ORIGINAL ARTICLE

Effect of capmatinib on the pharmacokinetics of digoxin and rosuvastatin administered as a 2-drug cocktail in patients with *MET*-dysregulated advanced solid tumours: A phase I, multicentre, open-label, single-sequence drug–drug interaction study

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Aims: Capmatinib, an orally bioavailable, highly potent and selective MET inhibitor, was recently approved to treat adult patients with metastatic nonsmall cell lung cancer with *METex14* skipping mutations. The study investigated the effect of capmatinib on the pharmacokinetics of a single oral dose of digoxin and rosuvastatin in patients with *MET*-dysregulated advanced solid tumours.

Methods: This was a multicentre, open-label, single-sequence study. An oral drug cocktail containing 0.25 mg digoxin and 10 mg rosuvastatin was administered to adult patients with *MET*-dysregulated advanced solid tumours on Day 1, and then on Day 22 with capmatinib. Between Days 11 and 32, capmatinib 400 mg was administered twice daily to ensure the attainment of steady state for drug–drug interaction assessment. Pharmacokinetics of cocktail drugs and safety of capmatinib were evaluated.

Results: Thirty-two patients were enrolled. Compared to digoxin alone, the geometric mean ratios (90% confidence interval) of area under the concentration–time curve from time zero to infinity and maximum concentration for digoxin plus capmatinib were 1.47 (1.28, 1.68) and 1.74 (1.43, 2.13), respectively. Compared to rosuvastatin alone, the geometric mean ratios (90% confidence interval) of area under the curve to infinity and maximum concentration for rosuvastatin plus capmatinib were 2.08 (1.56, 2.76) and 3.04 (2.36, 3.92), respectively. Most frequent adverse events (≥25% for all grades) were nausea, asthenia, constipation, vomiting, peripheral oedema and pyrexia. Most frequent Grade 3/4 adverse events (≥5%) were anaemia, pulmonary embolism, asthenia, dyspnoea, nausea and vomiting.

Conclusion: This study demonstrated that capmatinib is an inhibitor of P-gp and BCRP transporters, with clinically relevant drug–drug interaction potential. Capmatinib was well-tolerated and no unexpected safety concerns were observed.

KEYWORDS

capmatinib, digoxin, INC280, MET, pharmacokinetics, rosuvastatin

1 | INTRODUCTION

Dysregulation of MET-pathway has been implicated in the pathogenesis of several human cancers including papillary renal cell carcinoma and thyroid, prostate, lung, breast, ovarian, and gastrointestinal malignancies[1–4] and in the development of resistance to chemotherapy and radiotherapy, leading to poor clinical outcomes.[5–8] The dysregulation of MET pathway may occur by different mechanisms including gene mutation, amplification, overexpression and constitutive activation.[9]

Capmatinib, an orally bioavailable, highly potent and selective MET inhibitor, was recently approved to treat adult patients with metastatic nonsmall cell lung cancer (NSCLC) harboring MET exon 14 (*METex14*) skipping mutations.[10] Capmatinib has also shown in vitro and in vivo activities across a range of tumour models with *MET* amplification and/or overexpression.[11,12] Phase I and Phase II studies have shown a manageable safety and robust efficacy profile of capmatinib, both as monotherapy and in combination with other anticancer therapies, in patients with solid tumours.[13–20]

The therapeutic dose of capmatinib is 400 mg twice daily. Following oral administration, capmatinib absorbed rapidly with time to maximum plasma concentration (T_{max}) of 1–2 hours. The steady state was expected to be reached by Day 3 of consecutive twice daily dosing. Capmatinib is mainly metabolized by CYP3A4 and aldehyde oxidase. In vitro, capmatinib inhibits p-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) with a IC50 of 12.0 μM and 16.4 μM, respectively. At the recommended phase II dose, capmatinib was predicted to inhibit P-gp and BCRP in vivo based on the ratio of capmatinib concentration in plasma and/or gut to the inhibitory constant, (Ki) ([I]/Ki [R]) for P-gp and BCRP, and lead to increase in concentration of P-gp or BCRP substrates.

In clinical trials, patient populations are selected with limited or no comorbidities and concurrent medications are not permitted, follow-up period is much narrower, and the toxicities are detected earlier, so patient populations enrolled may not accurately represent the general oncology population.[21] Multiple drug therapy is also common in patients with cancer to treat their cancer or to manage the adverse effects and comorbidities. Some of these drugs are substrates of P-gp and/or BCRP.[22] Understanding the *in vivo* drug–drug interaction (DDI) potential of capmatinib and substrates of P-gp or BCRP will inform the safe use of capmatinib in treating cancer patients. The purpose of this study was to investigate the effect of multiple doses of capmatinib on the pharmacokinetics of a single oral

What is already known about this subject

- Capmatinib is an orally bioavailable, highly potent and selective MET inhibitor with recent approval to treat adult patients with metastatic NSCLC with *METex14* skipping mutations.
- The pharmacokinetics of oral capmatinib has been characterized in multiple clinical trials previously.
- In vitro studies showed that capmatinib inhibits transporter P-gp and BCRP.

What this study adds

- Capmatinib inhibits P-gp and BCRP at a clinically relevant therapeutic dose.
- The results of this study will inform the safe use of P-gp and BCRP substrates when coadministration of capmatinib is required.

dose of digoxin and rosuvastatin, administered orally as a 2-drug cocktail in patients with *MET*-dysregulated advanced solid tumours.

2 | METHODS

2.1 | Study design

This multicentre, open-label, single-sequence study (NCT02626234) consisted of a molecular prescreening period, a screening/baseline period, a DDI phase and post-DDI phase or treatment phase (Figure 1).

