PCN26

Quantifying the Relative Clinical Value of Nivolumab Plus Ipilimumab Versus Sunitinib in First-Line Advanced or Metastatic Renal Cell Carcinoma With the Number Needed to Treat and Number Needed to Harm in Spain and Portugal

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Introduction

- Renal cell carcinoma (RCC) is a common urological malignancy that represents 85% of all kidney cancers. The incidence of kidney cancer in Spain and Portugal is 7.9 and 5.0 per 100,000 individuals, respectively[1]
- Approximately one-third of affected patients present with advanced or metastatic renal cell carcinoma (aRCC) at diagnosis, and an additional 20% of patients will go on to develop aRCC after surgery[2]
- Despite various available first-line treatments, 5-year survival is only approximately 12% in patients with distant metastases, indicating an unmet need for a treatment to extend patient survival[3]
- In the CheckMate 214 trial, nivolumab plus ipilimumab (NIVO+IPI) showed superior efficacy over sunitinib (SUN) in patients with previously untreated intermediate-risk or poor-risk aRCC, with longer overall survival (OS; median not reached vs 26.6 months; hazard ratio, 0.66, $P < 0.0001$) and higher objective response rates (ORRs; 42% vs 29%, $P = 0.0001$). In addition, NIVO+IPI was associated with fewer grade 3–4 AEs than was SUN[4,5]
- On the basis of the results of CheckMate 214, combination immunotherapy with first-line NIVO+IPI was approved by the European Commission for previously untreated patients with intermediate/poor-risk aRCC in January 2019[6]
- To optimize treatment decision making, it is useful to quantify the clinical benefits and risks associated with NIVO+IPI and SUN using measures such as the number needed to treat (NNT) and number needed to harm (NNH)
  - NNT is the number of patients who would need to be treated with a specific treatment to achieve an additional positive outcome versus a comparator
  - NNH is the number of patients who would need to be treated with a specific treatment to be harmed by an additional adverse event (AE) versus a comparator
- This study estimated the NNT and NNH for NIVO+IPI versus SUN in patients with previously untreated intermediate/poor-risk aRCC in Spain and Portugal

Methods

Data source and study population

- Individual patient-level data from CheckMate 214 (database lock date, August 3, 2018; minimum follow-up, 30 months) were used in this study
- OS, ORR per investigator, and grade 3–4 AEs for NIVO+IPI and SUN at 12, 24, and 36 months were estimated based on patient-level data
  - OS rates were obtained using Kaplan–Meier analyses among randomized patients with intermediate/poor-risk aRCC in CheckMate 214
  - ORRs were calculated as the number of patients with a complete response or a partial response divided by the total number of randomized patients with intermediate/poor-risk aRCC in CheckMate 214
- All-cause and treatment-related grade 3–4 AE rates were estimated based on the Kaplan–Meier analysis of time to first AE (all-cause or treatment-related) among the safety population in CheckMate 214. Time to first AE was defined as the time from initiating the study medication to the time of the first AE of interest

Calculation of NNT

- The NNTs comparing NIVO+IPI and SUN were assessed for OS and ORR at 12, 24, and 36 months
  - NNTs were calculated as the reciprocal of the absolute difference between NIVO+IPI and SUN in estimated OS rate or ORR
  - $\text{NNT} = \dfrac{1}{\textit{Absolute difference between NIVO+IPI and SUN in OS rate or ORR}}$

Calculation of NNH

- The NNHs between NIVO+IPI and SUN were assessed for all-cause and treatment-related grade 3–4 AEs at 12, 24, and 36 months
  - NNHs were calculated as the reciprocal of the absolute difference between the NIVO+IPI and SUN in estimated AE rate
  - $\text{NNH} = \dfrac{1}{\textit{Absolute difference between NIVO+IPI and SUN in AE rate}}$
- The calculations for the NNT, NNH, and their associated 95% confidence intervals (CIs) were based on the methods described in Altman et al[7]

