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Title

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Permalink

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Journal

Cancer chemotherapy and pharmacology, 82(4)

ISSN

0344-5704

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Publication Date

2018-10-01

DOI

10.1007/s00280-018-3672-y

Peer reviewed

A phase I trial of topotecan plus tivantinib in patients with advanced solid tumors

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Received: 26 April 2018 / Accepted: 17 August 2018
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Abstract

Purpose Tyrosine kinase inhibitors (TKI) that target MET signaling have shown promise in various types of cancer, including lung cancer. Combination strategies have been proposed and developed to increase their therapeutic index. Based on preclinical synergy between inhibition of MET and topoisomerase I, a phase I study was designed to explore the combination of topotecan with the MET TKI tivantinib.

Methods Eligible patients with advanced solid malignancies for which there was no known effective treatment received topotecan at doses of 1.0–1.5 mg/m²/day for five consecutive days in 21-day cycles with continuous, oral tivantinib given at escalating doses of 120–360 mg orally twice daily. Pharmacokinetic analyses of tivantinib were included. Circulating tumor cells (CTC) were collected serially to identify peripheral changes in MET phosphorylation.

Results The trial included 18 patients, 17 of whom received treatment. At the planned doses, the combination of topotecan and tivantinib was not tolerable due to thrombocytopenia and neutropenia. The addition of G-CSF to attenuate neutropenia did not improve tolerability. Greater tivantinib exposure, assessed through pharmacokinetic analysis, was associated with greater toxicity. No responses were seen. MET phosphorylation was feasible in CTC, but no changes were seen with therapy.

Conclusions The combination of topotecan and oral tivantinib was not tolerable in this patient population.

Keywords Tivantinib · ARQ-197 · Topotecan · MET phosphorylation · Circulating tumor cells

Introduction

Dysregulation of the MET signaling cascade is implicated in numerous types of cancer, in part due to its role in essential biologic processes such as cell survival, proliferation and

migration [1, 2]. With downstream effectors in the mitogen activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K) and nuclear factor- κ B pathways (NF- κ B), MET plays a central role in many transformed cells and consequently, remains an appealing therapeutic target [3, 4]. There are several MET inhibitors in development, including tivantinib (ARQ-197), a potent, orally bioavailable MET tyrosine kinase inhibitors (TKI).

While monotherapy with a MET TKI has shown promise in various cancer subtypes, including non-small cell lung cancer [5], combination strategies have been explored to increase the therapeutic index. Inhibition of MET and topoisomerase I, the target of the cytotoxic agent topotecan, resulted in a synergistic decrease in cell viability in preclinical small cell lung cancer (SCLC) models [6]. To explore this potential synergy, we designed a phase I trial of intravenous (IV) topotecan plus tivantinib.

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Materials and methods

Patients and design

This phase I trial (NCT01654965) was conducted under the U01 co-operative agreement between the California Cancer Consortium (CCC) and the National Cancer Institute (NCI). The study was conducted at seven centers in the United States and was approved by the institutional review boards at each institution. The primary objective of this study was to establish the recommended phase 2 dose (RP2D) for the combination of tivantinib and IV topotecan. Secondary objectives were to describe the toxicities of the combination, to characterize the pharmacokinetic behavior of tivantinib with concurrent IV topotecan, and explore the efficacy of this combination. The study included a dose-escalation portion and an expansion portion in patients with SCLC.

Eligible patients in the dose escalation portion had advanced solid malignancies refractory to or relapsed from standard therapies, or for which there was no known effective treatment. Eligible patients in the expansion portion had SCLC previously treated with platinum-based chemotherapy. Other inclusion criteria included ECOG performance status 0–2, adequate organ and marrow function, and ability to take oral medications. Patients with creatinine levels above the institutional normal range were required to have a calculated creatinine clearance of at least 60 ml/min. Patients who had received chemotherapy or radiotherapy within the past 4 weeks (6 weeks for nitrosoureas or mitomycin C) were excluded. Also excluded were patients with untreated brain metastases, active infection or other uncontrolled intercurrent illness.

This study was conducted in accordance with principles of the Declaration of Helsinki and Good Clinical Practice guidelines and with local ethics committee approval and was registered (NCT01654965). Written informed consent was obtained from all patients.

