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MET abnormalities in patients with genitourinary malignancies and outcomes with *c-MET* inhibitors

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Abstract

Purpose—To determine the prevalence of *MET* amplification and mutation among genitourinary (GU) malignancies and its association with clinical factors and responses to c-MET inhibitors.

Methods—Patients with genitourinary (GU) malignancies referred to the Phase I Clinic were evaluated for *MET* mutation and amplification and outcomes on protocols with *c-MET* inhibitors.

Results—*MET* amplification was found in 7 of 97 (7.2%) patients (4/27 renal [all clear cell], 1/18 urothelial and 2/12 adrenocortical carcinoma), with *MET* mutation/variant in 3 of 54 (5.6%) (2/20 RCC [1 clear cell and 1 papillary] and 1/16 prostate cancer). No demographic characteristics were associated with specific *MET* abnormalities, but patients testing positive for mutation or amplification had more metastatic sites (median, 4 vs. 3 for wild-type *MET*). Median overall

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survival after phase I consultation was 6.1 and 11.5 months for patients with and without a *MET* alteration, respectively (hazard ratio [HR] = 2.8; 95% CI, 1.1 to 6.9; *P*=.034). Twenty-nine (25%) patients were treated on a *c-MET* inhibitor protocol. Six (21%) had a partial response (prostate and RCC) and 10 (34%) had stable disease as best response. Median time to tumor progression was 2.3 months (0.4 – 19.7) for all treated patients with no responses in patients with a *MET* abnormality or single-agent *c-MET* inhibitor treatment.

Conclusion—*MET* genetic abnormalities occur in diverse GU malignancies and are associated with a worse prognosis in a phase I setting. Efficacy of *c-MET* inhibitors was more pronounced in patients without *MET* abnormalities and when combined with other targets/drugs.

Graphical abstract

MET mutation and/or amplification can be found in diverse GU malignancies, and is potentially targetable. We explored the prevalence of MET abnormalities and its association with demographics and targeted therapy response in patients with GU tumors. We found that patients with a *MET* alteration present poor survival in a phase I setting. Although c-MET inhibitors showed activity, efficacy of these drugs was more pronounced when combined with other targets and in the absence of *MET* alterations.

Keywords

bladder cancer; c-MET inhibitor; *MET* mutation; *MET* amplification; prostate cancer; renal cell cancer

Introduction

The *MET* oncogene encodes a transmembrane receptor with intrinsic tyrosine kinase activity.[1] The *c-MET* receptor is activated by its physiological ligand, hepatocyte growth factor (HGF)[2], leading to downstream signaling events involved in cancer growth, migration, metastasis and angiogenesis.[3-5] Recent data have shown that many solid tumors display MET/HGF pathway deregulation, actuated by various mechanisms, including *c-MET* overexpression, *MET* mutation, amplification and increased HGF secretion by the tumor microenvironment.[6-9]

Genitourinary (GU) malignancies frequently involve *c-MET* deregulation. In prostate cancer, *c-MET* overexpression is associated with higher Gleason grade and development of resistance to anti-hormonal therapies.[10,11] *MET* mutations are described both in hereditary and sporadic papillary renal cell carcinoma (RCC)[12]; in addition, *MET* amplification and overexpression is a newly described mechanism of resistance in RCC patients undergoing VEGFR inhibitor treatment.[13,14] In bladder cancers, phosphorylation of HGF/*c-MET* is associated with the development of metastasis and poor survival.[15] *c-MET* inhibitors are currently being tested for treating GU malignancies with promising initial results in prostate cancer and RCC.[16,17]

Although much of the available data highlight the importance of protein overexpression as a mechanism of c-*MET* deregulation in GU malignancies, genetic abnormalities, including mutation and amplification, may also play a role.[18] Additionally, molecular biomarkers that

could be used to select optimal patients for treatment with *c-MET* inhibitors are lacking. These limitations call for a better understanding of *MET* genetic abnormalities to further efficacious treatment with *c-MET* inhibitors in GU malignancies.[8]

We investigated *MET* status, including mutation and amplification, in patients with advanced RCC, prostate cancer, urothelial cancer and adrenocortical carcinoma referred to our Phase I Clinical Trials Program. We also explored the relationship between *MET* status, demographic and molecular data, and patient outcomes with *c-MET* inhibitor treatment.

