Matching-adjusted indirect comparison of health-related quality of life of nivolumab plus cabozantinib versus pembrolizumab plus axitinib in previously untreated advanced renal cell carcinoma

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Background

- The landscape for first-line (1L) advanced or metastatic renal cell carcinoma (aRCC) is rapidly evolving
  - Nivolumab plus cabozantinib (NIVO+CABO) and pembrolizumab plus axitinib (PEM+AXI) are currently recommended as standard of care, irrespective of risk group, by the European Association of Urology and the European Society for Medical Oncology, as well as the National Comprehensive Cancer Network in the United States[1-3]
  - NIVO+CABO and PEM+AXI have similar modes of action and have demonstrated a significant efficacy benefit versus sunitinib (SUN)
- As aRCC significantly impacts health-related quality of life (HRQoL), understanding HRQoL benefits of these 2 treatments is of interest to inform clinical decision making
- The objective of this study was to understand the comparative HRQoL benefits of NIVO+CABO versus PEM+AXI in patients with previously untreated aRCC
  - In the absence of head-to-head clinical trials directly comparing NIVO+CABO versus PEM+AXI, we conducted a matching-adjusted indirect comparison (MAIC) on the following patient-reported outcome (PRO) endpoints:
    - Change from baseline at week 30/31 (CHG) in EQ-5D-3L VAS (EQ-VAS) and Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) scores
    - Time to first deterioration (TTFD) in EQ-VAS and time to confirmed deterioration (TTCD) in EQ-VAS and FKSI-DRS scores
  - The selection of endpoints was restricted by their availability in trials informing comparison, eg, TTFD in FKSI-DRS score was reported in the CheckMate 9ER trial but not in the KEYNOTE-426 trial

Methods

Data source

- The evidence network included 2 trials with a common comparator (SUN): CheckMate 9ER (NCT03141177) and KEYNOTE-426 (NCT02853331)
  - CheckMate 9ER, a phase 3, randomized, open-label trial comparing NIVO+CABO (N = 323) versus SUN (N = 328) in adults with previously untreated (1L) aRCC[4,5]
  - KEYNOTE-426, a phase 3, randomized, open-label trial comparing PEM+AXI (N = 432) versus SUN (N = 429) in adults with treatment-naïve aRCC with clear cell histology[6,7]
  - The PROs for KEYNOTE-426 were published based on 12.8 months of median follow-up; therefore, the data from 18.1 months of median follow-up for CheckMate 9ER were chosen

Feasibility assessment

- The 2 studies were evaluated for feasibility to conduct an MAIC (**Table 1**)
  - Both were comparable in terms of study design, and both included the target population of interest (ie, adults with aRCC without prior systemic therapy for RCC)
  - Inclusion criteria were similar, with some differences: CheckMate 9ER also included patients with 1 prior adjuvant or neoadjuvant systemic therapy for completely resectable aRCC, while KEYNOTE-426 only included patients with no previous systemic treatment for advanced disease
    - Prior neoadjuvant/adjuvant therapy of targeted agents is acceptable if completed > 12 months before randomization
  - Median follow-up was longer in CheckMate 9ER (data cutoff March 30, 2021) versus KEYNOTE-426 (data cutoff August 24, 2018) (18.1 and 12.8 months, respectively)

