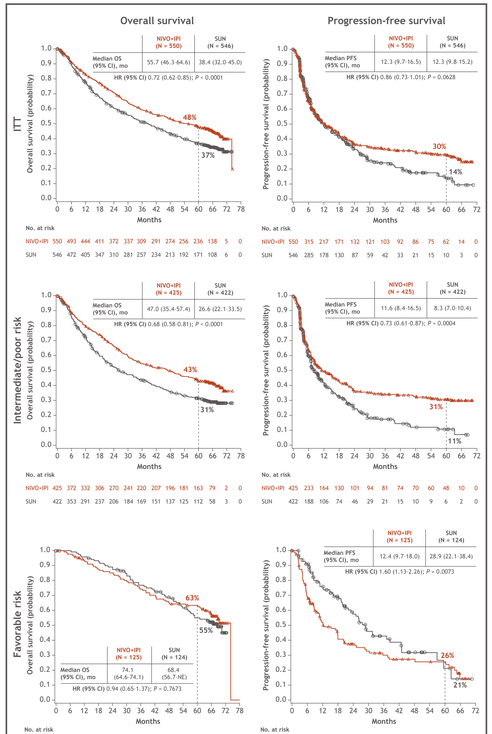
Patients

- 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[3-6]
- 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

- Superior OS with NIVO+IPI versus SUN was maintained in ITT (hazard ratio [HR], 0.72) and I/P (HR, 0.68) patients; the HR for OS in FAV patients was 0.94 (**Figure 1**)
- Five-year PFS probabilities with NIVO+IPI versus SUN were 30% versus 14% (ITT), 31% versus 11% (I/P), and 26% versus 21% (FAV) and appeared to stabilize above ~30% with NIVO+IPI for both ITT and I/P patients after 3 years (**Figure 1**)
- ORR (95% confidence interval [CI]) was 39% (35-44) with NIVO+IPI versus 32% (29-37) with SUN in ITT patients and 42% (37-47) versus 27% (23-31) in I/P patients, respectively. Among FAV patients, ORR (95% CI) was 30% (22-38) with NIVO+IPI versus 52% (43-61) with SUN
  - A higher proportion of patients achieved CR with NIVO+IPI versus SUN regardless of risk (ITT, 12% vs 3%; I/P, 11% vs 2%; FAV, 13% vs 6%)
  - More patients achieved CR and did not subsequently progress with NIVO+IPI (53/550, 9.6%) versus SUN (13/546, 2.4%)
- Median duration of response was notably longer with NIVO+IPI in all 3 populations (ITT, not reached [NR] vs 24.8 months; I/P, NR vs 19.7 months; FAV, 61.5 vs 33.2 months), and more patients had ongoing responses with NIVO+IPI across all risk groups (ITT, 63% vs 50%; I/P, 64% vs 50%; FAV, 59% vs 52%)

Figure 1. OS and PFS in ITT patients and by IMDC intermediate/poor and favorable risk



NE, not estimable.

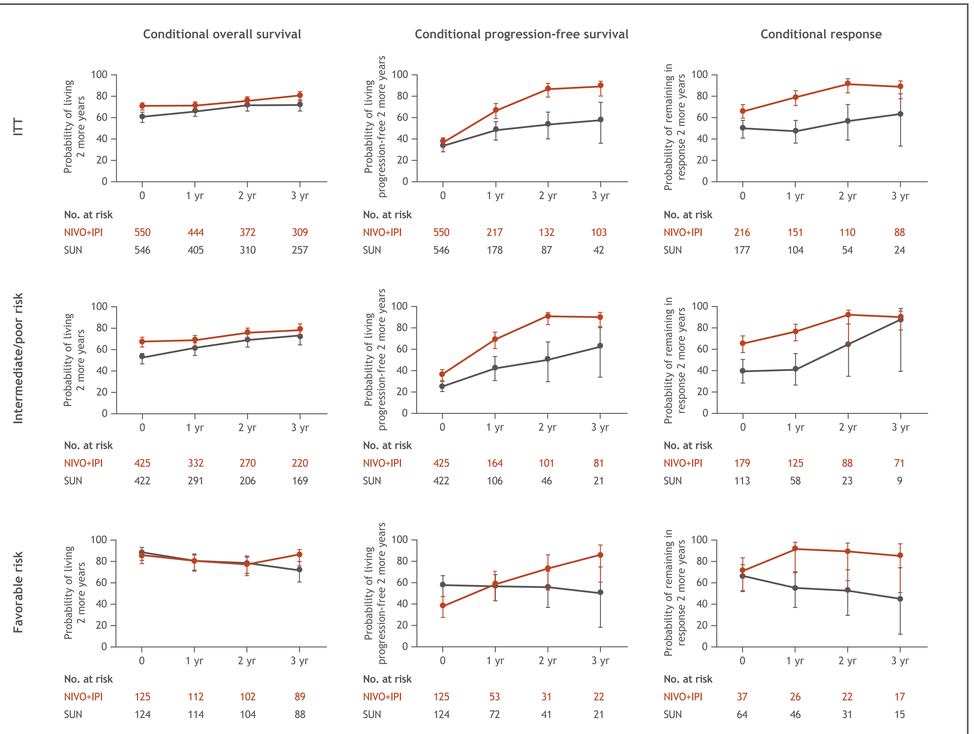
Conditional survival outcomes with NIVO+IPI versus SUN