Patients and Methods

Patients

We retrospectively reviewed the electronic medical records of consecutive patients with advanced prostate, RCC, urothelial and adrenocortical carcinoma referred to the Phase I at The University of Texas MD Anderson Cancer Center starting in May 2010 until January 2013. Patients were eligible for inclusion in data analysis if a primary diagnosis of any of these GU malignancies was confirmed and a tumor sample from a primary site or metastatic lesion was sent for evaluation of *MET* mutation or amplification. This study and all associated treatments were conducted in accordance with the guidelines of the MD Anderson Institutional Review Board.

Tissue samples and molecular analysis

MET mutation/variant and amplification were investigated in archival formalin-fixed, paraffin-embedded tissue blocks obtained from diagnostic and/or therapeutic procedures. Samples from primary or metastatic lesions were accepted. All histologies were centrally reviewed at MD Anderson. *MET* mutation or variant analysis was performed in different Clinical Laboratory Improvement Amendment-certified laboratories as part of a gene panel analysis or in a single test. Information about mutations in additional oncogenes was also included for analysis.

MET amplification was analyzed via fluorescence in situ hybridization (FISH). Copy numbers were expressed as gene copy number in relation to *CEP7*, a gene located near the centrosome of the same chromosome. *MET* was considered amplified when the *MET*/CEP7 signal ratio was ≥ 2.0 or when this ratio was < 2.0 but there were > 20 copies of *MET* signals and/or clusters in > 10% of the tumor nuclei counted.

Treatment and evaluation

Patients referred to the Phase I Clinic were enrolled in clinical trials judged to be clinically appropriate by attending physicians. Treatment continued until disease progression, withdrawal of consent by the patient, clinical judgment deeming the necessity of removing a patient from a clinical trial, or development of unacceptable toxicity or death. Clinical assessments were performed as specified in each protocol, typically before the initiation of therapy and then at a minimum at the beginning of each new treatment cycle. All radiographs were read in the Department of Radiology at MD Anderson and reviewed in the

Phase I Department tumor measurement clinic. Responses were categorized using RECIST on the basis of specific protocol requirements[19,20] and were reported as best response.

Statistical analysis

All statistical analysis was reviewed by our statistician (KH). Patient characteristics including demographics, tumor type, *MET* mutation and/or amplification status and associated genetic abnormalities were summarized using frequency distributions and percentages. Time to tumor progression (TTP) was defined as the interval from the start of therapy to treatment discontinuation for disease progression or death related to disease progression. Overall survival (OS) was assessed starting from the date of the first appointment in the Phase I Clinic using Kaplan-Meier curve analysis.

Results

Patient characteristics

A total of 118 patients with advanced RCC, prostate cancer, urothelial and adrenocortical cancers were analyzed for *MET* mutation/variant (53 patients) or amplification (97 patients). Among these patients, 33 were tested simultaneously for both genetic abnormalities. Thirty-eight (32%) patients had RCC (21 clear cell, 5 papillary, 3 medullary, 2 chromophobe, 2 Xp11 translocation, 2 sarcomatoid-predominant and 3 unclassified histologic subtypes), 46 (39%) prostate cancer, 22 (19%) urothelial cancer, and 12 (10%) adrenocortical cancer. Their median age at diagnosis was 55 years (range 16-75 years), and 99 (84%) were Caucasians, 11 (9%) were black, and 8 (7%) were Hispanic. Detailed patient characteristics according to *MET* status are shown In Table 1.

