Clinical Trials: Targeted Therapy

Clinical Cancer Research

First-in-Human Phase I Study of the Selective MET Inhibitor, Savolitinib, in Patients with Advanced Solid Tumors: Safety, Pharmacokinetics, and Antitumor Activity

Hui K. Gan[1,2,3], Michael Millward[4], Ye Hua[5], Chuan Qi[5], Yang Sai[5], Weiguo Su[5], Jian Wang[5], Lilin Zhang[5], Melanie M. Frigault[6], Shethah Morgan[7], Liu Yang[8], and Jason D. Lickliter[9,10]

Abstract

Purpose: Aberrant activation of MET (hepatocyte growth factor receptor) signaling is implicated in the tumorigenesis of human cancers. This phase I study assessed the safety, tolerability, and MTD of the potent and selective MET inhibitor, savolitinib (AZD6094, HMPL-504, volitinib).

Patients and Methods: This open-label, multicenter dose-escalation and -expansion study evaluated oral savolitinib for patients with locally advanced or metastatic solid tumors. A 3 + 3 design assessed repeated daily (QD) and twice daily (BID) dosing schedules. The dose-expansion phase included 12 patients. Primary objectives were to evaluate the safety, tolerability, MTD, and dose-limiting toxicities (DLT) of savolitinib. Secondary and exploratory objectives included pharmacokinetics, biomarker research, and antitumor activity.

Results: Overall, 48 patients were enrolled. Four patients had DLTs following QD savolitinib (600 mg $N = 1$, 800 mg $N = 1$, and 1,000 mg $N = 2$); the MTD was 800 mg QD and not reached for BID dosing. The recommended phase II dose (RP2D) was 600 mg QD. The most frequent adverse events were nausea (30 patients, 63%), vomiting (20 patients, 42%), fatigue (20 patients, 42%), and peripheral edema (15 patients, 31%). At 600 mg QD, C_{max} was 2,414.8 ng/mL, AUC was 17053.9 h·ng/mL, and there was no apparent drug accumulation. Three patients with papillary renal cell carcinoma (PRCC) and MET aberrations had partial responses with durations from 39 to 147 weeks.

Conclusions: The tolerability profile of savolitinib was acceptable and the RP2D was established as 600 mg QD. Preliminary antitumor activity was demonstrated supporting further study in patients with PRCC.

Introduction

MET [hepatocyte growth factor (HGF) receptor] is a key regulator of angiogenesis, cell survival, invasion, and proliferation and is expressed on the epithelial cells in numerous organs including the kidney, bone marrow, and liver (1). Dysregulation of the HGF/MET signaling pathway has been implicated in the tumorigenesis of a variety of human cancers (2). Binding of the ligand HGF to its receptor activates the MET tyrosine kinase, leading to the initiation of a cascade of downstream signals including activation of the Ras/Raf/MEK/ERK and PI3K/Akt pathways (1). Activating MET mutations and *MET* gene amplification have been reported in various malignancies including gastric carcinomas, gliomas, and prostate cancer (3–5). *MET* amplification is also a potential mechanism for the development of treatment resistance of [EGFR-mutant non–small-cell lung cancer (NSCLC) with the EGFR inhibitors, erlotinib, gefitinib, and osimertinib (3, 6, 7)]. Recent studies have also linked MET dysregulation with papillary renal cell carcinoma (PRCC; refs. 8–10).

Various strategies to inhibit the HGF/MET signaling pathway have been explored. mAbs directed against HGF and MET, such as rilotumumab, onartuzumab, and emibetuzumab have demonstrated antitumor activity in early-phase clinical trials (11, 12). Further developments include the small-molecule tyrosine kinase inhibitors crizotinib, cabozantinib, and foretinib, multikinase inhibitors that inhibit a number of intracellular pathways, including MET (13–15).

Savolitinib (previously referred to as AZD6094, HMPL-504 and volitinib) is a potent and highly selective small-molecule inhibitor of MET tyrosine kinase (16). Savolitinib effectively inhibited the *in vitro* activity of recombinant MET (IC_{50} value of 4 nmol/L) and the *in vitro* growth of gastric cell lines with dysregulated MET signaling (17). Also, MET signaling was reduced and tumor regression observed following savolitinib treatment of *in vivo*

[1]Department of Medical Oncology, Austin Health and Olivia Newton-John Cancer Research Institute, Melbourne, Victoria, Australia. [2]School of Cancer Medicine, La Trobe University School of Cancer Medicine, Melbourne, Australia. [3]Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia. [4]University of Western Australia, Perth, Australia and Linear Clinical Research, Perth, Australia. [5]Hutchison MediPharma Ltd, Shanghai, P.R. China. [6]Oncology Translational Science, IMED Biotech Unit, AstraZeneca, Boston, Massachusetts. [7]AstraZeneca, Cambridge, United Kingdom. [8]AstraZeneca, Shanghai, P.R. China. [9]Monash Medical Center, Bentleigh East, Victoria, Australia. [10]Nucleus Network, Melbourne, Victoria, Australia.

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Corresponding Author: Hui K. Gan, Olivia Newton-John Cancer Research Institute, Melbourne, Victoria 3084, Australia. Phone: 613-9496-9925; Fax: 613-9457-6698; E-mail: hui.gan@onjcri.org.au

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Translational Relevance

This first-in-human study of savolitinib (previously referred to as AZD6094, HMPL-504, and volitinib) in patients with advanced solid malignancies established the recommended dose as 600 mg QD and confirmed the observed safety profile was as expected for the drug based on its pharmacology. Evidence of antitumor activity with savolitinib was seen in some patients, in particular, three partial responses were observed among patients with PRCC, which tested positive for *MET* gene copy number gain. A phase II trial of savolitinib in patients with advanced or metastatic PRCC including analysis of treatment response by MET status biomarker was conducted on the basis of the data presented here (ClinicalTrials.gov identifier: NCT02127710) and has been published [Choueiri TK, et al. J Clin Oncol 2017;35 (26):2993—3001] and a phase III trial to assess the efficacy and safety of savolitinib versus sunitinib in patients with MET-driven, unresectable and locally advanced, or metastatic PRCC is underway (ClinicalTrials.gov identifier: NCT03091192).

human xenograft tumor models of MET-amplified gastric cancer and PRCC (17, 18).

