European Journal of Cancer 170 (2022) 158–168

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Impact of *MET* status on treatment outcomes in papillary renal cell carcinoma: A pooled analysis of historical data

Laurence Albiges [a,b,*,1], Daniel Y.C. Heng [c,1], Jae Lyun Lee [d,1], Stephen Walker [e,2], Anders Mellemgaard [f], Lone Ottesen [g,3], Melanie M. Frigault [h,4], Anne L'Hernault [i], Jonathan Wessen [f], Toni Choueiri [j,5], Mathilde Cancel [k,5], Sabina Signoretti [l,m,5]

[a] *Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA*
[b] *Department of Cancer Medicine, Institut Gustave Roussy, Université Paris Saclay, Villejuif, France*
[c] *Department of Medical Oncology, Tom Baker Cancer Center, University of Calgary, Calgary, Alberta, Canada*
[d] *Department of Oncology, Asan Medical Center and University of Ulsan College of Medicine, Seoul, South Korea*
[e] *Syneos Health, Charlotte, NC, USA*
[f] *Oncology R&D, AstraZeneca, Cambridge, UK*
[g] *Targovax Asa, Oslo, Norway*
[h] *Vincerx Pharma, Inc., Palo Alto, CA, USA*
[i] *Precision Medicine and Biosamples, Oncology R&D, AstraZeneca, Cambridge, UK*
[j] *Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA*
[k] *Department of Medical Oncology, CHU Bretonneau Centre, University of Tours, Tours, France*
[l] *Harvard Medical School, Boston, MA, USA*
[m] *Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA*

Received 24 March 2022; accepted 14 April 2022
Available online 28 May 2022

* *Corresponding author:* Department of Cancer Medicine, Institut Gustave Roussy, Université Paris Saclay, 114 rue Edouard Vaillant, 94805 Villejuif, France. Fax: +33 1 42 11 53 05.

E-mail address: laurence.albiges@gustaveroussy.fr (L. Albiges), Daniel.Heng@albertahealthservices.ca (D.Y.C. Heng), jaelyun@amc.seoul.kr (J.L. Lee), stephen.walker@syneoshealth.com (S. Walker), anders.mellemgaard@astrazeneca.com (A. Mellemgaard), Loneott@dadlnet.dk (L. Ottesen), melanie.frigault@gmail.com (M.M. Frigault), anne.lhernault@astrazeneca.com (A. L'Hernault), jonathan.wessen@astrazeneca.com (J. Wessen), Toni_Choueiri@DFCI.HARVARD.EDU (T. Choueiri), cancel@univ-tours.fr (M. Cancel), ssignoretti@bwh.harvard.edu (S. Signoretti).

[1] co-lead authors. [2] Formerly Oncology R&D, AstraZeneca, Cambridge, UK. [3] Formerly Translational Medicine, Oncology R&D, AstraZeneca, Waltham, MA, USA. [4] Formerly Precision Medicine and Biosamples, Oncology R&D, AstraZeneca, Cambridge, UK. [5] co-senior authors.

https://doi.org/10.1016/j.ejca.2022.04.021

KEYWORDS
Biomarkers;
Clinical-stage research;
Drug targets;
Genitourinary cancers;
MET;
PRCC;
Sunitinib

Abstract ***Background:*** Papillary renal cell carcinoma (PRCC) represents 15% of RCCs but has no indicated therapies, with limited biomarker-based data to inform targeted treatment. *MET* alterations may be key; > 80% of PRCC tumours show *MET* upregulation. The objective of this study was to assess *MET* status in PRCC and its impact on clinical outcomes.
Methods: This retrospective, observational study included patients with locally advanced/metastatic PRCC from three international registries. *MET* status was determined retrospectively by next generation sequencing (NGS) of archival tissue. *MET*-driven was defined as *MET* and/or *hepatocyte growth factor* amplification, chromosome 7 gain, and/or *MET* kinase domain mutations. Objectives included progression-free survival (PFS) and overall survival (OS) by *MET* status using a Cox proportional hazards model.
Results: Of 308 patients, 305 received first-line treatment; most commonly sunitinib (n = 208; 68%), then everolimus (n = 40; 13%). Of 179 patients with valid NGS results, 38% had *MET*-driven and 49% *MET*-independent tumours (13% unevaluable). In the *MET*-driven versus *MET*-independent subgroups, respectively, of sunitinib-treated patients, median PFS was numerically longer, though not statistically significantly; PFS: 9.2 months (95% confidence interval [CI]: 5.4–13.2) versus 5.7 months (95% CI: 4.3–7.4), hazard ratio (HR) = 0.67; 95% CI: 0.41–1.08. There was no difference between the OS of each subgroup.
Conclusions: *MET*-driven PRCC may respond to targeted agents. However, the presence of *MET* alterations did not appear to be predictive for outcomes in response to current therapies, which are not biomarker-driven, compared with *MET*-independent tumours.

1. Introduction

Among the histologic subtypes of renal cell carcinoma (RCC), non-clear cell RCC (non-ccRCC) accounts for up to 25% of all renal malignancies [1,2]. Papillary RCC (PRCC), classified as type I or II, is the most common variant of non-ccRCC, accounting for approximately 15% of all RCC [1,3].

There are few published phase III randomised controlled studies for non-ccRCC or PRCC [4] and hence no therapies specifically indicated for PRCC treatment. Current evidence for targeted treatment of patients with non-ccRCC, including PRCC, are extrapolated from real-world evidence and subgroup analyses from RCC studies with focus on the multi-target tyrosine kinase inhibitors (TKIs) (such as sunitinib) and the mechanistic target of rapamycin (mTOR) inhibitors (such as everolimus), which were initially developed for ccRCC treatment [4]. Phase II studies have demonstrated varying and limited activity of everolimus and sunitinib in patients with metastatic PRCC or other non-ccRCC [4–10]. More recent studies in advanced/metastatic PRCC include a prospective phase II study of the vascular endothelial growth factor receptor-TKI, axitinib, which demonstrated initial activity in some patients, particularly those with type II PRCC [11], and the randomised phase III SAVOIR study which investigated the efficacy and safety of savolitinib, a potent and highly selective MET-TKI [12–14], versus sunitinib, in patients with *MET*-driven tumours [15].