Met abnormalities

Seven out of 97 (7.2%) patients demonstrated a *MET* gene amplification by FISH. The prevalence of *MET* amplification was 14.8% (4 out of 27) in RCC (all clear cell), 5.5% (1 out of 18) in urothelial cancer and 17% (2 out of 12) in adrenocortical cancer. None of the 40 patients with prostate cancer tested positive for amplification. The copy number of the *MET* gene in relation to CEP7 ranged from 1.1 to 6.8 (Table 2). Of note, the patient with a ratio of 1.1 was positive because more than 10% of cancer cells had more than 20 copies of the *MET* gene. A *MET* mutation/variant was detected in 3 out of 54 patients (5.6%), 2 out of 20 (10%) with RCC (one with clear cell and one with papillary RCC) and 1 out of 16 (6.2%) with prostate cancer. All mutations detected were N375S, which was previously described as germline in nature[21] (Table 2).

Comparison of clinical and mutational characteristics

In the overall study population, 94 (80%) patients were male and 24 (20%) were female. The 3 patients with a *MET* variant, but only 4 (57%) out of 7 patients with amplification, were male. There were no differences in ethnicity among the patients with a *MET* abnormality and the overall population (Table 1). Patients harboring a *MET* abnormality had a median of 4 (3-5) metastatic sites compared to 3 (0-6) sites in wild-type patients; of note, all patients with a *MET* variant presented with bone metastasis and 2 out of 3 (67%) had brain metastasis, while only 2 out of 50 (4%) in the *MET* wild-type group developed central

metastasis. A lower proportion of bone metastasis (2 out of 7, 29%) and a higher proportion of lung metastasis (6 out of 7, 85%) were seen in *MET* amplified patients.

Concomitant mutations

MET amplification and mutation were mutually exclusive in the 33 patients tested for both abnormalities simultaneously. Five out of 10 patients with *MET* abnormalities had concomitant mutations, including *p53* mutations (2 patients), *PTEN* loss (3 patients) and a *VHL* mutation (1 patient with RCC) (Table 2). These mutations were also detected in MET wild-type patients, suggesting no differences between groups. The prevalence of mutations in other important oncogenes in the overall patient population was: 0 out of 81 patients for *KRAS*, 1 out of 66 (1.5%) for *EGFR*; 2 out of 77 (2.6%) for *BRAF*; and 5 out of 101 (5%) for *PIK3CA*. None of the patients positive for those mutations had a *MET* genetic abnormality, although not all of them were tested for both mutation and amplification.

Analysis of survival of MET positive patients

For survival analysis we compared the group of patients who tested positive for either a *MET* mutation/variant or amplification (*MET* positive group, 10 patients) with patients who tested negative for both abnormalities (*MET* negative group, 28 patients). Patients with *MET* mutation and *MET* amplification were grouped altogether after considering that individual survival data was similar between both groups (Table 2). Median OS from the day patients were initially seen in our Phase I Clinic was 6.1 and 11.5 months, for *MET* positive and negative patients, respectively, with an estimated hazard ratio (HR) of 2.8 (95% CI, 1.1 to 6.9; P=.034; Figure1). Patients received different treatments after phase I consult at the discretion of the physician.

Treatment of patients with c-MET inhibitors

Of the 118 study patients, 29 were treated on phase I protocols that contained a *c-MET* inhibitor (16 prostate cancer, 9 RCC, 3 urothelial cancer and 1 adrenocortical cancer). We further divided these patients into those treated on protocols with *c-MET*-specific inhibitors as a single agent (9 patients) and protocols targeting pathways in addition to *c-MET*. These included protocols containing multikinase inhibitors (with *c-MET* inhibitory activity) or treatment combinations containing a *c-MET* inhibitor (20 patients). Response rates were recorded according to RECIST criteria and are shown in Figure 2A. Six patients (21%) had a partial response and 10 (34%) had stable disease as their best response. Responses varied according to tumor type (25% for prostate and 22% for RCC, whereas no responses were registered for other GU malignancies), and all responses occurred in patients who had no *MET* genetic abnormalities and who had been treated with either a multikinase inhibitor or on a combination protocol (Table 3). The median TTP on c-MET inhibitors was 2.3 months (range, 0.4 – 19.7). An apparently shorter TTP was observed in patients harboring *MET* abnormalities (median TTP of 1.6 months, range 0.9-3.1) versus wild-type patients (median TTP 4.3 months, range 0.7-19.7) and when treated with single-agent *c-MET*-specific inhibitors (median TTP 1.43 months, range 0.7-3.1) versus when treated with combined targets (median TTP 5.4, range 0.7-19.7) (Table 3 and Figure 2B). We analyzed the prevalence of concomitant mutations in subgroups with different responses to c-MET inhibitors. The only apparent difference was on *TP53* prevalence. Three out of four (75%) of