Treatment

Treatment was administered on an outpatient basis. Topotecan was administered IV over 30 min on days 1–5 of a 21-day cycle with dexamethasone and an anti-emetic premedication. Tivantinib was given orally, twice daily, on a continuous schedule starting on day 1. The study explored combinations with tivantinib at doses between 120 and 360 mg orally twice daily with topotecan at doses of 1.0–1.5 mg/m²/day (Table 1). Initially, up to four dose levels were planned: three escalation doses and one de-escalation dose. The study was amended after completing

Table 1 Dose escalation schedule

Dose level	Dose of tivantinib (mg BID)	Dose of IV topotecan (mg/m ² /day)
Level – 1	120	1.0
Level 1	240	1.0
Level 2	240	1.5
Level 3	360	1.5
Level A1 ^a	120	1.0
Level A2 ^a	120	1.5

^aMandatory G-CSF support starting on cycle 1

the first two dose levels (levels 1 and – 1) to include two additional dose levels (A1 and A2) with mandatory use of granulocyte-colony stimulating factor (G-CSF) given subcutaneously at least 24 h after completion of topotecan. Treatment could continue until disease progression, unacceptable toxicity, delays in treatment for over 21 days, or the need for more than two dose reductions.

Study assessments

Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) criteria, version 4.0. Dose limiting toxicity (DLT) was at least possibly attributable to the regimen of tivantinib and topotecan and defined as: Grade 3 + thrombocytopenia, Grade 3 + neutropenia associated with fever or a clinically significant infection or lasting more than 7 days, or any clinically significant Grades 3 or 4 toxicity excluding Grades 3 or 4 nausea or vomiting despite maximal antiemetic therapy; Grades 3 or 4 diarrhea despite anti-diarrheal therapy; and Grade 3 fatigue. Any treatment-related toxicity resulting in a delay of treatment for over 21 days was also considered a DLT. Patients who during cycle 1 received less than 80% of the planned doses of either tivantinib or topotecan for reasons other than toxicity and did not experience a DLT were replaced for the purposes of evaluating the dose level for dose escalation/de-escalation decisions.

Patients underwent radiographic evaluation and tumor measurements at baseline and then after every two cycles. Confirmatory scans were required at 6 weeks following initial documentation of an objective response. Overall response was graded according to RECIST v1.1. Overall complete response (CR) and partial response (PR) were considered objective responses. Blood was collected for tivantinib pharmacokinetic (PK) analysis during the first cycle on day 1 prior to tivantinib or topotecan administration, on day 5 prior to tivantinib or topotecan administration (12 h after the evening tivantinib dose on day 4) and after topotecan and tivantinib administration (at 2, 3, 4, and 8 h). Tivantinib concentrations were

measured using high-performance liquid chromatography (HPLC) and tivantinib steady-state plasma pharmacokinetics were calculated including $C_{\max}$ (ng/ml), $AUC_{0-8\text{ h}}$ (ng $\times$ h/ml), $AUC_{0-\infty}$ (ng $\times$ h/ml), and Cl_{sys} (l/h).

Pharmacodynamics

Blood for analysis of circulating tumor cells (CTCs) was collected pre-study, on day 2 of treatment, prior to cycle 3 of treatment and within 2 weeks of last treatment. At these specified time points, 7.5 ml of peripheral blood was drawn by standard venipuncture into two CellSave tubes. Tubes underwent Ficoll-Hypaque centrifugation to deplete red blood cells and to isolate the “buffy coat” layer containing CTCs and white blood cells (WBCs). The buffy coat was then passed through a slot microfilter using a constant low-pressure delivery apparatus. The microfilter-captured cells were fixed in 10% formalin and subjected to immunofluorescent (IF) staining. The cells were stained for cytokeratin (Cam 5.2, BD), DAPI (Sigma), pC-Met (Abcam), and p-FAK (Santa Cruz). Captured CTCs (DAPI⁺Cam5.2⁺) were enumerated. Intensity of pC-Met and p-FAK staining in confirmed CTCs was graded as negative, 1+, 2+ or 3+ and recorded at each timepoint.