Results

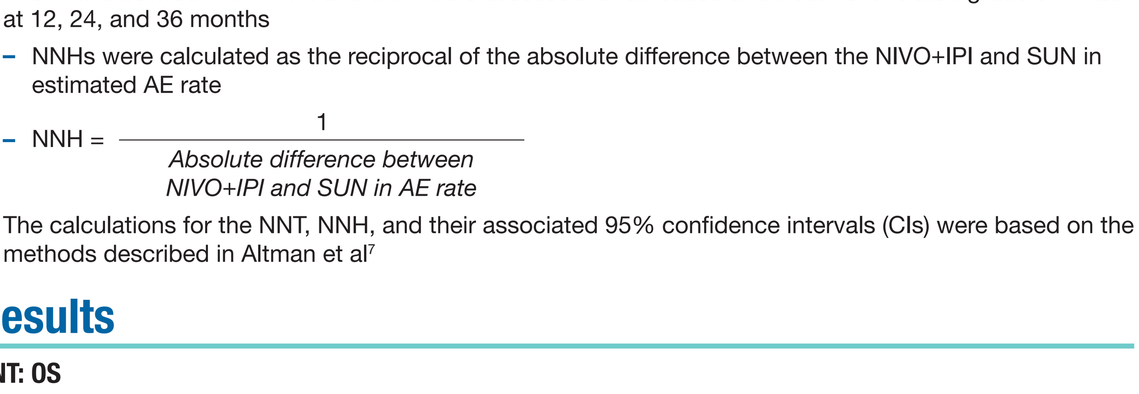
NNT: OS

- The OS rates were higher for NIVO+IPI versus SUN at all time points (80.1% vs 72.2%, 66.4% vs 52.6%, and 54.6% vs 43.5% at 12, 24, and 36 months, respectively)
- The OS rate was 7.9% higher for NIVO+IPI than SUN at month 12; the rate difference was 13.9% at month 24 and 11.1% at month 36
- At month 12, 1 death would be prevented if 12.67 patients were treated with NIVO+IPI instead of SUN. The NNT to prevent 1 death with NIVO+IPI versus SUN was reduced to 7.21 patients at month 24 and 9.00 patients at month 36 (**Figure 1**)

NNT: ORR per investigator

- The ORRs were also higher for NIVO+IPI versus SUN at all time points (41.4% vs 27.3%, 41.6% vs 29.4%, and 41.9% vs 29.4% at 12, 24, and 36 months, respectively)
- The difference between NIVO+IPI versus SUN in ORR was 14.2% at month 12, 12.3% at month 24, and 12.5% at month 36
- The NNT to achieve 1 additional responder with NIVO+IPI versus SUN was 7.06 patients at month 12, 8.15 patients at month 24, and 8.00 patients at month 36 (**Figure 1**)

Figure 1. NNT of NIVO+IPI versus SUN at months 12, 24, and 36



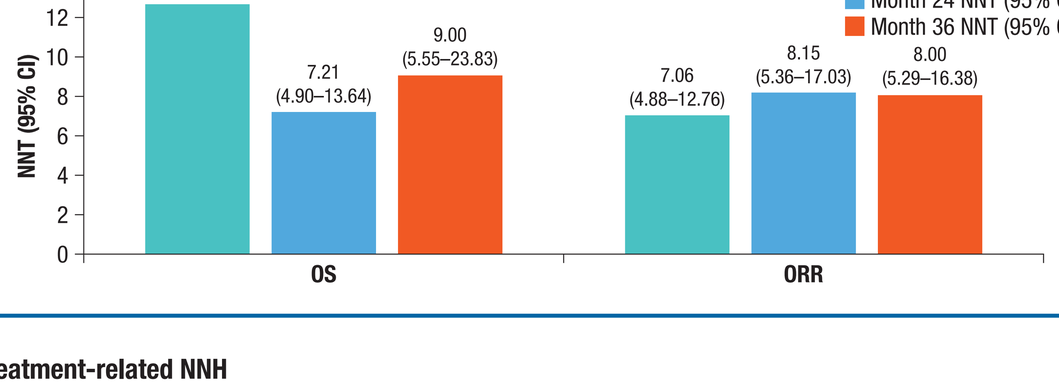
Treatment-related NNH

- The treatment-related grade 3–4 AEs were lower for NIVO+IPI versus SUN at all time points (49.1% vs 73.3%, 58.0% vs 78.7%, and 58.7% vs 78.7% at 12, 24, and 36 months, respectively)
- The rates of treatment-related grade 3–4 AEs were 24.2% lower for NIVO+IPI than SUN at month 12, 20.7% lower at month 24, and 20.0% lower at month 36
- For every 4.13 patients treated with NIVO+IPI instead of SUN, 1 fewer patient would have experienced a treatment-related grade 3–4 AE over 12 months. The NNH of treatment-related grade 3–4 AEs is 4.84 patients and 5.01 patients at 24 and 36 months, respectively (**Figure 2**)