We present the results of the first-in-human phase I trial of savolitinib in patients with advanced solid tumors. The study was designed to evaluate the safety, tolerability, and MTD of savolitinib, with the additional exploratory objectives of evaluating pharmacokinetics, biomarker research, and antitumor activity.

Patients and Methods

Study design and objectives

This was a phase I, open-label, multicenter dose-escalation and -expansion study of oral savolitinib in patients with locally advanced or metastatic solid tumors (ClinicalTrials.gov identifier: NCT01773018). The dose-escalation phase (Fig. 1) determined the MTD. The starting dose of 100 mg was chosen based on preclinical studies of savolitinib. The study utilized a 3 + 3 design with a total of nine cohorts. The initial cohorts received a single dose of savolitinib (100, 200, 400, 600, 800, or 1,000 mg) followed by a 7-day wash-out period, prior to starting repeated once daily (QD) dosing. Twice daily (BID) dosing of savolitinib was also assessed (300, 400, and 500 mg), exploring total daily doses between 600–1,000 mg. The duration of each continuous treatment cycle was 21 days. Following determination of the MTD, the dose-expansion phase commenced with the enrollment of 12 additional patients (Fig. 1).

Patients who completed the first treatment cycle and dose-limiting toxicity (DLT) observation period were considered to have completed the trial. After completion of the first cycle, patients with acceptable toxicity and ongoing clinical benefit could continue to receive savolitinib for up to 1 year or longer, at the discretion of the investigator and with the sponsor's agreement.

The primary objectives were to evaluate the safety, tolerability, MTD, and DLTs of savolitinib. The secondary objective was to describe the pharmacokinetics of savolitinib. Exploratory objectives included assessment of antitumor activity and collection of tumor biopsies and blood samples for biomarker and mutation analysis.

Patients

Eligible patients had a histologically or cytologically documented, incurable, locally advanced or metastatic solid tumor that had either progressed, failed to respond to standard systemic therapy, or had no standard or effective existing therapy. Other important eligibility criteria included the following: adults $\geq$18 years of age and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with poor hematologic status, who were pregnant, had received cancer treatment within 4 weeks of the first dose of savolitinib, had a history of significant liver disease, had previous or current exposure to a MET inhibitor, were excluded. Patients with poor liver or renal function were also excluded. Poor liver function was defined as total bilirubin >1.5$\times$ the upper limit of normal (ULN) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >2.5$\times$ ULN (patients with Gilbert disease and serum bilirubin levels $\leq$3$\times$ ULN and normal AST, ALT) could be enrolled and patients with documented liver metastases could have AST and/or ALT levels $\leq$5$\times$ ULN at screening]. Poor renal function was defined as serum creatinine >1.5$\times$ ULN (patients with a creatinine clearance of $\geq$50 mL/minute based on a documented 24-hour urine collection were eligible). The protocol did not mandate specific tumor types or evidence of MET dysregulation at baseline. However, patients with PRCC, NSCLC, colorectal cancer (for whom EGFR inhibitors had failed), breast cancer, and hepatocellular carcinoma were preferred for enrollment during the dose-expansion phase. A later protocol amendment (August 14, 2014) restricted the patient population of this phase to patients with cancers associated with MET dysregulation using local MET FISH testing for *MET* gene copy number gains.

All patients provided written, informed consent prior to participating in the study. The study was performed in accordance with ethical principles that originate from the Declaration of Helsinki and were consistent with International Committee on Harmonisation Good Clinical Practice guidelines, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. The protocol was reviewed and approved by the Human Research Ethics Committee at each study site. The first patient was enrolled on February 15, 2012 and the last patient completed the study on December 23, 2015.

Safety assessments

All adverse events (AE) during this study, including those leading to determination of DLTs, were graded according to the NCI Common Terminology Criteria for Adverse Events (Version 3.0). All AEs and serious AEs (SAE) were collected from the first study dose of savolitinib until 30 days after the last dose of savolitinib or study discontinuation/termination, whichever was later. A DLT was defined as one of the following toxicities: any nonhematologic toxicity $\geq$grade 3, grade 4 neutropenia lasting >7 days, febrile neutropenia [defined as absolute neutrophil count (ANC) <1,000 cells/mm^3 and fever $\geq$38.5°C or documented infection $\geq$grade 3 with ANC $\leq$1,000 cells/mm^3], grade 4 thrombocytopenia (lasting >48 hours or requiring intervention or associated with increased bleeding), and dose interruption for >14 days due to toxicity. The MTD was defined as the maximum dose at which no more than one of six patients in a single cohort experienced a DLT in the first cycle.