Baseline evaluations were performed within 28 days prior to the first dose of the probe drugs (digoxin and rosuvastatin). In the DDI phase (Day 1 to Day 32), a single oral dose of 2 probe drugs was administered as a 2-drug cocktail on Day 1. No treatment was administered from Day 2 to Day 10 (washout phase). From Day 11 to Day 21, capmatinib tablets (400 mg twice daily, given 12 hours apart) were administered on a continuous dosing schedule. On Day 22, the
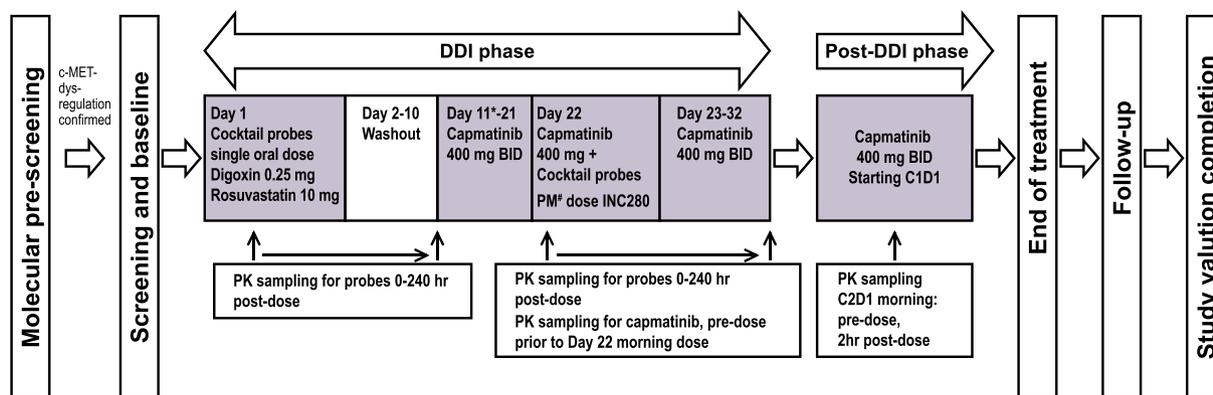
FIGURE 1 Study schema. BID, twice daily; C, cycle; D, day; DDI, drug–drug interaction; PK, pharmacokinetics; PM, post morning

2 probe drugs and capmatinib were administered together. Administration of capmatinib 400 mg twice daily was continued until the end of the DDI phase (from Day 23 to Day 32). From Day 22 onwards, pharmacokinetic samples were collected relative to the end of the probe drugs ingestion for measurement of digoxin, rosuvastatin and capmatinib plasma concentrations at various time points during the DDI phase. All patients who entered the DDI phase were required to have an end of phase visit after the DDI phase. After completion of the DDI phase, patients were allowed to continue treatment with capmatinib 400 mg twice daily, administered orally on continuous 21-day cycles. All patients who entered the post-DDI phase were required to have an end of treatment visit. When the patient discontinued from the post-DDI phase, the end of treatment visit was performed as soon as possible and within 7 days of the last dose.

Patients were contacted for a safety follow-up 30 days after the last dose of study treatment, regardless of the reason for discontinuation from study treatment. Any adverse events (AEs) or serious adverse events (SAEs) occurred after discontinuation of study treatment and follow-up on resolution of ongoing AEs were recorded. If the study drug was discontinued for reasons other than documented disease progression or withdrawal of consent, patients were followed-up with tumour assessments until progression determined by investigator's assessments, start of new anticancer therapy or death.

2.2 | Patients

Adult patients (≥18 years) with *MET*-dysregulated advanced solid tumours refractory to currently available therapies or for which no effective therapy was available were enrolled in this study. *MET*-dysregulation was defined as either *MET* amplification (determined by fluorescence in situ hybridization or quantitative polymerase chain reaction with a gene copy number ≥4) or *MET* overexpression (determined by *MET* immunohistochemistry intensity score +3 in ≥50% of tumour cells) or *MET* mutation (leading to exon

14 deletion). Other inclusion criteria included availability of at least 1 measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1, and an adequate organ function. Prior to receiving capmatinib, patients must have recovered from any previous anticancer treatment-related toxicities to Grade ≤1 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. However, patients with any grade of alopecia were eligible.

Patients were excluded if they had known hypersensitivity to digoxin or rosuvastatin or any of the excipients of capmatinib, digoxin or rosuvastatin or have inadequate organ function. Patient receiving following treatments were excluded: digoxin or rosuvastatin within 21 days prior to the beginning of the DDI phase (Day 1) and for the duration of the DDI phase; strong or moderate in vivo inhibitors and inducers of CYP3A4 that cannot be discontinued at least 1 week prior to the start of treatment with capmatinib and for the duration of the study; in vivo inhibitors or inducers of P-gp or BCRP within 30 days prior to starting study treatment, or during the DDI phase; medicines with a known risk of prolonging the QT interval; unstable or increasing doses of corticosteroids; proton pump inhibitors within 7 days prior to starting study treatment or during the DDI phase; thoracic radiotherapy to lung fields ≤4 weeks prior to starting the capmatinib or patients who did not recover from radiotherapy-related toxicities; major surgery (except video-assisted thoracic surgery and mediastinoscopy) within 4 weeks prior (2 weeks for resection of brain metastases) to starting capmatinib or patients who did not recover from side-effects of such procedure; homeopathic or naturopathic medicines (except vitamin supplements) within 5 days prior to the days of blood sample collection for pharmacokinetic assessment in the DDI phase (i.e., Day 5 to Day 10 and Day 17 to Day 32 of the DDI phase).

This clinical study was designed and implemented in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonization, with applicable local regulations. The study protocol and all amendments were reviewed by the independent ethics

committee or institutional review board for each centre. All patients provided written informed consent before screening.

2.3 | Blood sample collection and bioanalysis

Blood samples (3, 7 or 10 mL per sample) for measurement of plasma concentration of digoxin and rosuvastatin were collected before the administration of capmatinib (Day 1 to Day 11 of DDI phase) and after the administration (Day 22 to Day 32 of DDI phase), at various time points (predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hours postdose). Blood samples for measurement of pharmacokinetics of capmatinib were collected during the DDI phase (predose on Day 22) and post-DDI phase (predose and 2 hours postdose on Cycle 2 Day 1).

Plasma concentrations of digoxin, rosuvastatin and capmatinib were determined using a validated liquid chromatography–tandem mass spectrometry assay with a lower limit of quantification of approximately 0.05, 0.05 and 1.00 ng/mL for digoxin, rosuvastatin and capmatinib, respectively. The details of bioanalytical method is presented in Appendix S1.

2.4 | Efficacy evaluations

Antitumour activity of capmatinib was evaluated by Investigator's assessment per RECIST 1.1 with computed tomography scans conducted every 6 weeks.

2.5 | Safety evaluations

Safety assessments included incidence of AEs and SAEs. Data on AEs/SAEs were collected at every visit and coded using the latest version of Medical Dictionary for Regulatory Activities version 20.1 and were graded using CTCAE version 4.03. All patients were followed-up for AEs/SAEs for at least 30 days following the last dose of study treatment.

2.6 | Pharmacokinetics and statistical analysis

A sample size of 18 evaluable patients was selected to provide reasonable precision for the estimation of the effect of capmatinib on pharmacokinetics of digoxin and rosuvastatin, assuming the intrapatient coefficient of variation (CV) of digoxin (44.7%) and rosuvastatin (31.5%). Using these intrapatient CV% estimates and a sample size of 18, the half-width of the 90% confidence intervals (CIs) for treatment difference comparison (capmatinib + digoxin vs digoxin alone; capmatinib + rosuvastatin vs rosuvastatin alone) on the log scale was 0.247 for digoxin and 0.178 for rosuvastatin. These calculations were based on t-distribution with 1-sided α-level of .05 and N – 1 degrees of freedom. Due to the strict evaluability criteria

and the requirement to conduct the DDI test at steady state, the total number of patients enrolled was expected to be approximately 32.

