3-1-2022

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Recommended Citation

Patnaik A, Gadgeel S, Papadopoulos KP, Rasco DW, Haas NB, Der-Torossian H, Faltaos D, Potvin D, Tassell V, Tawashi M, Chao R, and O'Dwyer PJ. Phase I Study of Glesatinib (MGCD256) in Combination with Erlotinib or Docetaxel in Patients with Advanced Solid Tumors. Target Oncol 2022.

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Targeted Oncology (2022) 17:125–138
https://doi.org/10.1007/s11523-022-00875-0

ORIGINAL RESEARCH ARTICLE

Phase I Study of Glesatinib (MGCD265) in Combination with Erlotinib or Docetaxel in Patients with Advanced Solid Tumors

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Accepted: 3 March 2022 / Published online: 28 March 2022

Abstract

Background Oncogenic drivers in solid tumors include aberrant activation of mesenchymal epithelial transition factor (MET) and AXL.

Objective This study investigated the safety and antitumor activity of glesatinib, a multitargeted receptor tyrosine kinase inhibitor that inhibits MET and AXL at clinically relevant doses, in combination with erlotinib or docetaxel.

Patients and Methods The phase I portion of this open-label, multicenter study included two parallel arms in which ascending doses of oral glesatinib (starting dose 96 mg/m^2) were administered with erlotinib or docetaxel (starting doses 100 mg once daily and 50 mg/m^2, respectively) using a modified 3 + 3 design. Maximum tolerated dose (MTD) was based on dose-limiting toxicities (DLTs) during the first 21-day treatment cycle. Enrollment focused on patients with solid tumor types typically associated with MET aberration and/or AXL overexpression. The primary objective was to determine the safety profile of the treatment combinations. Antitumor activity and pharmacokinetics (PK) were also assessed.

Results Ten dose levels of glesatinib across three glycolate formulations (unmicronized, micronized, or micronized version 2 [V2] tablets) available during the course of the study were investigated in 14 dose-escalation cohorts ($n = 126$). MTDs of unmicronized glesatinib plus erlotinib or docetaxel, and micronized glesatinib plus erlotinib were not reached. Micronized glesatinib 96 mg/m^2 plus docetaxel exceeded the MTD. Further dosing focused on glesatinib micronized V2: maximum administered dose (MAD) was 700 mg twice daily with erlotinib 150 mg once daily or docetaxel 75 mg/m^2 every 3 weeks. DLTs, acceptable at lower glesatinib (micronized V2) dose levels, occurred in two of five and two of six patients at the MADs of glesatinib + erlotinib and glesatinib + docetaxel, respectively. Across all cohorts, the most frequent treatment-related adverse events were diarrhea (glesatinib + erlotinib: 84.1%; glesatinib + docetaxel: 45.6%), fatigue (46.4%, 70.4%), and nausea (30.4%, 35.1%). The objective response rate was 1.8% and 12.0% in all glesatinib + erlotinib and glesatinib + docetaxel cohorts, respectively.

Conclusions The safety profile of glesatinib plus erlotinib or docetaxel was acceptable and there were no PK interactions. MADs of glesatinib 700 mg twice daily (micronized V2) with erlotinib 150 mg once daily or docetaxel 75 mg/m^2 every 3 weeks exceeded the MTD by a small margin. Modest signals of efficacy were observed with these treatment combinations in non-genetically selected patients with advanced solid tumors.

Clinical Trials Registration ClinicalTrials.gov NCT00975767; 11 September 2009.

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Key Points

This was a phase I, open-label, dose-escalation study of glesatinib, a multitargeted inhibitor of mutant and wild-type MET, AXL, and other receptor tyrosine kinases, in a non-genetically selected population of patients with advanced solid tumors.

The study demonstrated modest efficacy, an acceptable safety profile, and no pharmacokinetic interactions for glesatinib glycolate formulations in combination with either erlotinib or docetaxel; exposure was suboptimal.

Further investigation of glesatinib, to be reported separately, focused on free-base formulations, aimed to improve drug bioavailability in patients with MET-activating alterations.