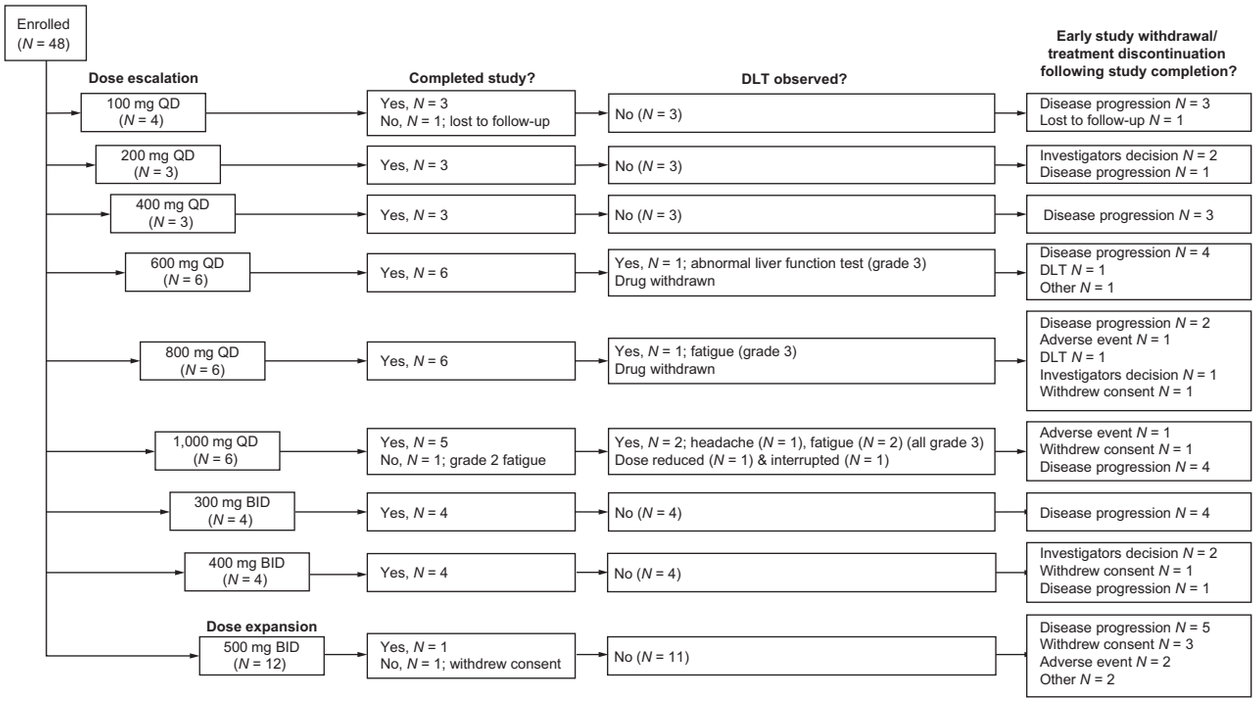

Figure 1.

Patient disposition (dose escalation and expansion). The study followed a 3 + 3 design with each cohort containing between 3 and 6 patients and a total of 48 patients being treated. The DLT observation period was 21 days. The decision to escalate dosing was decided based upon the review of any observed DLTs.

Medical, surgical, and demographic history were collected at screening. Vital signs, physical examinations, 12-lead electrocardiogram, and all clinical laboratory tests were recorded at screening and various time points throughout cycles 1–3 and every second cycle thereafter until study completion or early termination.

Pharmacokinetic assessments

Blood samples were taken to determine the plasma concentrations of savolitinib and its metabolites analyzed using a prevalidated LC/MS-MS assay. Samples were collected predose and at 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 30, and 48 hours postdose following single doses. For multiple doses, samples were collected on days 1, 8, 15, and 21 [predose and at 0.5, 2, 4, 6, 8, and 12 (BID) or 24 (QD) hours postdose, with the 12 (BID) or 24 (QD) hour sample being taken prior to the next dose]. Pharmacokinetic values were processed according to standard noncompartmental analytical procedures, using Phoenix WinNonlin v6.4 (Pharsight Corporation) and Microsoft Excel 2010 (Microsoft Corporation) software. The plasma concentration–time profile was used to determine pharmacokinetic parameters for savolitinib and the two major metabolites, M2 (active, with a potency 3–6-fold less than savolitinib for p-MET inhibition and tumor cell growth inhibition in a variety of tumor cells with MET amplification) and M3 (inactive), including area under the plasma concentration–time curve (AUC), maximum plasma concentration (C_{max}), oral clearance (CL/F), apparent volume of distribution (Vd/F), time to reach C_{max}, accumulation ratio, and elimination half-life ($t_{1/2}$).

Antitumor activity

Tumor assessments were performed according to RECIST (Version 1.0) at screening, the start of cycle 3, and every second cycle thereafter until savolitinib discontinuation. The objective tumor response for target and nontarget lesions was assessed using the RECIST criteria of complete response (CR), partial response (PR), incomplete response/stable disease (SD), and progressive disease (PD). Progression-free survival (PFS) was defined as the length of time from the date of the first dose of savolitinib until the earliest date of disease progression or death (from any cause). Antitumor activity was assessed in all patients with at least one postbaseline tumor assessment (tumor evaluable population).

Biomarker analyses

MET status was assessed as a retrospective exploratory analysis using formalin-fixed paraffin-embedded (FFPE) archival tissue. *MET* gene copy number and MET mutations were determined by using DNA next-generation sequencing (NGS; Foundation Medicine Inc) and amplifications were confirmed with MET FISH (Abbott Probe). Archival tumor FFPE sections were also analyzed by IHC for total MET protein expression (Ventana SP144 Ab).

Statistical considerations

The study had a planned enrollment of approximately 44–56 patients, with 34–46 patients in the dose-escalation stage and approximately 10 patients in the dose-expansion stage. Descriptive statistics were used to measure the safety, pharmacokinetics, and preliminary signs of activity of savolitinib. The safety population consisted of all the enrolled patients who received at least one dose of savolitinib. All patients had samples taken and

measured for pharmacokinetics. Analysis of antitumor response was performed on the tumor evaluable population (all patients with at least one postbaseline tumor assessment). PFS was analyzed using the Kaplan–Meier method.

