

**Correlation of c-MET Expression with PD-L1
Expression in Metastatic Clear Cell Renal Cell
Carcinoma Treated by Sunitinib First-Line Therapy**

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1 **Correlation of c-MET expression with PD-L1 expression in metastatic clear cell renal cell carcinoma**
2 **treated by sunitinib first-line therapy**

3
4 **Short title: c-MET in metastatic renal carcinoma**

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36 **ABSTRACT**

37 **Background:** Clear cell renal cell carcinoma (ccRCC) are highly metastatic. Cabozantinib, an antiangiogenic
38 tyrosine kinases inhibitor, targeting c-MET, proved interesting results in metastatic ccRCC treatment.

39 **Objective:** To better understand c-MET role, we assessed its status in a population of patients with metastatic
40 ccRCC.

41 **Patients and methods:** For this purpose, c-MET expression was studied by immunohistochemistry (IHC), *c-*
42 *MET* copy number alteration, by fluorescence in situ hybridization (FISH) and *c-MET* mutation, by next
43 generation sequencing (NGS) in a retrospective cohort of 90 primary ccRCC of patients with metastases treated
44 by first-line sunitinib. The expression of c-MET was correlated with pathological, immunohistochemical
45 (VEGFA, CAIX, PD-L1), clinical and molecular criteria (*VHL* status) by univariate and multivariate analyses
46 and to clinical outcome using Kaplan Meier curves compared by log-rank test.

47 **Results:** 31.1% of ccRCC had c-MET low expression (absent to weak intensity by IHC) versus 68.9% with high
48 expression (moderate to strong intensity). The high expression of c-MET was associated with a gain in FISH
49 analyses ($p = 0.0284$) without amplification. No mutation was detected in NGS. Moreover, high c-MET
50 expression was associated with lymph node metastases ($p=0.004$), sarcomatoid component ($p=0.029$), VEGFA
51 overexpression ($p=0.037$) and PD-L1 ($p=0.001$), the only factor that remained independently associated
52 ($p<0.001$) after logistic regression. No difference was observed in clinical outcome.

53 **Conclusion:** This study is the first to analyse c-MET status in metastatic ccRCC. The high expression of c-MET
54 in the majority of ccRCC and its independent association with PD-L1 expression, may suggest a potential benefit
55 from c-MET inhibitors and targeted immunotherapy in combination.

56

57 Key points:

- 58 • This study is the first to assess c-MET status, in metastatic renal carcinoma treated with anti-angiogenic
59 therapy.
- 60 • The high expression of c-MET was observed in the majority of patients and independently associated
61 with the overexpression of PD-L1.
- 62 • These findings may suggest a potential benefit from the combination of c-MET inhibitors and targeted
63 immunotherapy.

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70 1. INTRODUCTION

71
72 Renal cell carcinoma (RCC) is the most common form of kidney cancer with more than 270 000 cases diagnosed
73 worldwide and an estimated of 110 000 deaths from this tumour annually [1]. The most frequent histological
74 subtype is clear cell RCC (ccRCC), representing 70% of all renal cancers [2]. This subtype is a highly aggressive
75 tumour, as 40 to 50% of patients with ccRCC develop metastases: 20 to 30% of patients have metastatic disease
76 at diagnosis, while 30% of patients who have local RCC will develop metastases during follow-up [3].

77 Inactivation of the von Hippel–Lindau (*VHL*) tumour-suppressor protein has been described in more than 80% of
78 ccRCC, resulting in the stabilization of Hypoxia Inducible Factor (HIF) and the up-regulation of vascular
79 endothelial growth factor (VEGF) production [4]. A better understanding of the molecular pathways involved in
80 ccRCC contributed to the development of anti-angiogenic drugs, such as sunitinib or pazopanib, but long-
81 standing responses are rare [5, 6].

82 New strategies to treat metastatic ccRCC are in development. The first strategy is based on targeted
83 immunotherapy using checkpoint inhibitors (such as anti-PD-1/PD-L1). A recent clinical trial demonstrated
84 nivolumab (an anti-PD-1) superiority over everolimus, an inhibitor of mammalian target of rapamycin (mTOR),
85 in second-line treatment [7]. Another approach uses a novel antiangiogenic tyrosine kinase inhibitor (TKI),
86 cabozantinib, which has the particularity to target c-MET and also showed interesting results in second-line
87 treatment compared to everolimus [8].

