The impact of antibiotic (Ab) exposure on clinical outcomes in patients with metastatic renal cell carcinoma (mRCC) treated with immune checkpoint inhibitors (ICI) or VEGF targeted therapy (VEGF-TT):
Results from the International mRCC Database Consortium (IMDC)

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Background

- Retrospective studies have shown an association between Ab exposure and inferior clinical outcomes in patients receiving ICI across various tumor types, including mRCC[1-5]
- It is unclear whether Ab exposure has a unique association with ICI or is an independent prognostic marker, regardless of treatment
- We sought to examine Ab exposure and its association with clinical outcomes in patients with mRCC treated with ICI compared to VEGF-TT

Methods

- Using the IMDC dataset, we identified patients treated with ICI or VEGF-TT alone in the first to fourth line settings from 2009-2020 across 3 North American academic centers
- Ab exposure was defined as antibiotics administered within 60 days prior to initiation of the corresponding line of therapy
  - ➢ Antibiotics given for a duration <24 hours (e.g. perioperative antibiotics) were excluded
- Outcome measures of interest were response rate (RR), time to treatment failure (TTF) and overall survival (OS)
- Multivariable Cox regression analysis was performed to control for imbalances in IMDC risk factors, histology, and treatment line

Results

- 748 patients with mRCC were included
  - ➢ 427 patients were treated with ICI (ICI or ICI/VEGF-TT combination)
    - o Atezolizumab, Atezolizumab + Bevacizumab, Atezolizumab + Cabozantinib, Avelumab + Axitinib, Nivolumab, Nivolumab + Ipilimumab, Nivolumab + Ipilimumab + Cabozantinib, pembrolizumab, Pembrolizumab + Axitinib, Pembrolizumab + Lenvatinib, Pembrolizumab + Lenvatinib + Everolimus
    - o 13% (56/427) were exposed to Ab
  - ➢321 patients were treated with VEGF-TT
    - o Axitinib, Cabozantinib, Pazopanib, Sunitinib
    - o 15% (48/321) were exposed to Ab

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Table 1: Baseline Characteristics and IMDC Risk Factors

	ICI (N=427)			VEGF-TT (N=321)		
	Ab (N=56)	No Ab (N=371)	P-value	Ab (N=48)	No Ab (N=273)	P-value
Age in years (IQR)	61 (54-67)	60 (53-67)	0.37	61 (55-67)	60 (53-67)	0.19
Male	44/56 (79%)	274/370 (74%)	0.47	39/48 (81%)	213/273 (78%)	0.61
Liver metastasis	10/54 (19%)	61/353 (17%)	0.82	7/47 (15%)	51/259 (20%)	0.44
Bone metastasis	19/55 (35%)	109/358 (30%)	0.54	14/261 (5%)	4/47 (9%)	0.40
Brain metastasis	2/53 (4%)	21/348 (6%)	0.51	15/47 (32%)	76/262 (29%)	0.69
nccRCC*	7/55 (13%)	70/364 (19%)	0.25	4/43 (9%)	43/260 (17%)	0.22
Sarcomatoid features	11/53 (21%)	47/346 (14%)	0.17	6/37 (13%)	34/243 (14%)	0.72
Nephrectomy	48/55 (87%)	293/371 (79%)	0.15	37/48 (77%)	229/273 (84%)	0.25
IMDC Risk Groups						
Favourable	7/49 (14%)	55/305 (18%)	**0.03**	3/44 (7%)	29/231 (13%)	**0.01**
Intermediate	23/49 (47%)	185/305 (61%)		19/44 (43%)	139/231 (60%)	
Poor	19/49 (39%)	65/305 (21%)		22/44 (50%)	63/231 (27%)	

Figure 1: OS and TTF in ICI and VEGF-TT with and without Ab

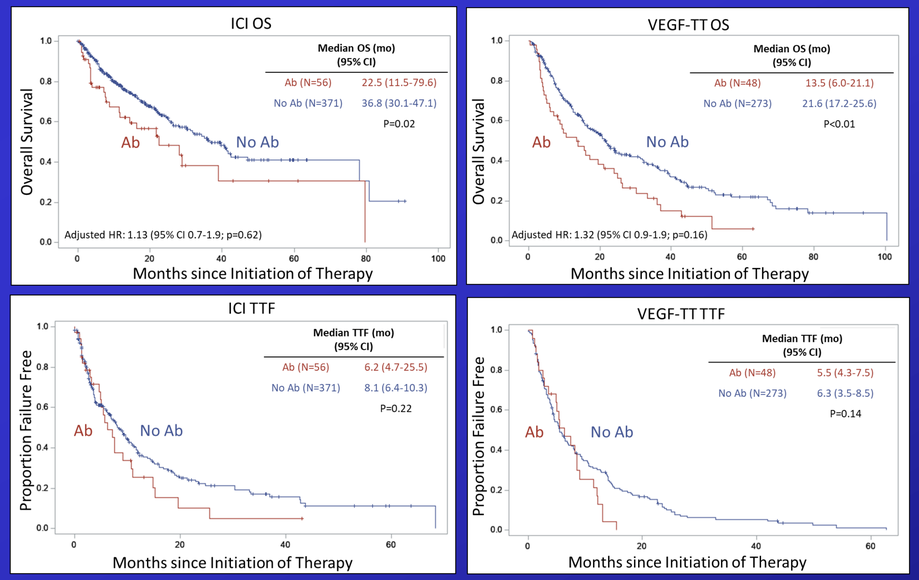

Table 2: Lines of therapy included

Line of Therapy	1	2	3	4
ICI	244 (57%)	143 (33%)	37 (10%)	3 (1%)
VEGF-TT	155 (48%)	124 (39%)	35 (11%)	7 (2%)

Table 3: RR for ICI and VEGF-TT

	ICI (N=427)			VEGF-TT (N=321)		
	Ab (N=56)	No Ab (N=371)	P-value	Ab (N=48)	No Ab (N=273)	P-value
RR (%)	36	38	0.81	21	24	0.66

Table 4: Multivariable analysis of OS

	Hazard Ratio (95% CI)	P-Value
ICI	1.1 (0.7-1.9)	0.69
VEGF-TT	1.3 (0.9-1.9)	0.16

- Treatment modality did not modify the effect of Ab exposure on OS (p=0.84)

Conclusions

- The proportion of patients receiving systemic antibiotics >24 hours duration in this real-world cohort was 13-15%
- Ab exposure was associated with worse IMDC risk scores in both cohorts
- Ab exposure was associated with inferior OS in both ICI and VEGF-TT cohorts on univariable analysis
- After adjusting for IMDC risk factors, histology, and treatment line, we were unable to find an independent association between Ab exposure and OS in multivariable analysis for either cohort
- It is possible that Ab exposure represents a poor prognostic factor independent of systemic treatment modality

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