

# FACTORS THAT MODIFY THE EFFECT OF MONO- OR COMBINATION PD-1/PD-L1 INHIBITOR THERAPIES ON SURVIVAL OUTCOMES IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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## BACKGROUND

- Programmed death-1 and programmed death-ligand 1 (PD-1/PD-L1) are immune checkpoint inhibitors (ICIs) widely used in the treatment of metastatic renal cell carcinoma (mRCC) and other cancers.
- There is a lack of understanding regarding which patient factors predict response to these therapies.
- Understanding which predictive factors influence ICI treatments can aid in patient selection for PD-1/PD-L1 inhibitor therapy, and improve survival outcomes in mRCC.

## OBJECTIVES

- To conduct a systematic literature review of studies examining factors that modify clinical efficacy of PD-1 or PD-L1 inhibitors among patients diagnosed with mRCC.
- To quantitatively synthesize the magnitude to which each predictive factor modifies the effect of PD-1/PD-L1 inhibitors.

## METHODS

### 1) Search Strategy

- Electronic databases MEDLINE and COCHRANE were searched on September 3<sup>rd</sup>, 2019.

### 2) Inclusion Criteria

- mRCC patient population.
- Studies published in English from 2006 onwards.
- Phase II/III RCTs with subgroup analyses of any baseline characteristic with respect to mono- or combo- PD-1/PD-L1 inhibitor therapies.