Statistical methods

Evaluation of the dose levels followed the standard 3 + 3 dose escalation rules [7]. Dose escalation considerations were based on course 1 data only. The maximum tolerated dose (MTD) was to be the highest dose level tested at which 0/6 or 1/6 patients experienced DLT (that was possibly, probably, or definitely related to one or both of the study drugs) with at least 2/3 or 2/6 patients encountering DLT at the next higher dose. The RP2D would not exceed the MTD but may be below the MTD, based on additional considerations such as cumulative toxicities.

To examine the association between the PK parameters and hematologic toxicity, neutropenia was grouped as Grades 0–3 vs. Grade 4, and thrombocytopenia was grouped as Grades 0–1 vs. Grades 2–4—in both cases, taking the maximum grade over all courses. Plots and exact logistic regression were used to describe the patterns; the Wilcoxon Rank Sum test was used to compare PK values between patients with or without Grade 3 + thrombocytopenia or Grade 4 neutropenia.

Results

Patient characteristics

Eighteen patients were enrolled from August 2012 through September 2014. No patients were determined to be

ineligible after enrollment, but one patient never began treatment and is not included in this report. Characteristics of the 17 patients who were treated are provided in Table 2. The median age was 63 years (range 26–77). The ECOG performance status for all patients was between zero (5 patients) and one (12 patients). There were six patients with primary lung cancer (3 with non-small cell lung cancer and 3 with SCLC), three with ovarian cancer, two with pancreatic cancer, and one patient with each of the following: liver, soft tissue, cervical, uterine, prostate, and urothelial.

Dose escalation and toxicity

A summary of the dose escalation is provided in Table 3. At dose level 1, the first patient experienced two DLTs in the first cycle: Grade 3 thrombocytopenia and grade 4 neutropenia persisting for more than 7 days. The patient recovered and received cycle 2. The second patient also had two DLTs in the first cycle: Grade 4 thrombocytopenia and a neutropenic fever. This patient's therapy was delayed for more than 21 days due to disease progression. The third patient at

Table 2 Summary of patient characteristics

	Number of patients
Patients treated	17
Age at on-study (years)	
Median	63
Range	26–77
Gender	
Female	8
Male	9
Race	
African American	2
Caucasian	11
Hispanic	4
ECOG performance status	
0	5
1	12
2	0
Primary site	
Liver	1
Pancreas	2
Lung/pleura	6
Connective, subcutaneous and other soft tissues	1
Cervix uteri	1
Uterus	1
Ovary	3
Prostate	1
Bladder	1

Table 3 Summary of dose escalation/de-escalation

Dose level: tivantinib dose	Number of patients		Number of. started cycles median (range)	No pts. w/DLT	Dose limiting toxicity (DLT) description	Best responses during therapy (RECIST v1.1)
	Treated	Evalu-able for DLT				
1: 240 mg BID	3	3	2 (1–3)	2	DLT #1: G3 thrombocytopenia and G4 neutropenia persisting over 7 days DLT #2: G4 thrombocytopenia and a neutropenic fever	1 SD 2 PD
– 1: 120 mg BID	8	6 ^a	2.5 (1–12)	2	DLT #1: G3–4 neutropenia lasting > 7 days DLT #2 : G4 thrombocytopenia	4 SD 2 PD 2 NA
A1: 120 mg BID with G-CSF	6	4 ^a	3 (1–12)	2	DLT #1: G3 thrombocytopenia DLT #2: G4 thrombocytopenia, G4 febrile neutropenia, G4 neutro-penia	3 SD 3 PD

SD stable disease, PD progressive disease, NA not assessed (off early for clinical deterioration or death)

^aReceived less than 80% of cycle 1 study drug

dose level 1 did not have a DLT, although there was a dose reduction due to Grade 3 neutropenia that did not last more than 7 days; the patient then received cycle 2. Based on two DLTs, the dose was de-escalated to level – 1 (Table 1).