The pharmacokinetic analysis was based on patients in the pharmacokinetic analysis set. Three separate sets were considered; 1 for each of the probe drugs (digoxin and rosuvastatin) and 1 for capmatinib. For each of the probe drugs, all patients who provided an evaluable pharmacokinetic profile for all periods (first period after the cocktail administration and second period after administration of cocktail + capmatinib) were included for analysis. A profile was considered evaluable if patient received the planned dose of capmatinib on Day 22 and at least 3 consecutive days prior to coadministration with probe drugs; received planned dose of probe drugs, did not vomit within 4 hours after receiving capmatinib or probe drugs and provided at least 1 primary pharmacokinetic parameter (area under the concentration–time curve from time zero to infinity [AUC_{inf}] or to the last quantifiable concentration [AUC_{last}] or maximum concentration [C_{max}]) for probe drugs. Pharmacokinetic analysis set for capmatinib included all patients who provided at least 1 evaluable concentration for capmatinib; a concentration was evaluable if patients received the same dose of capmatinib at least 3 consecutive days prior to sampling, did not vomit within 4 hours after receiving capmatinib, and had predose samples collected before the next dose administration and 9–15 hours after the last dose administration.

Pharmacokinetic parameters were estimated by a noncompartmental method using Phoenix WinNonlin 6.4 (Pharsight, Mountain View, CA). The log-transformed pharmacokinetic parameters (AUC_{last}, AUC_{inf} and C_{max}) were analysed using a linear mixed model to assess the effect of multiple doses of capmatinib on the pharmacokinetics of a single oral dose of each of the probe drugs separately. The model included treatment (probe + capmatinib and probe alone) as a fixed effect and patient as a random effect. Point estimates of treatment differences and the corresponding 90% CIs were calculated and anti-logged to obtain the point estimates and 90% CI for the geometric means ratio of the probe + capmatinib vs probe alone on the original scale.

3 | RESULTS

3.1 | Patient disposition

A total of 32 patients were enrolled in the study. Of these, 26 patients (81.3%) completed the DDI phase. The reasons for DDI phase discontinuation were AEs (two patients [6.3%]), physician's decision (two patients [6.3%]), disease progression (one patient [3.1%]) and death (one patient [3.1%], Table 1). Of the 2 patients who discontinued the DDI phase due to AEs, 1 had experienced Grade 3 blood bilirubin and Grade 4 encephalopathy (both nontreatment related), and another patient had experienced Grade 3 abdominal pain and Grade 3 vomiting, both were treatment related.

A total of 27 patients (84.4%) entered the treatment (post-DDI) phase, all of whom discontinued the study; the primary reason for

TABLE 1 Patient disposition

Disposition/reason	All patients n = 32 n (%)
Pharmacokinetic phase (DDI phase)	
Completed	26 (81.3)
Entered post-DDI (treatment) phase	26 (81.3)
Discontinued from PK phase	6 (18.8)
Entered post-DDI (treatment) phase	1 (3.1)
Entered post-treatment follow-up phase	1 (3.1)
Primary reason for discontinuation from PK phase	
Adverse event	2 (6.3)
Physician decision	2 (6.3)
Progressive disease	1 (3.1)
Death	1 (3.1)
Post-DDI (treatment) phase	
Discontinued from post-DDI (treatment) phase	27 (84.4)
Primary reason for discontinuation from treatment phase	
Progressive disease	20 (62.5)
Physician decision	3 (9.4)
Death	2 (6.3)
Adverse event	1 (3.1)
Lost to follow-up	1 (3.1)
Post-treatment follow-up	
Discontinued from post-treatment follow-up	1 (3.1)
Primary reason for discontinuation from post-treatment follow-up	
Protocol deviation	1 (3.1)

Abbreviations: DDI, drug–drug interaction; PK, pharmacokinetic

discontinuation was progressive disease (PD; 20 patients [62.5%]). Three patients (9.4%) discontinued from the treatment phase (post-DDI) due to physician decision and 1 patient each (3.1%, each) discontinued due to AE (Grade 3 pulmonary embolism; nontreatment related) and being lost to follow-up. Two patients (6.3%) died during the post-DDI phase: 1 due to PD and another due to Grade 3 respiratory tract infection (nontreatment related). One patient (3.1%) entered the post-treatment follow-up phase. However, this patient was discontinued due to protocol deviation. The patient received rosuvastatin during the DDI phase except on Day 1 and Day 22. All 32 patients enrolled in the study were included in the full analysis set and safety set. Of these, 25 (78.1%), 24 (75.0%) and 17 (53.1%) patients were included in pharmacokinetic analysis set for digoxin, rosuvastatin, and capmatinib, respectively.

3.2 | Patient demographics and disease characteristics

The median age of the patients who participated in the study was 61.5 years (range: 38–81 years). Patients were equally divided by sex, and almost all were Caucasian (30 patients [93.8%]). Most patients (24 [75%]) had an ECOG PS of 1. The median body mass index was 23.95 kg/m^2 (range: 17.1–35.7).

The most frequent primary site of cancer was colon (10 patients [31.3%]), followed by lung (8 patients [25%]), oesophagus, oral cavity, pancreas and rectum (2 patients [6.3%] each); other cancers (1 patient [3.1%], each; Table 2). Predominant tumour histology was adenocarcinoma (22 patients [68.8%]). A majority of the patients had metastatic (stage IV) disease at initial diagnosis (18 patients [56.3%]) and at study entry (27 patients [84.4%]). Key sites of metastatic disease included lung (21 patients [65.6%]), liver (19 patients [59.4%]), bone, lymph nodes, and peritoneum (6 patients [18.8%], each). All patients had *MET* dysregulation at study entry, with some having had >1 *MET* alteration. *MET* mutation was reported in 4 patients (9.4%; all had *METex14*), *MET* overexpression in 24 (75%) and *MET* amplification in 14 (43.8%) patients.