Results

Patient population and drug exposure

A total of 48 patients were enrolled and 45 patients (94%) completed the study (first treatment cycle; 21 days). Three patients (6%) did not complete the study due to withdrawal of consent ($N = 1$), grade two fatigue ($N = 1$), and lost to follow-up ($N = 1$; Fig. 1). The majority of patients (85%) had metastatic disease and the most common primary tumor locations were the kidney ($N = 18$; 38%) and large bowel ($N = 9$; 19%; Table 1).

After study completion, the primary subsequent reason for savolitinib discontinuation was radiologically confirmed disease progression (27 patients, 56%). Other reasons were withdrawal of consent (6 patients, 12.5%), investigator decision (5 patients, 10.4%: 3 patients with suspected disease progression, 1 patient with worsening liver function tests due to biliary obstruction by the tumor, and 1 patient with a growing tumor and problematic nausea), AEs (4 patients, 8.3%), DLT (2 patients 4.2%), lost to follow-up (1 patient, 2.1%) and other (3 patients, 6.3%: 2 patients with suspected disease progression and 1 patient due to sponsor ending study). Patients with suspected disease progression were withdrawn on clinical grounds before radiological progression. There appeared to be no relationship between the savolitinib dose and frequency of study withdrawal or treatment discontinuation following study completion (Fig. 1).

Safety

No immediate DLTs were observed following a single dose of savolitinib of between 100 and 1,000 mg (followed by a 7-day wash-out period). In the subsequent QD dosing cohorts that began treatment 1 week after the single dose of savolitinib, five grade 3 DLTs, all considered related to treatment, were experienced by 4 patients (8%); fatigue ($N = 1$ at 800 mg QD, $N = 2$ at 1,000 mg QD), headache ($N = 1$ at 1,000 mg QD), and abnormal liver function test (increased AST and ALT; $N = 1$ at 600 mg QD; Fig. 1). When considering any treatment-emergent AE (TEAE), whether or not related to study treatment, QD dosing resulted in withdrawal of savolitinib in 10 patients (21%) and dose interruption or reduction in 17 patients (35%). Treatment modification due to a grade 3 TEAE occurred in 9 patients who experienced 14 events, of which eight were considered possibly or probably related to savolitinib. The MTD of savolitinib was determined to be 800 mg QD. For BID dosing, there were no DLTs observed up to 500 mg BID (total daily dose 1,000 mg), and it was considered therapeutically unnecessary to proceed with further dose escalation. Therefore, the MTD for BID dosing was not reached.

TEAEs occurring in ≥5% of patients, whether or not considered related to savolitinib treatment, are shown in Table 2. Of those AEs considered related to savolitinib, the most common were nausea (28 patients, 58%), fatigue (18 patients, 38%), vomiting (16 patients, 33%), peripheral edema (11 patients, 23%), and diarrhea (6 patients, 13%). Overall, 29 patients (60%) experienced an AE ≥grade 3, including increased ALT ($N = 4$), increased AST ($N = 3$), and fatigue ($N = 3$; Table 2). In determining the recommended phase II dose (RP2D), the incidence of TEAEs ≥grade 3 was considered. These were 7 events in 4 patients (57%) at 600 mg QD, 7 events in 5 patients (71%) at 800 mg QD, and 18 events in 11 patients (92%) at 500 mg BID. In addition, there were five events of abnormal liver function test that occurred in the 500 mg BID cohort outside of the DLT period. Consequently, the RP2D was determined to be 600 mg QD.

AEs ≥grade 3 considered related to savolitinib are shown by dose in Table 3 and SAEs are shown in Supplementary Table S1. A total of 19 patients (40%) reported 29 SAEs. Five SAEs were considered probably related to savolitinib: abnormal liver function test (two events) and individual events of increased ALT, pyrexia, and fatigue. Two further SAEs, small intestinal obstruction and pyrexia, were considered possibly drug related. The frequency of SAEs did not appear to be clearly related to the dose of study drug (Table 3). Seven patients each experienced one grade 4 AE; five events were considered probably not drug related and two events, increased ALT and abnormal liver function test, were considered probably drug related. Three patients (6%) died during the study as a result of disease progression.

Table 1. Demographic and baseline characteristics

	Safety population ($N = 48$)
Mean age, years (SD)	60.0 (11.9)
Gender (female), *N* (%)	19 (40)
Ethnicity, *N* (%)	
Asian	5 (10)
Caucasian	43 (90)
ECOG performance status	
0	24
1	24
Primary cancer diagnosis, *N* (%)	
Renal cell carcinoma	
Papillary	14 (29)
Clear cell	3 (6)
Translocation Xp11	1 (2)
Colorectal	9 (19)
Gastric	3 (6)
Mesothelioma	3 (6)
Non–small-cell lung carcinoma	3 (6)
Thyroid	3 (6)
Pancreatic	2 (4)
Other tumors[a]	7 (15)
Prior anticancer treatment (yes), *N* (%)	34 (71)

[a]Primary cancer diagnosis: adenoid cystic carcinoma, breast cancer, gallbladder cancer, melanoma, ovarian cancer, thymic carcinoma, and adenocarcinoma of unknown primary (each $N = 1$).