All-cause NNH

- The all-cause grade 3–4 AEs were also lower for NIVO+IPI versus SUN at all time points (68.5% vs 85.4%, 78.0% vs 91.4%, and 82.3% vs 92.6% at 12, 24, and 36 months, respectively)
- The rates of all-cause grade 3–4 AEs with NIVO+IPI were 16.9% lower at month 12, 13.4% lower at month 24, and 10.3% lower at month 36 compared with SUN
- The NNH of all-cause grade 3–4 AEs is 5.93 patients, 7.47 patients, and 9.71 patients at 12, 24, and 36 months, respectively (**Figure 2**)

Figure 2. NNH of SUN versus NIVO+IPI at months 12, 24, and 36[a]

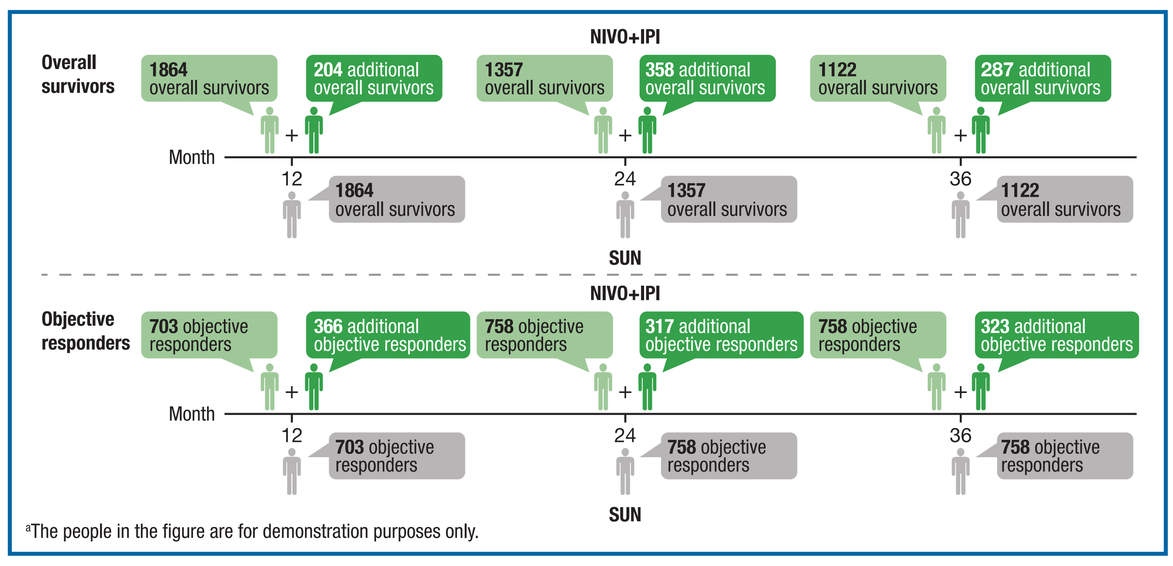


[a]Because the SUN group had higher grade 3–4 AE rates versus NIVO+IPI, the comparative NNH of SUN versus NIVO+IPI (instead of NIVO+IPI vs SUN) were presented. This could be interpreted as the number of patients that need to be treated by NIVO+IPI instead of SUN in order to prevent 1 fewer patient from experiencing a grade 3–4 AE.

