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Safety and activity of IT-139, a ruthenium-based compound, in patients with advanced solid tumours: a first-in-human, open-label, dose-escalation phase I study with expansion cohort

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ABSTRACT

Objective This phase I clinical study (NCT01415297) evaluated the safety, tolerability, maximum-tolerated dose (MTD), pharmacokinetics and pharmacodynamics of IT-139 (formerly NKP-1339) monotherapy in patients with advanced solid tumours. IT-139, sodium trans-(tetrachlorobis(1H-indazole)ruthenate(III)), is a novel small molecule that suppresses the stress induction of GRP78 in tumour cells. GRP78 is a key regulator of misfolded protein processing, and its upregulation in tumours is associated with intrinsic and drug-induced resistance.

Methods Forty-six patients with advanced solid tumours refractory to treatment received intravenous infusions of IT-139 on days 1, 8 and 15 for every 28 days, and doses were evaluated across nine cohorts at 20, 40, 80, 160, 320, 420, 500, 625 and 780 mg/m^2.

Results Overall, IT-139 was well tolerated. The treatment-emergent adverse events (AEs) occurring in ≥20% of patients were nausea, fatigue, vomiting, anaemia and dehydration. The majority of patients had AEs that were ≤grade 2, regardless of relationship with the study drug. Of the total 38 efficacy-evaluable patients, one patient with a carcinoid tumour achieved a durable partial response. Nine additional patients achieved stable disease. The MTD was determined to be 625 mg/m^2. IT-139 exhibited first-order linear pharmacokinetics.

Conclusions IT-139 demonstrated a manageable safety profile at the MTD and modest anti-tumour activity in this study of patients with solid tumours refractory to treatment. The lack of dose-limiting haematological toxicity and the absence of neurotoxicity position IT-139 well for use in combination with a broad spectrum of anticancer drugs.

Trial registration number NCT01415297.

Key questions

What is already known about this subject?

- IT-139 is a first-in-class, ruthenium-based, small molecule that in preclinical studies showed anti-tumour activity, including those resistant to different classes of anticancer agents, and synergism with a broad array of cancer therapeutics.
- Independent preclinical studies show IT-139 suppressing the stress induction of GRP78 in tumour cells.
- GRP78 is a key regulator of misfolded protein processing, and its upregulation in tumours is associated with intrinsic and drug-induced resistance.
- Only one other ruthenium compound NAMI-A, imidazolium-(*trans*-DMSO-imidazole-tetrachlororuthenate), has completed phase I/II clinical trials, but with a markedly different safety profile.

What does this study add?

- IT-139 is a novel modulator of GRP78, a master regulator of drug resistance and tumour progression.
- This study is the first to show the safety and tolerability of a ruthenium-based drug with a toxicity profile and the mechanism of action, unlike that of platinum.
- We provide the basis for future clinical studies that will combine IT-139 with other anticancer agents to overcome resistance and exploit the synergy seen in preclinical models.

How might this impact on clinical practice?

- IT-139 is a novel ruthenium compound that can be administered over long periods of time in the clinic with moderate and manageable toxicity.
- Although the single-agent anticancer activity of IT-139 against tumours was modest, we anticipate that when combined clinically with chemotherapy or targeted agents, we will see an increase in anti-tumour activity of these agents through inhibition of GRP78-induced drug resistance.

INTRODUCTION

Whether a chemotherapeutic or a targeted agent, the emergence of resistance is the greatest challenge to the success of anti-cancer agents. The search for an agent that would be active against resistant tumours led to the discovery and development of the

ruthenium-based small-molecule drug, IT-139 (formerly NKP-1339).[1–4] Early studies viewed ruthenium compounds as being similar to platinum, but it has since become increasingly clear that ruthenium derivatives have quite different pharmacodynamic profiles.[5–7] In vitro studies have elucidated that the mechanism of action and cytotoxicity is not that seen with the DNA-platinum adducts, and a wide range of ruthenium agents has been synthesised.[8] To date, only one other ruthenium drug, NAMI-A, has been studied in clinic trials where it was moderately tolerated as monotherapy, but in a phase I/II combination study with gemcitabine, it exhibited less activity in combination than with gemcitabine therapy alone .[9 10] IT-139 exhibits a markedly different preclinical and clinical profile, in terms of both anti-tumour activity and side effects, and we propose that this arises from IT-139's novel mechanism of action.

