Effectiveness of first-line immune checkpoint inhibitors in advanced non-clear cell renal cell carcinoma

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Background

- Immune checkpoint inhibitors (ICI) have demonstrated impressive activity in metastatic clear-cell renal cell carcinoma (ccRCC) and have become standard treatment options in this setting
- **Non-clear cell renal cell carcinomas (nccRCC)** account for approximately 25% of all primary kidney malignancies, and represent a clinically, pathologically, and biologically diverse group of RCC subtypes
- Data supporting the effectiveness of ICI based therapy in non-clear cell RCC is more limited, as most prospective randomized trials excluded this population
- The primary aim of this study is to describe the real-world effectiveness of first-line ICI based therapies in metastatic nccRCC

Methods

- We performed a retrospective analysis of the International Metastatic RCC Database Consortium (IMDC) and included all patients with non-clear cell histology
- Patients were classified into 3 groups based on type of first-line therapy: ICI based therapy (in monotherapy or in combination), vascular endothelial growth factor targeted therapy (VEGF-TT) monotherapy, or mammalian target of rapamycin (mTOR) inhibitor monotherapy.
- Outcome measures of interest were:
  - Objective response rate (ORR)
  - Time to treatment failure (TTF)
  - Overall survival (OS)
- Multivariable Cox regression analysis was performed to adjust for imbalances in pre-specified prognostic covariates, including IMDC risk group, age, and histologic subtype

Results

- We identified 1181 patients with metastatic nccRCC
- Based on first-line therapy, 78.2% received VEGF-TT, 15.8% mTOR inhibitors, and 5.5% ICI based therapy (41.5% in monotherapy, 30.8% doublet-ICIs and 27.7% an ICI combined with VEGF-TT)

Table 1: Baseline Characteristics

		VEGF targeted therapy (N=924)	mTOR targeted therapy (N=186)	ICI based therapy (N=65)
Histologic subtype	Papillary	452 (57.5%)	112 (64.4%)	26 (40.6%)
	Chromophobe	115 (14.3%)	27 (15.5%)	12 (18.8%)
	Unclassified	168 (20.9%)	25 (14.4%)	16 (25.0%)
	Collecting Duct	19 (2.4%)	5 (2.9%)	6 (9.4%)
	Translocation	39 (4.9%)	5 (2.9%)	4 (6.2%)
Age yrs (median)		60	60	62
Male		670 (72.5%)	121 (65.1%)	38 (58.5%)
Nephrectomy		745 (80.6%)	136 (73.1%)	49 (75.4%)
Sarcomatoid features		106 (11.5%)	34 (18.3%)	13 (20.0%)
IMDC risk group	Favourable	181 (19.6%)	20 (10.8%)	14 (21.5%)
	Intermediate	503 (54.4%)	109 (58.6%)	34 (52.3%)
	Poor	240 (26.0%)	57 (30.6%)	17 (26.2%)
Liver metastases		213 (23.1%)	54 (29.0%)	15 (23.1%)
Bone metastases		295 (31.9%)	57 (30.6%)	26 (40.0%)
Brain metastases		42 (4.5%)	9 (4.8%)	1 (1.5%)

Table 2: Type of First-Line Therapy

VEGF targeted therapy (N=924)	mTOR targeted therapy (N=186)	ICI based therapy (N=65)
Sunitinib (n=632, 68.4%)	**Temsirolimus (n=141, 75.8%)**	**Nivo + Ipi (n=20, 30.8%)**
Pazopanib (n=171, 18.5%)	**Everolimus (n=45, 24.2%)**	**Atezo + Bev (n=14, 21.5%)**
Sorafenib (n=72, 7.8%)		**Nivo (n=13, 20.0%)**
Cabozantinib (n=12, 1.3%)		**Pembro (n=13, 20.0%)**
Other (n=37, 4%)		**Other (n=5, 7.7%)**

Figure 1: Overall Survival (OS)

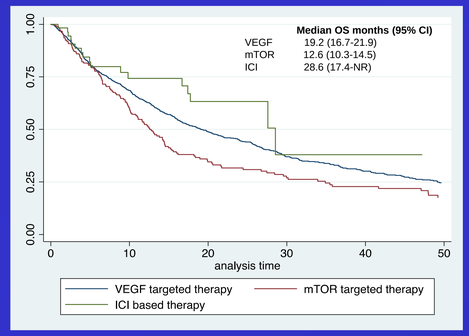

Figure 2: Time to Treatment Failure (TTF)

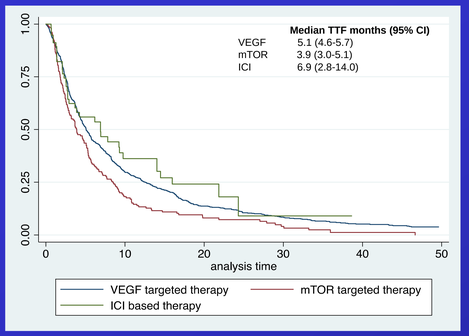

Table 3: Multivariable Analysis for OS and TTF

Overall Survival	Hazard Ratio (95% CI)*	P value
ICI vs. VEGF	0.58 (0.35-0.94)	0.03
ICI vs. mTOR	0.48 (0.29-0.80)	0.005
Time to Treatment Failure (TTF)	**Hazard Ratio (95% CI)***	**P value**
ICI vs. VEGF	0.72 (0.51-1.0)	0.06
ICI vs. mTOR	0.54 (0.37-0.78)	0.001

*Adjusted for IMDC risk group, histologic subtype, and age

Table 4: Objective response rate (ORR)

	VEGF targeted therapy	mTOR targeted therapy	ICI based therapy	P value
Entire population	17.8%	5.8%	25%	0.001
Papillary	13.0%	3.7%	31.6%	0.002
Chromophobe	20.6%	13.6%	9.1%	0.527
Unclassified	15.2%	0	33.3%	0.03

Conclusions

- Immune checkpoint inhibitor (ICI) based therapy appears to be associated with improved OS compared to VEGF and mTOR targeted therapy in treatment naïve metastatic non-clear cell RCC, even after adjustment for IMDC risk, histology and age
- The ORR of 25% in the entire population is consistent with the existing literature of ICI therapy in nccRCC, with lower responses seen in the chromophobe subgroup and higher responses seen in the papillary subgroup
- The study population was predominately papillary RCC, and the effectiveness of ICI based therapy in other less common histologic subtypes remains inconclusive
- These results need to be confirmed in prospective randomized trials

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References Lee et al ASCO 2019, Chahoud et al The Oncologist 2019