Pharmacokinetics

Following a single oral dose of savolitinib, $t_{1/2}$ (geometric mean) ranged from 3.77 hours (200 mg, $N = 3$) to 6.80 hours (800 mg, $N = 6$; Fig. 2A), the geometric mean CL/F ranged from approximately 32.95 L/h to 48.33 L/h and the apparent Vd/F was approximately 227.64 to 325.41 L. The geometric mean $t_{1/2}$, C_{max}, and AUC to the last detectable concentration are shown for single doses as well as repeated QD and BID dosing in Supplementary Table S2. QD dosing (100–1,000 mg) and BID dosing (300 mg and 400 mg) did not lead to accumulation of savolitinib. At 500 mg BID, some accumulation of savolitinib was observed (accumulation ratios were 1.312 and 1.420 for days 15 and 21, respectively). Formation of the two major metabolites, M2 (active) and M3 (inactive), occurred rapidly and the elimination

Table 2. TEAEs reported by ≥5% patients as grade 1–2, ≥grade 3, or any grade overall and considered related to savolitinib treatment

	Safety population ($N = 48$)					
AE, *N* (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any grade considered related to treatment[a]**
Any TEAE	47 (98)	33 (69)	27 (56)	7 (15)	1 (2)	38 (79)
	Grade 1–2		**Grade ≥3**			**Any grade considered related to treatment[a]**
Any SAE (including death)	2 (4)[b]		17 (35)			6 (13)
Treatment discontinuation due to any AE	2 (4)[b]		8 (17)			–
Dose modification due to any AE	6 (13)		11 (23)			–
TEAEs reported by ≥5% patients						
Nausea	30 (63)		0			28 (58)
Vomiting	20 (42)		0			16 (33)
Fatigue	17 (35)		3 (6)			18 (38)
Peripheral edema	13 (27)		2 (4)			11 (23)
Constipation	14 (29)		0			1 (2)
Diarrhea	11 (23)		0			6 (13)
Chest pain	8 (17)		1 (2)			0
Decreased appetite	8 (17)		0			6 (13)
Upper respiratory tract infection	6 (13)		0			0
Dizziness	6 (13)		0			1 (2)
Headache	5 (10)		1 (2)			2 (4)
Cough	6 (13)		0			1 (2)
Deep vein thrombosis	1 (2)		5 (10)			0
Abdominal pain	5 (10)		0			0
Arthralgia	5 (10)		0			0
Pyrexia	1 (2)		3 (6)			2 (4)
Urinary tract infection	3 (6)		1 (2)			0
ALT increased	0		4 (8)			2 (4)
AST increased	1 (2)		3 (6)			2 (4)
Insomnia	3 (6)		1 (2)			0
Dyspnea	4 (8)		0			2 (4)
Erythema	4 (8)		0			0
Gastro-esophageal reflux disease	3 (6)		0			0
Edema	3 (6)		0			4 (8)
Blood creatinine increased	3 (6)		0			1 (2)
Back pain	3 (6)		0			0
Rash	3 (6)		0			2 (4)

[a]Events considered possibly or probably related to study treatment.
[b]Grade 1–2 AEs considered serious were one instance each of scrotal edema and pyrexia, which led to interruption or withdrawal of savolitinib dosing.

half-lives of these two metabolites were similar to that of the parent compound. Figure 2B shows the mean concentration of savolitinib over time following repeated QD dosing.

Antitumor activity

In the tumor evaluable population ($N = 39$), 3 patients achieved a PR (8%; Fig. 3A). Nineteen patients (49%) had a best response of SD. Fifteen patients (39%) had PD and 2 patients (5%) had no evaluable lesions. The 3 patients who achieved a PR all had PRCC, with 2 patients receiving 600 mg QD and 1 patient 1,000 mg QD (Supplementary Fig. S1 shows tumor response in 1 patient treated with 600 mg QD). The PRs were durable with 1 patient (*MET* focal amplification) remaining on study for 75 weeks and 2 patients (chromosome 7 gain) for 39 and 147 weeks.

Table 3. Summary of AEs ≥grade 3 by dose considered related to study treatment

AE, *N* (%)	**100 mg QD ($N = 4$)**	**200 mg QD ($N = 3$)**	**400 mg QD ($N = 5$)**	**600 mg QD ($N = 7$)**	**800 mg QD ($N = 7$)**	**1,000 mg QD ($N = 6$)**	**Total QD ($N = 32$)**	**300 mg BID ($N = 4$)**	**400 mg BID ($N = 4$)**	**500 mg BID ($N = 12$)**	**Total BID ($N = 20$)**	**Safety population ($N = 48$)**
Fatigue	0	0	0	0	1	2	3 (6)	0	0	0	0	3 (6)
Edema peripheral[a]	0	0	1	1	0	0	2 (4)	2	0	0	2 (4)	4 (8)
Liver function test abnormal[b]	0	0	0	1	0	0	1 (2)	0	0	5[c]	5 (10)	6 (12)
Pyrexia	0	0	0	1	0	0	1 (2)	1[d]	0	0	1 (2)	2 (4)
Headache	0	0	0	0	0	1	1 (2)	0	0	0	0	1 (2)
Lymphopenia	0	0	0	1	0	0	1 (2)	0	0	0	0	1 (2)
Small intestinal obstruction	0	0	0	0	1	0	1 (2)	0	0	0	0	1 (2)

[a]Includes penile edema ($N = 1$), swelling ($N = 1$), and edema peripheral ($N = 2$).
[b]Includes ALT increased ($N = 2$), AST increased ($N = 2$), and abnormal liver function test ($N = 2$).
[c]One patient had a grade 4 event of ALT increased that after 7 days of onset reduced to a severity of grade 3; this event has only been counted once in this table.
[d]Patient was receiving reduced dosing (200 mg BID) at time of event.