Increased levels of markers in the unfolded protein response (UPR) are emerging as important advocates for drug resistance.[11 12] The protein GRP78/BiP/HSPA5 is the master regulator of the UPR, and numerous studies show that the levels are highly increased in several cancers.[13–18] Acute endoplasmic reticulum (ER) stress, induced by hypoxia and anticancer drugs, triggers the upregulation of the misfolded protein chaperone GRP78 to counter the insult and initiate mechanisms for cell survival.[12 19–21] The activity of IT-139 downregulates GRP78's stress response, thereby inhibiting the survival response [22] and rendering tumour cells more vulnerable to cytotoxic therapy. Recent in vitro studies with IT-139 show marked synergy when used in combination with different classes of cancer drugs, and preclinical in vivo data support a unique toxicity profile and improved anti-tumour effects in combination studies.[23 24]

The aim of this first-in-human, open-label, phase I, dose-escalation trial was to define the safety profile, maximum-tolerated dose (MTD), pharmacokinetic (PK) parameters and initial anti-tumour activity of IT-139 in patients with advanced solid tumours refractory to treatment.

METHODS

Patients, Study Design and Treatment

This study was a first-in-human, open-label, phase I, dose-escalation trial designed to define the safety profile, MTD, PK parameters and initial anti-tumour activity of IT-139 (formerly NKP-1339) (sodium trans-(tetrachlorobis(1indazole)ruthenate(III))) in patients with advanced solid tumours refractory to treatment. Patients were enrolled from the Sarah Cannon Research Institute, Nashville, Tennessee, USA, and the Scottsdale Healthcare Clinical Research Institute/Translational Genomics Research Institute (TGen), Scottsdale, Arizona, USA. Eligibility criteria were those standardly used in phase I studies in adults with refractory solid tumours.

Screening assessments were done at the clinical site within 2 weeks prior to initial dosing and included a medical history, physical examination, vital signs, Eastern Cooperative Oncology Group performance status (ECOG PS), body surface area (BSA), audiology testing, complete blood count, comprehensive serum chemistry, urinalysis, pregnancy test, radiological tumour assessments and an ECG.

The conduct of all aspects of the study, including the methods for obtaining informed consent, was in accordance with the principles in the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practices (ICH E6), and applicable Food and Drug Administration regulations/guidelines set forth in Title 21 CFR Parts 11, 50, 54, 56 and 312. The patients gave written informed consent for all clinical and research aspects of the study before enrolment.

IT-139, sodium trans-(tetrachlorobis(1H-indazole) ruthenate(III)), was supplied as a sterile, non-preserved, lyophilised powder. Each 100 mg vial of the product contained IT-139, mannitol and sodium citrate/citric acid. IT-139 was reconstituted with normal saline given by intravenous infusion. Infusion duration was 30 min for volumes <500 mL and 60–90 min for >500 mL on days 1, 8 and 15, for every 28 days, which constituted a cycle of therapy. The starting dose of IT-139 was 20 mg/m^2 chosen in accordance with the ICH S9 guidance documents. The human dose was based on one-sixth the highest non-severely toxic dose in dogs, which were the most sensitive species. Dosing was based on BSA calculated at the beginning of each treatment cycle. Actual weight was used to calculate the BSA for all patients. Premedication consisting of dexamethasone 10 mg intravenously and a 5-HT antagonist (eg, ondansetron and granisetron) intravenously at standard doses prior to each IT-139 infusion was recommended. IT-139 was administered to one patient and incrementally escalated in one additional patient at each dose level using a doubling scheme until ≥grade 2 toxicity was encountered. The cohorts at the dose level in which a ≥grade 2 toxicity occurred and subsequent dose levels used the traditional 3+3 design. A total of 25 patients could be enrolled in an expansion cohort at the defined MTD of IT-139.

Study outcomes

The primary objectives of this study were to investigate the safety of multiple escalating doses of IT-139 and to define MTD when administered by intravenous infusion. The secondary objectives were to estimate the PK parameters after a single and repeated escalating doses. Preliminary evidence of anti-tumour activity was assessed through the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Safety

The incidence of adverse events (AEs) and dose-limiting toxicities (DLTs) were recorded and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events V.3.0. Defined DLTs were monitored at each visit. Decisions to initiate dose escalation or cohort expansion were made after discussion and agreement

among the sponsor's medical monitor and investigators. Assessments of all AEs, drug-related and non-drug-related, were monitored for 30 days after discontinuation of IT-139 treatment or until an ongoing AE was resolved or deemed to continue indefinitely.

Pharmacokinetics

The PK evaluation included individual patient serum concentrations versus time and derived parameters for IT-139. Plasma sampling was performed in cycle 1 for all patients and analysed for total ruthenium (Ru) (free and bound) and for any identified metabolites or derivatives of interest. Plasma samples for all 28 patients were drawn on days 1, 2 and 8 of cycle 1 prior to infusion and after infusion at 15 min, 30 min, 1 hour, 2 hours, 4 hours, 6–8 hours, 10–12 hours, 24 hours and pre-dose day 8. Samples were analysed by Maxxam Analytics International Corporation, Burnaby, British Columbia, Canada.

