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UPDATED NETWORK META-ANALYSIS OF TREATMENTS IN FIRST-LINE ADVANCED/METASTATIC INTERMEDIATE- OR POOR-RISK RENAL CELL CARCINOMA

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Introduction

- Renal cell carcinoma (RCC) forms in cells in the lining of small tubules in the kidney that filter blood. RCC is the most common type of kidney cancer, accounting for 80-90% of all kidney malignancies.[1]
- Despite available therapies, life expectancy for patients with advanced or metastatic RCC is short, with a 5-year survival rate of only 10-15%[2], indicating a high unmet need for a new treatment option.
- Nivolumab plus ipilimumab was the first immuno-oncology combination therapy to show a significant OS benefit compared to the standard of care, sunitinib, in intermediate and poor risk patients. The phase 3 CheckMate 214 randomized controlled trial (NCT02231749), with a minimum follow-up of 18 months, showed a significant overall survival benefit versus sunitinib.[3]
- A network meta-analysis (NMA) has been conducted by Laliman et al.[4] to compare the efficacy of nivolumab plus ipilimumab versus 1L RCC therapies in intermediate and poor patients. The NMA by Laliman et al. was based on the initial 18-month results of the CheckMate 214 study.[3]
- As new data from the CheckMate 214 trial, with a minimum follow-up of 30 months has become available[5], an update of the previously conducted NMA is needed.

Objective

- To update a previously conducted NMA by Laliman et al. (2018)[4] with more mature survival data from the CheckMate 214 30-month DBL.[5]

Methods

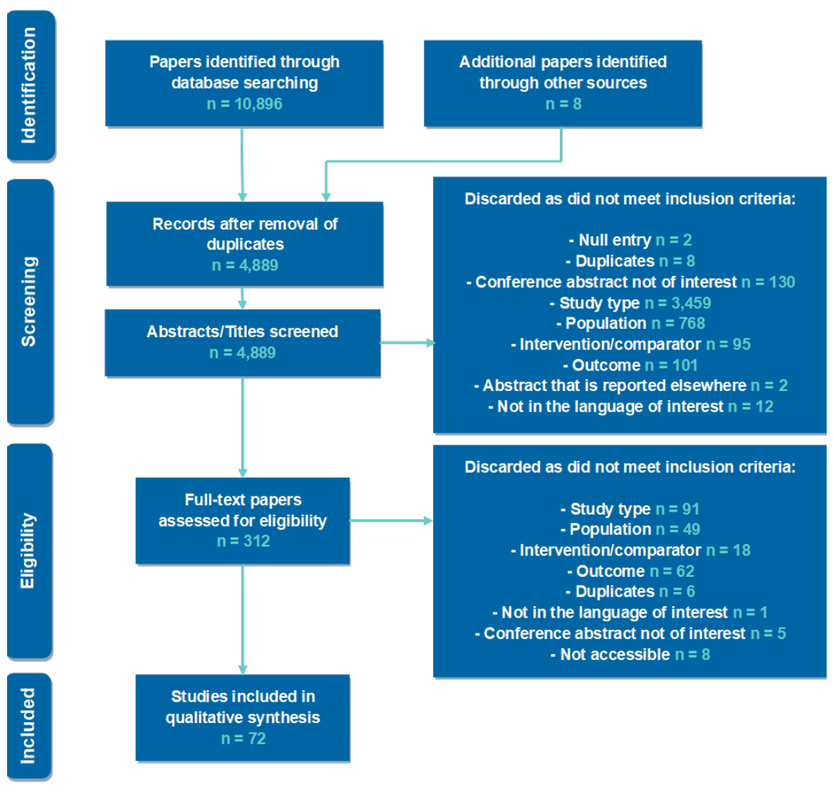
- The NMA update was based on a systematic literature review (SLR) that was conducted by Bregman et al. on March 15th 2018[7] following the NICE guidelines[6] to identify relevant randomized controlled trials (RCTs) involving first-line treatments for previously untreated, advanced or metastatic RCC.
- The outcomes of interest were progression-free survival (PFS) and overall survival (OS).
- Relative efficacy was estimated based on hazard ratio (HR) and evaluated using Bayesian probabilities, in line with the previous NMA and using methods in line with NICE guidelines.[7-8]
- The models were run in WinBUGS with three chains with a burn-in of 100,000 iterations. Inferences were based on 10,000 further iterations for both the fixed effects and random effects models.
- Two sensitivity analyses were carried out:
  - For PFS, the Motzer 2013 study was excluded from the main analysis and included in a sensitivity analysis, as this study only reported a HR in the intermediate (instead of intermediate and poor) prognosis population between pazopanib and sunitinib.
  - For OS, the Motzer 2014 study was included in the main analysis and excluded in a sensitivity analysis, since the HR for this comparison was obtained through a letter to the editor. As the letter only reported separate HRs in intermediate and poor prognosis populations, HRs were aggregated and used in the main analysis.