In addition to the limited clinical evidence for targeted treatment in PRCC, there are few biomarker-based clinical study data available to inform prognosis and treatment selection for patients with PRCC. However, there is additional evidence that dysregulation of the signalling pathway for the hepatocyte growth factor (HGF) receptor *MET* plays an important role in PRCC [16]. *MET* upregulation has been identified in approximately 80% of PRCC tumours, *MET* mutations, including those in its tyrosine kinase domain have been identified in patients with PRCC, and a gain of chromosome 7 copy number, the gene locus of both *MET* and *HGF*, is also present in a high proportion of patients with PRCC [3,16,17]. MET inhibition may therefore be a potential target for PRCC drug development, as supported by studies with savolitinib and multikinase inhibitors, foretinib and crizotinib, which include MET-inhibitory activity, showing that patients with *MET*-driven PRCC versus non-*MET*-driven PRCC are more likely to have a treatment response [18–21].

To further understand the prognostic value of *MET* alterations in PRCC, this retrospective molecular epidemiology study investigated the impact of *MET* status on outcomes in patients with locally advanced/metastatic PRCC receiving targeted therapies, to consider *MET* as a viable option for development of a novel targeted treatment for PRCC.

2. Methods

2.1. Study design and patients

We conducted a retrospective, large, international, observational study assessing demographic and clinical

data and archival tissue samples from previously treated patients with locally advanced/metastatic PRCC. Data and samples were collected from three sources as described in the Supplementary material. Data from the patients' medical records or case report forms, were retrospectively collected from the time of PRCC diagnosis until progression, death, last follow-up, or lost to follow-up (whichever occurred first). Details of the retrospective *MET* status analysis are provided in the Supplementary material.

Inclusion criteria included patients aged $\geq$ 18 year with histologically confirmed locally advanced/metastatic PRCC (type I, type II, and unspecified) who had received sunitinib and/or other systemic anti-cancer therapies for their PRCC. Patients with minor clear cell components (< 50%) were permitted provided that the dominant and presumed primary histology was papillary. Patients' data with retrospective tissue samples were excluded if any of the above inclusion criteria were not fulfilled. All patients had to provide informed consent for their tissue samples to be used.

This study was performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practices, Good Pharmacoepidemiology Practices and the applicable legislation on non-interventional studies and/or observational studies. The final protocol was approved or given a favourable opinion by the Ethics Committee/Institutional Review Board/Independent Ethics Committee, as applicable for sites without previous consent in place.

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

2.2. Objectives

The primary objective was to estimate the effect of *MET* status on progression-free survival (PFS) and time to treatment failure (TTF). The secondary objectives were to estimate the effect of *MET* status on overall survival (OS), outcome differences (PFS, OS, and TTF) with sunitinib and other anti-cancer systemic therapies by line of therapy, and the effect of *MET* status and line of therapy on outcome differences (PFS, OS, and TTF) from anti-cancer systemic therapies. Objective response rate (ORR) for anti-cancer systemic therapies by *MET* status was assessed as an exploratory objective.

2.3. Statistical methods

The full analysis set (FAS) comprised all enrolled patients providing informed consent to participate in the study. Here, data are presented for the *MET* analysis set comprising all patients who provided informed consent and whose tumour sample was tested by next generation sequencing (NGS). All analyses were descriptive in nature. The number of line of therapies, treatment patterns and baseline characteristics (age, gender, Karnofsky performance status, disease stage, liver metastases) were reported for the overall population and by *MET* status.

Definitions and methodologies for PFS, TTF, OS, and ORR and further details of a sensitivity analysis for the primary endpoint are provided in the Supplementary material.

3. Results

3.1. Patient disposition and characteristics

3.1.1. Overall population

Overall, 308 patients were included in the FAS of whom 96 (31%) patients were still alive at data cut-off (October 16, 2018) (Table 1). Overall, 305 patients received first-line treatment, most commonly sunitinib in 208 (68%) patients, followed by everolimus in 40 (13%) patients (Table 1). Patients received first-line treatment between 2005 and 2017, with 93% receiving it between 2007 and 2015. All other first-line treatments were reported in < 10% of patients (Fig. 1). Second-line treatment was received by 214 (69%) patients, most commonly everolimus (n = 63, 20%) followed by sunitinib (n = 46, 15%) and temsirolimus (n = 35, 11%).

3.1.2. MET analysis set

Of 308 patients enrolled, *MET* status was analysed in 179 (58%) patients with 129 (42%) patients excluded from the *MET* analysis set (Table 1). In this *MET* analysis set (n = 179), 68 (38%) patients had *MET*-driven tumours, 88 (49%) patients had *MET*-independent tumours and 23 (13%) patients had an unevaluable chromosome 7 ploidy analysis (Tables 1 and 2); therefore, their status was unknown. Similar to the overall population of the patients with *MET*-driven tumours, 45 (66%) patients received sunitinib as first-line treatment and 5 (7%) patients received everolimus (Table 2). The remaining patients received temsirolimus (n = 8, 12%), pazopanib (n = 4, 6%), sorafenib (n = 3, 4%), foretinib (n = 2, 3%) or bevacizumab (n = 1, 1%). From these findings, this report will focus predominantly on endpoint analyses in patients receiving sunitinib as this was the largest patient group with *MET* status analysed and clinically reflects the standard first-line treatment. A second analysis of endpoints was performed in patients receiving any-line everolimus, as the next largest patient group with available *MET* status.

In the *MET* analysis set, the majority of patients were male (n = 141, 79%) with a median (range) age of 60.3 (16.9, 83.0) years and were stage III or IV at initial diagnosis (n = 130, 73%) (Table 2). Characteristics were generally well balanced between the *MET*-driven and *MET*-independent groups except for a greater proportion

Table 1
Patient disposition for the full analysis set.