Pharmacodynamics

Exploratory pharmacodynamic markers (reticulocyte counts, transferrin (TFn), TFn receptor, ferritin, serum iron and total iron-binding capacity) and optional biomarker samples were obtained at baseline and on day 1 after every two cycles.

Efficacy

Tumour response assessments by CT were scheduled at baseline and after every two cycles of treatment. Patients with stable disease or better were allowed to continue IT-139 treatment until confirmation of progressive disease (PD) (according to RECIST V.1.1) or if another withdrawal criterion was met.

Statistical analysis

All analyses of data from this study were descriptive (without p value generation) as the study was not powered for inferential analyses and no formal hypothesis testing was performed. Continuous variables were presented by the sample size (n), mean, SD, median, minimum and maximum. Categorical variables were presented with summary statistics by count and percentage. SASV.9.1 software was used for all analyses. All patients who received any study treatment were included in the safety analyses.

Table 1 Patient characteristics

Characteristics	Patients (n) (n=46)
Age, years	
Median	61
Range	28–78
Sex	
Male	25
Female	21
Ethnicity	
Caucasian	42
African American	3
Other	1
Eastern Cooperative Oncology Group performance score	
0	22
1	24
Tumour types	
Colorectal	11
Non-small cell lung	9
Carcinoid neuroendocrine	5
Head and neck squamous cell	5
Breast	3
Gastro-oesophageal	2
Ovarian	2
Pancreatic	2
Gall bladder	1
Cervical	1
Lung (not specified)	1
Adrenocortical	1
Small round cell desmoplastic	1
Thymic	1
Unknown primary	1
Prior treatment*	
Chemotherapy	44
Octreotide	3
Radiation	30
Surgery	45
Number of previous systemic regimens	
Median	6
Range	1–14

*Patients could have received more than one previous treatment type.

RESULTS

Patients

This study enrolled 46 patients in two study centres in the USA (table 1). The study was closed by agreement of the sponsor and study investigators after the completion of treatment for the last patient. The majority of patients were heavily pretreated and had PD at study entry.

Forty-six patients were treated with IT-139 across nine cohorts, with doses ranging from 20 to 780 mg/m^2 (see online supplementary table S1). Eighteen patients participated in the expansion cohort treated at 625 mg/m^2, which was determined to be the MTD. Most patients received one or two cycles of treatment (n=37, 80%). One patient with carcinoid neuroendocrine remained on treatment for 25 cycles (71 doses) and for a total of 100 weeks of treatment. Another patient with a carcinoid tumour completed nine cycles of therapy on study and had stable disease with control of symptoms. After the study was closed, the patient was enrolled in a compassionate use protocol and received an additional six cycles of therapy. Standard premedication to prevent fever/chills/rigours was allowed. Thirty-eight of the 46 patients receiving study treatment (83%) received premedication. Two patients at the highest dose tested, 780 mg/m^2 , had their dose reduced by decision of the investigator.

Safety

There were 42 patients (91%) who had at least one AE that was considered by the investigator to be related to the study drug. The maximum severity of any AE experienced by the majority of patients was ≤ grade 2 (59%). Seventeen patients (37%) had AEs that were grade 3 and no patients experienced grade 4 (table 2). There were no treatment-related deaths. Treatment-emergent AEs occurring in ≥20% of patients were nausea (48%), fatigue (46%), vomiting (39%), anaemia (22%) and dehydration (22%) (see online supplementary table S2).

Fifteen patients (33%) experienced a serious adverse event (SAE). Five SAEs in four patients were determined by the investigator to be related to study treatment: atrial fibrillation, aspiration pneumonia and vomiting in one patient each,, and acute abdomen and hypotension in one patient. Five patients (11%) had an AE that led to treatment discontinuation: asthenia, atrial fibrillation, back pain, mental status changes and pneumonia.

No clinically meaningful post-baseline trends related to dose level or cumulative exposure were noted in vital signs, physical examinations, neurological function (including audiology studies), ECOG PS or clinical laboratory results for chemistry and haematology. Creatine clearance was stable over time and across all dose levels. There was no evidence of drug-related renal toxicity. Three patients (on four blood draws) were found to have discoloured serum, green in colour, at the time of a draw, without any clinical correlates.

There was evidence for QTc prolongation, regardless of antiemetic use, after IT-139 infusion in one patient at the 780 mg/m^2 dose level, which returned to baseline at day 8 post-infusion. In addition, there was evidence for PR prolongation.