Benefit/risk profiles in Spain and Portugal

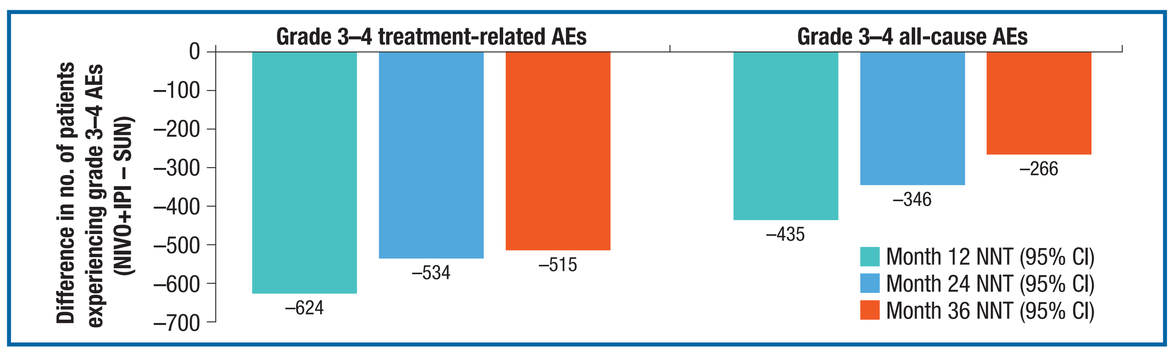
- In Spain, there are an estimated 2582 patients eligible for first-line aRCC treatment. If all eligible patients in Spain were treated with NIVO+IPI instead of SUN,
  - At month 12, there would be 204 additional overall survivors, 366 additional objective responders, 624 fewer patients experiencing treatment-related grade 3–4 AEs, and 435 fewer patients experiencing all-cause grade 3–4 AEs
  - Similar trends in survivors, responders, and patients experiencing AEs were observed at months 24 and 36 (**Figures 3** and **4**)

Figure 3. The number of overall survivors and objective responders assuming all 2582 patients eligible in Spain are treated with NIVO+IPI or SUN[a]



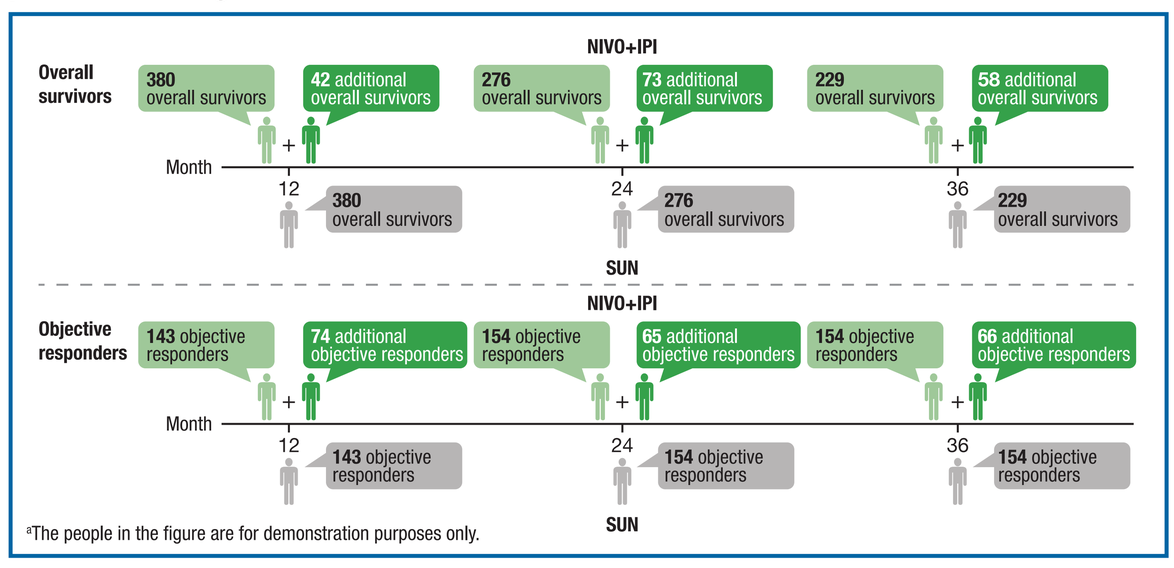
[a]The people in the figure are for demonstration purposes only.