88 The tyrosine kinase receptor c-MET is a proto-oncogene involved in tumour angiogenesis, proliferation and
89 metastasis. The dysregulation of c-MET and its ligand, hepatocyte growth factor (HGF), has been implicated in a
90 range of malignancies including renal cancers [9-11]. c-MET can be activated through several mechanisms such
91 as the mutation of the tyrosine kinase receptor domain or gene amplification and protein overexpression [6].
92 Although cabozantinib is a promising therapy, c-MET status has never been assessed in metastatic ccRCC.

93 The aim of the present study was to verify whether c-MET is activated in metastatic ccRCC in order to optimize
94 the use of c-MET inhibitors in such tumours. For this purpose, we assessed c-MET status in a retrospective
95 cohort of 90 patients with metastatic ccRCC treated by first-line sunitinib therapy.

96

97 2. MATERIALS AND METHODS

98 2.1 Patients and pathological analysis

99 Primary ccRCC-specimens were collected from 90 patients undergoing nephrectomy in 2 French University
100 Hospitals (Rennes, n=46 and Bordeaux, n=44 from UroCCR database) from 1997 to 2013 with metastases that
101 appeared between 2005 and 2013. When the metastases appeared, these patients were treated with
102 antiangiogenic sunitinib (Sutent®) therapy, as a first-line treatment. For each case, clinical, biological and
103 radiological features were obtained from referring physicians and medical records. The response to treatment
104 was assessed using response evaluation criteria in solid tumours (RECIST), the first evaluation was assessed
105 after 2 cycles of sunitinib (3 months). The study protocol was approved by the local advisory board (CNIL
106 declaration receipt 1812601v0) and informed consent was obtained from each patient. The macroscopic and
107 histological parameters analysed were tumour size, nucleolar grade according to the International Society of

108 Urological Pathology (ISUP) grading system, sarcomatoid component, tumour necrosis and microvessel
109 invasion. Tumour stage was defined according to the latest International Union Against Cancer 2009
110 classification. For each tumour, formalin-fixed paraffin-embedded (FFPE) and frozen samples were available.

111

112 2.2 Immunohistochemistry

113 For each ccRCC case, a representative slide of the tumour with the highest nucleolar grade and the
114 corresponding paraffin block was selected. Four μm -thick whole tissue sections were cut and mounted on glass
115 slides (Superfrost+, Menzel Glazer). The preparations were dried for 1 hour at 58°C, and then overnight at 37°C.
116 The sections were deparaffinized with toluene and rehydrated with ethanol. The preparations were pretreated and
117 immunostained using Ventana Benchmark XT. c-MET (Anti-Total c-MET, SP44, Rabbit Monoclonal Primary
118 Antibody, ready-diluted, Ventana, Roche, Switzerland), VEGFA (Anti-VEGF antibody, sc-152, dilution 1/100 ;
119 Santa Cruz Biotechnology, Santa Cruz, CA, USA), CAIX (Anti-CAIX antibody, ab15086, dilution 1/1500,
120 Abcam, Cambridge, UK), PD-L1 (Anti-PD-L1 antibody, clone 130021, dilution 1/200, RD System,
121 Minneapolis, USA) and PD1 (anti-PD-1 antibody, clone NAT105, dilution 1:50; Abcam, Cambridge, UK)
122 expressions were assessed by immunohistochemistry as previously described [12-15]. The reactivity of antibody
123 was revealed with HRP-labeled polymer conjugated secondary antibody using diaminobenzidine (DAB) as
124 chromogen (Sigma-Aldrich, France). Appropriate positive and negative controls were used. Two pathologists
125 (SM, SFKJ) and one uropathology expert (NRL) independently scored immunomarkers expression. The cut-off
126 for positive cases was 30% of tumour cells for VEGF and 85% for CAIX as previously described [16, 17]. For
127 PDL1, absent (0), weak (1), moderate (2) and strong expression (3) were reported and cases were then
128 subdivided into negative (score 0–1) or positive (score 2–3) subgroups [15]. For PD1, immunostaining density
129 was evaluated in tumour-infiltrating lymphocytes and was semi-quantified as absent (0), rare (1), moderate (2) or
130 dense (3); cases were then subdivided into negative (score 0–1) or positive (score 2–3) subgroups [18, 14]. For c-
131 MET IHC, membranous and cytoplasmic staining were considered. The intensity of the staining was scored as
132 absent (0), weak (1), moderate (2) or strong (3) as previously assessed [15]. For statistical analysis, c-MET
133 expression was considered high when moderate or strong staining was observed and low when the staining was
134 absent or weak.