	Number (in %) of patients			
	IMDC[a] (n = 72)	AMC (n = 40)	GETUG (n = 196)	Total (N = 308)
Patients with treatment data	69 (96)	40 (100)	196 (100)	305 (99)
Time from tissue extraction to first-line therapy, n (in %)				
After first-line	1 (1)	2 (5)	3 (2)	6 (2)
0–1 month	4 (6)	2 (5)	4 (2)	10 (3)
1–3 months	25 (35)	7 (18)	39 (20)	71 (23)
3–6 months	7 (10)	5 (13)	16 (8)	28 (9)
6–12 months	7 (10)	6 (15)	22 (11)	35 (11)
> 12 months	21 (29)	11 (28)	56 (29)	88 (29)
Missing	4 (6)	7 (18)	56 (29)	67 (22)
Patients receiving first-line treatment[b]				
Total	69 (96)	40 (100)	196 (100)	305 (99)
Sunitinib	33 (46)	17 (43)	158 (81)	208 (68)
Everolimus	1 (1)	1 (3)	38 (19)	40 (13)
Patients receiving second-line treatment[b]				
Total	42 (58)	30 (75)	142 (72)	214 (69)
Everolimus	4 (6)	6 (15)	53 (27)	63 (20)
Sunitinib	12 (17)	3 (8)	31 (16)	46 (15)
Temsirolimus	7 (10)	6 (15)	22 (11)	35 (11)
Patients receiving third-line treatment[b]				
Total	23 (32)	6 (15)	86 (44)	115 (37)
Everolimus	10 (14)	0	20 (10)	30 (10)
Sorafenib	1 (1)	0	32 (16)	33 (11)
MET status				
MET-driven[c]	21 (29)	9 (23)	38 (19)	68 (22)
MET-independent[d,e]	21 (29)	21 (53)	46 (23)	88 (29)
MET-, no *FH*, or *VHL* mutation	15 (21)	12 (30)	35 (18)	62 (20)
MET+/-, *FH* mutation	3 (4)	8 (20)	5 (3)	16 (5)
MET+/-, *VHL* mutation	3 (4)	1 (3)	6 (3)	10 (3)
Chromosome 7 ploidy analysis invalid	7 (10)	4 (10)	12 (6)	23 (7)
Missing[f]	23 (32)	6 (15)	100 (51)	129 (42)
Patients alive	67 (93)	13 (33)	16 (8)	96 (31)

AMC = Asan Medical Center; FH = fumarate hydratase; GETUG = Groupe Français d'Etude des Tumeurs Uro-Génitales; HGF = hepatocyte growth factor; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; *MET* = hepatocyte growth factor receptor; VHL = *von Hippel–Lindau tumour suppressor*.

[a] Three patients from the IMDC did not have treatment data.

[b] Treatments reported in < 10% of patients in all groups are not reported.

[c] *MET*-driven tumours were defined as any of the following alterations alone or in combination: *MET* amplification, chromosome 7 copy number gain above the ploidy of the rest of the genome in the same sample, *MET* kinase domain mutations, and *HGF* amplification.

[d] *MET*-independent tumours were defined as those not having the above mentioned alterations, or having *MET* alterations in combination with *FH* or *VHL* mutations.

[e] One patient in the *MET*-independent subgroup from IMDC did not have any treatment data.

[f] Missing due to the tumour tissue not being available (missing or no informed consent was received) or the next generation sequencing sample failing to pass the quality control check.

of type II tumours in the MET-independent group versus MET-driven (Table 2). In the overall *MET* analysis set, 76 (42%) patients had a chromosome 7 gain, 18 (10%) had a *fumarate hydratase* mutation, 12 (7%) possessed a *MET* mutation, 10 (6%) showed *MET*-amplification, 10 (6%) had a *von Hippel–Lindau tumour suppressor* mutation, and 6 (3%) had amplified *HGF* (these categories are not mutually exclusive).

3.2. Sunitinib-treated patients

3.2.1. Effect of MET status on PFS and TTF

The incidence of progression and treatment failure events was similar between sunitinib-treated patients with *MET*-driven and *MET*-independent tumours (Table 3). Median PFS and TTF were numerically longer in the *MET*-driven subgroup versus the *MET*-independent subgroup although the differences were not statistically significant (Fig. 2A and B; Table 3). A sensitivity analysis to assess for potential confounding was conducted for PFS and TTF and showed similar results to that determined in the primary analysis (Supplementary Table S1).

3.2.2. Effect of MET status on OS

The incidence of deaths was similar between sunitinib-treated patients with *MET*-driven and *MET*-

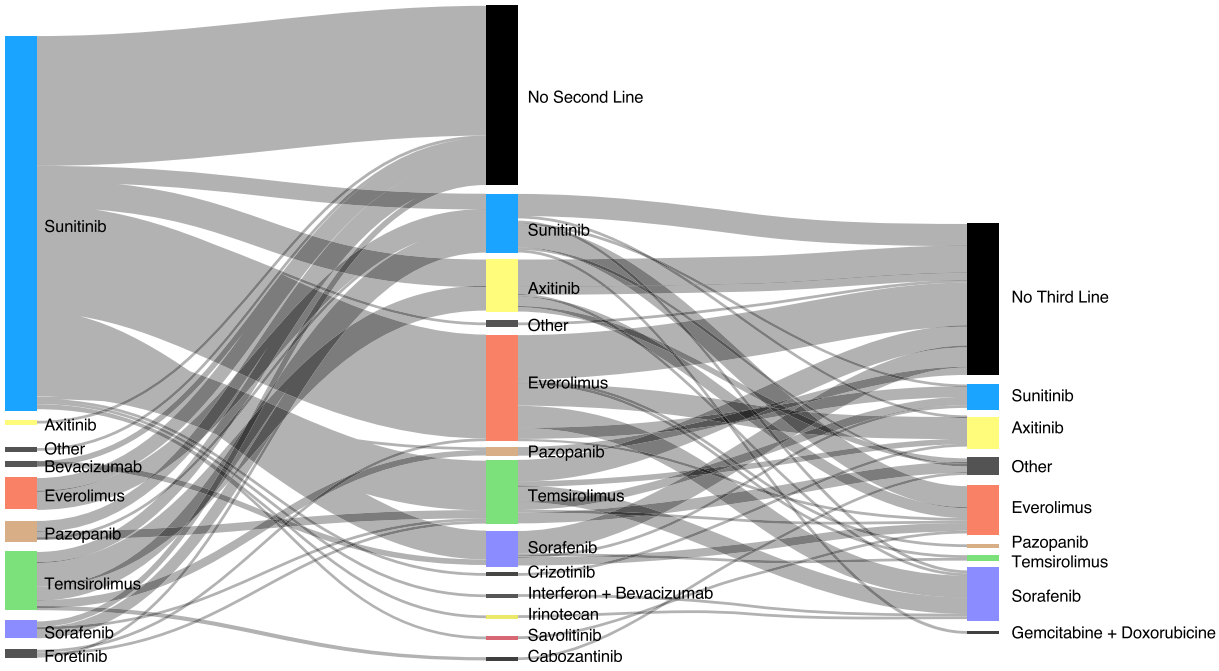

Fig. 1. Patient treatment flow

independent tumours and no difference in median OS was detected between these subgroups (Table 3; Fig. 2C).

3.2.3. Effect of *MET* status on ORR

No difference in ORR was observed between sunitinib-treated patients in the *MET*-driven (n = 5, 9%) and *MET*-independent subgroups (n = 6, 8%); the adjusted ORR was 7.8% versus 7.0%, respectively, odds ratio 1.13; 95% CI: 0.31–3.98; p = 0.846. A complete response was reported in 1 (1%) patient in the *MET*-independent subgroup and no patients in the *MET*-driven subgroup. A total of 5 (9%) patients in the *MET*-driven subgroup and 5 (7%) patients in the *MET*-independent subgroup had a partial response.