patients with PD on a c-MET protocol and tested for TP53 alteration were positive for mutation, while none of the four patients with SD or PR tested positive.

Discussion

We detected *MET* gene amplification in 7.2% of 97 patients and a *MET* genetic mutation/variant in 5.6% of 54 patients with GU malignancies. The prevalence of *MET* amplification was highest in RCC (14.8%) and adrenocortical carcinoma (17%), whereas a genetic variant was more frequent in RCC (10%). These abnormalities were mutually exclusive among patients tested simultaneously for both. Of the 29 patients treated on a protocol containing a *c-MET* inhibitor, 21% had a partial response.

Data from the Catalog of Somatic Mutations in Cancer (COSMIC) database revealed a low prevalence of *MET* mutations in prostate cancer (3.6%), in which *c-MET* activation was especially mediated by *c-MET* overexpression in the setting of androgen deprivation.[11,22] In addition, there was a 2.3% prevalence of *MET* mutations in urothelial cancers, 3% in RCC and none in adrenocortical carcinomas. The *MET* mutation has been described as being germline in virtually all patients with hereditary papillary RCC and somatic in up to 13% of patients with sporadic papillary renal cell cancer (PRCC).[23] Data concerning *MET* gene amplification in GU malignancies is however very scarce in the literature. Trisomy of chromosome 7, where the *MET* gene is located, has been detected in some patients with PRCC.[24] We described a higher prevalence of *MET* genetic abnormalities in GU malignancies than previous reports, which could be due to selection bias as our patient population was composed of those with advanced disease.

All mutations described here were N375S, which occurs in the extracellular semaphorin domain of the *MET* gene. This alteration was previously described as a germline mutation (variant)[21], and for this reason we did not perform a matched normal tissue analysis for confirmation. Although considered to be germline, it has functional implications through conferring a reduced affinity of the *c-MET* receptor to HGF and resistance to the apoptotic effects of a *c-MET* inhibitor.[21] Therefore, this variant is important for patients with GU malignancies especially when using a *c-MET* inhibitor for treatment is being considered. Accordingly, the 2 patients with this variant in our study had no responses to *c-MET* inhibitor treatment. It is important to note that only one of the 2 patients with RCC and a N375S mutation/variant had a papillary subtype. This patient had no personal history of multiple tumors or a family history of papillary RCC, which precludes the diagnosis of the hereditary form of the disease.

Substantial data correlate activation of the *c-MET* pathway with aggressiveness and a worse prognosis in different malignancies. A retrospective series of patients with gastroesophageal tumors showed *MET* amplification associated with a higher tumor grade and worse survival.[25] A deleterious effect of *MET* genetic abnormalities was also described in ovarian cancer[26]. In prostate cancer, *c-MET* overexpression is associated with a higher Gleason grade, whereas *c-MET* activation conferred a worse prognosis in urothelial cancer.[10,15] Our series also demonstrated a shorter OS for patients with either a *MET* mutation/variant or amplification compared to wild-type patients (6.1 months vs. 11.5 months) after they

presented to our Phase I Clinic. This finding highlights the inherent challenges that these patients represent vis-à-vis treatment selection.