The median time from initial diagnosis to first study treatment was 25.23 months (range: 8.6 to 124.2) and the median time from most recent relapse/progression to the first study treatment was 1.99 months (range: 0.7 to 7.1). All patients enrolled in the study received at least 1 prior antineoplastic therapy. Overall, 31 patients (96.9%) received prior antineoplastic chemotherapy. Eleven patients (34.4%) received 2 prior lines of chemotherapy, 3 patients (9.4%) received 3 prior lines of chemotherapy, and 15 patients (46.9%) received 4 or more lines of prior chemotherapy; 68.8% of patients received chemotherapy in a therapeutic setting as prior antineoplastic therapy. The best response to last therapy in patients receiving prior antineoplastic therapy excluding surgery was predominantly PD, which was noted in 21 patients (65.6%), and 84.4% of patients received concomitant medications.

3.3 | Pharmacokinetics of digoxin

The geometric and arithmetic mean concentration-time profiles of digoxin are shown in Figure 2. Digoxin concentration was higher throughout 72-hour sampling with coadministration of capmatinib *vs* digoxin alone. The pharmacokinetic parameters are summarized in Table 3. Coadministration of capmatinib increased digoxin AUC_{inf}, AUC_{last} and C_{max} by 47, 63 and 74%, respectively, compared to digoxin alone. The geometric mean ratios (90% CI) were 1.47 (1.28, 1.68) for AUC_{inf}, 1.63 (1.42, 1.89) for AUC_{last} and 1.74 (1.43, 2.13) for C_{max} (Table 4). Slightly longer half-life (T1/2) was observed with coadministration of capmatinib (61.4 h) compared to digoxin alone (47 h) as the elimination slope was parallel in general. T_{max} was not affected by capmatinib.

3.4 | Pharmacokinetics of rosuvastatin

The geometric and arithmetic mean concentration–time profiles of rosuvastatin are shown in Figure 2. The concentration of rosuvastatin was higher throughout the 72-hour timeframe

TABLE 2 Patient demographics and disease characteristics at baseline

Characteristic	All patients $n = 32$ n (%)
Age (y), median (range)	61.5 (38–81)
Sex, n (%)	
Female	15 (46.9)
Male	17 (53.1)
Race, n (%)	
White	30 (93.8)
Unknown	2 (6.3)
BMI (kg/m^2), median (range)	23.95 (17.1–35.7)
ECOG performance status, n (%)	
0	8 (25.0)
1	24 (75.0)
Primary site of cancer, n (%)	
Colon	10 (31.3)
Lung	8 (25.0)
Oesophagus	2 (6.3)
Oral cavity	2 (6.3)
Pancreas	2 (6.3)
Rectum	2 (6.3)
Bladder	1 (3.1)
Duodenum	1 (3.1)
Kidney	1 (3.1)
Skin melanoma	1 (3.1)
Small intestine	1 (3.1)
Uterus	1 (3.1)
Stage at study entry, n (%)	
III	1 (3.1)
IIIB	2 (6.3)
IV	27 (84.4)
IVB	2 (6.3)
Type of lesion per investigator assessment at baseline, n (%)	
Both target and nontarget	22 (68.8)
Target only	10 (31.3)
Number of metastatic sites of cancer, median (range)	3 (1–7)
***MET* dysregulation**	
MET overexpression	24 (75)
MET amplification	14 (43.8)
MET mutation	3 (9.4)
Prior anticancer medications, n (%)	
Any	32 (100)
Chemotherapy	31 (96.9)
Surgery	17 (53.1)
Radiotherapy	14 (43.8)
Number of prior chemotherapy regimens, n (%)	
1	3 (9.4)

TABLE 2 (Continued)

Characteristic	All patients $n = 32$ n (%)
2	11 (34.4)
3	3 (9.4)
≥4	15 (46.9)
Type of last therapy, n (%)	
Chemotherapy	19 (59.4)
Targeted therapy	7 (21.9)
Radiotherapy	3 (9.4)
Surgery	5 (15.6)
Other	6 (18.8)
Best response to last therapy[a], n (%)	
Stable disease	3 (9.4)
Progressive disease	21 (65.6)
Not applicable	14 (43.8)
Unknown	2 (6.3)

[a]Best response at last therapy was set to 'Not applicable' if the type of last therapy was surgery.
BMI, Body mass index; ECOG, Eastern Cooperative Oncology Group.

following capmatinib coadministration with the more significant difference observed in the absorption phase (first 12 h). The elimination slope was very similar with or without coadministration of capmatinib. The pharmacokinetic parameters for rosuvastatin are summarized in Table 3. Coadministration of capmatinib increased the geometric means of AUC_{inf}, AUC_{last} and C_{max} by 108, 103 and 204%, respectively, compared to rosuvastatin alone. The geometric mean ratios (90% CI) were 2.08 (1.56, 2.76) for AUC_{inf}, 2.03 (1.61, 2.56) for AUC_{last} and 3.04 (2.36, 3.92) for C_{max} (Table 4). The elimination half-life was not affected by capmatinib.

3.5 | Pharmacokinetics of capmatinib

The geometric mean predose concentration of capmatinib on Day 22 (DDI phase) was 407 ng/mL. On Cycle 2 Day 1 (post-DDI phase), the geometric mean predose and 2 hour postdose concentrations of capmatinib were 529 and 3960 ng/mL, confirming that steady state has been obtained.

3.6 | Efficacy assessments

No patient achieved a complete response (CR) or partial response (PR). Eight (25%) patients had stable disease (SD) as best overall response, while 17 (53.1%) had PD. Response was unknown for 7 patients (21.9%). The disease control rate (CR + PR + SD) was 25% (Table 5).

FIGURE 2 Geometric mean and arithmetic mean (SD) concentration–time profiles. (A) Digoxin with and without capmatinib; (B) rosuvastatin with and without capmatinib


