A single-arm biomarker-based phase II trial of savolitinib in patients with advanced papillary renal cell cancer

Toni K. Choueiri[1], Elizabeth R. Plimack[2], Hendrik-Tobias Arkenau[3], Eric Jonasch[4], Daniel Y.C. Heng[5], Thomas Powles[6], Melanie M. Frigault[7], Edwin Clark[7], Amir Handzel[7], Humphrey Gardner[7], Shethah Morgan[8], Laurence Albiges[9], Sumanta Kumar Pal[10]

[1]Dana-Farber Cancer Institute, Boston, MA, USA, [2]Fox Chase Cancer Center, Philadelphia, PA, USA, [3]Sarah Cannon Research Institute, London, UK, [4]MD Anderson Cancer Center, Houston, TX, USA, [5]Tom Baker Cancer Centre, Calgary, AB, Canada, [6]Barts Cancer Institute, London, UK, [7]AstraZeneca, Waltham, MA, USA, [8]AstraZeneca, Cambridge, UK, [9]Institute Gustave Roussy, Paris, France, [10]City of Hope, Duarte, CA, USA

Background and introduction

- Renal cell carcinoma (RCC) is a heterogeneous disease of several histological subtypes with different genetic and biochemical characteristics.
  - Of the non-clear cell renal carcinomas, papillary RCC (PRCC) is the most common.[1]
- Prognosis for patients with advanced PRCC is poor, due to the limited efficacy of currently available therapies,[2, 3] which were mainly developed for clear cell RCC.
- MET and its ligand, hepatocyte growth factor, are known to play an important role in the molecular events underlying oncogenesis in PRCC.[4, 5]
- Savolitinib (AZD6094, HMPL-504, volitinib) is a potent, selective MET inhibitor which has shown activity in patients with MET-driven PRCC in a phase I study.[6]
- Here, we report results of a phase II study of savolitinib for patients with PRCC, in whom anti-tumor activity was correlated with MET pathway alterations (Clinicaltrials.gov identifier: NCT02127710).

Patients and methods

- This was a single-arm, multicenter, global, phase II study designed to evaluate the safety and efficacy of savolitinib in patients with PRCC, irrespective of prior treatment.
  - Primary objective was to assess the objective response rate (ORR) to savolitinib in all patients with PRCC and by MET status.
  - Secondary objectives included change in target lesion tumor size from baseline, progression-free survival (PFS) and duration of response (DoR).
- Key inclusion criteria included histologically confirmed locally advanced or metastatic PRCC, predicted life expectancy ≥12 weeks, age ≥18 years and adequate hematologic, hepatic and renal function.
- Exclusion criteria included prior or current MET inhibitor treatment.
- The recommended dose of savolitinib (600 mg orally QD) was given continuously until RECIST version 1.1 defined progression or treatment discontinuation criteria were met. A treatment cycle was defined as 21 days.
- MET abnormalities were centrally assessed by Next Generation Sequencing of archival tumor tissue analyzed using a targeted gene panel.[7]
- A sample size of 50 patients in the MET-driven patient population would detect an ORR >10% at a 90% two-sided confidence level with at least 80% power assuming the true response rate is 25% or better.
  - Analyses of outcome measures were descriptive and tests for significance differences were conducted between the MET-driven and MET-independent subgroups.
  - End of study for ORR was 29 January 2016; data cut-off for PFS and DoR was 27 June 2016.

Results

- Overall, 111 PRCC patients were enrolled and 109 received at least one dose of savolitinib (Table 1).
- PRCC was MET-driven in 44 (40%) patients and MET-independent in 46 (42%).
  - MET status was unknown in 19 (17%) patients.