1 Introduction

Binding of hepatocyte growth factor (HGF) to mesenchymal epithelial transition factor (MET) receptor tyrosine kinase activates downstream signaling pathways involved in morphogenic, proliferative, and antiapoptotic processes [1]. Aberrant MET activation can be triggered by *MET* amplification as well as a range of *MET* mutations, including exon 14 skipping mutations that result in constitutive activation of MET [2]. Overexpression of MET or heightened MET activity can contribute to tumor progression by promoting tumor cell survival, proliferation and migration, epithelial-mesenchymal transition (EMT), and angiogenesis [3]. *MET* exon 14 skipping mutations and amplification are reported in patients with non-small cell lung cancer (NSCLC) and are also observed at varying incidences across other solid tumors, including, but not limited to, colon cancer, gastric cancer, prostate cancer, and renal cell carcinoma [4–6]. Importantly, tumors with *MET* amplification and *MET* exon 14 skipping alterations are associated with poor prognosis [7].

Aberrant MET activation has been identified as a mechanism of resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). This occurs by activating EGFR-independent phosphorylation of ErbB3 and the PI3K/AKT pathway, providing a bypass resistance mechanism [8, 9]. Consequently, co-targeting EGFR and MET has the potential to prevent this crosstalk and overcome resistance in some patients. This is supported by a phase 1b study in which partial responses (PRs) were observed in patients with MET-amplified NSCLC treated with the EGFR TKI osimertinib, and savolitinib, an MET TKI [10]. Activation of other bypass signaling pathways has also been implicated in resistance to EGFR TKIs, including ErbB2, fibroblast growth factor receptor, insulin-like growth factor 1 receptor, and AXL [11]. High expression of AXL has been linked with tumor growth, EMT, and metastasis and is associated with poor prognosis in a range of tumors, including lung cancer [12–18]. Furthermore, in NSCLC cells, AXL has been shown to interact with EGFR and HER3 and maintain cell survival following exposure to EGFR TKIs. Moreover, in in vivo models, an AXL inhibitor plus EGFR TKI reduced tumor size and delayed tumor regrowth compared with an EGFR TKI alone [19].

Glesatinib (MGCD265) is an investigational receptor TKI of mutant and wild-type forms of MET, along with AXL, MER proto-oncogene tyrosine kinase (MERTK), vascular endothelial growth factor receptor (VEGFR), and the platelet-derived growth factor receptor (PDGFR) family in preclinical studies [20]. At clinically achievable doses, MET and AXL were identified as the most relevant glesatinib targets based on pharmacodynamic and preliminary clinical data [20]. Single-agent glesatinib was shown to induce robust tumor regression in patient-derived NSCLC xenograft models with *MET* exon 14 deletion and *MET* amplification as putative oncogenic drivers [20]. The present study investigated the safety profile of glesatinib, across different formulations based on emerging data, in combination with the EGFR TKI erlotinib or the frequently used taxane docetaxel, in patients with advanced solid tumors. The antitumor activity of these treatment combinations was also evaluated in patients with advanced solid tumors who were not genetically selected for MET/AXL alterations such as skipping mutations or amplification, or expression.

2 Methods

2.1 Study Design and Patient Population

This open-label, multicenter study evaluated glesatinib in combination with erlotinib or docetaxel. We enrolled non-genetically selected patients ≥ 18 years of age with histologically or cytologically confirmed advanced metastatic or unresectable solid malignancy that was refractory to standard therapy/unlikely to achieve clinical benefit, or who had declined standard therapy. All patients had documented progressive disease (PD) during or following their most recent treatment, and evaluable disease (either measurable or non-measurable by Response Evaluation Criteria in Solid Tumors [RECIST] v1.1). Patients also had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate renal, hepatic and bone marrow function. Key

exclusion criteria were anticancer treatment within 4 weeks of the first study treatment; prior treatment with a MET inhibitor or anti-HGF therapy; uncontrolled concurrent illness including serious infection, hypertension or endocrine disease; stroke or transient ischemic attack in the prior 6 months; history of bleeding diathesis, coagulopathy or cardiovascular illness; and QT interval corrected for heart rate (QTc) > 470 ms.