Table 1. Summary of study characteristics

	CheckMate 9ER	KEYNOTE-426
Clinical trial ID	NCT03141177	NCT02853331
Population	Adults with previously untreated aRCC	Adults with treatment-naïve aRCC with clear cell histology
Intervention	NIVO+CABO	PEM+AXI
Comparator	SUN	SUN
Study design	Phase 3, randomized, open label Stratification by • IMDC prognostic score (0 [favorable risk] vs 1-2 [intermediate risk] vs 3-6 [poor risk]) • Tumor PD-L1 expression (≥ 1% vs < 1% or indeterminate) • Geographic region (US/Canada/western Europe/ northern Europe vs rest of the world)	Phase 3, randomized, open label Stratification by • IMDC risk group (favorable vs intermediate vs poor) • Geographic region (North America vs western Europe vs rest of the world)
Region	Multinational	Multinational
Key eligibility criteria	• Adults aged 18 years or older • Histological confirmation of RCC with a clear cell component, including patients who may also have sarcomatoid features • Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC stage IV) RCC • No prior systemic therapy for RCC, except for 1 prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets VEGF or VEGF receptors, and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy	• Adults aged 18 years or older • Newly diagnosed stage IV or recurrent RCC with clear cell histology • No previous systemic treatment for advanced disease • Measurable disease per RECIST v1.1 • Karnofsky performance status score of 70 or higher at baseline
Primary outcomes	PFS	OS and PFS
Secondary outcomes	• OS • ORR • Incidence of AEs, SAEs, deaths, and laboratory abnormalities, change from baseline in laboratory values	• ORR • DCR • DOR • PFS rate at month 12, 18, 24 • OS rate at month 12, 18, 24 • Mean change from baseline to week 54 in EORTC QLQ-C30 • Time to deterioration in FKSI-DRS
Exploratory outcomes	• HRQoL (FKSI-19 TS, FKSI-DRS, FKSI-DRS-P, FKSI-DRS-E, FKSI-TSE, FKSI-FWB, EQ-5D-3L VAS and utility) • Potential predictive biomarkers of clinical response • Pharmacokinetics • Immunogenicity • PFS-2	• PFS, ORR, DOR, and DCR per irRECIST as assessed by BICR • EQ-5D-3L UK Utility • Pharmacokinetics • Identify molecular determinants of response or resistance
Study population[a]	651 (NIVO+CABO, 323; SUN, 328)	861 (PEM+AXI, 432; SUN, 429)
Median follow-up (range), months	18.1 (10.6-30.6)	12.8 (0.1-22.0)
Main publication	Choueiri TK, et al. 2021[4]	Rini BI, et al. 2019[6]

[a]Number of patients randomized.
AE, adverse event; AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; FKSI-19 TS, FKSI-19 total score; FKSI-DRS-P, FKSI-disease related symptoms physical; FKSI-DRS-E, FKSI-disease related symptoms emotional; FKSI-TSE, FKSI-treatment side effects; FKSI-FWB, FKSI-functional well being; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PFS-2, second progression-free survival; SAE, serious adverse event.

MAIC methodology

- TTFD and TTCD were defined based on definitions from CheckMate 9ER
  - TTFD: time from the date of randomization to the date of the first deterioration in PRO scores of at least of 1 threshold unit (7 points for EQ-VAS and 3 points for FKSI-DRS) versus the baseline score
  - TTCD: time from the date of randomization to the date of the first deterioration in PRO scores of at least of 1 threshold unit (7 points for EQ-VAS and 3 points for FKSI-DRS) versus the baseline score if the deterioration of at least 1 threshold unit versus the baseline score is also confirmed at the next consecutive scheduled visit common for both arms (at least 6 weeks apart) or followed by dropout, resulting in missing data
- The individual patient-level data (IPD) from CheckMate 9ER was reweighted to mimic the KEYNOTE-426 trial population
- Hazard ratios (HRs) for TTFD and TTCD and baseline to week 30 least squares mean differences (LSMD) in these outcomes were re-estimated for CheckMate 9ER using a weighted population and indirectly compared with those in KEYNOTE-426 via a Bayesian framework
- An anchored MAIC[8] was conducted using IPD from CheckMate 9ER and aggregate published data from KEYNOTE-426
- Outcomes included FKSI-DRS and EQ-VAS
- CheckMate 9ER patients were matched to KEYNOTE-426 patients on the following 5 variables evaluated as being both clinically and statistically relevant for a particular endpoint:
  - Age (TTCD EQ-VAS, TTCD FKSI-DRS)
  - Geographic region (CHG FKSI-DRS)
  - IMDC risk category (all endpoints)
  - Sites of metastatic disease (TTFD EQ-VAS, TTCD FKSI-DRS, CHG FKSI-DRS)
  - Prior nephrectomy (all endpoints)