Interestingly, despite the promising activity of *c-MET* inhibitors in the overall patient population with GU malignancies reported in our study, these agents showed no activity in the few patients presenting with *MET* genetic abnormalities. As demonstrated in preclinical models, the N375S mutation may confer resistance to *c-MET* inhibitors [21] and our data suggest that resistance might also occur *in vivo*. Additionally, two patients with *MET* amplification were treated with c-MET inhibitors and both presented tumor progression as best response. There is debate about the threshold of *MET* gene amplification that can cause *c-MET* addiction by cancer cells and susceptibility to *c-MET* inhibitors. Of note, the RCC patient with the highest detected FISH ratio in our series (MET/CEP7 = 6.8) received a *c-MET* inhibitor and developed tumor progression within 2 months of therapy. It is important to note that in our study patients had access to c-MET inhibitors during dose escalation of phase I trials, and optimal biologic dose might not be reached yet. In a phase II study of foretinib (a dual c-MET/VEGFR2 inhibitor) in PRCC no responses were seen in the 2 patients with *MET* amplification.[16] In the same study, *MET* germline mutations were greatly associated with better activity of the drug, but they were all considered activating mutations of *MET* gene, which are different than N375S variant as previously discussed. Therefore, further prospective data are warranted to better correlate *MET* genetic abnormalities with responses to *c-MET* inhibitors. It is important to note that this correlation may also be tissue dependent, as illustrated in gastroesophageal cancers.[27]

Finally, all responses in our study were observed when a *c-MET* inhibitor was combined with another targeted agent, either using a combination of drugs or a multikinase inhibitor. Some of the promising *c-MET* inhibitors in development are, in fact, multikinase inhibitors, including cabozantinib, which produced responses in prostate cancer[17] and RCC,[28] and foretinib, which showed activity in PRCC.[16] Although further prospective data are needed, this observation has importance for the development of *c-MET* inhibitors.

Our study is limited by its retrospective nature and because the small number of patients with *MET* mutation or amplification did not provide sufficient statistical power for drawing definitive conclusions. Indeed, most of our analysis is essentially descriptive and statistical tests were not applied due to insufficient power to draw conclusions. Further collaborative efforts are necessary to include a higher number of patients in order to confirm some of the possible findings suggested based on our results. Additionally, we did not compare *MET* genetic alterations with c-MET receptor expression levels, limiting some of our comparisons with previous studies.

These limitations notwithstanding, we showed that abnormalities of *MET* gene might be detected in GU malignancies and that patients with them had a worse prognosis, especially those being treated in a phase I setting. However, *c-MET* inhibition has promise, especially in prostate cancer and RCC, but further exploration of biomarkers of response and combined treatments is needed.

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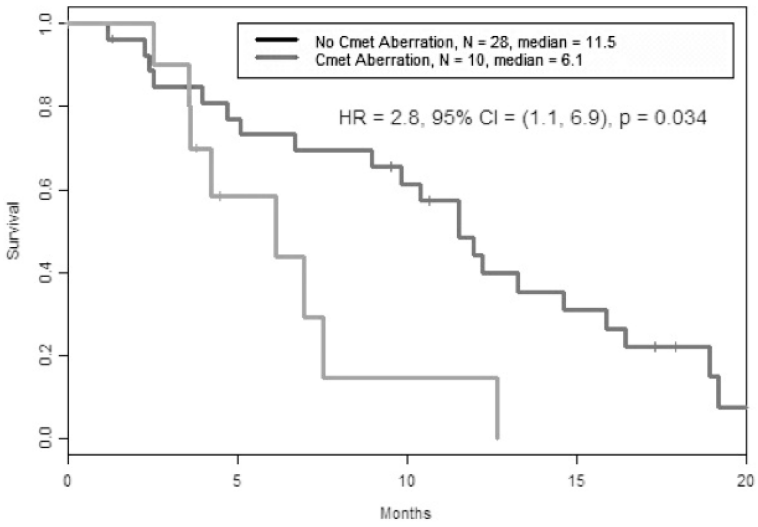

Figure 1.

Kaplan-Meier overall survival curves for patients with GU malignancies according to *MET* status starting from presentation in a phase I clinic.