The MTD was determined to be 625 mg/m^2. DLTs were observed for five (11%) patients. The DLTs were ≥ grade 2 cardiotoxicity for two patients (atrial fibrillation in the 320 mg/m^2 cohort and pericardial effusion in the 780 mg/m^2 cohort), and inability to complete cycle 1 due to any toxicity thought to be associated with investigational product for two patients in the 780 mg/m^2 cohort.

Pharmacokinetics

The PK parameters increased proportionally with dose. The mean half-life ($t_{1/2}$) was 113 hours (see online supplementary table S3). IT-139 had a mean total clearance (CL_{total}) of 164 mL/hour. The mean steady-state volume of distribution ($V_{d/ss}$) was 23.7 L or 0.312 L/kg. A very small percentage of the administered dose was excreted in the urine (mean: 1.14%). IT-139 exhibited first-order linear pharmacokinetics across the dose range that was evaluated in this trial (figure 1). The half-life values may not represent true terminal half-life as higher levels of accumulation were observed than predicted by the elimination rate constant derived from cycle 1 day 1 and cycle 1 day 8 data. There was no evidence of cumulative toxicity detected across dose levels.

Pharmacodynamics

Pharmacodynamic markers were analysed, including reticulocytes, TFn, TFn receptor, ferritin, serum iron and total iron-binding capacity. Twenty-two of the total patients (n=46) had data available that could be assessed, and no trends related to efficacy or safety were observed. Serum GRP78 levels were to be measured, but too few serial samples were collected for analysis.

Anti-tumour activity

The efficacy-evaluable population (n=38) included all patients who completed informed consent, received study

Table 2 Overall summary of adverse events

	Dose levels (mg/m^2)									
	20 (n=1)	40 (n=1)	80 (n=1)	160 (n=1)	320 (n=7)	420 (n=5)	500 (n=3)	625 (n=18)	780 (n=9)	Total patients (n=46)
Any adverse event	1	1	1	1	7	5	3	18	9	46
Related adverse event*	1	1	1	1	7	4	2	16	9	42
Maximum severity of adverse event										
Grade 1	1	0	1	1	1	1	1	4	1	11
Grade 2	0	1	0	0	3	2	2	4	4	16
Grade 3	0	0	0	0	3	2	0	9	3	17
Grade 4	0	0	0	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0	1	1	2
≥ Grade 3	0	0	0	0	3	2	0	10	4	19
Any serious adverse event	0	0	0	0	4	1	0	6	4	15
Related serious adverse event	0	0	0	0	1	0	0	1	2	4
Discontinued treatment due to adverse event	0	0	0	0	1	2	0	2	0	5

* Related to study drug as assessed by the investigator.

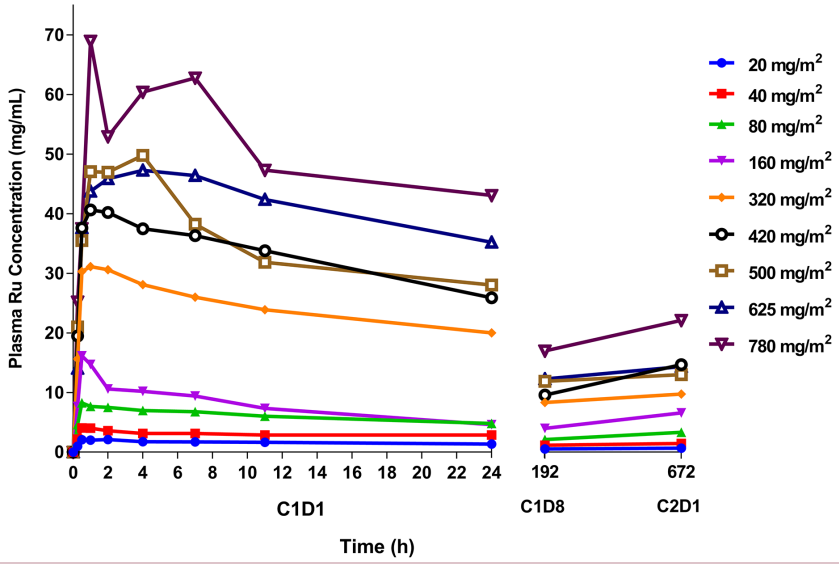

Figure 1 Mean plasma concentration-time profiles of ruthenium by dose on days 1, 8 and 28. Total ruthenium levels in plasma measured by Inductively Coupled Plasma Mass Spectroscopy (ICP-MS) during cycle 1 day 1 (C1D1), prefusion on cycle 1 day 8 (C1D8) and cycle 2 day 1 (C2D1).

medication and had at least one disease response assessment (figure 2). The disease control rate (defined as CR, PR or SD) was 26% (1 PR and 9 SD). The median duration of disease control was 9 weeks (1–98 weeks). Of the 10 patients who had disease control, three were patients with neuroendocrine tumours—two carcinoids and one gastrinoma (see online supplementary table 4). All three patients had ongoing disease control at the time the patients went off study. Target lesion size reductions were observed in 8 of 38 (21%) efficacy-evaluable patients (figure 3).

