Efficacy of immune checkpoint inhibitor (ICI) combination therapy as first-line (1L) treatment in metastatic renal cell carcinoma (mRCC).

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BACKGROUND

- Immune checkpoint inhibitor combination as 1L is the standard of care for patients with previously untreated mRCC.
- However, whether their efficacy is consistent across subgroups remains unclear.
- Therefore, we assessed the efficacy of ICI combination therapy by different clinically relevant subgroups using evidence from contemporary clinical trials.

METHODS

- MEDLINE and EMBASE were systematically searched through June 2023 to identify phase II/III randomized controlled trials (RCTs) assessing ICI combination therapies in 1L mRCC setting.
- Trials reporting efficacy by age, gender , PDL1 receptor status and international mRCC database consortium (IMDC) risk categories were included.
- Main efficacy outcomes included overall survival (OS), progression-free survival (PFS), and objective response rate (ORR).
- A random-effects meta-analysis was conducted to estimate summary effect estimates in each subgroup of interest.
- A p-value of interaction was computed to assess subgroup differences and a p-value <0.1 was considered as statistically significant.

RESULTS

- **Baseline characteristics**
  - A total of 4 trials with 3110 patients were included in the meta-analysis.
  - Updated data from all trials is reported here.
  - Approximately 75.3% patients were males, 38.8% were older than 65 years, 53% had PDL1 positive receptor status, and 75.3% were intermediate/poor risk.
- **Overall population**
  - In the overall population, ICI combination improved OS compared to sunitinib monotherapy.

TABLES & FIGURES

Table 1. Baseline trial characteristics

Trials	CLEAR	CHECKMATE 9ER	KEYNOTE 426	JAVELIN 101
Treatment	**Lenvatinib-Pembrolizumab**	**Cabozantinib-Nivolumab**	**Pembrolizumab-Axitinib**	**Avelumab-Axitinib**
Age in years - N (%)				
Age <65	Rx: 88 (45.3) Control: 134 (59.5)	Rx: 119 (62.3) Control: 151 (71.9)	Rx: 155 (59.6) Control: 192 (69)	Rx: 180 (66.4) Control: 207 (75.2)
Age ≥65	Rx: 72 (44.7) Control: 71 (53.7)	Rx: 88 (66.6) Control: 72 (61.0)	Rx: 109 (63.3) Control: 89 (58.9)	Rx: 117 (68.4) Control: 110 (65)
IMDC Risk Groups - N (%)				
Favorable	Rx: 96 (27) Control: 97 (27)	Rx: 74 (22.9) Control: 72 (22)	Rx: 138 (31.9) Control: 131 (30.5)	Rx: 94 (21.2) Control: 96 (21.6)
Intermediate /Poor	Rx: 243 (68.4) Control: 229 (64.1)	Rx: 249 (77) Control: 256 (78)	Rx: 294 (68) Control: 298 (69.4)	Rx: 343 (77.6) Control: 347 (78.1)
Sex - N (%)				
Male	Rx: 255 (72) Control: 275 (77)	Rx: 249 (77.1) Control: 232 (70.7)	Rx: 308 (71.3) Control: 320 (74.6)	Rx: 316 (71.4) Control: 344 (77.4)
Female	Rx: 100 (28) Control: 82 (23)	Rx: 74 (22.9) Control: 96 (29.3)	Rx: 124 (28.7) Control: 109 (25.4)	Rx: 126 (28.5) Control: 100 (22.5)
PDL1 status - N (%)				
PDL1 positive	Rx: 107 (30) Control: 119 (33)	Rx: 83 (25.7) Control: 83 (25.3)	Rx: 243 (59.3) Control: 254 (61.7)	Rx: 270 (61) Control: 290 (65.3)
PDL1 negative	Rx: 112 (32) Control: 103 (29)	Rx: 240 (74.3) Control: 245 (74.7)	Rx: 167 (40.7) Control: 158 (38.3)	Rx: 132 (29.8) Control: 120 (27)

Table 2. Subgroups analysis

	OS HR (95% CI)	P value of interaction	PFS HR (95% CI)	P value of interaction	ORR RR (95% CI)	P value of interaction
IMDC Status						
Favorable risk	1.00 (0.82;1.22)	0.002	0.79 (0.53;1.16)	0.23	2.61 (1.87;3.66)	0.47
Intermediate/Poor risk	0.71 (0.64;0.78)		0.60 (0.49;0.73)		3.04 (2.41;3.84)	
Age						
Age < 65 years	0.65 (0.56;0.77)	0.17	0.53 (0.41;0.67)	0.24	1.85 (0.66;5.18)	0.92
Age >= 65 years	0.79 (0.64;0.98)		0.66 (0.50;0.88)		1.74 (0.83;3.66)	
Sex						
Male	0.73 (0.64;0.84)	0.79	0.55 (0.42;0.73)	0.52	2.71 (2.06;3.58)	0.93
Female	0.69 (0.49;0.98)		0.63 (0.49;0.81)		2.76 (1.99;3.84)	
PDL1 Status						
PDL1 Positive	0.78 (0.68;0.90)	0.53	0.57 (0.45;0.72)	0.55	2.63 (1.64;4.22)	0.73
PDL1 Negative	0.73 (0.61;0.87)		0.64 (0.47;0.88)		2.39 (1.83;3.11)	

RESULTS

- **Subgroup analysis**
  - The results for overall survival are provided below. The results for PFS and ORR are provided in Table 1.
  - **IMDC risk groups**
    - ICI combination therapy significantly improved OS compared to sunitinib monotherapy in intermediate-poor risk population (hazard ratio: 0.71; 95% CI: 0.64-0.78) but not in the favorable risk population (1.00;0.82-1.22).
    - There was statistically significant effect modification by IMDC risk (P:0.002).
  - **Age**
    - Similarly, there was a significant improvement in OS for patients <65 years (0.65; 0.56-0.77) and in patients >65 years (0.79;0.64-0.98).
    - There was no statistically significant effect modification by age (P:0.17).
  - **Gender**
    - ICI combination therapy improved OS compared to sunitinib monotherapy in both female (0.69;0.49-0.98) and male patients (0.73;0.64-0.84).
    - However no statistically significant subgroup difference was observed (P:0.79).
  - **PDL1 status**
    - ICI combination therapy improved OS compared to sunitinib monotherapy in PDL1 positive (0.78;0.68-0.90) as well as PDL1 negative population (0.73;0.61-0.87).
    - However, no statistically significant difference was observed between the two groups (P:0.53).

CONCLUSIONS

- The results suggest that intermediate-poor risk disease may predict a higher magnitude of benefits for patients with mRCC contemplating treatment with immunotherapy combination