Dr. Joseph Varon - Research Inquiry #22

Fumarate Hydratase-Deficient Renal Cell Carcinoma Treatment |

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Research Inquiry

1. Which of the following therapeutic regimens has demonstrated to have the highest efficacy and success rate for treating Fumarate hydratase-deficient renal cell carcinoma?
Regimen 1: lenvatinib and pembrolizumab, Regimen 2: bevacizumab and erlotinib, Regimen 3: nivolumab and cabozantinib, Regimen 4: cabozantinib alone , Regimen 5: pazopanib alone

Conclusion

- **Given the absence of randomized control trials, the information presented below is primarily based on retrospective studies with small sample sizes, resulting wide variations in data about efficacy.**
- **The most comprehensive data pertains to Bevacizumab + Erlotinib treatment, notably from a single-arm phase II trial showcasing an ORR of 64% and a progression-free survival (PFS) of 21.1 months.**
- **Most studies did not report any adverse events, limiting the full assessment of safety profiles.**
- **According to Srinivasan et-al, 2020[4] the adverse effects involving Bevacizumab and Erlotinib ranged from mild symptoms like acneiform rash,**

diarrhea, and dry skin to more serious conditions (Grade ≥3) including proteinuria (13%), hypertension (34%) and gastrointestinal (GI) hemorrhage (1.2%). Similarly, Choi et-al, 2019[3] describe mild side effects like hypertension, proteinuria, ALT elevation, and dry skin, along with severe conditions (Grade ≥3) such as acneiform eruption (10%) and one fatal case of gastrointestinal hemorrhage (10%).

- **Treatments with Nivolumab and Cabozantinib were associated with mild to moderate adverse effects such as fatigue, palmar-plantar erythrodysesthesia syndrome, and hypertension.**

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Meta Medical Findings

The table below summarizes the efficacy evidence regarding the treatments mentioned in the query for Fumarate Hydratase-Deficient Renal Cell Carcinoma (FHdRCC). This include details on dosage (when specified), overall response rate (ORR), overall survival (OS), progression-free survival (PFS), time-to-treatment Failure (TTF) and adverse events:

Treatment	Author & Journal	Study Design	Treatment Regime	Results	Adverse Events	Notes
Lenvatinib + Pembrolizumab	Gleeson et-al. 2021[1] *Clinical Cancer Research* (Q1, IF 11.5)	Single-center retrospective analysis **(n=1)**	N.A	ORR: 100% Duration of Treatment: 25.5 months OS: N.A	N.A	-
Bevacizumab + Erlotinib	Carril-Ajuria et-al, 2021[2] *European Journal of Cancer* (Q1, IF 8.4)	Multicentre retrospective Analysis **(n=3)**	N.A	ORR: 30% TTF: 5.5 months OS for all treatment groups: 44 months	N.A	-
	Srinivasan et-al, 2020[4] *Journal of Clinical Oncology* (Q1, IF 45.3)	Interventional Phase II single-arm trial **(papillary RCC=83, HLRCC=42)**	Bevacizumab 10 mg/kg IV every 2 weeks, Erlotinib 150 mg p.o daily	ORR: 64% PFS: 21.1 months.	Acneiform rash, diarrhea, dry skin, proteinuria (13%), hypertension (34%), one instance of GI hemorrhage (1.2%)	Refers to Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC), a condition that includes FHdRCC and in which fumarate hydratase is absent.