135

136 2.3 Fluorescent *in situ* hybridization

137 FISH analyses were performed on the Rennes cohort (n=46). FISH analyses were performed on 4 μm sections of
138 FFPE tumour tissue with the ZytoLight[®] SPEC c-MET (7q31, Spectrum Green[®]) / CEN 7 (Spectrum Orange[®])
139 Dual Color Probe (Zytovision, Bremerhaven, Germany). One cytogeneticist (MABR) independently analysed
140 FISH. The slides were deparaffinized with xylene using a VP2000processor (Abbott, Wiesbaden, Germany). The
141 tissue was digested with pepsin (Dako, Les Ulis, France) for 6 min. The target DNA and probe were co-
142 denatured for 10 min at 75 °C using a programmable system (Thermobrite, Abbott Laboratories, North Chicago,
143 Illinois, USA) and probe hybridization was performed overnight in a humidified atmosphere at 37 °C. The slides
144 were analysed using a fluorescence microscope (BX61, Olympus, Rungis, France) and Isisimaging software
145 (Metasystems, Altlußheim, Germany) [19]. The entire hybridized surface was screened using a double band-
146 pass filter with an X63 objective and 50 non-overlapping tumour nuclei were examined. For the c-MET analysis,

147 gain (copy number alteration) was defined by strictly more than 2 c-MET signals and amplification was defined
148 according to UCCC (University of Colorado Cancer Center) scoring system [20].

149

150 2.4 Next generation sequencing

151 Small samples were collected from surgical specimens, frozen in liquid nitrogen and stored at -80°C until DNA
152 extraction. Genomic DNA was extracted using QIAamp DNA minikit (Qiagen, Courtaboeuf, France). DNA
153 quantity and quality were estimated by optical density (OD 260/280) measurement and 0,8% agarose gel
154 electrophoresis using standard protocols. Sequencing amplicon libraries were prepared using the TruSeq
155 Amplicon Cancer Panel (Illumina Inc., San Diego, California), according to the manufacturer's instructions.
156 DNA target preparation and enrichment were performed using the Access Array[®] polymerase chain reaction
157 (PCR) system (Fluidigm, San Francisco, USA). A 6-nucleotide "barcode" tag, specific to each sample and
158 Illumina-specific sequencing adaptors were attached using secondary PCR. Purified products were subsequently
159 pooled and sequenced on the Illumina MiSeq NGS instrument (Illumina Inc., San Diego, California). For the *c-*
160 *MET* gene, exons 2, 14, and 16 to 20 were fully sequenced to identify mutations in the tyrosine kinase domain.
161 For the *VHL* gene, the entire coding sequence and exon-intron junctions of exons 1, 2 and 3 were analysed.

162

163 2.5 Multiplex Ligation-dependant Probe Amplification

164 Methylation-Specific-MLPA (MS-MLPA) was used to detect CpG islands methylation in the *VHL* gene
165 promoter [21]. The SALSA MS-MLPA kit ME001B Tumour suppressor-1 was used to detect the aberrant
166 methylation of CpG-islands located in the promoter region of the *VHL* gene. The DNA (50–200 ng) was
167 denatured and the probes were allowed to hybridize (16h at 60°C). The *VHL* probes used for the methylation
168 quantification analysis contained one methylation-sensitive restriction site (HhaI) in the target recognition
169 sequence. Following hybridization, the samples were divided in half and one half of the samples was ligated,
170 whereas ligation was combined with HhaI digestion enzyme for the other part of the sample. This digestion
171 resulted in the ligation of only the methylated sequences. PCR was performed on all the samples and the
172 products were then analysed by electrophoresis. Reference unmethylated DNA samples, isolated from blood
173 from healthy volunteers, were included in each set of MLPA experiments. Unmethylated DNA will not generate
174 a signal, and a normal probe signal will be detected if the site is methylated.