At dose level – 1, the first patient experienced had a DLT: Grades 3–4 neutropenia lasting for more than 7 days. The next two patients were both properly dosed and did not have a DLT. After review of the first three patients, this dose level was expanded to enroll three more patients, but a decision was made to stagger entry by 2 weeks. The fourth patient was replaced since he did not receive 80% of both drugs. He experienced rectal hemorrhage attributed to hemorrhoids while receiving anticoagulation and discontinued therapy due to clinical decline. The next two patients were both properly dosed and did not have a DLT. A seventh patient also received less than 80% and therefore needed to be replaced. This patient experienced Grade 3 neutropenia and decreased WBC which did not persist for more than 7 days and therefore did not qualify as DLT. The eighth patient experienced a DLT in the first cycle: prolonged Grade 4 neutropenia and Grade 4 thrombocytopenia. His course was complicated by neutropenic sepsis and rhabdomyolysis. The patient died of acute renal failure and study accrual was suspended.

After discussion with the sponsor, G-CSF was added to attenuate the neutropenia and two additional doses (A1 and A2) were added (Table 1). At dose level A1, the first patient experienced at DLT: Grade 3 thrombocytopenia. The next 2 patients were evaluable and did not experience DLT. Dose level A1 was expanded to enroll three more patients. The fourth and fifth patients did not experience a DLT, but neither had received sufficient drug to be evaluable for DLT assessment. The sixth patient experienced Grade 4

thrombocytopenia and the Grade 3 febrile neutropenia. With two DLTs at level A1, the dose exceeded the MTD. The combination was not felt to be tolerable and the study was permanently closed with no MTD determined. The expansion cohort was not opened.

Toxicities observed are summarized in Table 4. With two exceptions at dose level A1 (fatigue and diarrhea), all Grade 3 or greater toxicities at least possibly attributed to treatment were hematologic. Decreasing the dose of tivantinib (from 240 to 120 mg twice daily) did not substantially decrease the frequency of Grade 3 or greater neutropenia or thrombocytopenia; nor did the use of G-CSF. As might be expected, patients who were able to continue treatment had fewer grade 3 or greater toxicities in subsequent cycles.

Pharmacokinetics

Twelve patients had adequate samples collected to allow calculation of tivantinib steady-state plasma pharmacokinetics. Table 5 summarizes the PK results. In the cohort of 11 patients treated at the MTD dose of 120 mg bid, the median steady state area under the curve (AUC) at 12 h was 12,031 ng h/ml (range 2697–50,290 ng h/ml), the median maximum plasma level was 1150 ng/ml (range 454–4550 ng/ml), and the median oral clearance was 10.0 l/h (range 2.4–44.5 l/h). A descriptive analysis was undertaken to examine the association between the PK values and the development of Grade 3 or greater thrombocytopenia or Grade 4 neutropenia. The patterns observed were as expected: higher toxicities were observed with greater tivantinib exposure. The associations were stronger for thrombocytopenia, but in this series, none of the associations were statistically significant at the

Table 4 Grade 3+ toxicities at least possibly related to treatment (for a specific toxicity, if a Grade 3+ toxicity was observed, then Grades 1 and 2 toxicities are also summarized)

Toxicity	Cycle 1			All subsequent cycles		
	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4
Dose level 1	<i>n</i> = 3			<i>n</i> = 2		
Anemia	2		1	1	1	
Lymphocyte count decreased	1		1		1	1
Neutrophil count decreased		1	2		2	
Platelet count decreased	1	1	1	2		
White blood cell decreased		1	2	1	1	
Dose level – 1	<i>n</i> = 8			<i>n</i> = 6		
Anemia	5			5	1	
Lymphocyte count decreased	1	1			1	
Neutrophil count decreased	3	1	3	2	2	
Platelet count decreased	4		1	3		
White blood cell decreased	3	2	2	3	1	
Dose level A1	<i>n</i> = 6			<i>n</i> = 5		
Anemia	2	2		3	1	
Febrile neutropenia			1			
Diarrhea	4			2	1	
Fatigue	2	1		3		
Lymphocyte count decreased	1	2		1		1
Neutrophil count decreased			3		1	
Platelet count decreased	4	1	1	3	1	
White blood cell decreased	1	1	2	2		