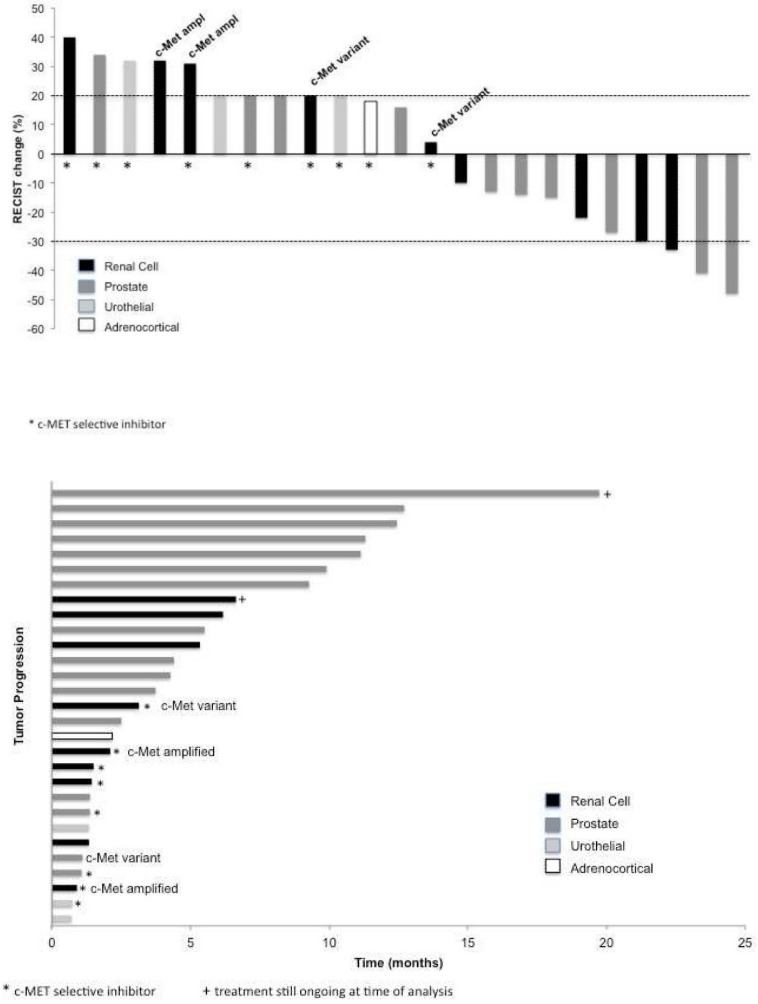

Figure 2.

Waterfall plot showing responses (A) and TTP (B) of patients with GU malignancies treated on a phase I protocol including a *c-MET* inhibitor. Patients harboring a *MET* genetic abnormality are indicate

Table 1

Demographic, molecular characteristics and metastatic sites in patients with GU malignancies stratified by *MET* mutation/variant and amplification status