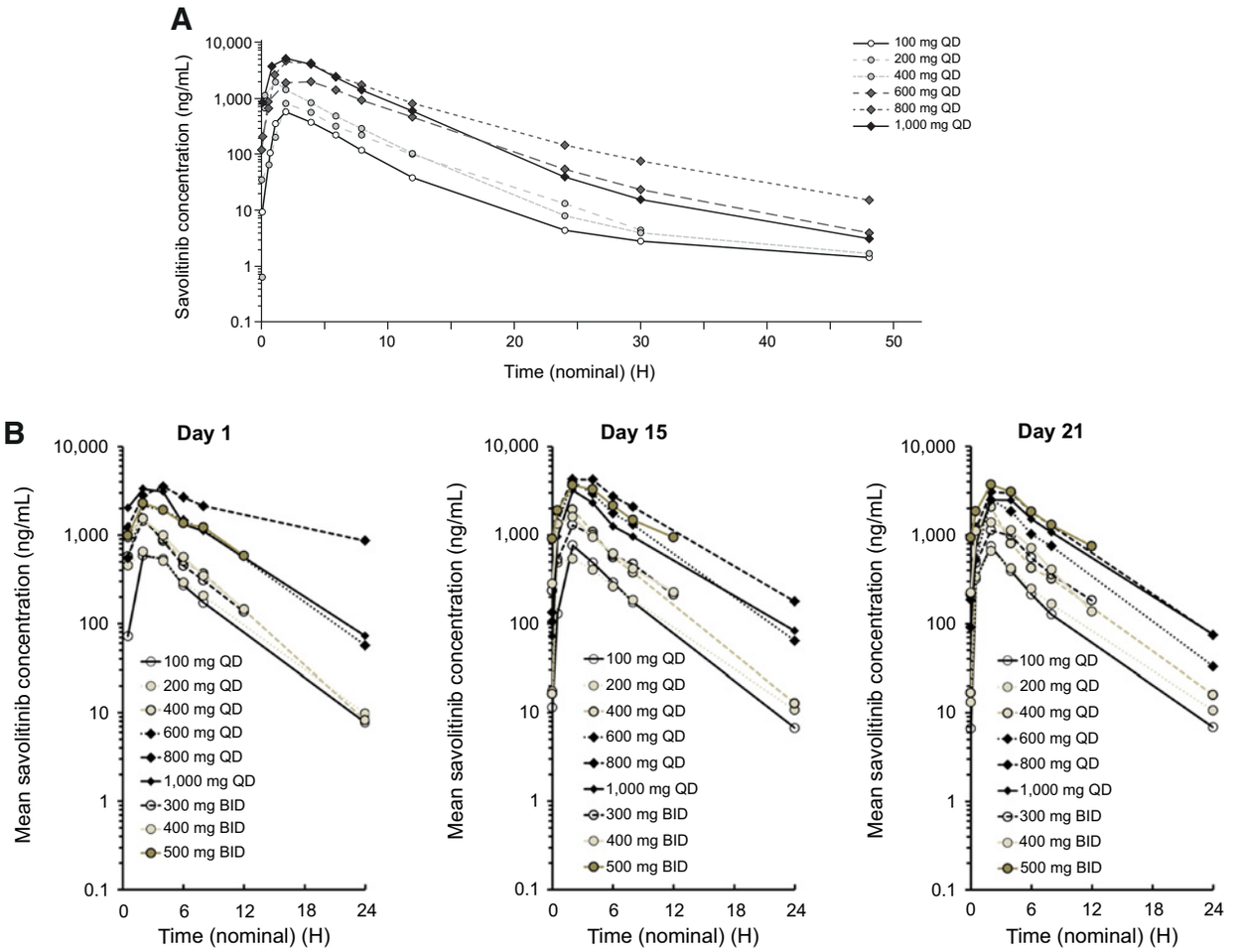

Figure 2.

Plasma concentration–time of savolitinib after a single dose of savolitinib (followed by ≥7-day wash-out period) at 100–1,000 mg (**A**) and following repeated QD dosing (**B**). Savolitinib reached peak concentration levels by 5 hours following administration. Concentration of savolitinib is shown on a log scale.

Overall, these patients achieved PFS of 17.1, 8.4, and ≥33.5 months, respectively.

Biomarkers

After finding that all responders to savolitinib ($N = 3$) had PRCC histology, retrospective exploratory biomarker analysis was performed on available archival samples from 12 patients to determine their tumor MET status (representative data are shown in Fig. 3B–D). NGS analysis was performed on tumor samples from patients with PRCC ($N = 8$), clear cell renal cell carcinoma (ccRCC; $N = 2$), colorectal cancer ($N = 1$), and thymoma (longest duration of SD; $N = 1$). Amongst these tumor samples, no *MET* gene mutations were identified. Notably, only those patients with PRCC with *MET* copy number changes (focal amplification or chromosome 7 gains) had a response to treatment with savolitinib (Fig. 3A). Samples from 2 patients with PRCC (one with no *MET* copy number change and one with *MET* focal amplification) did not have any on-treatment tumor measurements available for correlation to response. One patient with colorectal cancer had *MET* amplification and achieved a best response of SD with a decrease in tumor measurement of 29.7% from baseline (Fig. 3A).

Discussion

This first-in-human phase I study demonstrated that the selective MET tyrosine kinase inhibitor, savolitinib, was generally well tolerated in patients with locally advanced or metastatic solid tumors. The MTD of savolitinib was determined to be 800 mg for QD dosing and the MTD for BID dosing was not reached (maximum dose investigated was 500 mg BID). The RP2D was determined as 600 mg QD based on toxicity, incidence of TEAEs ≥grade 3 in severity, pharmacokinetic data, and the indication of antitumor activity at this dose. Preclinical modeling demonstrated phosphorylated-MET (pMET) inhibition at an effective concentration $(EC)_{50}$ of 0.35 ng/mL and EC90 of 3.2 ng/mL; this is equivalent to an EC_{90} of 6.5 ng/mL in humans (19). At 600 mg QD in humans, the minimal plasma concentration at steady-state exceeded this value [following 21-day continuous dosing, the median C_{min} (predose on day 1 of the 2nd treatment cycle) was