175

176 2.6 Statistical analysis

177 Chi² (or Fisher exact) and Mann-Whitney tests were performed to compare qualitative and quantitative
178 parameters respectively between groups. For logistic regression, we used a backward stepwise selection with
179 $p < 0.05$ inclusion criteria. For clinical outcome, we calculated PFS from the date of sunitinib introduction to the
180 date of progression and OS from the date of sunitinib introduction to the date of specific death or last contact. All
181 p-values were 2-sided, and p-values less than 0.05 were considered statistically significant. All statistical
182 analyses were performed using Stata 14.1 software (College Station, TX).

183

184 **3. RESULTS**

185 3.1 Patients and histological parameters

186 The mean age at diagnosis was 61 years (37-85). The mean tumour size was 8.7 cm with tumours ranging from 2

187 cm to 20 cm. A total of 69 patients (76.6%) had an ECOG performance status of 0. In 50 cases (55.5%),
188 metastases were present at diagnosis. Non-metastatic tumours at diagnosis developed metastases on average after
189 10.5 months (0-144 months). The mean follow-up was 43.9 months (1-171 months) from nephrectomy. Eighty-
190 five patients (94.4%) experienced progression and 71 patients (78.9%) died from their cancer. The mean follow-
191 up period was 25.9 months (range 1-76 months) from sunitinib introduction. The population characteristics and
192 pathological parameters are summarized in Table 1.

193

194 3.2 VHL status

195 VHL status was assessed in the entire cohort (n=90). All patients were negative for germ-line mutations. A *VHL*
196 gene mutation was observed in 64 cases (71.1%). Mutations occurred in exons 1, 2 and 3 in 28 (43.8%), 21
197 (32.8%) and 15 cases (23.4%) respectively. Stop, frameshift, missense, and splice site mutations were detected in
198 8 (12.5%), 34 (53.1%), 18 (28.1%) and 4 (6.3%) cases respectively. *VHL* promoter methylation occurred in 10
199 cases (11.1%). At least one or more *VHL* abnormalities (*VHL* inactivation) were observed in 74 cases (82.2%).

200

201 3.3 c-MET status

202 For c-MET immunostaining, 11.1% (n=10) of ccRCC cases were negative, while 20.0% (n=18) of ccRCC cases
203 had weak staining. Moderate staining was observed in 26.7% (n=24) of cases and strong staining was observed
204 in 42.2% (n=38) of cases. Overall, 31.1% (n=28) of tumours were considered low and 68.9% (n=62) of cases
205 were considered high for c-MET expression. In the NGS analysis for the 90 patients, *c-MET* status was assessed
206 in 90 tumours. DNA quality was acceptable for 75 samples and no mutation was identified. *c-MET* FISH status
207 was assessed in 39 out of 46 interpretable cases. Gains were observed without amplification of *c-MET*. Two
208 copies were observed. The mean percentage of cells with gains was significantly associated with c-MET high
209 expression (p=0.0284).

210

211 3.4 Correlation of c-MET expression with pathological, immunohistochemical and molecular characteristics and 212 clinical outcomes

213 Tumours with low or high c-MET expression and patients characteristics were summarized and compared in
214 Table 2. Overall, high c-MET expression was not associated with progression at first radiologic evaluation. High
215 c-MET expression was also associated with high ISUP nucleolar grade (p=0.037), lymph node status (p=0.004)
216 and sarcomatoid component (p=0.029). VEGFA and PD-L1 overexpression were also associated with high c-
217 MET expression (p=0.037 and p=0.001 respectively). CAIX expression was not associated with c-Met
218 expression. PD-L1 overexpression remained significantly associated after logistic regression (p<0.001, [2.3-
219 18.7]). The high expression of c-MET was not associated with VHL status (p=0.239). No differences were
220 observed between progression-free and overall survival according to c-MET expression (p=0.94 and p=0.73
221 respectively, Figure 4).