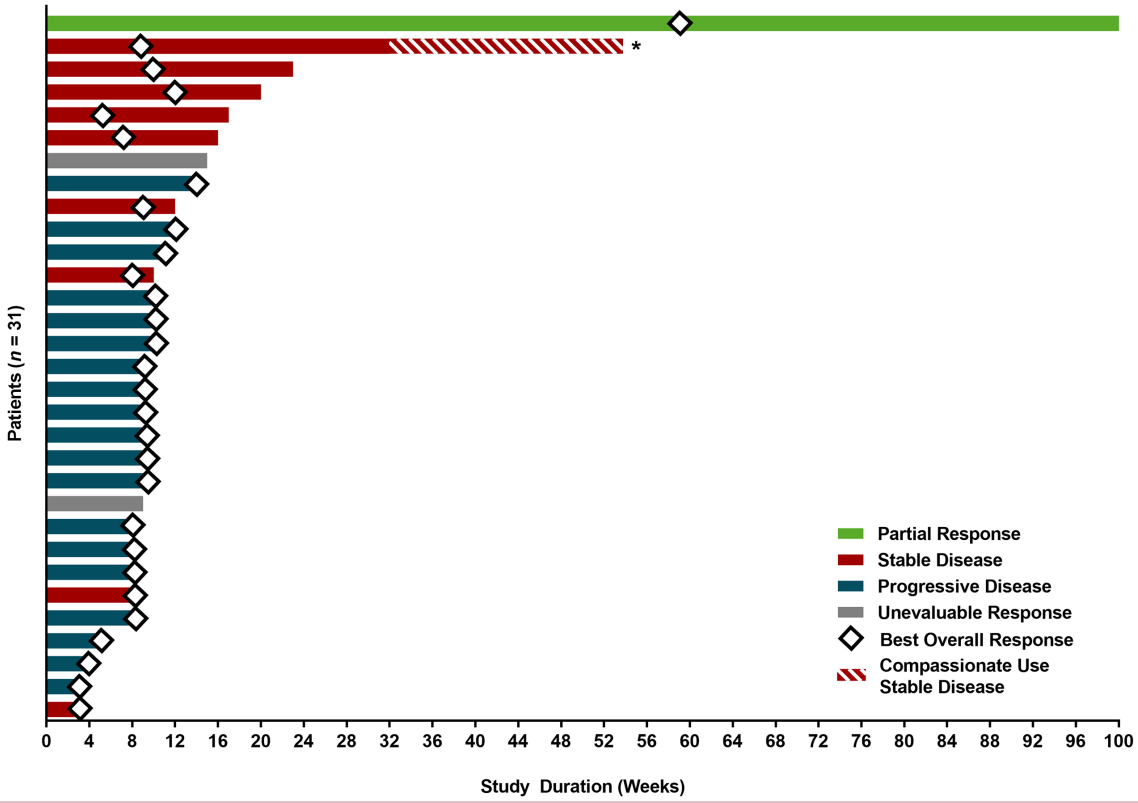

Figure 2 Plot with best overall response and study duration. Start time denotes the first dose of IT-139. Stop time denotes death or last follow-up if patient is still alive. Length of bars denotes study duration in weeks. Colour of bars shows best overall response. Diamonds mark the first instance of best overall response. *Hashed bar represents the time the patient was treated on a compassionate use extension study after completion of NCT01415297.