	Choi et-al, 2019[3] *Cancer Research and Treatment* (Q2, IF 4.6)	Multicenter Retrospective Analysis **(n=10)**	Bevacizumab 10 mg/kg IV every 2 weeks, Erlotinib 150 mg p.o daily	ORR: 50% PFS: 13.3 months OS: 14.1 months	Acneiform eruption, hypertension, proteinuria, ALT elevation, dry skin, one case of fatal GI hemorrhage (10%)	Refers to Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC), a condition that includes FHdRCC and in which fumarate hydratase is absent.
	Xu et-al, 2023[7] *European Urology* (Q1, IF 23.4)	Retrospective multicenter analysis **(n=12)**	N.A	ORR: 25% DCR: 67% PFS: 10 months	N.A	-
Nivolumab + Cabozantinib	Lee et-al, 2022[6] *Journal of Clinical Oncology* (Q1, IF 45.3)	Interventional single-center, single-arm, Phase II Trial **(n=47, including 5 FHdRCC)**	Cabozantinib 40 mg p.o daily, Nivolumab 240 mg IV every 2 weeks or 480 mg monthly.	ORR: 100% (5 patients) PFS: 12.5 months (5 patients) OS: 28 months (for the entire cohort)	Fatigue, palmar-plantar erythrodysesthesia syndrome, diarrhea, hypertension	Results refer to FHdRCC patients only for ORR and PFS, yet OS is for the entire cohort.
Cabozantinib	Carril-Ajuria et-al, 2021[2] *European Journal of Cancer* (Q1, IF 8.4)	Multicentre retrospective analysis **(n=10)**	N.A	ORR: 50% TTF: 14.0 months OS: N.A	N.A	-
	Gleeson et-al. 2021[1] *Clinical Cancer Research* (Q1, IF 11.5)	Single-center retrospective analysis **(n=5)**	N.A	ORR: 0% DOT: 2.2 months OS for all VEGF monotherapy: 13.2 months	N.A	-
	Xu et-al, 2023[7] *European Urology* (Q1, IF 23.4)	Retrospective multicenter analysis **(n=4)**	N.A	ORR: 0%	N.A	-

Pazopanib	Gleeson et-al. 2021[1] *Clinical Cancer Research* (Q1, IF 11.5)	Single center retrospective cohort study **(n=3)**	N.A	ORR: 33% Duration of Treatment: 8.1 months OS for all VEGF monotherapy: 13.2 months	N.A	-
	Xu et-al, 2023[7] *European Urology* (Q1, IF 23.4)	Retrospective multicenter analysis **(n=6)**	N.A	ORR: 17% DOT: 9.5 months DCR: 60%	N.A	-
	Carril-Ajuria et-al, 2021[2] *European Journal of Cancer* (Q1, IF 8.4)	Multicentre retrospective Analysis **(n=9)**	Combined for different TKIs: sorafenib, pazopanib, and axitinib. Dosage information is not available.	ORR: 64% TTF: 17.7 months OS: N.A	N.A	Results are for different TKIs: sorafenib, pazopanib, or axitinib

n=number; ORR=Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; TTF=Time-To-Treatment Failure; DCR=Disease Control Rate; DOT=Duration of Treatment; FHDRCC=Hydratase-Deficient Renal Cell Carcinoma; HLRCC=Hereditary Leiomyomatosis And Renal Cell Carcinoma; IV=Intravenous; P.O=Per Os; TKI=Tyrosine Kinase Inhibitors; VEGF=Vascular Endothelial Growth Factor; RCC=Renal Cell Carcinoma; IF=Impact Factor; N.A=Not Applicable.

It should also be noted that no standard of care exists for patients with FHdRCC, according to the National Comprehensive Cancer Network (NCCN). However, the NCCN guidelines do list Bevacizumab and Erlotinib as optional treatments for FHdRCC.[8]

According to a consensus article published by Holistic Integrative Oncology (journal not indexed in Scimago, JCR, or Scopus) in 2024, experts claim that monotherapies, including anti-vascular targeted drugs, mTOR inhibitors, and immune checkpoint inhibitors (ICIs), do not provide an adequate therapeutic response. **Therefore, the use of monotherapy is not recommended.** [10]

Furthermore, there are studies regarding different treatment options for FHdRCC which were not included in the query such as VEGF Inhibitors [1, 5, 9, 7], immune checkpoint inhibitors [1, 5], mTOR Inhibitors [10] and TKIs [7].

References

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