Novel Chromosome Copy Number Changes Predict Clinical Response to Sunitinib in Patients with Advanced Renal Cell Carcinoma

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BACKGROUND:

- Renal cell carcinoma is the 7th most common malignancy in men and 10th most common in women with clear cell renal cell carcinoma (ccRCC) as the most common subtype.[1]
- ccRCC is characterized by the loss of the Von Hippel-Lindau (VHL) tumor suppressor, which allows for the accumulation of the transcription factors Hypoxia Inducible Factor (HIF) 1α and 2α in the absence of hypoxia
- Inhibition of HIF dependent transcription targets has been an effective mechanism for the treatment of ccRCC with the FDA approval of multiple VEGF targeted agents (bevacizumab, sunitinib, pazopanib, sorafenib, axitinib)[2]

Sunitinib for ccRCC

- Approved in the 1st line setting after demonstrating and improved PFS and ORR compared to INF alone[3]
- 20-30% of tumors show primary resistant disease (PRD) with progression as the best response.[4]

OBJECTIVE:

- Identify the chromosomal copy number changes that are associated with sunitinib clinical response

MATERIALS & METHOD:

- **Design**
  - Whole genome comparative genomic hybridization (aCGH) of pretreatment tumor derived DNA
- **Study Population (MSK-76)**
  - Seventy six patients treated with sunitinib as monotherapy or in combination at MSKCC prior to 9/27/2010 with availability of banked fresh frozen tissue
  - Date of last analysis for OS and PFS – 3/24/2014
- **Publically Available ccRCC SNP Datasets**
  - **TCGA-436**: The Cancer Genome Atlas, 436 patients
  - **UT-240:** University of Tokyo, 240 patients
- **Whole genome comparative genomic hybridization (aCGH)**
  - DNA extracted from fresh frozen tissue specimens, and aCGH performed using 244K array (Agilent Technologies)
  - Sex matched normal DNA (Promega, Madison, WI) used as reference DNA
  - Segments defined by Rank Segmentation algorithm using Nexus Copy Number 7.5 (Biodiscovery Inc.)
  - Min average log ratio of 0.13 for gain and -0.13 for loss
  - Significantly enriched CNAs were determined between groups using Fisher's exact test ($P \leq 0.05$)
- **Data Analysis**
  - RECIST v1.1 assessment of objective response to therapy

STUDY DESIGN:

- **Aim 1: Identify differential CNAs between sunitinib responders and non-responders (MSK-76) based on RECIST response**
  - Differential CNAs were identified using the Fisher's exact test with p-value ≤ 0.05 and at least 15% different minimum threshold difference comparing PD vs. CR/PR/SD as best response or PD/SD vs. CR/PR as best response and at least a 25% different minimum threshold difference comparing PD vs. CR/PR as best response
  - Identified CNAs were independently tested for association with progression free survival (PFS) and overall survival (OS) in sunitinib treated population (MSK-76) and largely treatment naïve populations (TCGA-436 and UT-240) by Kaplan-Meier analysis
- **Aim 2: Identify differential CNAs for long term sunitinib responders based on PFS**
  - Differential CNAs were identified using Fisher's exact test with p-value ≤ 0.05 and at least 15% different threshold difference.
  - PFS cut off for sunitinib long term responders was defined at 18 months

TABLE 1. Demographics

	N (%)
MEDIAN AGE (RANGE) IN YEARS	60 (38-86)
SEX	
MALE	57 (75)
FEMALE	19 (25)
RACE	
WHITE, NON-HISPANIC	74 (97)
WHITE, HISPANIC	1 (1.3)
UNKNOWN	1 (1.3)
KPS	
≥ 80%	66 (89)
< 80%	8 (11)
FUHRMAN GRADE	
FUHRMAN GRADE I	1 (1.3)
FUHRMAN GRADE II	13 (17)
FUHRMAN GRADE III	23 (30)
FUHRMAN GRADE IV	23 (30)
NOT APPLICABLE	16 (21)
HISTOLOGIC VARIANTS	
SARCOMATOID	11 (14)
RHABDOID	5 (7)
TISSUE SITE	
KIDNEY	57 (75)
BONE	8 (11)
LUNG	3 (4)
LYMPH NODE	3 (4)
BRAIN	2 (3)
OTHER	3 (4)

TABLE 2. Treatment Course and Response

	N (%)
PATIENTS REMAINING ON THERAPY	4 (5)
TREATMENT REGIMEN	
SUNITINIB	60 (79)
SUNITINIB + BEVACIZUMAB	5 (7)
SUNITINIB + EVEROLIMUS	4 (5)
SUNITINIB + GEFITINIB	4 (5)
SUNITINIB + INF	3 (4)
BEST RESPONSE BY RECIST V1.1	
COMPLETE RESPONSE (CR)	2 (3)
PARTIAL RESPONSE (PR)	20 (27)
STABLE DISEASE (SD)	43 (57)
PROGRESSION OF DISEASE (PD)	10 (13)
MEDIAN PFS IN MONTHS (95% CI)	9.7 (6.9 - 11.9)
MEDIAN OS IN MONTHS (95% CI)	27.1 (19.9 - 36.7)