Results

Systematic literature review

- A total of 10,896 citations were captured from the electronic searches. After removal of the duplicates, 4,889 citations remained. Excluding the publications not meeting the selection criteria, 72 publications were included and extracted.[6] The SLR was not updated for the current update of the NMA.
- The PRISMA diagram of the SLR is reported in Figure 1.

Figure 1. PRISMA diagram of the SLR



Studies included in the NMA alongside CheckMate 214

- An overview of studies that were included in the NMA to be compared with nivolumab plus ipilimumab, based on the previously conducted feasibility assessment by Laliman et al. (2018), is shown in Table 1.

Table 1. Studies included in the NMA

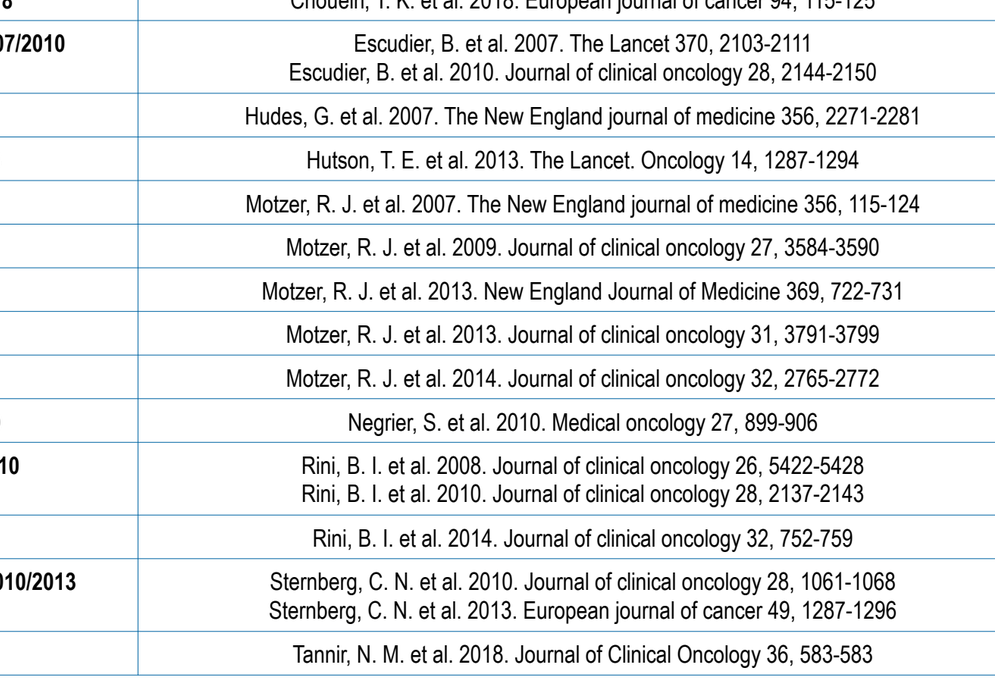
Author and year	Reference
Choueiri, 2018	Choueiri, T. K. et al. 2018. European journal of cancer 94, 115-125
Escudier, 2007/2010	Escudier, B. et al. 2007. The Lancet 370, 2103-2111 Escudier, B. et al. 2010. Journal of clinical oncology 28, 2144-2150
Hudes, 2007	Hudes, G. et al. 2007. The New England journal of medicine 356, 2271-2281
Hutson, 2013	Hutson, T. E. et al. 2013. The Lancet. Oncology 14, 1287-1294
Motzer, 2007	Motzer, R. J. et al. 2007. The New England journal of medicine 356, 115-124
Motzer, 2009	Motzer, R. J. et al. 2009. Journal of clinical oncology 27, 3584-3590
Motzer, 2013	Motzer, R. J. et al. 2013. New England Journal of Medicine 369, 722-731
Motzer, 2013	Motzer, R. J. et al. 2013. Journal of clinical oncology 31, 3791-3799
Motzer, 2014	Motzer, R. J. et al. 2014. Journal of clinical oncology 32, 2765-2772
Negrier, 2010	Negrier, S. et al. 2010. Medical oncology 27, 899-906
Rini, 2008/2010	Rini, B. I. et al. 2008. Journal of clinical oncology 26, 5422-5428 Rini, B. I. et al. 2010. Journal of clinical oncology 28, 2137-2143
Rini, 2014	Rini, B. I. et al. 2014. Journal of clinical oncology 32, 752-759
Sternberg, 2010/2013	Sternberg, C. N. et al. 2010. Journal of clinical oncology 28, 1061-1068 Sternberg, C. N. et al. 2013. European journal of cancer 49, 1287-1296
Tannir, 2018	Tannir, N. M. et al. 2018. Journal of Clinical Oncology 36, 583-583