Table 5 Tivantinib steady-state plasma pharmacokinetics

	<i>C</i> _{max} (ng/ml) ^a	AUC _{0–8 h} (ng × h/ml) ^a	AUC _{0–12 h} (ng × h/ml) ^a	Cl _{sys} (l/h) ^a
Dose level 1 (tivantinib 240 mg) (<i>n</i> = 1)	1430	7243	8907	26.9
Dose levels – 1 and A1 (tivan- tinib 120 mg) (<i>n</i> = 11)	1150 454–4550	8298 332–33,910	12,031 2697–50,290	10.0 2.4–44.5
All dose levels (<i>n</i> = 12)	1425 454–4550	7770 332–33,910	10,469 2697–50,290	11.8 2.4–44.5

^aMedian and range of observed values

0.05-level, possibly because of the small number of patients with PK values (see Figs. 1, 2).

Antitumor activity

No objective responses were seen. Seven of the 17 treated patients experienced a best response of stable disease. A median of 3 cycles were administered (range 1–12); 1 patient received 10 cycles and 2 patients received 12 cycles.

Fourteen (14) patients stopped protocol therapy due to progressive disease (PD) and 2 stopped due to clinical decline or early death.

Pharmacodynamics

Of the 14 patients with specimens collected for CTC analysis, 12 patients had detectable CTCs. There were no significant changes in pC-MET or p-FAK staining, though staining

Fig. 1 Distribution of PK parameters as a function of the maximum grade of thrombocytopenia experienced over all courses—with Grade grouped as 0–1 vs. 2–4. p values are two-sided-based on the Wilcoxon test, with p value calculation based on the normal approximation

Fig. 2 Distribution of PK parameters as a function of the maximum grade of neutropenia experienced over All courses-with Grade grouped as 0-3 vs. 4. *p* values are two-sided-based on the Wilcoxon test, with *p* value calculation based on the normal approximation

for these markers was found to be feasible on isolated CTCs (Fig. 3).

Discussion

MET is an increasingly relevant therapeutic target in oncology, holding a central role in cancer progression and drug resistance [8]. Tivantinib is a potent, orally bioavailable inhibitor of C-MET that has been explored in numerous cancer subtypes. As a single agent, tivantinib is well tolerated and in the phase I dose escalation study, no maximum tolerated dose was identified [9]. Monotherapy with tivantinib has led to prolonged periods of disease control, but the response rate has been low. No responses were seen in single arm studies of patients with germ cell tumors [10], gastric cancer [11], and hepatocellular carcinoma [12, 13] and a response rate of only 5% was noted in patients with triple-negative breast cancer [14].

Combining tivantinib with other active agents has been explored, including cytotoxic agents and targeted agents. These combinations have generally been well tolerated, including combinations of tivantinib plus gemcitabine

[15], irinotecan and cetuximab [16], erlotinib [17], sorafenib [18], and temsirolimus [19]. Based on preclinical synergy between MET inhibition and topoisomerase I inhibition, a combination of tivantinib plus topotecan had potential relevance, particularly in diseases where topotecan played a clinical role. This phase I study explored the combination of tivantinib and topotecan with plans to pursue the combination in a cohort of patients with SCLC. Unfortunately, in contrast to prior combination studies, the combination of tivantinib and topotecan was not well tolerated. While the phase I dose escalation study of tivantinib did not identify a maximum tolerated dose, DLTs were noted including leucopenia, neutropenia and thrombocytopenia. The hematologic toxicity overlaps with the well described myelosuppression associated with topotecan [20]. Patients at higher risk for topotecan toxicity were excluded from this study, including those with poor creatinine clearance [21] or a poor performance status; however these patients were not included in this trial. Other at-risk populations could have been included, including those with a poor nutritional status [22], which may have influenced the toxicity profile of this combination. The protocol was amended to include use of growth factors but

Fig. 3 CTC staining. Isolated CTC with CK expression (top left) with background cells identified by DAPI (top right). CTC was positive for pC-MET and pFAK

even with this support, the combination was not tolerated and the study was terminated.