(A) Digoxin with and without capmatinib
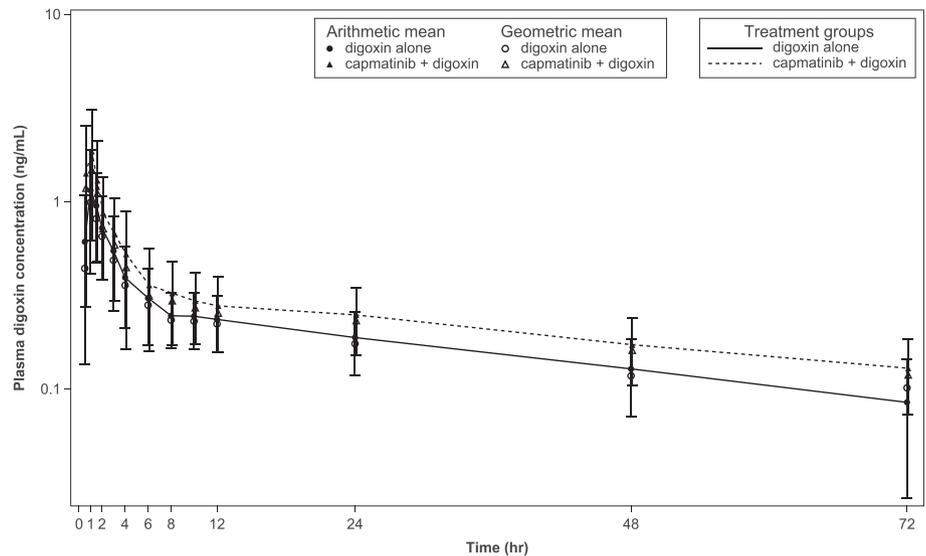
(B) Rosuvastatin with and without capmatinib
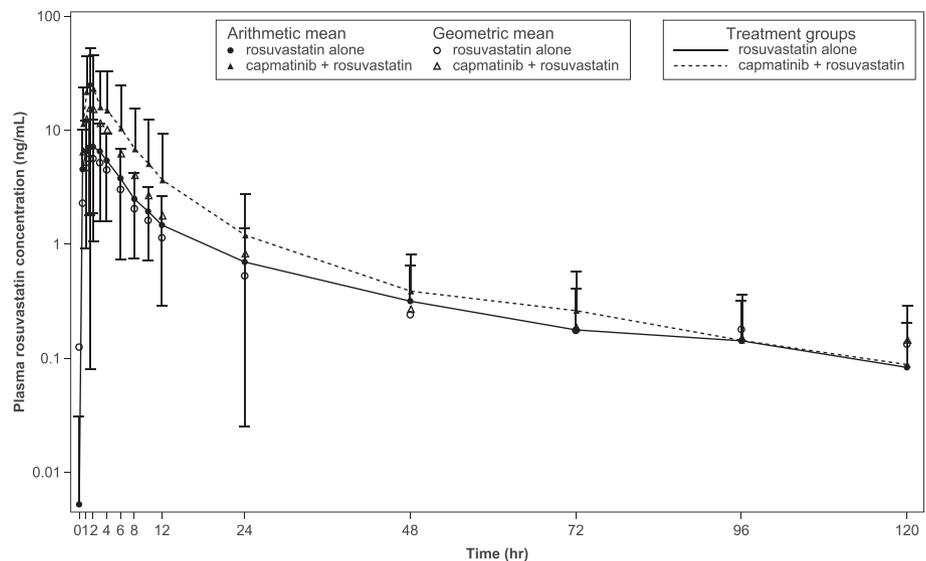
TABLE 3 Summary statistics of the pharmacokinetic parameters by treatment

Pharmacokinetic parameters	Digoxin alone $n = 25$		Capmatinib + digoxin $n = 25$		Rosuvastatin alone $n = 24$		Capmatinib + rosuvastatin $n = 24$	
	n	Geo-mean (geo-CV%)	n	Geo-mean (geo-CV%)	n	Geo-mean (geo-CV%)	n	Geo-mean (geo-CV%)
AUC_{inf}, ng h/mL	9	25.3 (36.3)	12	34.1 (37.9)	21	78.2 (73.4)	22	159 (99.8)
AUC_{last}, ng h/mL	25	14.6 (58.0)	25	23.8 (50.5)	24	71.0 (71.3)	24	144 (102.6)
C_{max}, ng/mL	25	1.12 (57.9)	25	1.95 (56.8)	24	7.72 (73.4)	24	23.5 (85.5)
T_{max}, h[a]	25	1.07 (0.500, 6.00)	25	1.00 (0.417, 4.08)	24	2.04 (0.500, 6.00)	24	1.55 (0.500, 9.93)
$T_{1/2}$, h	9	47 (29.8)	12	61.4 (25.7)	21	22 (73.8)	22	21.4 (56.6)

[a]Median (min, max) is reported for T_{max}.

n = number of patients with corresponding evaluable pharmacokinetic parameters.

AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last quantifiable concentration; C_{max}, maximum concentration; Geo-CV, geometric coefficient of variation; Geo-mean, geometric mean; $T_{1/2}$, elimination half-life determined as $0.693/\lambda z$; T_{max}, time to reach maximum plasma concentration; λz, terminal elimination rate constant;.

TABLE 4 Statistical comparison of primary pharmacokinetic parameters between probe drug (digoxin or rosuvastatin) and capmatinib with probe drug

PK parameter by probe drug	n	Adjusted geo-mean	Treatment comparison Geo-mean ratio (90% CI)
Digoxin			
AUC_{inf} (ng × h/mL)			
Probe drug alone	9	22.4	1.47 (1.28–1.68)
Probe drug + capmatinib	12	32.9	
AUC_{last} (ng × h/mL)			
Probe drug alone	25	14.6	1.63 (1.42–1.89)
Probe drug + capmatinib	25	23.8	
C_{max} (ng/mL)			
Probe drug alone	25	1.12	1.74 (1.43–2.13)
Probe drug + capmatinib	25	1.95	
Rosuvastatin			
AUC_{inf} (ng × h/mL)			
Probe drug alone	21	75.2	2.08 (1.56–2.76)
Probe drug + capmatinib	22	156	
AUC_{last} (ng × h/mL)			
Probe drug alone	24	71	2.03 (1.61–2.56)
Probe drug + capmatinib	24	144	
C_{max} (ng/mL)			
Probe drug alone	24	7.72	3.04 (2.36–3.92)
Probe drug + capmatinib	24	23.5	

n = number of patients with corresponding evaluable PK parameters.

Model is a linear mixed effects model of the log-transformed PK parameters. Included in the model were treatment as a fixed factor and patient as a random factor. The results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.

AUC_{inf}, area under the concentration–time curve from time zero to infinity; AUC_{last}, area under the concentration–time curve from time zero to the last quantifiable concentration; CI, confidence interval; C_{max}, maximum concentration; Geo-mean, geometric mean; PK, pharmacokinetic.

TABLE 5 Best overall response per investigator assessment (per RECIST 1.1)

Best overall response	All patients n = 32
Stable disease (SD), n (%)	8 (25.0)
Progressive disease (PD), n (%)	17 (53.1)
Unknown, n (%)	7 (21.9)
Disease control rate (CR + PR + SD + non-CR/non-PD), n (%) [95% CI]	8 (25.0) [11.5–43.4]

CI, confidence interval; CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

3.7 | Safety assessments

The median (range) percentage of the relative dose intensity was 100% (76.8–100.0), and the mean (±standard deviation) percentage was 98.28% (±4.82). The median actual dose intensity was 800 mg/day (range: 614.3, 800). The median duration of exposure for capmatinib was 7.14 weeks (range: 1.4 to 42.0) for all patients. 43.8% patients received capmatinib for a duration of 6 to 12 weeks.