Progression-free survival

- The SLR resulted in the identification of thirteen studies reporting PFS HR with their associated 95% CI or PFS Kaplan-Meier curves (allowing reconstruction and HR estimation using Guyot's algorithm)[9] in the population of interest. Fourteen therapies were included in the network of evidence (Figure 2).
- A fixed-effects model was applied for PFS, as the random effects models did not converge.
- Nivolumab plus ipilimumab significantly improved PFS compared to seven comparators: sunitinib, interferon, bevacizumab plus interferon, everolimus, temsirolimus, temsirolimus plus interferon and placebo. Full results for PFS are presented in Figure 2.

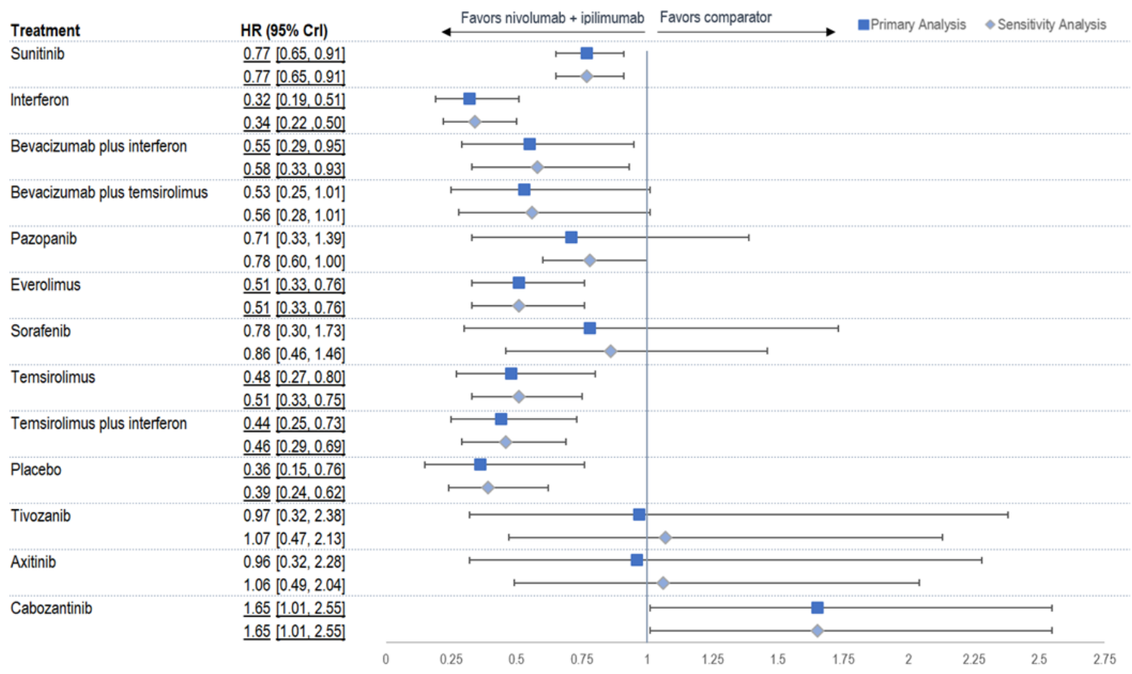
Figure 1. Network of evidence - PFS

AXI: axitinib
BEV: bevacizumab
CABO: cabozantinib
EVE: everolimus
IFN: interferon
IPI: ipilimumab