222

223 **4. DISCUSSION**

224 Antiangiogenic VEGF-targeted therapies have been approved as first-line treatment in metastatic ccRCC.
225 However, despite showing efficacy and survival benefit, almost 20 to 30% of patients develop early disease
226 progression [5]. Thus, tumour recurrence in metastatic ccRCC has been one of the major challenges in patients

227 treated with angiogenesis inhibitors, and explains the emergence of new strategies such as targeted
228 immunotherapy and TKI targeting new pathways such as HGF/cMET [10].

229 It is important to acknowledge the limitations of our study. Firstly, this a retrospective study with patients
230 included from 2 centers. The sample size is limited and partially explained by our rigorous inclusion criteria such
231 as homogeneous histology (ccRCC) and sunitinib as first line treatment. Secondly, as recognized by the
232 literature, immunohistochemistry usually experienced poor standardization; however, in the case of c-Met
233 antibody, this statement is limited as the same clone for c-MET antibody is widely used [20, 15, 9].

234 In the present study, we assessed c-MET status in a series of 90 patients with m-ccRCC treated by sunitinib as
235 first line treatment with a median follow-up of 43 months. High c-MET expression was found in 69% of
236 tumours. The FISH analysis revealed gains without *c-MET* amplification as previously found by Macher-
237 Goepfing *et al* [22]. We observed a significant correlation between the percentage of gains by FISH and c-
238 MET expression by IHC, suggesting a potential mechanism for overexpression of the protein detected by IHC
239 that could be inherited to metastatic tumour cells. Another explanation for c-MET overexpression may be related
240 to post-translational modification, as previously described for tyrosine kinase receptors [23]. NGS analysis
241 revealed no mutation on the c-MET gene, consistent with a previous study, unlike papillary RCC, particularly
242 type 1, which shows nearly 20% c-MET mutations [11, 22].

243 As previously described, c-MET expression has been associated with poor prognostic factors such as nucleolar
244 grade, sarcomatoid component and the presence of lymph nodes metastases [24]. A recent study by Peltola *et al.*
245 assessed that c-MET high expression was also associated with poor survival in patients with metastatic RCC
246 treated with sunitinib [25]. This difference may be explained by the non-homogeneous histology of the renal cell
247 carcinoma included. Indeed, in their population (n=137), n=107 were clear cell renal cell carcinoma, whereas
248 n=15 were non ccRCC and for 15 tumors, the histology was missing. Non ccRCC have different carcinogenesis
249 and there is no evidence whether first-line sunitinib is the optimal treatment in this subgroup [26, 27].

250 In our study, high c-MET expression was independently associated with PD-L1 by IHC. Shin *et al* first reported
251 an association between c-MET and PD-L1 expressions in non-selected ccRCC [15]. In the present cohort, this
252 association was observed in the primary ccRCC of patients with metastases. This cohort is more representative
253 of patients likely to benefit from the corresponding inhibitors. Moreover, the independent association we
254 identified, although limited by the sample size, gives argument for the combined use of c-MET inhibitors and
255 targeted immunotherapy. Indeed, cabozantinib and nivolumab combination is currently investigated
256 (NCT02496208) [28].

257 The HGF/cMET pathway has been described as an alternative antiangiogenic pathway that could be responsible
258 for early resistance to anti-VEGF therapy [29]. In addition, chronic sunitinib treatment was demonstrated to lead
259 to c-MET up regulation *in vitro* [30]. Consequently, we hypothesize that the response could be improved
260 targeting c-MET pathway as well. Nevertheless, MET overexpression was not associated with progressive
261 disease at first radiological evaluation, PFS and OS, in patients uniformly first-treated by sunitinib.

262 With *VHL* inactivation, HIF stabilization leads to the transcription of targeted genes, such as CAIX, VEGFA and
263 c-MET whose expression and suggesting a correlation between *VHL* status and HIF-targeted gene expression
264 [31, 32]. However, we did not observe a correlation between *VHL* inactivation (*VHL* mutation or promoter

265 methylation) and the expression of these targets genes suggesting the involvement of alternative pathways, such
266 as the MAP kinase and PI3K-AKT-mTOR pathways, in ccRCC oncogenesis, independent of *VHL* mechanisms
267 [33, 34].

268 In conclusion, the present study confirmed a high proportion of metastatic ccRCC showing a high c-Met protein
269 expression without association with sunitinib response. The independent association of c-MET expression with
270 PD-L1 expression, may suggest a potential benefit to the use of c-MET inhibitors with targeted immunotherapy
271 for these patients.