Sensitivity analysis

- The following additional variables reported in both studies were evaluated as potential effect modifiers, based solely on their statistical relevance for particular endpoint:
  - Gender
  - Race
  - Karnofsky score (based on Karnofsky Performance Scale)
  - Presence of sarcomatoid features
  - Number of organs involved with disease at baseline
  - RCC stage at initial diagnosis
  - Prior oncologic radiation
- Of these, the following variables identified as statistically relevant were added to the set of matching variables used in the primary analysis for these outcomes:
  - Gender (CHG VAS, CHG FKSI-DRS)
  - Karnofsky Performance Scale (TTCD FKSI-DRS, CHG FKSI-DRS)
  - Presence of sarcomatoid features (TTCD FKSI-DRS)
  - RCC stage at initial diagnosis (CHG VAS)
  - Prior oncologic radiation (TTCD FKSI-DRS, CHG FKSI-DRS)
- The IPD from CheckMate 9ER were reweighted using this extended set of matching variables, and models for TTCD FKSI-DRS, CHG VAS, and CHG FKSI-DRS were re-estimated

Results

Baseline characteristics

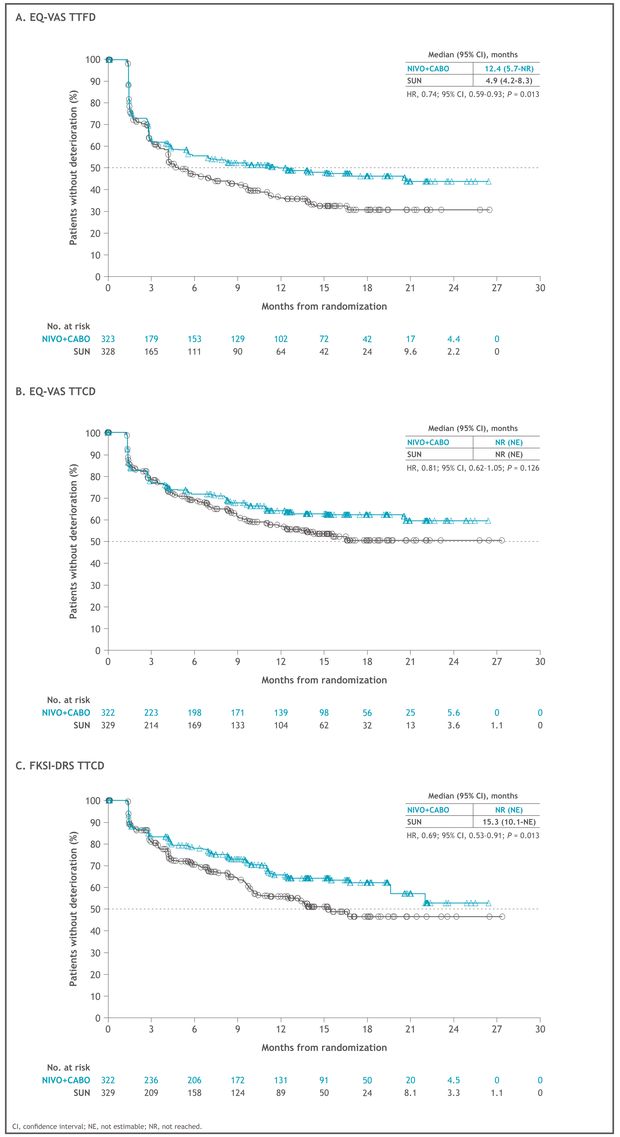
- A total of 651 CheckMate 9ER patients were matched to 861 KEYNOTE-426 patients using age, region, risk group, sites of metastatic disease, and prior nephrectomy
- Before matching, trial populations differed in several baseline characteristics
- After MAIC, selected baseline characteristics for matching were balanced across trials (**Table 2**)