Table 1. Patient demographics and baseline clinical characteristics

Characteristic	MET-driven (n=44)	MET-independent (n=46)	MET Unknown (n=19)	Total (N=109)
Age (years), median (range)	64 (23–87)	64 (29–75)	58 (37–80)	64 (23–87)
ECOG performance status, n (%)				
0	18 (41)	25 (54)	8 (42)	51 (47)
1	26 (59)	21 (46)	11 (58)	58 (53)
PRCC confirmation, n (%)*				
Yes	35 (80)	39 (85)	10 (53)	84 (77)
No	9 (20)	7 (15)	9 (47)	25 (23)
Renal cell classification, n (%)*				
Type 1 PRCC	12 (27)	2 (4)	2 (11)	16 (15)
Type 2 PRCC	23 (52)	37 (80)	8 (42)	68 (62)
Unclassifiable	9 (20)	7 (15)	9 (47)	25 (23)
Tumor grade, n (%)*†				
Low	0 (0)	4 (9)	1 (5)	5 (5)
Intermediate	8 (18)	11 (24)	5 (26)	24 (22)
High	12 (27)	15 (33)	4 (21)	31 (28)
Missing	24 (55)	16 (35)	9 (47)	49 (45)
MSKCC risk group, n (%)				
Favorable risk	3 (7)	10 (22)	2 (11)	15 (14)
Intermediate risk	28 (64)	14 (30)	7 (37)	49 (45)
Poor risk	2 (5)	4 (9)	4 (21)	10 (9)
Missing	11 (25)	18 (39)	6 (32)	35 (32)
Number of prior systemic therapies, n (%)				
0	26 (59)	23 (50)	11 (58)	60 (55)
1	12 (27)	10 (22)	3 (16)	25 (23)
2	3 (7)	5 (11)	2 (11)	10 (9)
≥3	3 (7)	8 (17)	3 (16)	14 (13)
Prior immunotherapy, n (%)	6 (14)	3 (7)	1 (5)	10 (9)
Prior radiotherapy, n (%)	9 (20)	10 (22)	3 (16)	22 (20)
Prior surgery, n (%)				
Nephrectomy	32 (73)	35 (76)	13 (68)	80 (73)
Lymphadenectomy	8 (18)	9 (20)	1 (5)	18 (17)
Adrenalectomy	4 (9)	4 (9)	2 (11)	10 (9)

*Based on central laboratory data. †Modified Fuhrman nuclear grade, low = grade 1 or 2, intermediate = grade 3 and high = grade 4. Percentages may not total 100% due to rounding. ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center.

Efficacy: Objective disease response

- In patients with MET-driven PRCC, 27 (61%) experienced some tumor shrinkage vs nine (20%) patients with MET-independent PRCC (Figure 1).
- All eight patients with a partial response (PR) had MET-driven PRCC, an ORR of 18% in this subset.
- Twenty-two (50%) patients with MET-driven PRCC achieved stable disease (SD).
- Overall in this study, eight (7%) patients had a confirmed PR and 38 (35%) had SD, Table 2. No complete responses were reported.

Figure 1. Best percentage change in tumor size from baseline according to MET status.

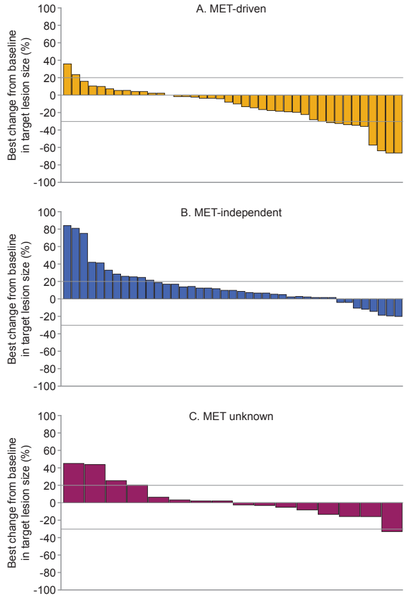


Table 2. Tumor responses in the overall treatment population and by MET status

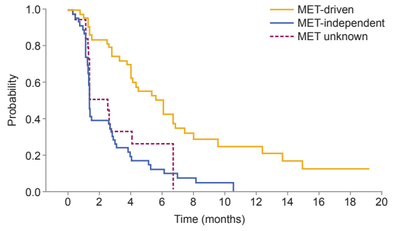
RECIST response, n (%)	MET-driven (n=44)	MET-independent (n=46)	MET Unknown (n=19)	Total (N=109)
PR†	8 (18)*	0 (0)	0 (0)	8 (7)
SD	22 (50)	11 (24)	5 (26)	38 (35)
PD	11 (25)	28 (61)	9 (47)	48 (44)
NE	3 (7)	7 (15)	5 (26)	15 (14)

*p=0.002 vs MET-independent subgroup (Fisher exact test). Responses assessed according to RECIST version 1.1. †Unconfirmed responses excluded. PD, progressive disease; NE, not evaluable.