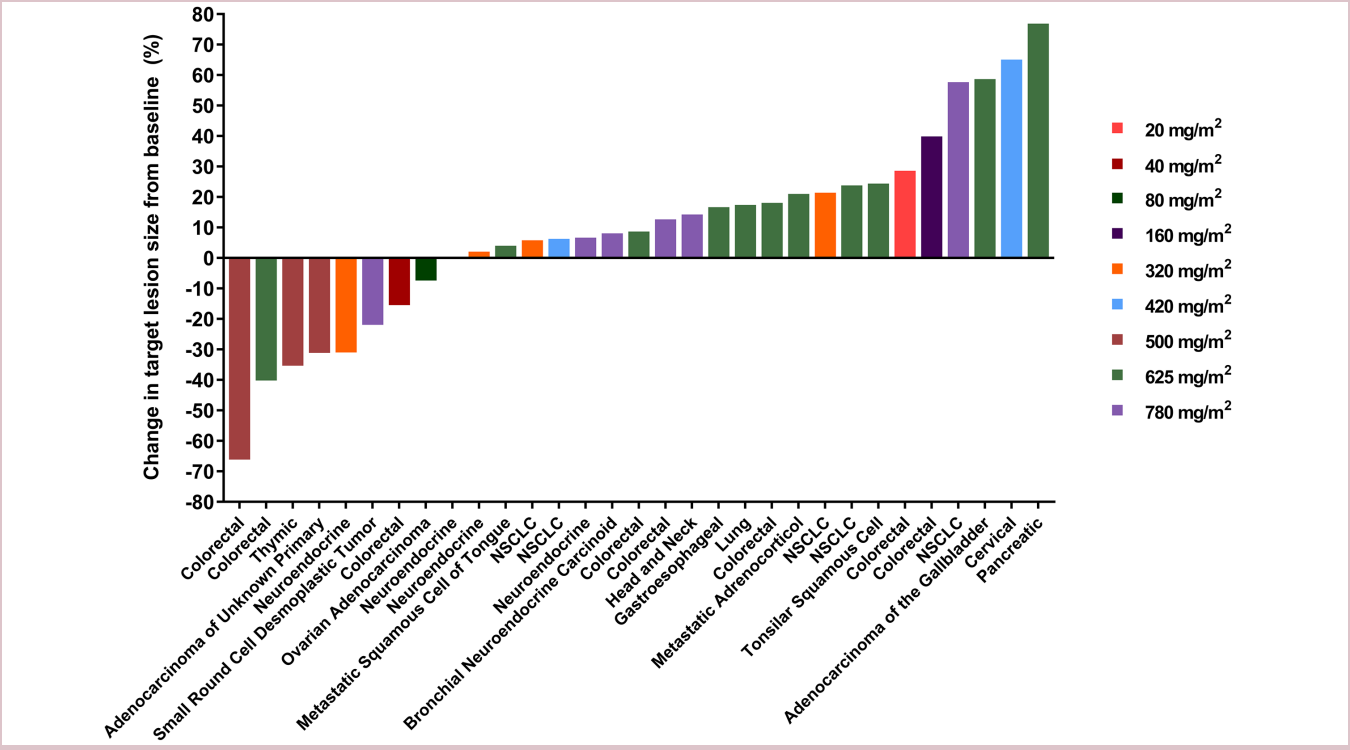

Figure 3 Change in target lesions from baseline stratified by cancer type.

DISCUSSION

This phase I clinical study (NCT01415297) evaluated the safety, tolerability, MTD, PK and pharmacodynamics of IT-139 monotherapy in patients with advanced solid tumours. Five patients experienced DLTs (11%), and the events in the 780 mg/m^2 cohort were determined to have formally exceeded the MTD and led to the determination of the 625 mg/m^2 cohort as the MTD. IT-139 was associated with manageable toxicities when administered every week at 625 mg/m^2 and below. There was a low incidence of clinically significant laboratory abnormalities for both chemistry and haematology values, and no adverse trends were observed based on cumulative exposure or dose level. There was no effect on platelets or white blood cells. No clinically meaningful post-baseline trends were noted in vital signs, physical examinations, neurological function tests, audiometry and ECOG PS. There was evidence for QTc prolongation that remained for up to 10 hours after IT-139 infusion at the highest dose tested, 780 mg/m^2 dose level, but generally returned to baseline at day 8 post-infusion. However, with regard to the evidence for PR prolongation, in the absence of a control group and the inability to exclude a chance effect, it is impossible to rule out an IT-139 effect on the PR interval. Analysis of exploratory PD markers as correlated with response was not performed as no trends in the markers chosen in this study were observed.

Administered weekly by intravenous on days 1, 8 and 15 of every 28-day cycle, IT-139 showed modest anti-tumour activity. Twenty-six percent of patients achieved disease control (one PR and nine SDs), with a median durability of about 9 weeks (range, 1–98). IT-139 particularly showed anti-tumour activity in patients with carcinoid neuroendocrine tumours where three of five patients had disease control (one PR and two SDs). The patient who achieved a PR was on treatment for a total of 100 weeks before being discontinued from the study due to an AE unrelated to study drug. The patient who received an additional five cycles of therapy on a compassionate use protocol maintained SD for a total of 54 weeks from initiation of therapy until PD was observed. Higher levels of accumulation of IT-139 were observed than predicted by the elimination rate constant derived from data collected. The half-life values may not represent true terminal half-life as higher levels of accumulation were observed than predicted by the elimination rate constant derived from cycle 1 D1 and cycle 1 D8 data. The PK profile suggests that less frequent dosing schedules at dose levels below the MTD could achieve desirable exposures in future clinical studies. Clearance was not related to body weight, but there was a relationship with body size, suggesting further dosing should be based on body size (mg/m^2). Future studies will explore additional PK data to determine the actual terminal half-life.