Table 2. Selected baseline characteristics before and after adjustment

Effect modifier, %[a]	CheckMate 9ER (unadjusted)	CheckMate 9ER (adjusted)[b]	KEYNOTE-426
IMDC risk category[a]			
Favorable	22.4	31.2	31.2
Intermediate	57.8	56.2	56.2
Poor	19.8	12.5	12.5
Prior nephrectomy			
Yes	69.9	83.0	83.0
No	30.1	17.0	17.0
Sites of metastatic disease			
Lymph node			
Yes	40.1	46.0	46.0
No	59.9	54.0	54.0
Liver			
Yes	19.4	15.9	15.9
No	80.6	84.1	84.1
Adrenal gland			
Yes	11.1	16.6	16.6
No	88.9	83.4	83.4
Age category			
< 65 years	61.6	62.5	62.5
≥ 65 years	38.4	37.5	37.5
Geographic region			
Rest of the world	51.0	51.6	51.6
US/Canada/western Europe	49.0	48.4	48.4

[a]Selected modifiers after reweighting matched the values reported from KEYNOTE-426 perfectly. Weights were generated separately for each endpoint.
[b]Effective sample sizes ranged from 557-582.

Figure 1. Weighted Kaplan-Meier curves for TTFD or TTCD of EQ-VAS and FKSI-DRS



CI, confidence interval; NE, not estimable; NR, not reached.

MAIC efficacy results

- After adjustment, HRs and LSMDs worsened for all PRO scores and HR for TTCD EQ-VAS became statistically nonsignificant, but the results still favored NIVO+CABO versus SUN (**Table 3**)

Table 3. PRO results before and after adjustment

Outcome	CheckMate 9ER (unadjusted)	CheckMate 9ER (adjusted)[b]	KEYNOTE-426
TTFD, HR (95% CI)[a]			
EQ-VAS	0.71 (0.56-0.89)[c]	0.74 (0.59-0.93)[c]	1.02 (0.86-1.20)
TTCD, HR (95% CI)[a]			
EQ-VAS	0.71 (0.55-0.94)[c]	0.81 (0.62-1.05)	1.12 (0.91-1.38)
FKSI-DRS	0.62 (0.46-0.82)[c]	0.69 (0.53-0.91)[c]	1.44 (1.14-1.82)
Change from baseline at week 30, LSMD (95% CI)[b]			
EQ-VAS	1.54 (−0.89 to 3.97)	1.15 (−1.19 to 3.50)	−1.4 (−3.90 to 1.10)
FKSI-DRS	1.64 (0.98-2.31)[c]	1.35 (0.70-2.00)[c]	−0.5 (−1.10 to 0.10)

[a]HR < 1 favors NIVO+CABO/PEM+AXI over SUN; HR > 1 favors SUN over NIVO+CABO/PEM+AXI.
[b]LSMD > 0 favors NIVO+CABO/PEM+AXI over SUN; LSMD < 0 favors SUN over NIVO+CABO/PEM+AXI.
[c]Statistically significant when the 95% CI does not contain 1 (for TTFD or TTCD) or 0 (for LSMD).

