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Association of Genetic Polymorphisms and Disease Outcome of Metastatic Renal Cell Cancer In Patients Treated with VEGF Targeted Agents

HARVARD MEDICAL SCHOOL

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OBJECTIVE

- **To evaluate the association of germline polymorphisms and the outcome of patients with metastatic renal cell cancer (mRCC) treated with VEGF targeted therapy.**

BACKGROUND

- **We have previously demonstrated that germline polymorphisms are associated with the risk of recurrence in patients with localized RCC. (Schutz et al., ASCO 2011:Abstr 4506).**
- **We hypothesized that gene polymorphisms in critical signaling pathways mighty impact the outcome of metastatic renal cell cancer (mRCC) patients (pts) treated with VEGF-targeted agents.**

METHODS

- A prospective observational study for germline genetic polymorphisms analysis
- Histologically-proven RCC patients with European-American ancestry were selected from Dana-Farber/Harvard Cancer Center.
- All patients had documented locally advanced or metastatic disease.
- All patients were treated with approved VEGF targeted agents: sunitinib, sorafenib, pazopanib or bevacizumab.
- Consent was collected from RCC patients for blood collection and DNA analysis
- Full baseline clinical and pathological data and follow-up data were prospectively collected
- 113 single nucleotide polymorphism (SNP) from 13 genes were selected based on their potential involvement in RCC pathogenesis, VEGF targeted therapy pharmacodynamics or pharmacokinetics: VEGFR2, HIF1A, HIF1B, HIF2A, VEGF, GLUT1, ABCB1, ABCG2, CYP3A4, CYP3A5, as well as the top 5 SNPs potentially associated with RCC recurrence in our previous study
- Tagging SNPs were selected from the HapMap database (V.2)
  - Minimum allele frequency (MAF) of 5%
  - Minimum pairwise correlation coefficient (r^2) of 80%
- Statistical analysis:
  - Progression free survival (PFS): time from start of VEGF targeted therapy to deasese progression or death.
  - Cox Proportional Hazards (PH) regression model evaluates the association between individual SNP and PFS
    - Univariate analysis (log-rank test) to identify SNPs potentially associated with PFS
    - Controlling for multiple comparisons using FDR measure (Storey's Q-value, with cutoff <20%)
  - Multivariate Cox PH model adjust for age, gender and clinical risk categories by MSKCC risk criteria.
  - Kaplan Meier estimates the distribution of PFS by genotype variants.

RESULTS

Table 1. Baseline patient and cohort characteristics (n=263).

Characteristic		*TOTAL (n=263)*
PFS (months)	Median (95% CI)	11.5 (9.4-13.2)
Age (years)	Median (range)	60.2 (25.9-88.2)
Gender	Male	185 (70%)
ECOG PS	0	125 (51%)
	1	94 (38%)
	≥2	26 (11%)
Histology	Clear cell	222 (90%)
	Other	26 (10%)
Previous Nephrectomy	Yes	236 (90%)
Number of metastatic sites	1	72 (28%)
	2	81 (31%)
	3	73 (28%)
	≥4	35 (13%)
Prior therapy	Yes	108 (42%)
	No	152 (58%)
VEGF targeted therapy	Sunitinib	140 (53%)
	Other	123 (47%)
Heng risk score	Favorable	45 (17%)
	Intermediate	95 (36%)
	Poor	61 (23%)
	Unknown	62 (24%)
MSKCC risk score	Favorable	82 (31%)
	Intermediate	101 (38%)
	Poor	75 (29%)
	Unknown	5 (2%)

Table 2. SNPs that were significantly associated with PFS with Log-rank p-value < 0.05.

		PFS (event rate=81%)	
Gene	*SNP Id*	*Log-rank p-value*	*Q-value (pFDR)*
VEGFR2	**rs2305948**	**0.002906**	**0.165121**
HIF2A	**rs11687512**	**0.002923**	**0.165121**
VEGFR2	rs7654599	0.01311	0.493814
GLUT1	rs3768042	0.022251	0.542561
VEGFR2	rs4576072	0.032208	0.542561
TNF	rs3093662	0.03527	0.542561
VEGF	rs10434	0.045697	0.542561
VEGFR2	rs2305949	0.047045	0.542561
VEGF	rs3025030	0.04885	0.542561
GLUT1	rs841853	0.049173	0.542561

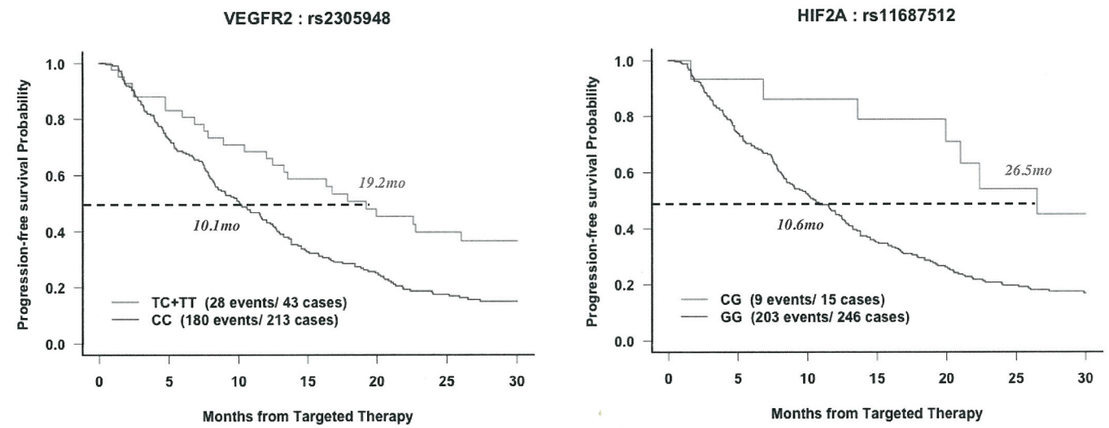
Table 3. Characteristics of the 2 selected SNPs in VEGFR2 and HIF2A.

Gene	*SNP Id*	*Minor homozygote*	*Heterozygote*	*Common homozygote*	*MAF*
VEGFR2	rs2305948 (C>T)	0.01	0.16	0.83	0.09
HIF2A	rs11687512 (G>C)		0.06	0.94	0.03

Table 4. Unadjusted and adjusted Cox PH model results of PFS endpoint by the 2 SNPs.

								MSKCC risk criteria	
Gene	*SNP Id*	*Genotype*	*Event*	*Patients*	*mPFS (mo.)*	*Unadjusted HR (95% CI)*	*P*	*Adjusted HR (95% CI)*	*P*
VEGFR2	rs2305948 (C>T)	TC+TT	28	43	19.2	0.55 (0.37-0.82)	0.003	0.56 (0.37-0.84)	0.005
		CC	180	213	10.1	Ref.		Ref.	
HIF2A	rs11687512 (G>C)	GC	9	15	26.5	0.36 (0.17-0.72)	0.003	0.33 (0.16-0.68)	0.002
		GG	203	246	10.6	Ref.		Ref.	

Figure 1. Kaplan-Meier plots of progression free survival by SNP variant in VEGFR2 and HIF2A genes.



CONCLUSIONS

1. Inherited variants may influence the PFS of patients with metastatic RCC treated with VEGF targeted agents.

2. Further validation of these findings is required.

3. If validated, these results could help identifying subset of patients that are more likely to remain progression free on treatment with VEGF targeted therapies.