All 32 enrolled patients experienced at least 1 AE, regardless of study drug relationship; of these, 18 patients (56.3%) had Grade 3/4 AEs (Table 6). The most frequent AEs regardless of study drug relationship (≥20% for all grades) were nausea (56.3%), asthenia (43.8%), constipation and vomiting (40.6%, each), peripheral oedema (28.1%), pyrexia (25%), anaemia, decreased appetite, and dyspepsia (21.9%, each). The most frequent Grade 3/4 AEs (≥5%) regardless of study drug relationship were anaemia and pulmonary embolism (9.4%, each), asthenia, dyspnoea, nausea and vomiting (6.3%, each). No clinically relevant alterations were observed in the electrocardiograph. Treatment-related AEs were reported in 25 patients (78.1%); of these, 8 (25.0%) had Grade 3/4 AEs. Most common treatment-related AEs (≥10%, all grades) were nausea and vomiting (34.4%, each), asthenia (18.8%), dyspepsia (15.6%) and peripheral oedema (12.5%). Most frequent treatment-related Grade 3/4 AE (≥5%) was vomiting (6.3%). AEs leading to study drug discontinuation were reported in 3 patients (9.4%); all of the events were grade 3/4 in severity. Treatment-related AEs leading to study drug discontinuation were Grade 3 abdominal pain and Grade 3 vomiting. AEs requiring dose adjustment or study drug interruption were reported in 13 patients (40.6%). The most frequent AE that led to dose

TABLE 6 All-grade adverse events (in >5% of patients) and Grade 3/4 adverse events, regardless of study drug relationship

Preferred term	All patients n = 33	
	All grades n (%)	Grade 3/4 n (%)
Total	32 (100)	18 (56.3)
Nausea	18 (56.3)	2 (6.3)
Asthenia	14 (43.8)	2 (6.3)
Constipation	13 (40.6)	0
Vomiting	13 (40.6)	2 (6.3)
Oedema peripheral	9 (28.1)	0
Pyrexia	8 (25.0)	1 (3.1)
Anaemia	7 (21.9)	3 (9.4)
Decreased appetite	7 (21.9)	1 (3.1)
Dyspepsia	7 (21.9)	0
Back pain	6 (18.8)	1 (3.1)
Diarrhoea	6 (18.8)	1 (3.1)
Dyspnoea	6 (18.8)	2 (6.3)
Increased blood bilirubin	5 (15.6)	1 (3.1)
Cough	5 (15.6)	0
Respiratory tract infection	5 (15.6)	1 (3.1)
Abdominal pain upper	4 (12.5)	0
Fatigue	4 (12.5)	0
Abdominal pain	3 (9.4)	1 (3.1)
Pulmonary embolism	3 (9.4)	3 (9.4)
Urinary tract infection	3 (9.4)	0
Vitamin K decreased	3 (9.4)	1 (3.1)
Blood albumin decreased	2 (6.3)	1 (3.1)
Candida infection	2 (6.3)	0
Depression	2 (6.3)	0
Headache	2 (6.3)	0
Hypotension	2 (6.3)	1 (3.1)
Lymphocyte count decreased	2 (6.3)	1 (3.1)
Rash	2 (6.3)	0
Vertigo	2 (6.3)	0
Weight decreased	2 (6.3)	0

Only adverse events occurring during treatment or within 30 days of the last dose of study treatment are reported.

adjustment or dose interruption was nausea (6.3%; both Grade ≤2 in severity).

Seventeen patients (53.1%) experienced SAEs of any grade, regardless of study drug relationship; of these, 13 patients (40.6%) had Grade 3/4 SAEs. Treatment-related SAEs were reported in 4 patients (12.5%). Most frequently reported treatment-related SAE was vomiting occurring in 3 patients (9.4%). Other treatment-related SAEs were anaemia, abdominal pain and malaise, reported in 1 patient each. In total, 8 patients (25.0%) died during the study; of these, 6 (18.8%) were on-treatment deaths. Of the on-treatment deaths,

2 (6.3%) were due to disease progression, 3 (9.4%) due to AEs with disease progression as contributing reason and 1 (3.1%) died due to AE (respiratory tract infection).

4 | DISCUSSION

In vitro data suggested that capmatinib can inhibit transporters P-gp (Ki of 12.0 μM) and BCRP (Ki of 8.20 μM; data on file). At the therapeutic dose of 400 mg twice daily, the estimated maximum luminal concentration in the gut was approximately 3880 μM (dose/250 mL), which was >300-fold of the Ki for P-gp and BCRP. Therefore, a clinical DDI study was considered necessary to confirm whether capmatinib is likely to inhibit intestinal P-gp and BCRP and potentially result in an increase in the absorption of P-gp and BCRP substrates. This study was thus conducted in patients with MET-dysregulated advanced solid tumours, and capmatinib was given as multiple doses until attaining steady stat,e which allows for an assessment of the maximum inhibition effect of capmatinib on P-gp and BCRP in the relevant patient population.

The 2 selected probe drugs (digoxin and rosuvastatin) were administered simultaneously as a 2-drug cocktail, as the cocktail approach offers advantages such as reduced study duration and increased efficiency[23] compared to the administration of individual probes in separate studies. Digoxin and rosuvastatin are established as sensitive probes to evaluate the potential impact of other drugs on P-gp and BCRP, and no interaction between these 2 probe drugs are expected.[24]

Digoxin is rapidly absorbed following oral administration, with peak serum concentrations occurring at 1–3 hours. Digoxin is mostly eliminated via urinary excretion as parent drug. The $T_{1/2}$ in healthy subjects with normal renal function is 1.5–2 days.[25,26] As the ratio between maximum unbound plasma concentration for capmatinib and Ki ([Imax,u]/Ki) for renal P-gp is 0.04 compared to the ratio of >300 for intestinal P-gp, capmatinib was not expected to inhibit renal clearance of digoxin. Thus, this study would reflect the inhibition of intestinal P-gp by capmatinib. Rosuvastatin is eliminated mainly through an efflux-mediated process in the gut and in bile with minimum metabolism. The $T_{1/2}$ is approximately 19 hours.[27,28] Based on the half-lives, a total of 21-day washout period was implemented between the first and second dose of probe drugs to allow a complete elimination of probe drugs. A long pharmacokinetic sampling schedule up to 240 hours has ensured the capture of complete pharmacokinetic profiles for both probe drugs.

The study population consisted of 32 patients with MET-dysregulated advanced solid tumours, who had been treated with at least 1 prior line of treatment. The pharmacokinetics of digoxin and rosuvastatin, considered independently, were comparable to those reported in literature reports.[25–30] Co-administration of capmatinib and digoxin increased C_{max}, AUC_{last} and AUC_{inf} by 74, 63 and 47%, respectively and coadministration of capmatinib and rosuvastatin increased the C_{max}, AUC_{last} and AUC_{inf} by 204, 103 and 108%, respectively.