Secondary efficacy endpoints

- In the treatment population, 82 (75%) patients progressed, died or discontinued therapy, and 27 (25%) continued to receive study drug or remained in follow-up at end of study.
- As of June 2016, patients with MET-driven PRCC had significantly longer median PFS than those with MET-independent disease: 6.2 (95% confidence interval [CI]: 4.1–7.0) months vs 1.4 (95% CI: 1.4–2.7) months, respectively (hazard ratio=0.33 [95% CI: 0.20–0.52]; p<0.0001, Figure 2).
- Of the eight patients exhibiting a PR, six were still responding to treatment at data cut-off, with a DoR of 2.4–16.4 months (median DoR not yet reached, 25th percentile is 4.2 months).
- 41 (38%) patients had died at time of data cut-off; overall survival data are currently not mature.

Figure 2. Kaplan-Meier estimates of PFS in patients with PRCC by MET status



Time (months)	0	1.4	2.8	4.1	5.5	6.9	8.3	9.7	11.1	12.5	13.9	15.2	16.6	18.0	19.4
No. at risk															
MET-independent	46	30	15	8	4	3	2	1	0						
MET-driven	44	39	29	20	13	9	6	6	4	3	3	3	0		
MET unknown	19	13	3	2	1	0									

Safety and tolerability

- The most common treatment-related adverse events (AEs) were nausea, fatigue and vomiting with the majority of events being grade 1–2 (Table 3).
  - Abnormal liver function tests were reported in 20% of patients.

Table 3. Overall incidence of AEs and those considered related to savolitinib treatment occurring in ≥5% of patients

AE, n (%)*	Treatment population (N=109)		
	Grade 1–2	Grade ≥3	Total
Any AE	57 (52)	51 (47)	108 (99)
Any treatment-related AE†	75 (69)	21 (19)	96 (88)
Any SAE			23 (21)
Death Related to PRCC or disease progression Considered treatment-related			 32 (29) 1 (<1)
Treatment discontinuation Due to any AE Due to any SAE Dose reduction due to any AE			 9 (8) 3 (3) 14 (13)
AEs considered treatment-related occurring in ≥5% of patients†	**Grade 1–2**	**Grade ≥3**	**Total**
Nausea	42 (39)	(0)	42 (39)
Fatigue	21 (19)	2 (2)	23 (21)
Vomiting	18 (17)	1 (<1)	19 (17)
Peripheral edema	17 (16)	1 (<1)	18 (17)
AST increased	9 (8)	3 (3)	12 (11)
Blood creatinine increased	12 (11)	0 (0)	12 (11)
ALT increased	7 (6)	5 (5)	11 (10)
Decreased appetite	10 (9)	1 (<1)	11 (10)
Diarrhea	9 (8)	0 (0)	9 (8)
Anemia	6 (6)	1 (<1)	7 (6)
Constipation	7 (6)	0 (0)	7 (6)
Dysgeusia	7 (6)	0 (0)	7 (6)
Mucosal inflammation	6 (6)	0 (0)	6 (6)
Proteinuria	5 (5)	1 (<1)	6 (6)
Stomatitis	5 (5)	0 (0)	5 (5)
Hyponatremia	2 (2)	3 (3)	5 (5)
Pruritus	5 (5)	0 (0)	5 (5)

*Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. †As assessed by the investigator. Grade of AEs reported according CTCAE version 4.03.

- A serious AE (SAE) occurred in 23 (21%) patients; three patients had four SAEs considered related to treatment;
  - Pneumonitis (grade 3), elevated transaminases (grade 4) and drug-induced liver injury (grade 4), each in one patient.
- There was one death due to hepatic encephalopathy.
- A total of 13 AEs in nine (8%) patients led to drug discontinuation.
  - Alanine aminotransferase (ALT) and peripheral edema (both in two patients) and individual events of increased aspartate aminotransferase (AST), proteinuria, pain, nausea, vomiting, fatigue and embolism.
- Fourteen patients (13%) had dose reductions due to an AE at some time during the study.

Summary and conclusions

- Savolitinib selectively inhibits MET-driven tumor progression in PRCC patients, with eight of 44 (18%) patients in this subgroup achieving a PR.
- PFS was significantly longer in patients with MET-driven PRCC compared with MET-independent disease (6.2 versus 1.4 months, respectively (p<0.0001).
- Treatment with savolitinib was generally well tolerated, with the majority of AEs being grade 1 or 2.
  - The three most common AEs were nausea, fatigue and vomiting.
  - The safety profile of savolitinib is broadly similar to other multikinase inhibitors in patients with RCC.[8-10]
- These data support the hypothesis that savolitinib has anti-tumor activity in patients with MET-driven PRCC.
  - MET status was more predictive of response to savolitinib in this study than classification of PRCC based on pathology e.g. Type 1 or 2.
- Further clinical investigation of savolitinib in this subgroup is warranted.

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