3.3. Everolimus-treated patients

No statistically significant difference was observed in PFS, TTF, and OS between everolimus-treated patients with *MET*-driven and *MET*-independent tumours (Supplementary Table S2). However, the low number of patients should be noted when interpreting the results; 11 (6%), 36 (20%) and 17 (9%) patients received everolimus as first-, second-, and third-line therapy, respectively.

3.4. Analysis of outcomes by line of therapy

Due to low patient numbers in the second and third lines of treatment, meaningful interpretation of other endpoints assessing differences in outcome by line of therapy and by *MET* status and line of therapy were not possible (Supplementary Fig. S1).

4. Discussion

Given the limited efficacy of current treatments for locally advanced/metastatic PRCC, identifying molecular biomarkers for predicting response to therapies is key to developing novel targeted treatments for optimal patient care. Our study, the first to report extensive *MET* molecular characterisation and its association with treatment outcome in this patient population, demonstrates that *MET* alterations are frequent in locally advanced/metastatic PRCC and in sunitinib-treated patients, PFS and TTF were numerically longer in those with *MET*-driven versus *MET*-independent tumours.

The proportion of tumour samples that were *MET*-driven or *MET*-independent was in line with those previously reported in a phase II study of PRCC (n = 109) where 40% and 42% of tumours were *MET*-driven and *MET*-independent, respectively [19]. The most frequent *MET* alterations were chromosome 7 gain (42%) followed by *MET* mutation (7%) and *MET* amplification (6%). High rates of chromosome 7 gain have also been reported in gene expression PRCC studies (47%–68%) [3,16], while slightly higher rates of *MET* mutations (11%–13%) have been reported in other PRCC studies [3,22].

In the overall population and MET analysis set, the most frequent first-line treatment was sunitinib, in line with treatment guidelines although supportive data are limited for PRCC [4,23]. In sunitinib-treated patients with known *MET* status, there was a trend for patients with *MET*-driven versus *MET*-independent tumours to have a longer PFS and TTF but the differences were not statistically significant. This trend may be explained by

Table 2
Patient demographics and baseline characteristics for the *MET* analysis set.

	MET-driven[a] (n = 68)	*MET*-independent[b] (n = 88)	Chr7 ploidy analysis invalid (n = 23)	Total (n = 179)
Data source, n (in %)				
IMDC	21 (31)	21 (24)	7 (30)	49 (27)
AMC	9 (13)	21 (24)	4 (17)	34 (19)
GETUG	38 (56)	46 (52)	12 (52)	96 (53)
Baseline characteristics				
Median (range) age, year	61.5 (30.6–83.0)	59.7 (20.1–79.5)	60.2 (16.9–81.6)[c]	60.3 (16.9–83.0)
Sex, n (in %)				
Female	15 (22)	15 (17)	7 (30)	37 (21)
Male	53 (78)	72 (82)	16 (70)	141 (79)
Missing	0	1 (1)	0	1 (1)
Histology				
Papillary type I	17 (25)	3 (3)	1 (4)	21 (12)
Papillary type II	32 (47)	54 (61)	14 (61)	100 (56)
Unspecified	19 (28)	31 (35)	8 (35)	58 (32)
Stage at diagnosis,[d] n (in %)				
1	6 (9)	11 (13)	0	17 (9)
2	9 (13)	3 (3)	0	12 (7)
3	25 (37)	29 (33)	11 (48)	65 (36)
4	19 (28)	34 (39)	12 (52)	65 (36)
Missing	9 (13)	11 (13)	0	20 (11)
First-line therapy characteristics				
KPS,[e] n (in %)				
≥ 90	35 (51)	46 (52)	13 (57)	94 (53)
80	19 (28)	15 (17)	5 (22)	39 (22)
70	5 (7)	6 (7)	2 (9)	13 (7)
< 70	3 (4)	7 (8)	1 (4)	11 (6)
Missing	6 (9)	13 (15)	2 (9)	21 (12)
Liver metastasis, n (in %)				
Yes	15 (22)	21 (24)	5 (22)	41 (23)
No	22 (32)	24 (27)	10 (43)	56 (31)
Missing	31 (46)	43 (49)	8 (35)	82 (46)
Line of therapy				
First-line therapy,[e] n (in %)				
Total	68 (100)	87 (99)	23 (100)	178 (99)
Sunitinib	45 (66)	63 (72)	19 (83)	127 (71)
Temsirolimus	8 (12)	10 (11)	2 (9)	20 (11)
Everolimus	5 (7)	6 (7)	0	11 (6)
Second-line therapy,[e] n (in %)				
Total	47 (69)	55 (63)	16 (70)	118 (66)
Sunitinib	9 (13)	10 (11)	1 (4)	20 (11)
Temsirolimus	10 (15)	9 (10)	3 (13)	22 (12)
Everolimus	9 (13)	19 (22)	8 (35)	36 (20)
Axitinib	8 (12)	9 (10)	1 (4)	18 (10)
Third-line therapy,[e] n (in %)				
Total	30 (44)	29 (33)	6 (26)	65 (36)
Sunitinib	4 (6)	5 (6)	0	9 (5)
Everolimus	13 (19)	2 (2)	2 (9)	17 (9)
Axitinib	4 (6)	5 (6)	2 (9)	11 (6)
Sorafenib	6 (9)	11 (13)	1 (4)	18 (10)

AMC = Asan Medical Center; Chr = chromosome; FH = fumarate hydratase; GETUG = Groupe Français d'Etude des Tumeurs Uro-Génitales; HGF = hepatocyte growth factor; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; KPS = Karnofsky performance status; *MET* = hepatocyte growth factor receptor; NA = not applicable; VHL = *von Hippel–Lindau tumour suppressor*.

[a] *MET*-driven tumours were defined as any of the following alterations alone or in combination: *MET* amplification, chromosome 7 copy number gain above the ploidy of the rest of the genome in the same sample, *MET* kinase domain mutations, and *HGF* amplification.

[b] *MET*-independent tumours were defined as those not having the above mentioned alterations, or having *MET* alterations in combination with *FH* or *VHL* mutations.

[c] One patient had an important protocol deviation: patient was < 18 years.

[d] Only metastatic information was available for the GETUG data.

[e] One patient in the *MET*-independent category from IMDC did not have any treatment data.

the distinct underlying biology as the *MET*-independent subgroup had predominantly type II histology, which is characterised by CDKN2A silencing, as well as a CpG island methylator phenotype in some cases, both associated with poor survival and prognosis [3,16]. No differences were observed in ORR or OS between the *MET*-

Table 3
Effect of *MET* status on PFS, TTF, and OS in sunitinib-treated patients (*MET* analysis set, all lines of therapy).