In preclinical studies, pharmacokinetics for tivantinib were evaluated and compared in mice, rats and dogs using different dosing routes, levels and formulations. In general, exposure to tivantinib increased as the dose was increased. The corresponding AUC_{0-inf} and C_{max} were generally not dose proportional. After multiple dosing in 7-day, 28-day, 8-week, and 26-week studies, there were no consistent changes in C_{max} and AUC values in rats or dogs, indicating that there was no marked accumulation of tivantinib after multiple dosings. The systemic exposures of tivantinib measured in patients enrolled on the current study were highly variable. As a result, the median steady-state AUC determined in our subjects receiving 120 mg bid was within the ranges of AUCs reported in patients taking 360 mg bid [9, 10, 23]. While we did not control for potential sources of pharmacokinetic variability such as CYP2C19 pharmacogenomic differences, potential drug–drug interactions, and possible food-effects on the oral absorption of tivantinib, it is unlikely that co-administration of topotecan contributed to the higher than expected tivantinib AUC since topotecan has not been shown to induce or inhibit cytochrome P450 enzymes (Hycamtin® prescribing information). Pharmacokinetic studies were not performed for topotecan but tivantinib is not associated with renal impairment, which could impact topotecan clearance. Furthermore, tivantinib has not been shown to have a significant interaction with substrates of CYP1A, CYP2C9, CYP2C19, CYP3A4 or P-glycoprotein [24].

Circulating tumor cells were isolated using a slot microfilter and detectable in 12 of 14 patients who provided specimens. Assaying pC-MET and p-FAK was feasible, though no meaningful conclusions can be made regarding changes in CTC number or phosphorylation of MET or FAK based on the small sample size.

It is worth noting that tivantinib may demonstrate activity independent of MET inhibition, as more recent studies suggest its primary mechanism is via tubulin depolymerization [25]. The strategy of combining a MET inhibitor with a topoisomerase inhibitor may still hold value, but avoiding overlapping hematologic toxicity will make for a better tolerated combination. While this combination was based on preclinical synergy and likely distinct pharmacokinetic pathways, the overlapping toxicity was too great for further development. Based on this phase I study, we do not recommend further study of the combination of tivantinib plus IV topotecan.

Acknowledgements Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under awards UM1 CA186717, P30CA033572 (including work performed in the Biostatistics Core and the Analytical Pharmacology Core), and P30CA014089 [including work performed in the

Circulating Tumor Cell (CTC) Research Core and the Biostatistics Core]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Research reported in this publication was also supported by an institutional research Grant from the American Cancer Society to the University of Southern California under award number ACS-IRG 53-5114-0188. The authors would also like to acknowledge the contributions of the additional co-investigators who contributed to the study: Dr. Anthony El-Khoueiry and Dr. Agustín García.

Funding This study was funded by the National Cancer Institute of the National Institutes of Health under awards UM1 CA186717, P30CA033572 (including work performed in the Biostatistics Core and the Analytical Pharmacology Core), and P30CA014089 (including work performed in the Circulating Tumor Cell (CTC) Research Core and the Biostatistics Core). Research reported in this publication was also supported by an institutional research Grant from the American Cancer Society to the University of Southern California under award number ACS-IRG 53-5114-0188.

Compliance with ethical standards

Conflict of interest SVL reports personal fees from Takeda, AstraZeneca, Bristol-Myers Squibb, Lilly, Taiho, and Celgene; grants from Bayer, Clovis, Corvus, Esanex, Lycera, Merck, Oncomed, Threshold, and Medimmune; and grants and personal fees from Genentech, Ignyta, and Pfizer, all outside the submitted work. BJG reports personal fees from Genentech. MK reports personal fees from AstraZeneca. DRG reports personal fees from Celgene, Guardant health, Lilly, Liquid Genomics/NANT and grants and personal fees from AstraZeneca/Medimmune and Genentech. Other authors report no relevant conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Haddad R, Lipson KE, Webb CP (2001) Hepatocyte growth factor expression in human cancer and therapy with specific inhibitors. *Anticancer Res* 21(6B):4243–4252
2. Maulik G et al (2002) Role of the hepatocyte growth factor receptor, c-Met, in oncogenesis and potential for therapeutic inhibition. *Cytokine Growth Factor Rev* 13(1):41–59
3. Sipeki S et al (1999) Phosphatidylinositol 3-kinase contributes to Erk1/Erk2 MAP kinase activation associated with hepatocyte growth factor-induced cell scattering. *Cell Signal* 11(12):885–890
4. Salgia R (2017) MET in lung cancer: biomarker selection based on scientific rationale. *Mol Cancer Ther* 16(4):555–565
5. Paik PK et al (2015) Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. *Cancer Discov* 5(8):842–849
6. Rolle CE et al (2014) Combined MET inhibition and topoisomerase I inhibition block cell growth of small cell lung cancer. *Mol Cancer Ther* 13(3):576–584
7. Storer BE (1989) Design and analysis of phase I clinical trials. *Biometrics* 45(3):925–937
8. Birchmeier C et al (2003) Met, metastasis, motility and more. *Nat Rev Mol Cell Biol* 4(12):915–925