- With NIVO+IPI, the probability of remaining alive 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 complete response and clinical subgroups

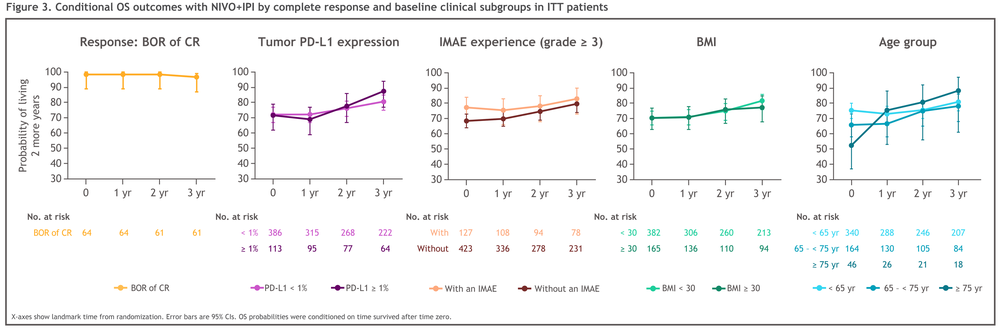
- Conditional OS estimates with NIVO+IPI remained high (> 96%) in ITT patients with CR from all landmark timepoints assessed (**Figure 3**)
- Conditional OS estimates with NIVO+IPI in ITT patients were largely similar regardless of tumor PD-L1 expression, grade ≥ 3 IMAE experience, or BMI, and estimates improved from time zero to year 3 in each subgroup (**Figure 3**)
- Conditional OS with NIVO+IPI varied to some extent across age groups in ITT patients (in particular at time zero), yet estimates consistently improved from time zero to year 3 (**Figure 3**)

Figure 2. Conditional OS, conditional PFS, and conditional response in ITT patients and by IMDC intermediate/poor and favorable 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.

Figure 3. Conditional OS outcomes with NIVO+IPI by complete response and baseline clinical subgroups in ITT patients



X-axes show landmark time from randomization. Error bars are 95% CIs. OS probabilities were conditioned on time survived after time zero.

Safety and HRQoL

- Comparable rates of treatment-related 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[3-6]
- HRQoL benefits continued to favor NIVO+IPI in ITT and I/P patients
  - The difference in mean change from baseline between treatment arms (NIVO+IPI vs SUN) in FKSI-19 total score was 1.87 (0.95-2.79, $P < 0.0001$) in ITT patients and 2.65 (1.60-3.70, $P < 0.0001$) in I/P patients
  - The difference in mean change from baseline between treatment arms (NIVO+IPI vs SUN) in FKSI-DRS subscale score was 0.47 (0.07-0.87, $P = 0.0224$) in ITT patients and 0.75 (0.28-1.22, $P = 0.0016$) in I/P patients

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
  - Five-year OS and PFS probabilities were higher, and more responses were durable with NIVO+IPI versus SUN across all IMDC risk groups
- 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 with NIVO+IPI in ITT patients with CR remained consistently high over time and improved from time zero to 3 years with NIVO+IPI in ITT patients stratified by tumor PD-L1 expression, grade ≥ 3 IMAE experience, BMI, and age
- The overall incidence of treatment-related AEs in the NIVO+IPI arm remained consistent with previous reports and the incidence of grade 3-4 treatment-related AEs remained lower with NIVO+IPI versus SUN with extended follow-up[3-6]
- Treatment with NIVO+IPI led to fewer symptoms and better HRQoL compared with SUN
- 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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Acknowledgments

- The patients and families who made this study possible
- The clinical study teams who participated
- We would like to acknowledge Jennifer McCarthy (Bristol Myers Squibb, Princeton, NJ, USA) for serving as protocol manager, and Heshani Desilva (Bristol Myers Squibb, Princeton, NJ, USA) for reviewing the clinical data
- Dako, an Agilent Technologies, Inc. company, for collaborative development of the PD-L1 IHC 28-8 pharmDx assay (Santa Clara, CA, USA)
- Bristol Myers Squibb (Princeton, NJ, USA) and Ono Pharmaceutical Company Ltd. (Osaka, Japan)
- The study was supported by Bristol Myers Squibb
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by Rachel Maddente, PhD, of Parexel, funded by Bristol Myers Squibb

Disclosures

- Dr Motzer reports consulting/personal/speaker fees and/or advisory relationships with AstraZeneca, Aveo Pharmaceuticals, Eisai, EMD Serono, Exelixis, Genentech/Roche, Incyte, Lilly Oncology, Merck, Novartis, and Pfizer, and trial funding/other fees from Bristol Myers Squibb, Eisai, Exelixis, Genentech/Roche, Merck, and Pfizer

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