IT-139 is a novel modulator of stress-induced GRP78, a chaperone protein responsible for supporting drug resistance and tumour progression. GRP78 is the master regulator of key stress transducers and has been identified for its role in autophagy, anti-apoptosis and cell survival. In normal cells, GRP78 resides in the ER and is

involved with cellular processes, such as protein folding and trafficking, and calcium homeostasis.[25 26] GRP78 is essential for embryonic cell growth, but *Grp78+/–* mice are capable of responding to ER stress, suggesting that GRP78 levels in normal cells can potentially be down-regulated without limiting a stress response through the role of GRP78.[27] Preclinical in vivo studies have confirmed IT-139 targets the upregulation of GRP78 in response to stress in tumour cells. Decrease in stress upregulated GRP78 levels translates to increased vulnerability and apoptosis of tumour cells. An independent group confirmed that IT-139 treatment inhibits GRP78 chemoresistance in a pancreatic ductal adenocarcinoma (PDAC) model. [28] When treated in combination with gemcitabine, sensitivity to cytotoxic drugs was restored in drug-resistant PDAC cells and increased cell death over gemcitabine treatment alone. In another independent study of an ex vivo lung metastases model, IT-139 targeting GRP78 in metastatic osteosarcoma cells saw a decrease in tumour burden after treatment.[29] Combination in vivo studies with cisplatin, 5-FU, oxaliplatin and vemurafenib all show increased anti-tumour efficacy in xenograft colorectal, lung[23] and melanoma models (unpublished data).

We see SD in this study and believe that because IT-139 targets a stress-response protein, its value will be in combination studies moving forward. Lack of neutropaenia or effects on platelets supports IT-139 as a promising candidate for combination therapy with agents that cause haematological toxicity. Phase I/II studies will explore IT-139 in combination with chemotherapeutic, targeted agents and potentially immunotherapy, given the role of GRP78 and ER stress in immunology.[30 31] In vitro and in vivo preclinical studies demonstrate potential for additive and synergistic combinations, and although the single-agent anticancer activity against tumours was modest, we anticipate that when combined clinically with chemotherapy or targeted agents, we will see an increase in anti-tumour activity and prolonged survival.

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Competing interests DVH discloses that he is a consultant for Intezyne Technologies, the sponsor of this study.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES

1. Dempke W, Voigt W, Grothey A, *et al*. Cisplatin resistance and oncogenes--a review. *Anticancer Drugs* 2000;11:225–36.
2. Galluzzi L, Senovilla L, Vitale I, *et al*. Molecular mechanisms of cisplatin resistance. *Oncogene* 2012;31:1869–83.
3. Jakupec MA, Keppler BK. Gallium and other main group metal compounds as antitumor agents. In: Sigel A, Sigel H, eds. *Metal ions in biological systems: volume 42: metal complexes in tumor diagnosis and as anticancer agents*. New York: Marcel Dekker, 2004:425–62.
4. Galanski M, Arion VB, Jakupec MA, *et al*. Recent developments in the field of tumor-inhibiting metal complexes. *Curr Pharm Des* 2003;9:2078–89.
5. Abid M, Shamsi F, Azam A, *et al*. Ruthenium complexes: an emerging ground to the development of metallopharmaceuticals for cancer therapy. *Mini Rev Med Chem* 2015;16:772–86.
6. Chen Y, Qin MY, Wang L, *et al*. A ruthenium(II) β-carboline complex induced p53-mediated apoptosis in cancer cells. *Biochimie* 2013;95:2050–9.
7. Mangiapia G, Vitiello G, Irace C, *et al*. Anticancer cationic ruthenium nanovectors: from rational molecular design to cellular uptake and bioactivity. *Biomacromolecules* 2013;14:2549–60.
8. Pizarro AM, Habtemariam A, Sadler PJ. Activation mechanisms for organometallic anticancer complexes. 2010;32:21–56.
9. Rademaker-Lakhai JM, van den Bongard D, Pluim D, *et al*. A phase I and pharmacological study with imidazolium-trans-DMSO-imidazole-tetrachlororuthenate, a novel ruthenium anticancer agent. *Clin Cancer Res* 2004;10:3717–27.
10. Leijen S, Burgers SA, Baas P, *et al*. Phase I/II study with ruthenium compound NAMI-A and gemcitabine in patients with non-small cell lung cancer after first line therapy. *Invest New Drugs* 2015;33:201–14.
11. Al-Rawashdeh FY, Scriven P, Cameron IC, *et al*. Unfolded protein response activation contributes to chemoresistance in hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2010;22:1099–105.
12. Roller C, Maddalo D. The molecular chaperone GRP78/BiP in the development of chemoresistance: mechanism and possible treatment. *Front Pharmacol* 2013;4:10.
13. Delpino A, Castelli M, Andrea Delpino MC. The 78 kDa glucose-regulated protein (GRP78/BIP) is expressed on the cell membrane, is released into cell culture medium and is also present in human peripheral circulation. *Biosci Rep* 2002;22:407–20.
14. Daneshmand S, Quek ML, Lin E, *et al*. Glucose-regulated protein GRP78 is up-regulated in prostate cancer and correlates with recurrence and survival. *Hum Pathol* 2007;38:1547–52.
15. Xing X, Lai M, Wang Y, *et al*. Overexpression of glucose-regulated protein 78 in colon cancer. *Clin Chim Acta* 2006;364:308–15.
16. Zhang J, Jiang Y, Jia Z, *et al*. Association of elevated GRP78 expression with increased lymph node metastasis and poor prognosis in patients with gastric cancer. *Clin Exp Metastasis* 2006;23:401–10.
17. Zheng HC, Takahashi H, Li XH, Xh L, *et al*. Overexpression of GRP78 and GRP94 are markers for aggressive behavior and poor prognosis in gastric carcinomas. *Hum Pathol* 2008;39:1042–9.
18. Koomägi R, Mattern J, Volm M. Glucose-related protein (GRP78) and its relationship to the drug-resistance proteins P170, GST-pi, LRP56 and angiogenesis in non-small cell lung carcinomas. *Anticancer Res* 1999;19:4333–6.
19. Little E, Ramakrishnan M, Roy B, *et al*. The glucose-regulated proteins (GRP78 and GRP94): functions, gene regulation, and applications. *Crit Rev Eukaryot Gene Expr* 1994;4:1–18.
20. Li J, Lee AS. Stress induction of GRP78/BiP and its role in cancer. *Curr Mol Med* 2006;6:45–54.
21. Dong D, Ni M, Li J, *et al*. Critical role of the stress chaperone GRP78/BiP in tumor proliferation, survival, and tumor angiogenesis in transgene-induced mammary tumor development. *Cancer Res* 2008;68:498–505.
22. Li J, Ni M, Lee B, *et al*. The unfolded protein response regulator GRP78/BiP is required for endoplasmic reticulum integrity and stress-induced autophagy in mammalian cells. *Cell Death Differ* 2008;15:1460–71.
23. Costich TL, Sethuraman J, Crouse R, *et al*. IT-139 holds potential for combination therapy. 2016, *Proceedings of the 107th Annual Meeting of the American Association for Cancer Research*. New Orleans, LA:AACR, 2016.
24. Sethuraman J, Crouse R, Costich TL, *et al*. IT-139 targets GRP78 in stressed cancer cells. 2016, *Proceedings of the 107th Annual Meeting of the American Association for Cancer Research*. New Orleans, LA:AACR, 2016.
25. Pfaffenbach KT, Lee AS. The critical role of GRP78 in physiologic and pathologic stress. *Curr Opin Cell Biol* 2011;23:150–6.
26. Lee AS. The ER chaperone and signaling regulator GRP78/BiP as a monitor of endoplasmic reticulum stress. *Methods* 2005;35:373–81.
27. Luo S, Mao C, Lee B, *et al*. GRP78/BiP is required for cell proliferation and protecting the inner cell mass from apoptosis during early mouse embryonic development. *Mol Cell Biol* 2006;26:5688–97.

28. Gifford JB, Huang W, Zeleniak AE, *et al*. Expression of GRP78, master regulator of the unfolded protein pesponse, increases chemoresistance in pancreatic ductal adenocarcinoma. *Mol Cancer Ther* 2016;15:1043–52.
29. Lizardo MM, Morrow JJ, Miller TE, *et al*. Upregulation of Glucose-Regulated protein 78 in metastatic cancer cells is necessary for lung metastasis progression. *Neoplasia* 2016;18:699–710.
30. Oida T, Weiner HL. Overexpression of TGF-ß 1 gene induces cell surface localized glucose-regulated protein 78-associated latency-associated peptide/TGF-ß. *J Immunol* 2010;185:3529–35.
31. Mahadevan NR, Zanetti M. Tumor stress inside out: cell-extrinsic effects of the unfolded protein response in tumor cells modulate the immunological landscape of the tumor microenvironment. *J Immunol* 2011;187:4403–9.