	Sunitinib-treated patients					
	PFS		TTF		OS	
	MET-driven (n = 40)[a]	*MET*-independent (n = 54)[a]	*MET*-driven (n = 54)	*MET*-independent (n = 71)	*MET*-driven (n = 54)	*MET*-independent (n = 71)
Total events, n (in %)	32 (80)	46 (85)	52 (96)	66 (93)	48 (89)	62 (87)
Censored patients, n (in %)	8 (20)	8 (15)	2 (4)	5 (7)	6 (11)	9 (13)
Median (95% CI), month[b]	9.2 (5.4–13.2)	5.7 (4.3–7.4)	6.2 (4.8–10.7)	5.6 (3.5–6.5)	17.1 (12.9–21.3)	13.9 (10.8–19.5)
HR (95% CI)[c]	0.67 (0.41–1.08)		0.79 (0.54–1.14)		1.09 (0.73–1.61)	

CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; *MET* = hepatocyte growth factor receptor; OS = overall survival; PFS = progression-free survival; TTF = time to treatment failure.
[a] Date of progression not collected in IMDC data therefore patient numbers are lower for PFS compared with TTF.
[b] Calculated using the Kaplan–Meier technique; CIs were derived based on Brookmeyer–Crowley method.
[c] The analysis was performed using a Cox model using a backward selection procedure and profile-likelihood confidence limits. The final model included the variables of *MET* status, line of therapy (first versus later), and Karnofsky performance status. A HR < 1 favoured *MET*-driven disease associated with a longer PFS, TTF, or OS than *MET*-independent disease.

driven and *MET*-independent subgroups. Overall, these data suggest that *MET* may be predictive for treatment outcomes with sunitinib in locally advanced/metastatic PRCC.

The MET-TKI savolitinib is currently under clinical development for PRCC to further explore *MET* tumour inhibition in *MET*-driven diseases [12,24]. Phase II data demonstrated savolitinib activity and tolerability in patients with *MET*-driven locally advanced/metastatic PRCC and molecular characterisation of *MET* status was more predictive of response than pathological classification [19]. The phase III SAVOIR study assessing savolitinib versus sunitinib in patients with *MET*-driven PRCC was conducted at the same time as this molecular epidemiology study [15]. A key assumption for SAVOIR was that *MET*-driven status in PRCC would be associated with a negative prognosis; however, the findings from the current study suggested that this may not be the case. This led to the conclusion that a much larger SAVOIR study would be needed to detect a difference between the treatment groups, and so SAVOIR recruitment was halted prematurely [15]. Despite the lower patient numbers (60 of the planned 180 patients were recruited), outcomes from SAVOIR

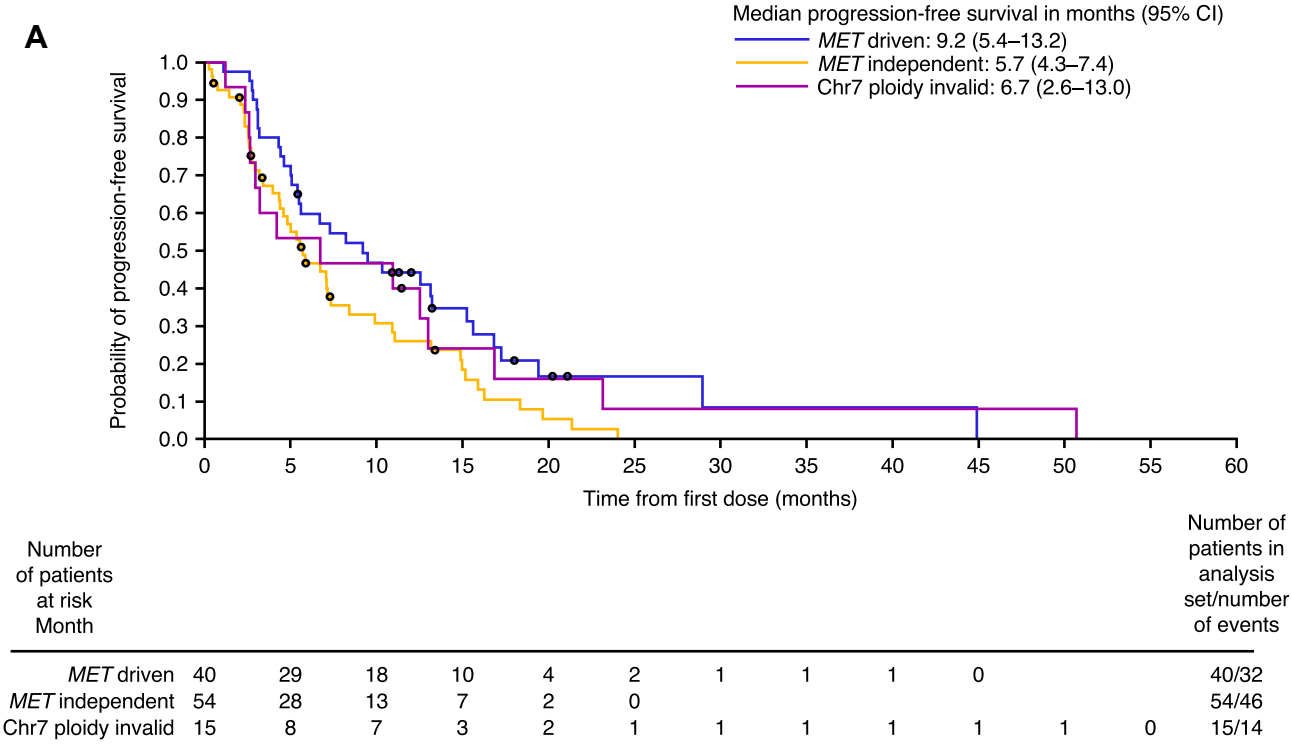

Fig. 2. Kaplan–Meier plot of (A) progression-free survival, (B) time to treatment failure, and (C) overall survival by *MET* status in sunitinib-treated patients (*MET* analysis set). Circle indicates a censored observation. Chr = chromosome; CI = confidence interval; *MET* = hepatocyte growth factor receptor.