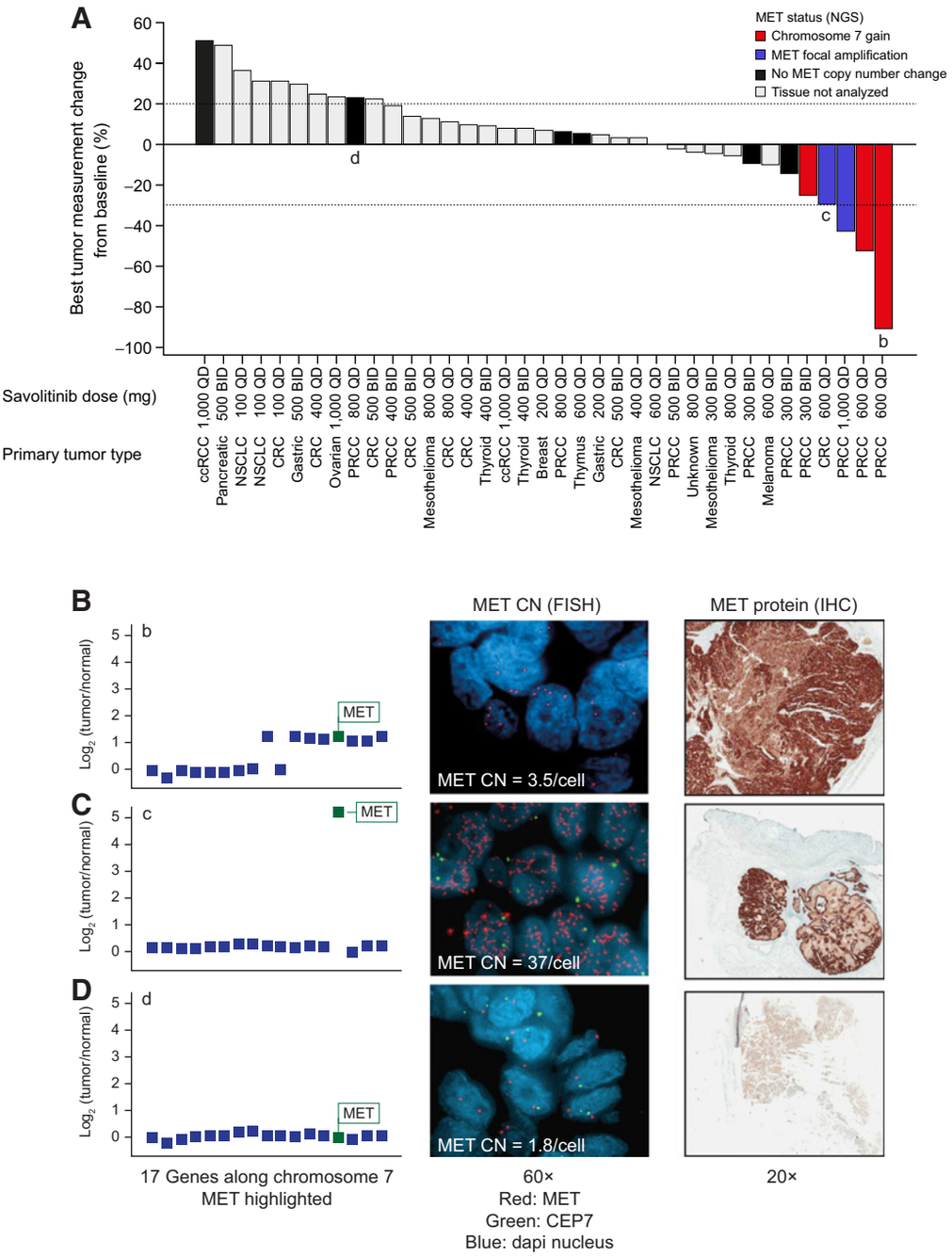

Figure 3.

Waterfall plot of best tumor response and MET biomarker analysis. **A,** Best tumor response from baseline according to assessment of *MET* copy number by NGS, tumor type, and savolitinib dose (tumor evaluable population, $N = 39$; 2 patients did not have evaluable lesions postbaseline). **B–D,** Representative data showing NGS assessment of chromosome 7 gain (**B**; PRCC patient with a PR), focal *MET* gain (**C**; patient with colorectal cancer with SD) and no change in chromosome 7 number or *MET* focal gain (patient with PRCC with PD) with examples of FISH (*MET* copy number) and IHC (MET protein expression) staining results (**D**). In the waterfall plot (**A**), these patients are labelled b, c and d, respectively. CN, copy number; CRC, colorectal cancer.

25.4 ng/mL; range 18.0–.6], providing the extensive and durable inhibition of pMET required to achieve optimal efficacy. In practice, this is considered to provide >90% pMET inhibition throughout the treatment cycle.

The most frequent drug-related AEs reported (nausea, vomiting, fatigue, peripheral edema, constipation, and diarrhea) were similar to those reported by other MET inhibitors (crizotinib, foretinib, cabozantinib; refs. 13–15). The majority of

fatigue and headache AEs were grade 1–2, and the few grade ≥3 events reported were limited to high doses of savolitinib (800 mg QD and 1,000 mg QD). Most events of fatigue were considered possibly or probably related to savolitinib; however, only events of grade 3 led to study withdrawal (3 patients with DLTs). As with other tyrosine kinase inhibitors, there is the potential for hepatotoxicity such as raised AST and/or ALT (13–15). This was seen in some patients following treatment with savolitinib, although such events generally resolved after stopping treatment with savolitinib. However, AEs frequently reported (≥20% in phase I, II, and III trials) with other less selective MET inhibitors (foretinib, cabozantinib), such as hypertension, hypophosphatemia, and proteinuria, were rarely reported (≤2%) with savolitinib. This is possibly due to the multikinase activity (including, VEGF, AXL, TIE–2 receptors) of foretinib and cabozantinib (14, 15, 20).