NIVO: nivolumab
PAZO: pazopanib
PBO: placebo
SOR: sorafenib
SUN: sunitinib
TEM: temsirolimus
TIV: tivozanib



-The turquoise colored box indicates the main treatment of interest.
-The underlined study indicates this study was included in a sensitivity analysis.
-For the study of Hudes et al. (2007), HRs were estimated using Guyot's algorithm.

Figure 2. Fixed-effects treatment HR nivolumab plus ipilimumab vs. comparators – PFS



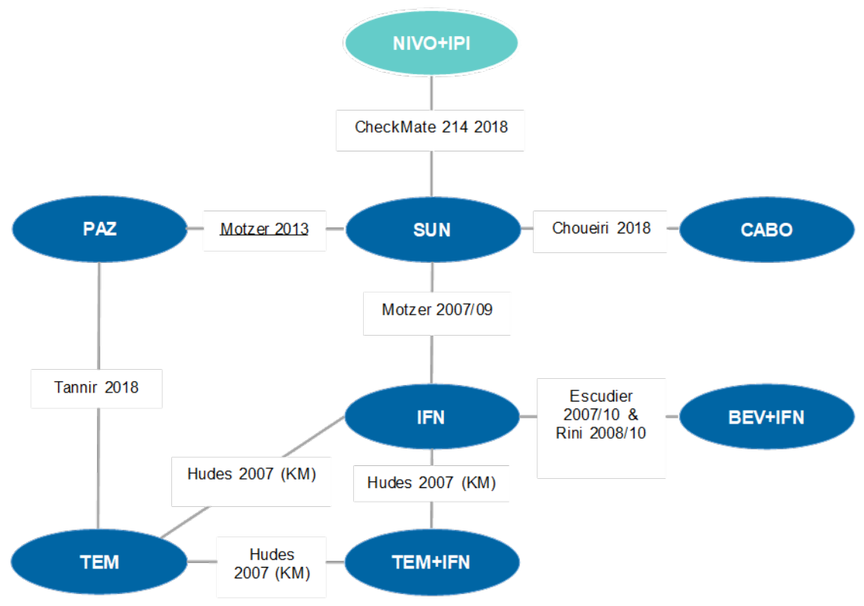
Note: underlined HRs are HRs with 95%CrIs not crossing the null value of 1.

Overall Survival

- The SLR resulted in the identification of seven studies reporting OS HR with their associated 95% CI or OS Kaplan-Meier curves (allowing reconstruction and HR estimation using Guyot's algorithm)[9] in the population of interest.
- Eight therapies were included in the network of evidence (Figure 3).