Digoxin was mainly cleared through glomerular filtration and renal tubular secretion via P-gp. As indicated above, the value of [Imax,u]/Ki for renal P-gp is 0.04, thus capmatinib is unlikely to inhibit renal tubular secretion of digoxin. Serum creatinine has been used widely as renal function biomarker clinically. Similar to what was observed in other capmatinib patient and healthy subject studies, low-grade creatinine increase was observed in some subjects in this study, and none of these events was considered clinically relevant and reported as AEs. The reversible creatinine increase was likely due to the inhibition of renal transporters multidrug and toxic compound extrusion 1 (MATE1) and MATE2k by capmatinib.[31] Approximately 10%–40% of the serum creatinine is cleared via active tubular secretion by renal transporters such as MATE, in addition to renal glomerular filtration.[32] In one of the capmatinib studies, cystatin C, a renal function biomarker cleared solely by glomerular filtration, was measured over the time following capmatinib treatment. No change in cystatin C level was observed, in contrast to transient increase of serum creatinine, which indicates that capmatinib does not affect the glomerular filtration (data on file). Therefore, effect of capmatinib on serum creatinine will not impact the evaluation of the inhibitory effect of capmatinib on P-gp using digoxin as a probe drug.

Different genotypes have been reported for ABCB1 gene, which leads to the postulation that it may contribute to the variability of P-gp expression and pharmacokinetics of P-gp substrates. However, most of the studies in the literature have failed to show the association of genotypes of ABCB1 with P-gp function or pharmacokinetics of P-gp substrate, such as digoxin. For those studies which showed an association, conflicting results were reported, thus inconclusive.[33,34] Genetic polymorphism was also reported for ABCG2 gene, which codes BCRP protein. Increase in rosuvastatin plasma concentration was linked to the most studied ABCG2 polymorphism Q141K.[35] In this study, patients were not genotyped for ABCB1 and ABCG2 genes. In the current study design, the cocktail drugs were given alone prior to coadministration of capmatinib for every patient, which served as their own control for DDI evaluation. Therefore, the influence of genotypes on the pharmacokinetic of probe drugs, if any, should not compromise the DDI evaluation.

In vitro, capmatinib showed inhibition of hepatic uptake transporter organic anion transporting polypeptide (OATP) 1B1 and OATP1B3 with Ki values of 5.1 and 5.2 μM, respectively (data on file). The DDI assessment resulted in R-values of 1.12 and 1.13, respectively, using calculated maximum unbound hepatic inlet concentration (fu,p × Iin,max), which indicated a low risk of inhibition (R = 1 + [(fu,p × Iin,max)/Ki]).[36] In this study, the probe substrate rosuvastatin is a substrate for BCRP and OATP, so the result obtained reflected the worst-case scenario of the impact on rosuvastatin pharmacokinetics by capmatinib. However, based on R-value assessment for BCRP and OATP, the increase of rosuvastatin exposure should be mainly due to the inhibition on BCRP with little or no contribution from the inhibition of OATP. Consistent with this, the rosuvastatin clinical pharmacokinetics data indicated that the increase occurred mainly in the absorption phase, with no/little change on the $T_{1/2}$ of rosuvastatin.

In this population with MET-dysregulated advanced solid tumours, no patient achieved CR or PR. Best overall response of SD was observed in 25% of the patients. While the predictive role of specific MET alterations, primarily METex14 skipping mutations, has recently become more established in some indications such as NSCLC, the predictive role of others, like MET amplification and over-expression, remain exploratory particularly in indications other than NSCLC. Taken altogether with the limited sample size of this study, which was not primarily designed or powered to evaluate antitumour activity of capmatinib, no conclusions can be made on efficacy of capmatinib in patients with MET-dysregulated advanced solid tumours.

The overall safety results of capmatinib in this study were mostly in line with those seen with other capmatinib studies conducted in patients with advanced solid malignancies with no new or unexpected safety concerns observed.[13–15,17] The most common treatment-related AEs were nausea and vomiting, asthenia, dyspepsia, and peripheral oedema, while treatment-related SAEs were vomiting, anaemia, abdominal pain and malaise. All these AEs were manageable by routine oncology patient monitoring and supportive care.

In summary, the clinical data from this study confirms that capmatinib is an inhibitor of P-gp and BCRP transporters, with clinically relevant DDI potential. In addition, capmatinib was well-tolerated by the study population with no major or new safety concerns.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[37,38]