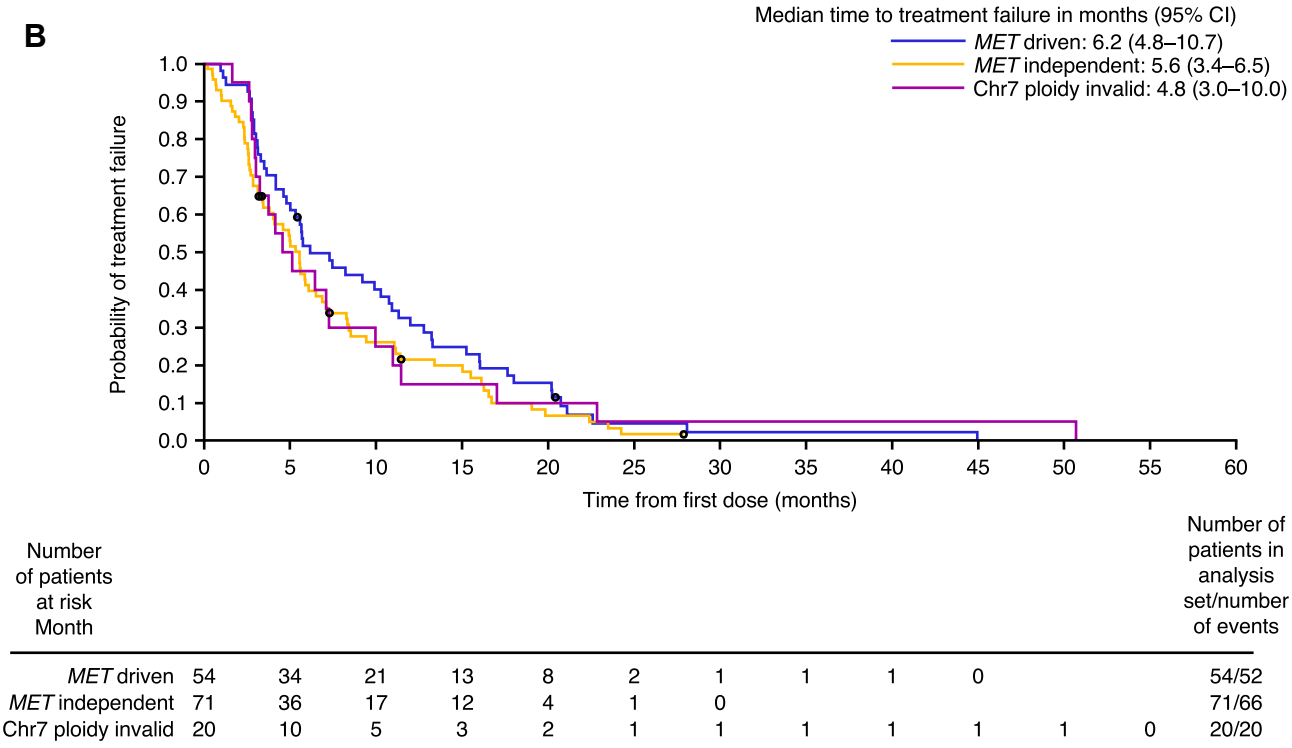

Fig. 2. (*continued*).

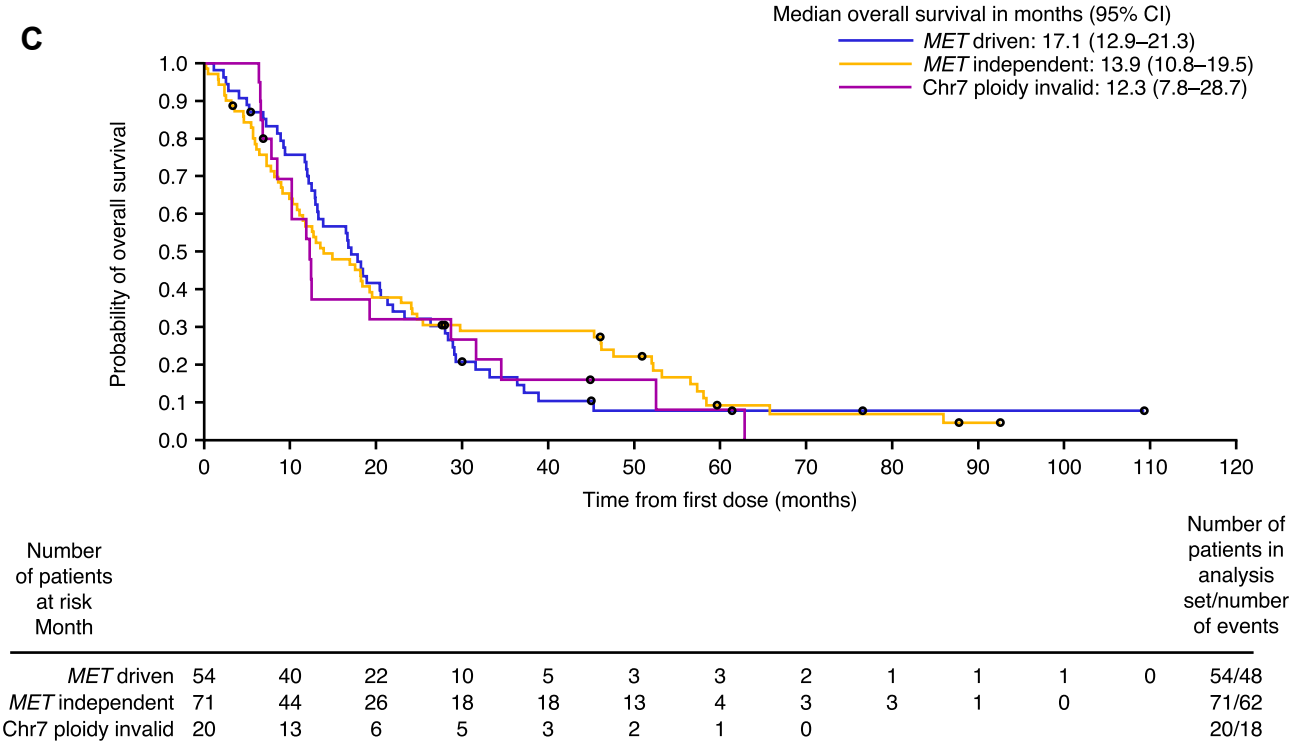

Fig. 2. (*continued*).

suggested that savolitinib had a superior safety and tolerability profile and numerically improved efficacy versus sunitinib. Median PFS was numerically higher with savolitinib (7.0 months [95% CI: 2.8–not calculated; n = 33]) versus sunitinib (5.6 months [95% CI: 4.1–6.9; n = 27]; HR = 0.71; 95% CI: 0.37–1.36; p = 0.31) and a higher ORR was observed with savolitinib (27%) versus sunitinib (7%) [15]. Further evidence suggesting that *MET* alteration status may be predictive of treatment response was observed in a phase II study of crizotinib in patients with advanced/metastatic PRCC type I (n = 23) where patients with *MET* mutations experienced a longer median treatment duration than those without (49 versus 15 weeks) [21]. Furthermore, a phase II study of foretinib (evaluable, n = 67) reported a partial response in 50% (5/10) versus 9% (5/57) of locally advanced/metastatic PRCC patients with and without a germline *MET* mutation, respectively [18].