Figure 3. Network of evidence - OS

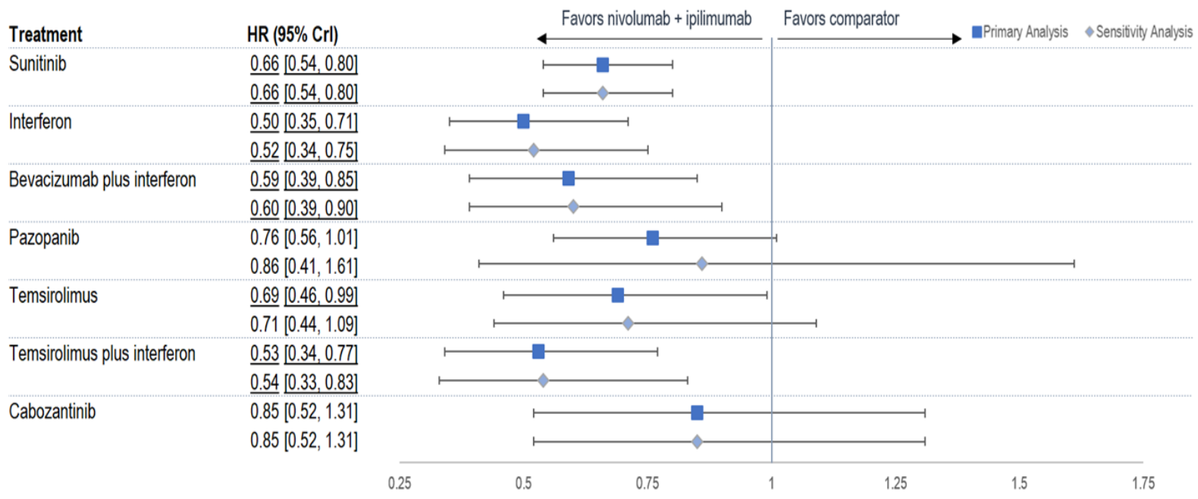
BEV: bevacizumab
CABO: cabozantinib
IFN: interferon
IPI: ipilimumab
NIVO: nivolumab
PAZO: pazopanib
SUN: sunitinib
TEM: temsirolimus



-The turquoise colored box indicates the main treatment of interest.
-The underlined study indicates this study was excluded in a sensitivity analysis.
-For the study of Hudes et al. (2007), HRs were estimated using Guyot's algorithm.

- A fixed-effects model was applied for OS, as the random effects models did not converge.
- Nivolumab plus ipilimumab was found to be numerically more effective than all comparators and significantly improved OS compared to five comparators: sunitinib, interferon, bevacizumab plus interferon, temsirolimus and temsirolimus plus interferon. Full results for OS are presented in Figure 4.

Figure 4. Fixed-effects treatment HR nivolumab plus ipilimumab vs. comparators – OS



Note: underlined HRs are HRs with 95%CrIs not crossing the null value of 1.

Discussion

- This study followed NICE guidelines to conduct the SLR and the NMA. There was available evidence to derive a network for the comparators most commonly used in clinical practice.
- For pazopanib, limited information on PFS was available as the main study comparing pazopanib to sunitinib (Motzer 2013) was only reporting HR in the intermediate population. Therefore, despite being able to connect the network through temsirolimus through the study by Tannir et al. (which had very low patient numbers), the HR of nivolumab with ipilimumab vs. pazopanib was associated with a large credible interval. This problem also extended to any treatment anchored to the network via pazopanib (placebo, sorafenib, tivozanib and axitinib).
- The previous limitation also extended to OS, as the sensitivity analysis shows that excluding the trial of Motzer et al. (2014) increased the credible intervals of pazopanib vs. sunitinib.
- All studies used the MSKCC scoring system, with the exception of CheckMate 214 and Alliance A03123 CABOSUN trials, which used the IMDC scoring system. Available literature[10] indicates a high level of concordance between the two scales.

Conclusions

- Nivolumab plus ipilimumab was found to be numerically more effective than all comparators and significantly improved OS compared to five comparators: sunitinib, interferon, bevacizumab plus interferon, temsirolimus and temsirolimus plus interferon.
- Nivolumab plus ipilimumab significantly improved PFS compared to seven comparators: sunitinib, interferon, bevacizumab plus interferon, everolimus, temsirolimus, temsirolimus plus interferon and placebo.
- Though nivolumab plus ipilimumab numerically favored most comparators, scarcity of data led to large credible intervals for some therapies, meaning that the effectiveness of nivolumab plus ipilimumab did not reach statistical significance for these therapies.
- Nivolumab plus ipilimumab was statistically superior to most comparators tested for OS and PFS; therefore, it represents a significant advance for 1L RCC patients when compared to existing therapies.
- This result aligns with the previous NMA, showing robustness of the efficacy estimates and benefit of nivolumab plus ipilimumab as 1L treatment for RCC.

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