9. Rosen LS et al (2011) A phase I dose-escalation study of tivantinib (ARQ 197) in adult patients with metastatic solid tumors. *Clin Cancer Res* 17(24):7754–7764
10. Feldman DR et al (2013) A phase 2 multicenter study of tivantinib (ARQ 197) monotherapy in patients with relapsed or refractory germ cell tumors. *Investig New Drugs* 31(4):1016–1022
11. Kang YK et al (2014) A phase II trial of a selective c-Met inhibitor tivantinib (ARQ 197) monotherapy as a second- or third-line therapy in the patients with metastatic gastric cancer. *Investig New Drugs* 32(2):355–361
12. Okusaka T et al (2015) Phase I study of tivantinib in Japanese patients with advanced hepatocellular carcinoma: distinctive pharmacokinetic profiles from other solid tumors. *Cancer Sci* 106(5):611–617
13. Santoro A et al (2013) A phase-Ib study of tivantinib (ARQ 197) in adult patients with hepatocellular carcinoma and cirrhosis. *Br J Cancer* 108(1):21–24
14. Tolaney SM et al (2015) Phase II study of tivantinib (ARQ 197) in patients with metastatic triple-negative breast cancer. *Investig New Drugs* 33(5):1108–1114
15. Pant S et al (2014) A phase I dose escalation study of oral c-MET inhibitor tivantinib (ARQ 197) in combination with gemcitabine in patients with solid tumors. *Ann Oncol* 25(7):1416–1421
16. Eng C et al (2016) A randomized, placebo-controlled, phase 1/2 study of tivantinib (ARQ 197) in combination with irinotecan and cetuximab in patients with metastatic colorectal cancer with wild-type KRAS who have received first-line systemic therapy. *Int J Cancer* 139(1):177–186
17. Sequist LV et al (2011) Randomized phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated non-small-cell lung cancer. *J Clin Oncol* 29(24):3307–3315
18. Puzanov I et al (2015) Phase 1 trial of tivantinib in combination with sorafenib in adult patients with advanced solid tumors. *Investig New Drugs* 33(1):159–168
19. Kyriakopoulos CE et al (2017) A phase I study of tivantinib in combination with temsirolimus in patients with advanced solid tumors. *Investig New Drugs* 35(3):290–297
20. Armstrong D, O'Reilly S (1998) Clinical guidelines for managing topotecan-related hematologic toxicity. *Oncologist* 3(1):4–10
21. O'Reilly S et al (1996) Phase I and pharmacologic study of topotecan in patients with impaired renal function. *J Clin Oncol* 14(12):3062–3073
22. Alexandre J et al (2003) Evaluation of the nutritional and inflammatory status in cancer patients for the risk assessment of severe haematological toxicity following chemotherapy. *Ann Oncol* 14(1):36–41
23. Yap TA et al (2011) Phase I trial of a selective c-MET inhibitor ARQ 197 incorporating proof of mechanism pharmacodynamic studies. *J Clin Oncol* 29(10):1271–1279
24. Tachibana M et al (2018) Evaluation of the pharmacokinetic drug interaction potential of tivantinib (ARQ 197) using cocktail probes in patients with advanced solid tumours. *Br J Clin Pharmacol* 84(1):112–121
25. Calles A et al (2015) Tivantinib (ARQ 197) efficacy is independent of MET inhibition in non-small-cell lung cancer cell lines. *Mol Oncol* 9(1):260–269