Figure 4. Difference in number of patients experiencing grade 3–4 AEs if all 2582 eligible patients with aRCC in Spain are treated by NIVO+IPI instead of SUN



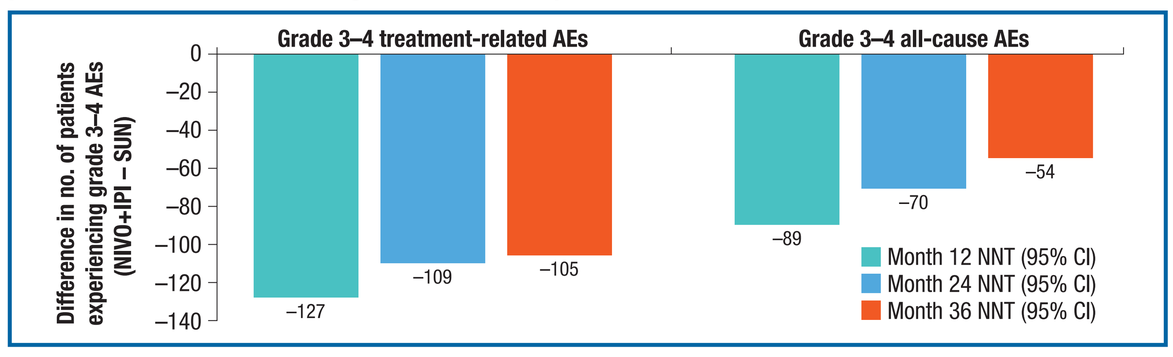
- In Portugal, there are an estimated 526 patients eligible for first-line aRCC treatment. If all eligible patients in Portugal were treated with NIVO+IPI instead of SUN,
  - At month 12, there would be 42 additional overall survivors, 74 additional objective responders, 127 fewer patients experiencing treatment-related grade 3–4 AEs, and 89 patients experiencing fewer all-cause grade 3–4 AEs
  - Similar trends in survivors, responders, and patients experiencing AEs were observed at months 24 and 36 (**Figures 5** and **6**)

Figure 5. The number of overall survivors and objective responders assuming all 526 eligible patients in Portugal are treated with NIVO+IPI or SUN[a]



[a]The people in the figure are for demonstration purposes only.

Figure 6. Difference in number of patients experiencing grade 3–4 AEs if all 526 eligible patients with aRCC in Portugal are treated by NIVO+IPI instead of SUN



Limitations

- The NNTs and NNHs were based on the CheckMate 214 patient population. The findings should be further validated in real-world patient populations
- The analyses were limited to 36 months due to data availability. Future analyses based on longer-term data are warranted to quantify the benefits and risks associated with NIVO+IPI beyond 3 years

Conclusions

- The NNT and NNH analyses demonstrated the benefits of NIVO+IPI over SUN in terms of both clinical efficacy and safety. Among previously untreated patients with intermediate/poor-risk aRCC, NIVO+IPI provides greater clinical benefits and is associated with a lower risk of grade 3–4 AEs compared with SUN
- The efficacy and safety benefits for NIVO+IPI versus SUN were sustained over 36 months
- If all eligible patients in Spain with aRCC receive NIVO+IPI instead of SUN, there would be 287 additional overall survivors, 323 additional objective responders, 515 fewer patients experiencing treatment-related grade 3–4 AEs, and 266 fewer patients experiencing all-cause grade 3–4 AEs over 36 months
- If all eligible patients in Portugal with aRCC receive NIVO+IPI instead of SUN, there would be 58 additional overall survivors, 66 additional objective responders, 105 fewer patients experiencing treatment-related grade 3–4 AEs, and 54 fewer patients experiencing all-cause grade 3–4 AEs over 36 months
- The results provide important evidence that could inform treatment decision making related to aRCC for payers and healthcare providers

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Acknowledgments

- Lei Yin and Zhaocheng Yi from Analysis Group for analytical support
- Bristol-Myers Squibb (Princeton, NJ) and ONO Pharmaceutical Company Ltd. (Osaka, Japan)
- This study was supported by Bristol-Myers Squibb
- All authors contributed to and approved the presentation; editorial assistance was provided by Parexel, funded by Bristol-Myers Squibb

Presented at ISPOR Europe 2019; November 2–6, 2019; Copenhagen, Denmark

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