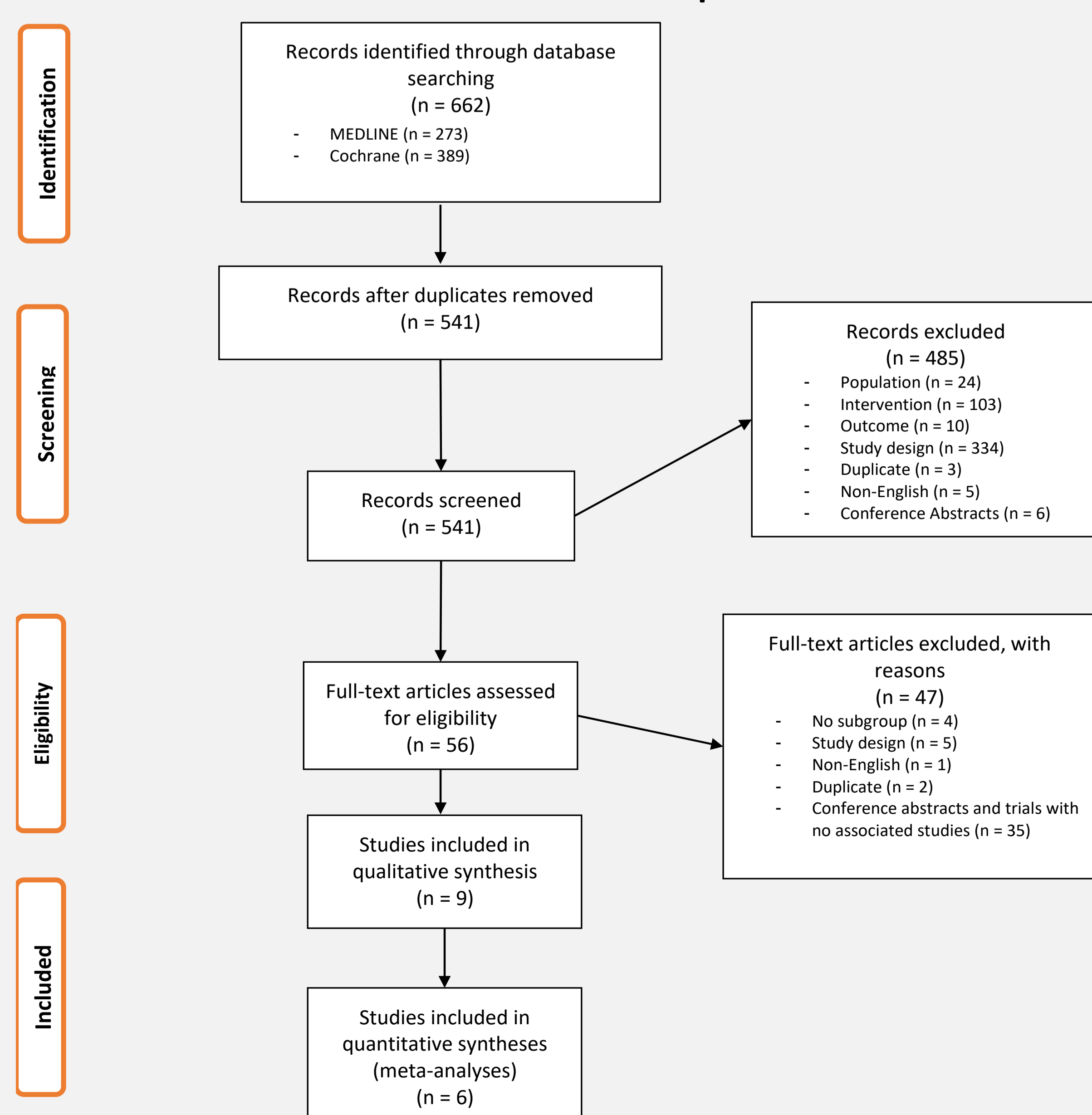
### 3) Screening & Data Extraction

- PRISMA reporting guidelines were followed.
- Screening was performed by 2 independent reviewers.
- From an initial 662 studies, **seven unique trials** were included.

### 4) Quantitative Analysis

- Random-effects pairwise meta-analyses were performed on the ratio of subgroup-specific hazard ratios, for commonly reported baseline variables.
- Forest plots were constructed using "Metafor" (R v3.5.0).

Figure 1: Six trials were included in the pairwise meta-analyses.