- Results from the MAIC favored NIVO+CABO versus PEM+AXI in all outcomes with statistically significant differences for FKSI-DRS and TTFD in EQ-VAS score (**Table 4**)
- NIVO+CABO compares favorably to PEM+AXI with significant improvement in disease-related symptoms and significant delay in TTFD for HRQoL (**Table 4**)
  - MAIC showed statistically significant benefit of NIVO+CABO versus PEM+AXI
    - TTFD in EQ-VAS score (HR, 0.73; 95% credible interval [CrI], 0.55-0.96)
    - TTCD in FKSI-DRS score (HR, 0.48; 95% CrI, 0.33-0.69)
    - Change from baseline in FKSI-DRS score (LSMD, 1.85; 95% CrI, 0.96-2.74)
- Results for TTCD and change from baseline for EQ-VAS score also favored NIVO+CABO, albeit they were not statistically significant (HR, 0.72; 95% CrI, 0.52-1.01; LSMD, 2.55; 95% CrI, −0.88 to 5.98; **Table 4**)

Table 4. Comparison of NIVO+CABO versus PEM+AXI in selected outcomes (TTFD, TTCD, change from baseline)

Outcome	MAIC results, NIVO+CABO vs PEM+AXI
TTFD, HR (95% CrI)[a]	
EQ-VAS	0.73 (0.55-0.96)[c]
TTCD, HR (95% CrI)[a]	
EQ-VAS	0.72 (0.52-1.01)
FKSI-DRS	0.48 (0.33-0.69)[c]
Change from baseline at week 30, LSMD (95% CrI)[b]	
EQ-VAS	2.55 (−0.88 to 5.98)
FKSI-DRS	1.85 (0.96-2.74)[c]

[a]HR < 1 favors NIVO+CABO over PEM+AXI; HR > 1 favors PEM+AXI over NIVO+CABO.
[b]LSMD > 0 favors NIVO+CABO over PEM+AXI; LSMD < 0 favors PEM+AXI over NIVO+CABO.
[c]Statistically significant results when the 95% CrI does not contain 1 (for TTFD or TTCD) or 0 (for LSMD).

- The sensitivity analyses, consistent with the primary results, showed favorable results for NIVO+CABO versus PEM+AXI across all endpoints
  - Sensitivity analyses revealed
    - Increased benefits of NIVO+CABO versus PEM+AXI in TTCD in FKSI-DRS score versus the primary analysis (HR, 0.36; 95% CrI, 0.25-0.52), which was statistically significant
    - A statistically significant change from baseline in FKSI-DRS score favoring NIVO+CABO versus PEM+AXI (LSMD, 1.90; 95% CrI, 1.01-2.79), which was similar in magnitude to the primary analysis
    - Change from baseline for EQ-VAS score favoring NIVO+CABO, albeit, as in the primary analysis, this was not statistically significant (LSMD, 2.43; 95% CrI, −0.99 to 5.85)
  - No additional modifiers were identified in sensitivity analysis for TTFD in EQ-VAS and TTCD EQ-VAS scores

Strengths and limitations

- The strengths of this study include that it was adjusted for differences in patient characteristics between the 2 trials, and that it used the Bayesian approach, which offers more conservative estimates and is preferred by many health technology assessment bodies
- Whereas the MAIC methodology assumes that adjustment is made for all prognostic factors and treatment effect modifiers, unknown or unobserved prognostic factors, treatment effect modifiers, or other differences may still exist between studies.[9] This is a known limitation of population adjustment methods, which should be considered when interpreting results
- Another limitation of this study includes the limited published HRQoL data from KEYNOTE-426 and the 2-week difference in HRQoL data collection in the 2 studies relative to SUN dosing
  - In CheckMate 9ER, the PRO data were collected only on the beginning of the SUN cycle; however, for KEYNOTE-426, data were collected in the beginning and end of the cycle, which may have captured more AEs in the SUN arm, and impacted TTFD and perception of treatment burden associated with SUN

Conclusions

- In patients with 1L aRCC, MAIC analyses suggest that NIVO+CABO demonstrated a statistically significant improvement in disease-related symptoms (as measured by FKSI-DRS) and significantly delayed deterioration in HRQoL compared with PEM+AXI
- These results, combined with the significant efficacy benefits and favorable safety profile of NIVO+CABO versus SUN, may further inform treatment decisions of clinicians and patients with 1L aRCC

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Disclosures

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