COMPETING INTERESTS

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REFERENCES

1. Schmidt L, Duh FM, Chen F, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. *Nat Genet*. 1997;16(1):68-73.
2. Di Renzo MF, Olivero M, Martone T, et al. Somatic mutations of the MET oncogene are selected during metastatic spread of human HNSC carcinomas. *Oncogene*. 2000;19(12):1547-1555.
3. Christensen JG, Schreck R, Burrows J, et al. A selective small molecule inhibitor of c-Met kinase inhibits c-Met-dependent phenotypes in vitro and exhibits cytoreductive antitumor activity in vivo. *Cancer Res*. 2003;63(21):7345-7355.
4. Davis IJ, McFadden AW, Zhang Y, et al. Identification of the receptor tyrosine kinase c-Met and its ligand, hepatocyte growth factor, as therapeutic targets in clear cell sarcoma. *Cancer Res*. 2010;70(2):639-645.
5. Akervall J, Guo X, Qian CN, et al. Genetic and expression profiles of squamous cell carcinoma of the head and neck correlate with cisplatin sensitivity and resistance in cell lines and patients. *Clin Cancer Res*. 2004;10(24):8204-8213.
6. Lal B, Xia S, Abounader R, Laterra J. Targeting the c-Met pathway potentiates glioblastoma responses to gamma-radiation. *Clin Cancer Res*. 2005;11(12):4479-4486.
7. Liu X, Yao W, Newton RC, Scherle PA. Targeting the c-MET signaling pathway for cancer therapy. *Expert Opin Investig Drugs*. 2008;17(7):997-1011.
8. Cappuzzo F, Marchetti A, Skokan M, et al. Increased MET gene copy number negatively affects survival of surgically resected non-small-cell lung cancer patients. *J Clin Oncol off J am Soc Clin Oncol*. 2009;27(10):1667-1674.
9. Sierra JR, Tsao MS. c-MET as a potential therapeutic target and biomarker in cancer. *Ther Adv Med Oncol*. 2011;3(1_suppl):S21-S35.
10. US Food and Drug Administration. Capmatinib oral tablet prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213591s000lbl.pdf. Accessed on 18 May 2020.
11. Liu X, Wang Q, Yang G, et al. A novel kinase inhibitor, INCB28060, blocks c-MET-dependent signaling, neoplastic activities, and cross-talk with EGFR and HER-3. *Clin Cancer Res*. 2011;17(22):7127-7138.
12. Baltschukat S, Engstler BS, Huang A, et al. Capmatinib (INC280) is active against models of non-small cell lung cancer and other cancer types with defined mechanisms of MET activation. *Clin Cancer Res*. 2019;25(10):3164-3175.
13. Schuler MH, Berardi R, Lim W-T, et al. Phase (Ph) I study of the safety and efficacy of the cMET inhibitor capmatinib (INC280) in patients (pts) with advanced cMET+ non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2016;34(15_suppl):9067-9067.
14. Wu YL, Zhang L, Kim DW, et al. Phase Ib/II study of capmatinib (INC280) plus gefitinib after failure of epidermal growth factor receptor (EGFR) Inhibitor therapy in patients with EGFR-mutated, MET factor-dysregulated non-small-cell lung cancer. *J Clin Oncol off J am Soc Clin Oncol*. 2018;36(31):3101-3109.
15. Wolf J, Han J, Nishio M, et al. PS04.06 GEOMETRY Mono-1: Phase II, multicenter study of MET inhibitor capmatinib (INC280) in EGFR wt, MET-dysregulated advanced NSCLC. *J Thorac Oncol*. 2017;12(11):S1578-S1579.
16. Bang Y-J, Su W-C, Nam D-H, et al. Phase I study of the safety and efficacy of INC280 in patients with advanced MET-dependent solid tumors. *J Clin Oncol*. 2014;32(15_suppl):2520-2520.
17. Esaki T, Hirai F, Makiyama A, et al. Phase I dose-escalation study of capmatinib (INC280) in Japanese patients with advanced solid tumors. *Cancer Sci*. 2019;110(4):1340-1351.
18. Bang YJ, Su WC, Schuler M, et al. Phase 1 study of capmatinib in MET-positive solid tumor patients: Dose escalation and expansion of selected cohorts. *Cancer Sci*. 2020;111(2):536-547.
19. Qin S, Chan SL, Sukeepaisarnjaroen W, et al. A phase II study of the efficacy and safety of the MET inhibitor capmatinib (INC280) in patients with advanced hepatocellular carcinoma. *Ther Adv Med Oncol*. 2019;11:1-12. https://doi.org/10.1177/1758835919889001
20. Reungwetwattana T, Liang Y, Zhu V, Ou SI. The race to target MET exon 14 skipping alterations in non-small cell lung cancer: The Why, the How, the Who, the Unknown, and the Inevitable. *Lung Cancer (Amsterdam, Netherlands)*. 2017;103:27-37.
21. Feliu J, Heredia-Soto V, Girones R, et al. Can we avoid the toxicity of chemotherapy in elderly cancer patients? *Crit Rev Oncol Hematol*. 2018;131:16-23.
22. van Leeuwen RW, van Gelder T, Mathijssen RH, Jansman FG. Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective. *Lancet Oncol*. 2014;15(8):e315-e326.
23. Turpault S, Brian W, Van Horn R, et al. Pharmacokinetic assessment of a five-probe cocktail for CYPs 1A2, 2C9, 2C19, 2D6 and 3A. *Br J Clin Pharmacol*. 2009;68(6):928-935.
24. Otani N, Wakuda H, Imai H, et al. No effect of digoxin on rosuvastatin pharmacokinetics in healthy subjects: utility of oita combination for clinical drug-drug interaction study. *Clin Transl Sci*. 2019;12(5):513-518.
25. Einfeld SL, Piccinin AM, Mackinnon A, et al. Psychopathology in young people with intellectual disability. *JAMA*. 2006;296(16):1981-1989.
26. Tye C, McEwen FS, Liang H, et al. Long-term cognitive outcomes in tuberous sclerosis complex. *Dev Med Child Neurol*. 2020;62(3):322-329.

27. Krueger DA, Northrup H. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol*. 2013;49(4):255-265.

28. Nabbout R, Belousova E, Benedik MP, et al. Epilepsy in tuberous sclerosis complex: Findings from the TOSCA Study. *Epilepsia Open*. 2019;4(1):73-84.

29. Martin PD, Kemp J, Dane AL, Warwick MJ, Schneck DW. No effect of rosuvastatin on the pharmacokinetics of digoxin in healthy volunteers. *J Clin Pharmacol*. 2002;42(12):1352-1357.

30. Lee E, Ryan S, Birmingham B, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. *Clin Pharmacol Ther*. 2005;78(4):330-341.

31. Wolf J, Seto T, Han JY, et al. Capmatinib in MET Exon 14-Mutated or MET-Amplified Non-Small-Cell Lung Cancer. *N Engl J Med*. 2020;383 (10):944-957.

32. Lepist EI, Zhang X, Hao J, et al. Contribution of the organic anion transporter OAT2 to the renal active tubular secretion of creatinine and mechanism for serum creatinine elevations caused by cobicistat. *Kidney Int*. 2014;86(2):350-357.

33. Hsin CH, Stoffel MS, Gazzaz M, et al. Combinations of common SNPs of the transporter gene ABCB1 influence apparent bioavailability, but not renal elimination of oral digoxin. *Sci Rep*. 2020;10(1):12457-12468.

34. Leschziner GD, Andrew T, Pirmohamed M, Johnson MR. ABCB1 genotype and PGP expression, function and therapeutic drug response: a critical review and recommendations for future research. *Pharmacogenomics J*. 2007;7(3):154-179.

35. Heyes N, Kapoor P, Kerr ID. Polymorphisms of the Multidrug Pump ABCG2: A Systematic Review of Their Effect on Protein Expression, Function, and Drug Pharmacokinetics. *Drug Metab Dispos*. 2018;46 (12):1886-1899.

36. US Food and Drug Administration. In vitro metabolism- and transporter-mediated drug-drug interaction studies: guidance for industry. [Draft Guidance 2017]. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-metabolism-and-transporter-mediated-drug-drug-interaction-studies-guidance-industry. Accessed on 18 May 2020.

37. Alexander SPH, Fabbro D, Kelly E, et al. The Concise Guide to PHARMACOLOGY 2019/20: Catalytic receptors. *Br J Pharmacol*. 2019;176 (Suppl 1):S247-s96.

38. Alexander SPH, Kelly E, Mathie A, et al. The Concise Guide to PHARMACOLOGY 2019/20: Transporters. *Br J Pharmacol*. 2019;176 (Suppl 1):S397-s493.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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