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284 **COMPLIANCE WITH ETHICAL STANDARDS SECTION**

285 **Informed consent**

286 Informed consent was obtained from all individuals participants included in the study.

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290 **Conflict of interest**

291 The authors have no conflict of interest to declare.

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300

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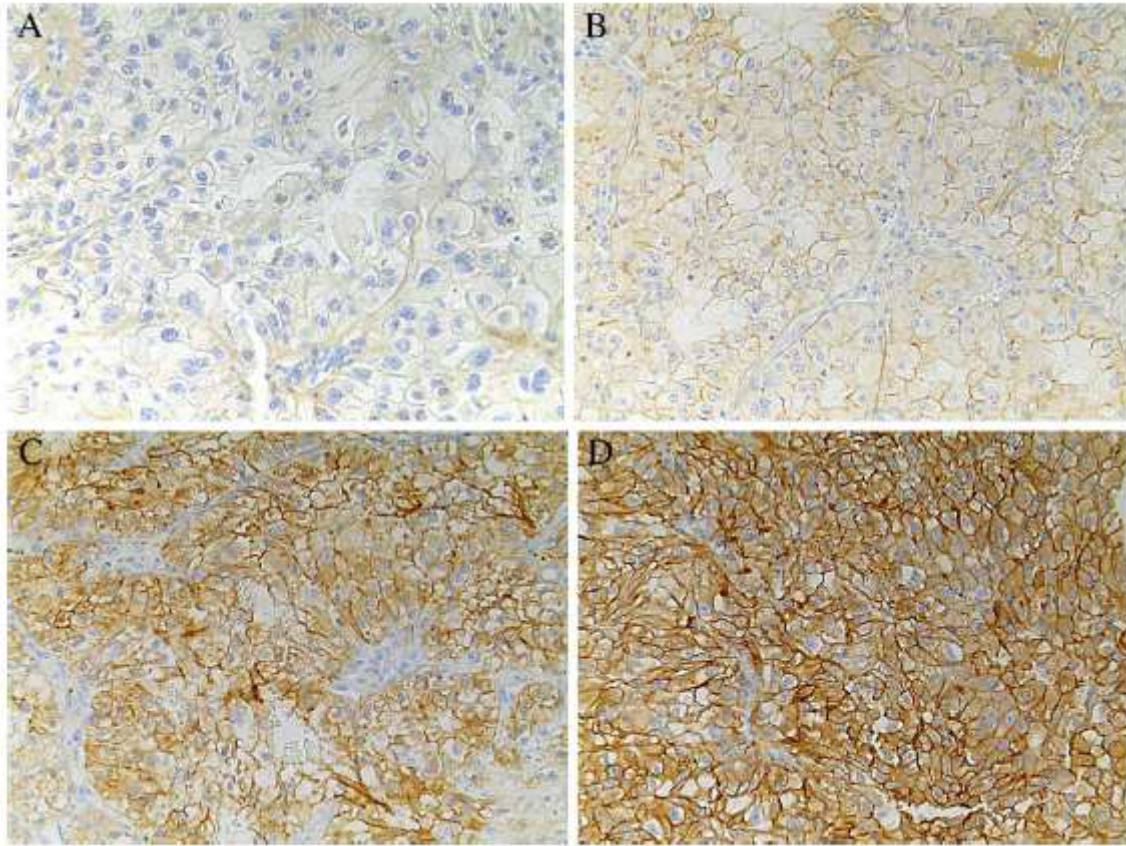
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400 **FIGURE LEGENDS**



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402 **Figure 1: Intensity of c-MET expression:**