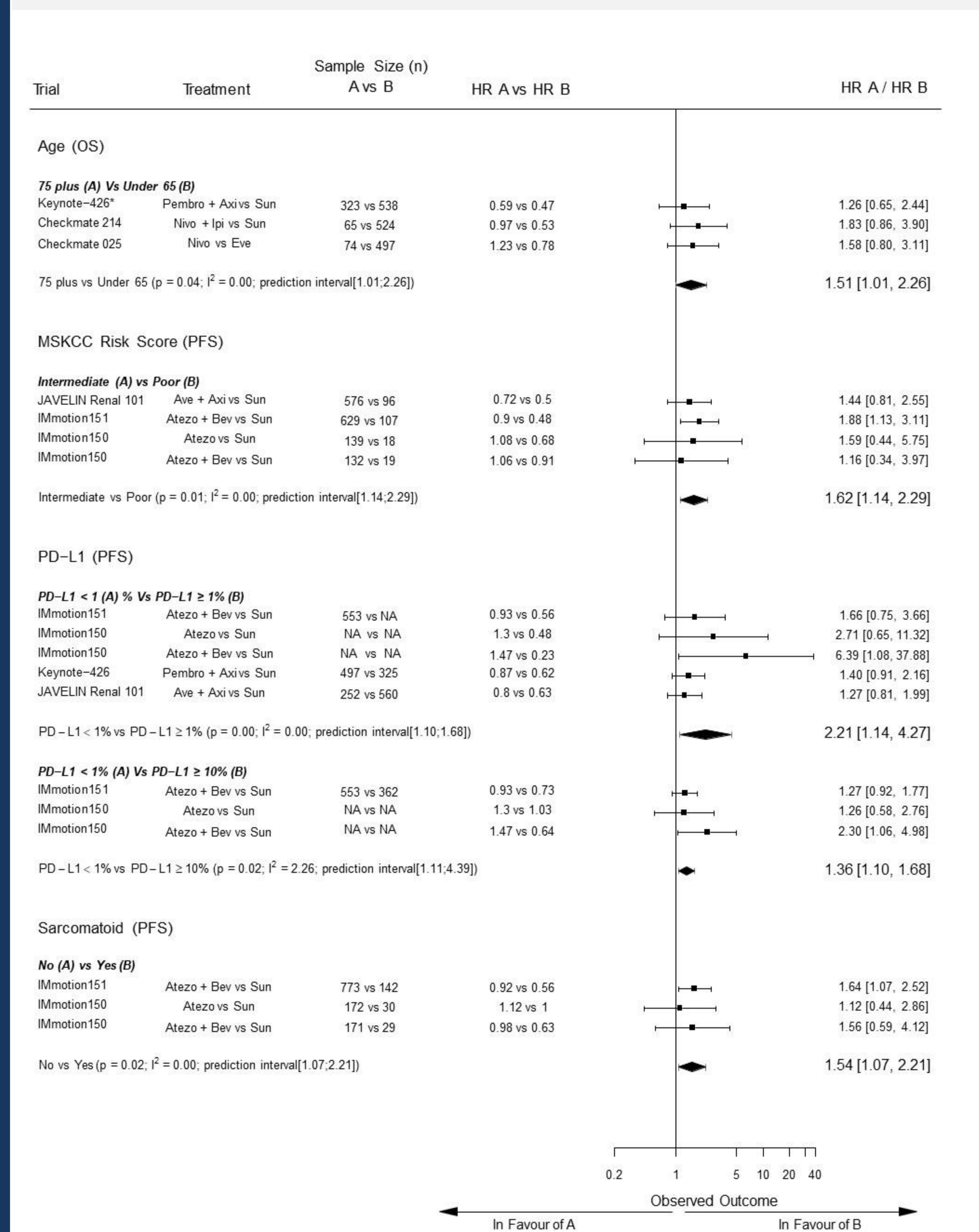


## RESULTS

Table 1: Descriptive characteristics of the included trials (n=7).

| Trial                           | Phase | PD-1/PD-L1 Inhibitor(s)                           | Comparator(s) | Reported Outcomes | Examined Subgroups  |
|---------------------------------|-------|---|---------------|-------------------|---|
| NCT01354431 (Motzer 2015)       | II    | Nivolumab   | N/A           | OS, PFS           | -PD-L1  |
| IMmotion150 (McDermott 2018)    | II    | i) Atezolizumab + Bevacuzimab<br>ii) Atezolizumab | Sunitinib     | PFS               | -IMDC Risk Score<br>-Liver Metastases<br>-MSKCC Risk Score<br>-PD-L1<br>-Sarcomatoid Presence                       |
| Checkmate 025 (Motzer 2015)     | III   | Nivolumab   | Everolimus    | OS, PFS           | -Age<br>-Bone Metastases<br>-IMDC Risk Score<br>-Liver Metastases<br>-MSKCC Risk Score<br>-PD-L1<br>-Region<br>-Sex |
| Checkmate 214 (Motzer 2018)     | III   | Nivolumab + Ipilimumab                            | Sunitinib     | OS, PFS           | -Age<br>-Bone Metastases<br>-IMDC Risk Score<br>-Lung Metastases<br>-PD-L1<br>-Region<br>-Sex                       |
| IMmotion151 (Rini 2019)         | III   | Atezolizumab + Bevacuzimab                        | Sunitinib     | OS, PFS           | -IMDC Risk Score<br>-Liver Metastases<br>-MSKCC Risk Score<br>-PD-L1<br>-Sarcomatoid Presence                       |
| Keynote-426 (Rini 2019)         | III   | Pembrolizumab + Axitinib                          | Sunitinib     | OS, PFS           | -Age<br>-IMDC Risk Score<br>-PD-L1<br>-Region<br>-Sex   |
| JAVELIN Renal 101 (Motzer 2019) | III   | Avelumab + Axitinib                               | Sunitinib     | PFS               | -Age<br>-IMDC Risk Score<br>-MSKCC Risk Score<br>-PD-L1<br>-Region<br>-Sex  |

Figure 2: Baseline variables that demonstrated evidence of effect modification on the efficacy of PD-1/PD-L1 inhibitors.



\*Keynote-426 compared age subgroups of 65 plus and under 65.

\*\*Missing subgroup sample size data was reported as "NA".

## CONCLUSION

- Older age, intermediate MSKCC risk scores, low levels of PD-L1 expression, and sarcomatoid tumour differentiation demonstrated reductions in PD-1/PD-L1 inhibitor treatment efficacy.
- Research on the predictive factors that modify ICI treatment efficacy is needed to improve survival outcomes in mRCC.