TABLE 3. CNAs Identified by RECIST Response

ABERRATION	GENOMIC COORDINATES	RESPONDER (%)*	NON-RESPONDER (%)*
		CR-PR-SD (N=65)	PD (N=10)
del 3p26.3-p26.1	chr3: 0 - 4,117,195	67	30
amp 6p21.2	chr6: 36,832,241 - 37,259,712	0	20
del 8p23.2-p12	chr8: 4,409,852 - 30,971,236	39	0
del 8p12	chr8: 33,165,574 - 33,573,405	34	0
amp 22q11.1-q13.33[1]	chr22: 14,700,000 - 51,304,566	2	20
		CR-PR (N=22)	SD-PD (N=53)
amp 1q23.2-q23.3	chr1: 159,494,469 - 160,842,508	0	19
amp 1q25.3	chr1: 183,569,490 - 183,745,076	0	19
del 4q13.1-q13.3	chr4: 63,635,383 - 75,519,857	32	11
del 4q25	chr4: 113,396,008 - 113,777,943	40	15
del 4q31.3	chr4: 151,254,493 - 152,157,479	36	13
amp 5q14.3	chr5: 87,908,292 - 88,460,429	45	21
del 10q23.33	chr10: 94,441,090 - 94,590,081	32	11
del 11p13	chr11: 32,470,266 - 33,264,911	22	2
del 15q21.2	chr15: 50,532,334 - 50,583,961	29	8
del 18q11.1	chr18: 17,200,000 - 18,597,696	41	17
amp 18q23	chr18: 73,273,206 - 73,284,717	18	2
amp 20p13 - p12.3	chr20: 2,417,712 - 6,148,197	34	12
del 22q13.1 - q13.2	chr22: 40,876,072 - 42,473,631	31	8
		CR-PR (N=22)	PD (N=10)
del 4q25	chr4: 113,396,008 - 113,792,319	40	0
del 4q28.1 - q28.2	chr4: 128,751,673 - 129,170,210	39	0
del 8p21.1	chr8: 27,842,332 - 28,497,749	36	0
del 10q21.3-q22.1	chr10: 69,552,141 - 70,661,672	36	0
del 10q23.32 - q23.33	chr10: 93,805,007 - 94,433,385	36	0

*Weighted Frequency Average, [1]Joining of 6 closely located CNAs

TABLE 4. PFS and OS Association of CNAs Identified by RECIST

ABERRATION	MSK-76 OS	MSK-76 PFS	TCGA-436 OS	UT-240 OS
CR-PR-SD (N=65) vs. PD (N=10)				
Higher in Responders				
del 3p26.3-p26.1	0.04	0.41	N/A[1]	0.40
Higher in Non-Responders				
amp 6p21.2	0.01	< 0.001	0.81	< 0.001
amp 22q11.1-q13.33**	0.27	0.06	0.90	0.50
CR-PR (N=22) vs. SD-PD (N=53)				
Higher in Responders				
del 4q13.1-q13.3	0.88	0.07	0.02[3]	0.004[3]
amp 18q23	0.06	0.47	0.63	N/A[2]
CR-PR (N=22) vs. PD (N=10)				
Higher in Responders				
del 8p21.1	0.71	0.06	0.44	0.55

[1]Poor coverage of region within dataset
[2]Too few events to calculate p-value
[3]Opposite trend as in MSK-76
**Joining of 6 closely located CNAs

Sunitinib Treated | Predominately Sunitinib Naïve

TABLE 5. CNAs Identified by Long Term Sunitinib PFS Response

ABERRATION	GENOMIC COORDINATES	RESPONDER (%)*	NON-RESPONDER (%)*
		PFS > 18 months (N=21)	PFS < 18 months (N=55)
del 1p32.3	chr1: 53,463,025 - 53,481,250	19	3
del 10q21.3-q22.1	chr10: 64,677,478 - 70,936,862	32	10
del 11p11.2	chr11: 48,054,287 - 48,183,545	24	5
del 13q12.11-q13.3	chr13: 20,623,796 - 37,309,428	19	4
del 13q14.11	chr13: 41,188,484 - 41,894,200	24	5
del 13q22.2-q32.1	chr13: 76,606,175 - 95,122,885	19	4
del 13q32.1-q34	chr13: 95,549,694 - 115,169,878	19	3
amp 18q23	chr18: 73,273,206 - 73,284,717	19	4
del 21q21.1-q21.3	chr21: 20,546,232 - 30,666,748	19	0
del 21q22.2	chr21: 40,596,014 - 41,037,072	19	3

*Weighted Frequency Average

CONCLUSIONS:

- aCGH analysis of sunitinib treated patient reveal multiple novel CNAs associated with clinical response.
- Identified CNAs from sunitinib treated patients did not correlate to OS in predominately sunitinib naïve populations, suggesting these reflect sunitinib response and not sunitinib-independent biology.
- Distribution CNAs associated with sunitinib outcomes is heterogenous and may suggest multiple mechanisms for response and resistance.
- These CNAs warrant further investigation and may provide insight into mechanisms of resistance.

CONFLICTS OF INTEREST:

B.G and J.H. are full time employees and stock/stock option holders of Cancer Genetics Inc.

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