403 A) Absence of c-MET expression, IHC x100

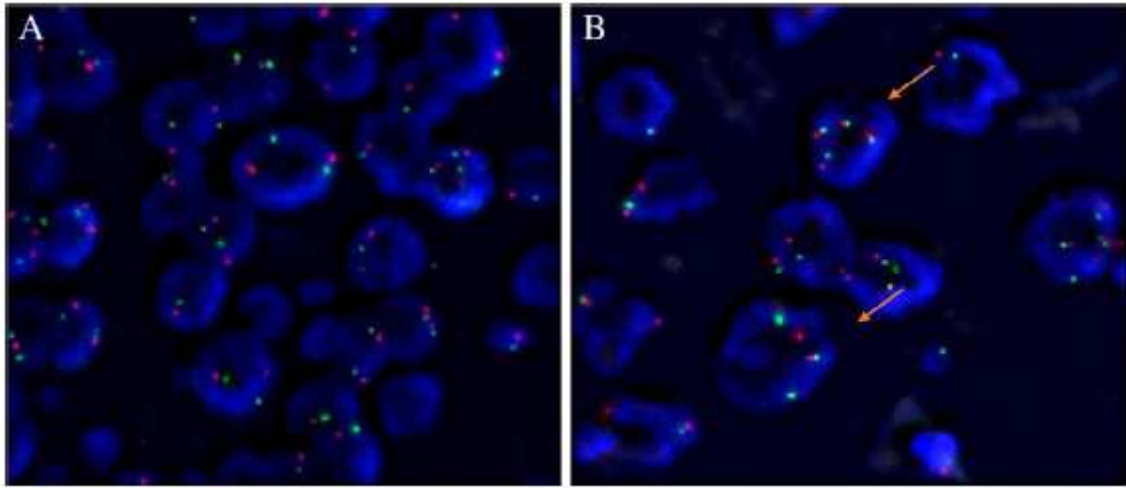
404 B) Low expression of c-MET in tumor cells, IHC x100

405 C) Moderate expression of c-MET in tumor cells, IHC x100

406 D) High expression of c-MET in tumor cells, IHC x100

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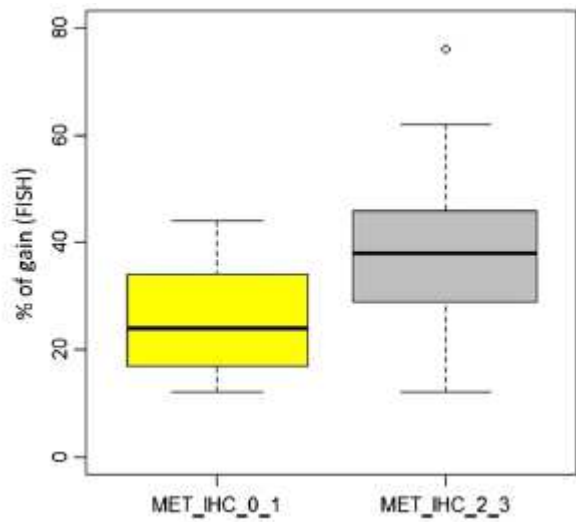


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Figure 2: FISH analysis

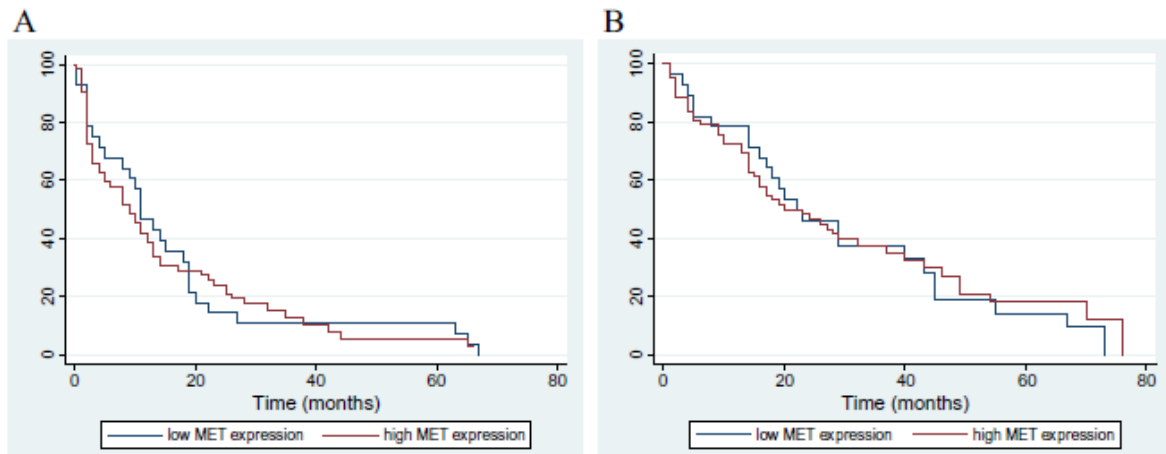
A) Nuclei with a normal hybridization pattern (2 green and 2 orange signals)

B) Nuclei with a c-MET gain exhibit more than 2 green signals (arrows).