Attempts to identify the role of immuno-oncology therapy in PRCC are also ongoing. The role of single agent programmed death-(ligand) 1 inhibitors seems to be debated in patients with metastatic PRCC with ORRs ranging from 8% to 27% [25–28]. However, immuno-oncology therapy in combination with a targeted therapy such as a MET inhibitor may have the potential to enhance the immunomodulatory role of the targeted therapy. In the phase II CALYPSO study, durvalumab in combination with savolitinib in patients with metastatic PRCC (n = 41) was associated with an ORR of 27%, and a median PFS and OS of 4.9 months (95% CI: 2.5–12.0) and 12.3 months (95% CI: 5.8–21.3), respectively [29]. Amongst patients with MET-driven disease, the combination was associated with an ORR of 57%, a median PFS and OS of 10.5 months (95% CI: 2.9–15.7) and 27.4 months (95% CI: 7.3–NR) [30]. Further investigations are therefore needed to fully characterise the utility of *MET* alterations for predicting treatment response in patients with metastatic PRCC.

Several limitations should be highlighted for this study. Real-world data generation can lack standardised imaging intervals to accurately define disease progression. The study also lacks centralised molecular pathology review. There was also a low number of patients and a short follow-up time, making it difficult to interpret PFS and ORR data. Meaningful data interpretation by line of therapy and by *MET* status was also not possible due to limited patient numbers in the second- and third-lines of treatment. It is not known whether the differences in outcome on therapy could be influenced by histology type; the greater proportion of patients with type II histology in the MET-independent group compared with the MET-dependent group (61% versus 47%) could have influenced treatment outcome. Furthermore, *MET* overexpression by immunohistochemical analysis could not be carried out due to limited tissue availability.

To our knowledge, this molecular epidemiology study is one of the largest to date and contributes to the relatively limited knowledge on the epidemiology, natural history, and treatment outcomes for locally advanced/metastatic PRCC, a rare disease without specifically approved treatments. The data demonstrate that *MET* alterations in locally advanced/metastatic PRCC may have the potential to impact treatment outcomes such as PFS and TTF, although our results showed limited effect on OS. Therefore, *MET*-driven tumours may not be prognostic for outcomes versus *MET*-independent tumours for current targeted treatments, which are not biomarker-driven.

Financial support

The study was funded by AstraZeneca.

Declaration of interests

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests:

L. Albiges reports research funding from Bristol-Myers Squibb; consultancy/advisory roles with Bristol-Myers Squibb, Novartis, Amgen, Ipsen, Roche, Pfizer, Merck, MSD, and AstraZeneca; and travel/accommodation expenses from Bristol-Myers Squibb and MSD.

D.Y.C. Heng reports receiving consulting fees and grants/funding from AstraZeneca, Pfizer, Novartis, BMS, Merck, Ipsen, Exilexis.

J.L. Lee holds ownership interest in Myovant Sciences and Black Diamond Therapeutics, reports advisory council/consultancy for MSD Korea, BMS Korea and Janssen and has received honoraria for Astellas, Sanofi Aventis, Ipsen Korea and AstraZeneca.

J.L. Lee also reports receiving grants/funding from Pfizer Korea, Roche, Genetech, Bayer, AstraZeneca, Seattle Genetics, and Janssen.

S. Walker declares employment and holds ownership interest in AstraZeneca.

A. Mellemgaard is an employee of AstraZeneca.

L. Ottesen, A. L'Hernault, J. Wessen declare employment and hold ownership interest in AstraZeneca.

M.M Frigault declares employment and holds ownership interest in AstraZeneca, and reports patent ownership.

T. Choueiri holds ownership interest in Tempest and Pionyr, reports advisory council/consultancy for KidneyCan and has received honoraria and consulting fees from Pfizer, BMS, Exelixis, Merck, EMD, Novartis, and Lilly.

T. Choueiri also reports receiving grants/funding from Pfizer, BMS, Exelixis; declares financial support from Dana-Farber/Harvard Cancer Center Kidney

SPORE (2P50CA101942-16) and Program 5P30CA006516-56, the Kohlberg Chair at Harvard Medical School and the Trust Family, Michael Brigham, and Loker Pinard Funds for Kidney Cancer Research at DFCI.

M. Cancel reports receiving consulting fees from Sanofi Aventis, and travel accommodation/expenses from Amgen and Novartis.

S. Signoretti reports receiving commercial research grants from Bristol-Myers Squibb, AstraZeneca, and Exelixis and Novartis; is a consultant/advisory board member for Merck, AstraZeneca, Bristol-Myers Squibb, CRISPR Therapeutics AG, AACR, and NCI; and receives royalties from Biogenex.

Authors' contributions

L. Albiges, D.Y.C. Heng, L. Ottesen, M.M. Frigault, T. Choueiri, M. Cancel, S. Signoretti**: Conceptualization**.

J.L. Lee, L. Ottesen, M.M. Frigault, J. Wessen, T. Choueiri, M. Cancel: **Methodology**.

J. Wessen: **Software**.

A. Mellemgaard, M. Cancel: **Validation**.

L. Albiges, D.Y.C. Heng, A. Mellemgaard, L. Ottesen, J. Wessen, S. Signoretti: **Formal analysis**.

L. Albiges, J.L. Lee, A. Mellemgaard, A. L'Hernault, M. Cancel: **Investigation**.

L. Albiges, J.L. Lee, S. Walker, T. Choueiri, M. Cancel: **Resources**.

A. Mellemgaard, J. Wessen: **Data curation**.

L. Ottesen, J. Wessen: **Visualization**.

S. Walker, A. Mellemgaard, L. Ottesen, T. Choueiri: **Supervision**.

S. Walker, T. Choueiri: **Project administration**.

T. Choueiri: **Funding acquisition**.

All authors contributed equally: **Writing - Original Draft**.

All authors reviewed the literature. All authors critically reviewed the manuscript and approved the final version for submission: **Writing - Review & Editing**.

Acknowledgments

Thanks to all the patients and their families.

The authors would like to acknowledge Vincent Haddad for assistance in study design and Remy Verheijen for assistance in data analysis.