Interestingly, 3 patients with PRCC obtained a PR in this study (two in the 600 mg QD cohort and one in the 1,000 mg QD cohort), therefore supporting the selection of the monotherapy RP2D of 600 mg QD. During this trial, patients had not been selected on the basis of MET status; a subsequent analysis of MET status was undertaken, comparing responders with nonresponders. Interestingly, none of the responding patients had activating MET mutations, but they did have *MET* gene copy number increases (chromosome 7 gains or *MET* focal gene amplification) and high MET protein expression. Intriguingly, 1 patient with colorectal cancer who had received four prior lines of treatment, achieved a best response of SD, over 5.5 months of treatment, with a 29.7% decrease in tumor size from baseline and had *MET* gene amplification and protein overexpression. Indeed, MET is a promising biomarker for PRCC with the concept of targeting MET previously proposed in a phase II trial with foretinib, and with recent research reporting MET abnormalities in Type II PRCC; a subtype previously thought to be unrelated to MET (8, 10). Interest in MET inhibitors for the treatment of PRCC is increasing, and an ongoing phase II randomized trial is comparing several MET kinase inhibitors, including savolitinib, cabozantinib, and crizotinib, for the treatment of locally advanced or metastatic kidney cancer (www.ClinicalTrials.gov; NCT02761057). Entry criteria do not include *MET* amplification or mutation, although tumor response by MET abnormality and expression level is being assessed. Furthermore, recent studies have looked at identifying biomarkers associated with the pathologic stage of PRCC (21). This is important as it has been shown that outcomes for PRCC, as well as being inferior to ccRCC, can be stratified into risk groups according to the International Metastatic Renal Cell Carcinoma Database Consortium prognostic model; the definition of additional biomarkers will only serve to strengthen such prognostic models (22).

On the basis of the results of this first-in-man study, a phase II single-arm trial of savolitinib in patients with advanced or metastatic PRCC was conducted (ClinicalTrials.gov identifier: NCT02127710). The study included analysis of treatment response by MET status biomarker, with MET-driven status being defined as any of: *MET* copy number gain (either chromosome 7 gain or a *MET* focal amplification of ≥6 copies), *HGF* gene amplification (≥6 copies), or MET kinase domain mutations (allele frequency >5%; ref. 23). The phase II study found savolitinib monotherapy at 600 mg QD to have an acceptable safety and tolerability profile in patients with PRCC with the most commonly reported AEs (nausea, fatigue, vomiting, and peripheral edema) similar to those reported in this study. Increases in ALT and AST were similar between studies; 10%–11% of patients in the phase II study and 8% in this study. Savolitinib demonstrated favorable antitumor activity with 61% ($N = 27$) of patients with MET-driven PRCC reported to have experienced some tumor shrinkage compared with 20% ($N = 9$) of patients with MET-independent PRCC. Moreover, patients with MET-driven PRCC demonstrated a significantly higher objective response rate of 18% (8 PRs) compared with MET-independent PRCC (0%; $P = 0.002$). Savolitinib treatment of patients with MET-driven PRCC led to a longer median PFS compared with patients with MET-independent PRCC [6.2 months, 95% confidence interval (CI), 4.1–7.0 months versus 1.4 months, 95% CI, 1.4–2.7 months; ref. 24]. The safety of savolitinib has also been explored in other phase I studies in combination with osimertinib and gefitinib. The monotherapy toxicity profile of savolitinib at active doses makes combinations with other targeted therapies, such as osimertinib, feasible and such combination regimens are currently being investigated with preliminary data demonstrating a potentially acceptable tolerability profile (25, 26).

Although this study met its predetermined primary and secondary endpoints, it does have some limitations. Firstly, as this study was primarily designed to evaluate the safety and tolerability profile of savolitinib, care must be taken when interpreting initial antitumor results due to the exploratory nature of these findings. In addition, only a very small number of patients with MET-driven PRCC were enrolled, so conclusions cannot be drawn in this study regarding the antitumor characteristics of savolitinib in such a patient population, although the results of the phase II trial described above were in line with these findings (22).

In summary, oral administration of savolitinib in patients with locally advanced or metastatic solid tumors was generally well tolerated, and may have an advantageous toxicity profile compared with less selective agents. Results from this study suggest that savolitinib exhibits antitumor activity in patients with dysregulated MET signaling, particularly for PRCC. As survival for patients with PRCC with monotherapy remains poor (23, 27, 28), the outcomes of a phase III study evaluating the efficacy and safety of savolitinib compared with sunitinib in MET-driven PRCC (ClinicalTrials.gov identifier: NCT03091192), will be of interest.

Disclosure of Potential Conflicts of Interest

M. Millward is a consultant/advisory board member for AstraZeneca. M.M. Frigault has ownership interests (including patents) at AstraZeneca. S. Morgan has ownership interests (including patents) at AstraZeneca. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: M. Millward, Y. Hua, C. Qi, Y. Sai, W. Su, M.M. Frigault, J.D. Lickliter

Development of methodology: C. Qi, Y. Sai, M.M. Frigault, J.D. Lickliter

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H.K. Gan, M. Millward, C. Qi, M.M. Frigault, S. Morgan, L. Yang, J.D. Lickliter

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.K. Gan, M. Millward, Y. Hua, C. Qi, Y. Sai, M.M. Frigault, S. Morgan, L. Yang, J.D. Lickliter

Writing, review, and/or revision of the manuscript: H.K. Gan, M. Millward, Y. Hua, C. Qi, Y. Sai, J. Wang, L. Zhang, M.M. Frigault, S. Morgan, J.D. Lickliter

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.K. Gan, Y. Hua, Y. Sai, J. Wang, M.M. Frigault, S. Morgan
Study supervision: Y. Hua, C. Qi, L. Zhang, S. Morgan

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