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Figure 3: Percentage of gains (FISH) according to c-MET expression (IHC).



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420 **Figure 4: Progression-free survival (PFS) and overall survival (OS) after sunitinib according to c-MET**
 421 **expression in metastatic ccRCC:**

422 A) PFS: median survival: low: 11months, high: 9 months (p=0.828)

423 B) OS: median survival: low: 22 months, high: 20 months (p=0.860)

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449 **TABLE LEGENDS**

Characteristics	No	%
Age (years)		
Mean	61.3	
Range	37-85	
Sex		
Male	34	37.8%
Female	56	62.2%
Heng score		
Favorable	20	22.2%
Intermediate	43	47.8%
Poor	27	30.0%
T stage		
T1	14	15.6%
T2	8	8.9%
T3	63	70.0%
T4	5	5.6%
N stage		
N0	75	83.3%
N1-N2	15	16.7%
M stage		
M0	40	44.4%
M1	50	55.6%
Tumor size (cm)		
Mean	9.6	
Range	2-20	
ISUP nucleolar grade		
Grade 2	7	7.8%
Grade 3	33	36.7%
Grade 4	50	55.6%
RECIST 1		
Complete response	1	1.1%
Partial response	27	30.0%
Stable disease	34	37.8%
Progressive disease	28	31.1%

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452 **Table 1. Summary of the clinical and histopathological characteristics of 90 patients with metastatic**

453 **ccRCC treated by first line sunitinib.**

Variables	MET low (n = 28)	%	MET high (n = 62)	%	p-value
Clinical and radiological data					
Age > 65 years	14	50.0%	23	37.1%	0.249†
Good/intermediate prognosis (Heng score)	21	75.0%	42	67.7%	0.487†
Distant lymph node metastasis	11	39.3%	28	45.2%	0.603†
Pulmonary metastasis	22	78.6%	46	74.2%	0.655†
Bone metastasis	17	60.7%	31	50.0%	0.346†
Liver metastasis	8	28.6%	13	21.0%	0.430†
Cerebral metastasis	7	25.0%	12	19.4%	0.544†
Multiple metastasis	22	78.6%	47	75.8%	0.774†
Progressive disease (RECIST)	7	25.0%	21	33.9%	0.400†
Pathological analysis					
Size >7 cm	19	67.9%	39	62.9%	0.649†
Nucleolar ISUP grade 4	11	39.3%	39	62.9%	0.037†
Sarcomatoid component	2	7.1%	17	27.4%	0.029†
Tumor necrosis	20	71.4%	51	82.3%	0.244†
Microvascular invasion	13	46.4%	28	45.2%	0.911†
T3-T4 stage	22	78.6%	46	74.2%	0.655†
Hilar fat infiltration	11	39.3%	31	50.0%	0.346†
Peri-renal fat infiltration	16	57.1%	29	46.8%	0.362†
Venal invasion	12	42.9%	29	46.8%	0.730†
N1-N2 stage	0	0.0%	15	24.2%	0.004‡
M1 stage	13	46.4%	37	59.7%	0.242†
Immunohistochemistry					
CAIX >85%	7	25.0%	21	33.9%	0.400†
VEGFA >30%	11	39.3%	39	62.9%	0.037†
PD-L1 (2-3 intensity) *	13	46.4%	53	85.5%	0.001†
PD-1 (2-3 density)	11	39.3%	37	59.7%	0.073†
VHL status					
VHL mutation	23	82.1%	41	66.1%	0.121†
Promoter methylation	2	7.1%	8	12.9%	0.718‡
VHL inactivation	25	89.3%	49	79.0%	0.239†

†, χ^2 test; ‡, Fisher exact test

RECIST 1: First RECIST evaluation, CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

*Independent variable after logistic regression

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Table 2. Summary of histopathological and immunohistochemical characteristics and VHL status of tumors according to c-MET expression.