The authors would also like to acknowledge Bernadette Tynan, MSc, of Ashfield MedComms, an Ashfield Health company, for medical writing support that was funded by AstraZeneca, Cambridge, UK in accordance with Good Publications Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.04.021.

References

[1] Bellmunt J, Dutcher J. Targeted therapies and the treatment of non-clear cell renal cell carcinoma. Ann Oncol 2013;24:1730–40.
[2] Albiges L, Flippot R, Rioux-Leclercq N, Choueiri TK. Non-clear cell renal cell carcinomas: from shadow to light. J Clin Oncol 2018;36:3624–31.
[3] Linehan WM, Spellman PT, Ricketts CJ, et al. Comprehensive molecular characterization of papillary renal-cell carcinoma. N Engl J Med 2016;374:135–45.
[4] Ljungberg B, Albiges L, Bensalah K, et al. EAU guidelines. Arnhem, The Netherlands: EAU Guidelines Office; 2019.
[5] Lee JL, Ahn JH, Lim HY, et al. Multicenter phase II study of sunitinib in patients with non-clear cell renal cell carcinoma. Ann Oncol 2012;23:2108–14.
[6] Koh Y, Lim HY, Ahn JH, et al. Phase II trial of everolimus for the treatment of nonclear-cell renal cell carcinoma. Ann Oncol 2012;24:1026–31.
[7] Ravaud A, Oudard S, De Fromont M, et al. First-line treatment with sunitinib for type 1 and type 2 locally advanced or metastatic papillary renal cell carcinoma: a phase II study (SUPAP) by the French Genitourinary Group (GETUG). Ann Oncol 2015;26:1123–8.
[8] Escudier B, Molinie V, Bracarda S, et al. Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. Eur J Cancer 2016;69:226–35.
[9] Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. Lancet Oncol 2016;17:378–88.
[10] Tannir NM, Jonasch E, Albiges L, et al. Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): a randomized multicenter phase 2 trial. Eur Urol 2016;69:866–74.
[11] Negrier S, Rioux-Leclercq N, Ferlay C, et al. Axitinib in first-line for patients with metastatic papillary renal cell carcinoma: results of the multicentre, open-label, single-arm, phase II AXIPAP trial. Eur J Cancer 2020;129:107–16.
[12] Jia H, Dai G, Weng J, et al. Discovery of (S)-1-(1-(Imidazo[1,2-a]pyridin-6-yl)ethyl)-6-(1-methyl-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazine (volitinib) as a highly potent and selective mesenchymal-epithelial transition factor (c-Met) inhibitor in clinical development for treatment of cancer. J Med Chem 2014;57:7577–89.
[13] Gavine PR, Ren Y, Han L, et al. Volitinib, a potent and highly selective c-Met inhibitor, effectively blocks c-Met signaling and growth in c-MET amplified gastric cancer patient-derived tumor xenograft models. Mol Oncol 2015;9:323–33.
[14] Hua Y, Shen L, Gan H, et al. Abstract CT305: phase I studies of a selective cMet inhibitor AZD6094 (HMPL504/volitinib) in patients with advanced solid tumors. Cancer Res 2015;75:CT305.
[15] Choueiri TK, Heng DYC, Lee JL, et al. Efficacy of savolitinib vs sunitinib in patients with MET-driven papillary renal cell carcinoma: the SAVOIR phase 3 randomized clinical trial. JAMA Oncol 2020;6:1247–55.
[16] Albiges L, Guegan J, Le Formal A, et al. MET is a potential target across all papillary renal cell carcinomas: result from a large molecular study of pRCC with CGH array and matching gene expression array. Clin Cancer Res 2014;20:3411–21.

[17] Jeffers M, Schmidt L, Nakaigawa N, et al. Activating mutations for the Met tyrosine kinase receptor in human cancer. Proc Natl Acad Sci U S A 1997;94:11445–50.

[18] Choueiri TK, Vaishampayan U, Rosenberg JE, et al. Phase II and biomarker study of the dual MET/VEGFR2 inhibitor foretinib in patients with papillary renal cell carcinoma. J Clin Oncol 2013;31:181–6.

[19] Choueiri TK, Plimack E, Arkenau HT, et al. Biomarker-based phase II trial of savolitinib in patients with advanced papillary renal cell cancer. J Clin Oncol 2017;35:2993–3001.

[20] Gan HK, Millward M, Hua Y, et al. First-in-human phase I study of the selective MET inhibitor, savolitinib, in patients with advanced solid tumors: safety, pharmacokinetics, and antitumor activity. Clin Cancer Res 2019;25:4924–32.

[21] Schoffski P, Wozniak A, Escudier B, et al. Crizotinib achieves long-lasting disease control in advanced papillary renal-cell carcinoma type 1 patients with MET mutations or amplification. EORTC 90101 CREATE trial. Eur J Cancer 2017;87:147–63.

[22] Schmidt L, Junker K, Nakaigawa N, et al. Novel mutations of the MET proto-oncogene in papillary renal carcinomas. Oncogene 1999;18:2343–50.

[23] Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30:706–20.

[24] Schuller AG, Barry ER, Jones RD, et al. The MET inhibitor AZD6094 (savolitinib, HMPL-504) induces regression in papillary renal cell carcinoma patient-derived xenograft models. Clin Cancer Res 2015;21:2811–9.

[25] Koshkin VS, Barata PC, Zhang T, et al. Clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma. J Immunother Cancer 2018;6:9.

[26] Chahoud J, Msaouel P, Campbell MT, et al. Nivolumab for the treatment of patients with metastatic non-clear cell renal cell carcinoma (nccRCC): a single-institutional experience and literature meta-analysis. Oncologist 2020;25:252–8.

[27] De Vries-Brilland M, Gross-Goupil M, Seegers V, et al. Are immune checkpoint inhibitors a valid option for papillary renal cell carcinoma? A multicentre retrospective study. Eur J Cancer 2020;136:76–83.

[28] McDermott DF, Lee JL, Ziobro M, et al. Open-label, single-arm, phase II study of pembrolizumab monotherapy as first-line therapy in patients with advanced non-clear cell renal cell carcinoma. J Clin Oncol 2021;39:1029–39.

[29] Rodriguez CS, Larkin JMG, Patel P, et al. Overall survival results for durvalumab and savolitinib in metastatic papillary renal cancer. J Clin Oncol 2020;38:619.

[30] Rodriguez CS, Larkin J, Patel PM, et al. Clinical activity of durvalumab and savolitinib in MET-driven, metastatic papillary renal cancer. J Clin Oncol 2021;39:4511.