Characteristic	Not mutated (*n*=50) (%)	Mutated (*n*=3) (%)	Not amplified (*n*=90) (%)	Amplified (*n*=7) (%)
Age At Diagnosis: Median (IQR)	56 (25-72)	56 (54-62)	56 (16-75)	48 (19-67)
Prior Therapies: Median (IQR)	3 (0-8)	3 (3-4)	3 (0-10)	3 (1-6)
Diagnosis (n)				
Renal Cell (38)	18 (36)	2 (67)	23 (26)	4 (57)
Urothelial (22)	12 (24)	0 (0)	17 (19)	1 (14)
Prostate (46)	14 (28)	1 (33)	40 (44)	0 (0)
Adrenocortical (12)	6 (12)	0 (0)	10 (11)	2 (29)
Gender				
Male	40 (80)	3 (100)	75 (83)	4 (57)
Female	10 (20)	0 (0)	15 (27)	3 (43)
Ethnicity (%)				
Black	4 (8)	0 (0)	8 (9)	0 (0)
Hispanic	4 (8)	1 (33)	6 (7)	1 (14)
Caucasian	42 (84)	2 (67)	76 (84)	6 (86)
Metastasis (%)				
# Metastatic sites – median (range)	3 (1-6)	4 (3-5)	2 (0-6)	4 (3-4)
Liver	29 (58)	1 (33)	37 (41)	4 (57)
Lungs	26 (52)	2 (67)	35 (39)	6 (85)
Bone	29 (58)	3 (100)	60 (67)	2 (29)
Central Nervous System	2 (4)	2 (67)	4 (4)	0 (0)
Peritoneum	7 (14)	0 (0)	6 (7)	2 (29)
Lymph nodes	23 (46)	2 (67)	13 (14)	2 (29)
Site of mutational analysis				
Primary tumor	31 (62)	0 (0)	55 (61)	5 (71)
Metastatic tumor	19 (38)	2 (67)	35 (39)	2 (29)
Unknown	0 (0)	1 (33)	0 (0)	0 (0)
Additional genetic alterations				
PIK3CA mutation	2/47 (4)	0/3 (0)	4/79 (5)	0/7 (0)
TP53 mutation	7/31 (23)	1/2 (50)	5/21 (24)	1/1 (100)
PTEN loss	7/19 (37)	1/2 (50)	21/70 (30)	2/6 (33)
HER amplification	1/23 (4)	0/1 (0)	1/27 (4)	0/0 (0)
EGFR mutation	1/37 (3)	0/3 (0)	0/43 (0)	0/5 (0)
BRAF mutation	1/40 (3)	0/3 (0)	1/53 (2)	0/5 (0)

Table 2

Pathological and molecular characteristics of patients presenting *MET* abnormalities and outcomes on *c-MET* inhibitors

Patient No.	Diagnosis	Histology	Grade	Mutation/ Copy Number	Concomitant Mutations	Best Response	TTP (mos)	OS (mos)[1]
***c-Met* amplified**								
1	RCC	Clear Cell	Fuhrman 4	2.27	PTEN loss	-	-	3.6
2	RCC	Clear Cell	Fuhrman 4	2.7	-	-	-	7.5
3	RCC	Clear Cell[2]	Fuhrman 4	2.79	-	PD	1	2.5
4	RCC	Clear Cell	Fuhrman 4	6.8	TP53	PD	2	6.9
5	Urothelial	TCC	High Grade	5.91	PTEN loss	-	-	4.2
6	Adrenocortical	Carcinoma	-	1.1[3]	-	-	-	12.7
7	Adrenocortical	Carcinoma	-	2.68	-	-	-	6.1
***c-Met* Mutated**								
8	RCC	Papillary	Fuhrman 3	N375S	-	SD	3	3.8
9	RCC	Clear Cell	Fuhrman 4	N375S	VHL	-	-	4.4
10	Prostate	Adenocarcinoma	Gleason 8	N375S	PTEN loss, TP53	PD	1	3.6

[1] OS was measured staring from phase I consult;

[2] sarcomatoid differentiation;

[3] more than 10% of cancer cells with more than 20 copies of the *c-MET* gene

Table 3

Treatment outcomes of patients with GU malignancies treated with *c-MET* inhibitors under a phase I protocol

Characteristic	Response Rate (%)	Time to Tumor Progression Median/Range (mos)
All population (*n*=29)		3.1 (0.7-19.7)
PR	6 (21)	
SD	10 (34)	
PD	13 (45)	
By tumor type		
RCC	2/9 (22)	2.1 (0.9-6.6)
Prostate	4/16 (25)	5 (1-19.7)
Urothelial	0/3 (0)	0.73 (0.7-1.3)
Adrenocortical	0/1 (0)	2.2
By *MET* abnormality		
Variant/amplification	0/4 (0)	1.6 (0.9-3.1)
No abnormality[1]	6/25 (24)	4.3 (0.7-19.7)
By type of c-MET trial		
c-MET specific inhibitor	0/9 (0)	1.43 (0.7-3.1)
Multi-kinase inhibitor or combination	6/20 (30)	5.4 (0.7-19.7)

[1] negative for either *MET* mutation or amplification or both