While there were no genetic selection criteria for the phase I dose-escalation cohorts, enrollment focused on patients with specific cancer types (including NSCLC, prostate cancer, gastric cancer) and patients with other solid tumors typically associated with MET alterations such as skipping mutations or amplification, or AXL overexpression.

The phase I portion of the study (modified 3 + 3 design) included two parallel arms in which ascending doses of oral glesatinib (starting dose 96 mg/m^2) were administered with either erlotinib or docetaxel (treatment assignment was based on the investigator's judgment) at starting doses of 100 mg once daily and 50 mg/m^2 every 3 weeks, respectively. Glesatinib was administered either once daily or twice daily, either fasted (no food for 2 h prior to or 1 h after dosing) or with food, depending on the cohort, and was initially supplied as an unmicronized glycolate formulation. Based on available data during the study, a micronized glesatinib glycolate formulation was provided followed by a version 2 (V2) micronized tablet containing sodium lauryl sulphate, aimed at improving the consistency of particle size and absorption, respectively.

If no dose-limiting toxicities (DLTs; defined below) were observed in the first patient cohort during Cycle 1, a new cohort of three or four patients was enrolled at dose level 2 (glesatinib 96 mg/m^2 plus erlotinib 150 mg once daily or docetaxel 75 mg/m^2 every 3 weeks) (Fig. 1). If one of three or four patients experienced a DLT at dose level 1 then up to four additional patients were to be enrolled at that dose level, and if one or fewer of six of these patients experienced a DLT then a new cohort was enrolled (at dose level 2). Subsequent dose escalations are described in Fig. 1. If ≥ 33% of six or more patients experienced a DLT at any dose level, the maximum tolerated dose (MTD) would be exceeded. Study treatment (21-day cycles) was continued until unacceptable toxicity, disease progression/recurrence, or withdrawal of consent. Dose modifications of glesatinib, erlotinib, or docetaxel were permitted for adverse events (AEs) considered related to study medication.

Phase I expansion cohorts were planned at the MTD or maximum administered dose (MAD) in each study arm in patients genetically selected for MET and/or AXL alterations, along with a phase II randomized portion of the study, investigating glesatinib plus erlotinib versus glesatinib plus docetaxel in patients with MET and/or AXL altered NSCLC, but were not conducted (see below).

The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, and local regulatory requirements. The study protocol was approved by the Institutional Review Boards at each participating study site.

2.2 Study Endpoints and Assessments

The phase I primary objective was to determine the safety profile of glesatinib in combination with erlotinib or docetaxel, including the MTD/MAD and DLTs. Evaluation of antitumor activity and pharmacokinetics (PK) of glesatinib plus erlotinib or docetaxel were included as secondary objectives.

Safety assessment included evaluation of AEs, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0, laboratory assessments, physical examinations, vital signs, and electrocardiograms/multiple gated acquisition scans. DLTs were defined as any of the following AEs occurring during Cycle 1 that were considered possibly, probably, or definitely related to glesatinib: Grade 4 neutropenia for ≥ 7 days; Grade 3 or higher febrile neutropenia; Grade 4 thrombocytopenia (or anemia or bleeding episode requiring platelet transfusion); Grade 3 or higher clinically significant, non-hematologic toxicity unrelated to the underlying malignancy; severe hypertension (≥ 180/120 mmHg); sustained uncontrolled hypertension (150–179/100–119 mmHg for ≥ 14 days or causing a treatment delay of ≥ 4 days); and any toxicity other than Grade 3 neutropenia that resulted in a treatment delay of ≥ 6 or ≥ 12 doses of glesatinib administered on once-daily or twice-daily schedules, respectively, that was of sufficient severity to be considered a DLT.

Tumor evaluations using magnetic resonance imaging or computed tomography scans were performed every two cycles. Progression-free survival (PFS) was assessed using Kaplan–Meier methodology (time from first study treatment to first documented disease progression or death), and objective response rate (ORR) was evaluated per RECIST v1.1 and/or other appropriate criteria [21]. Blood samples for PK assessments were obtained during Cycle 1 (days 1, 2, 3, and 8) and Cycle 2 (days 1, 2, and 3); day 1 PK samples were obtained at five timepoints in both cycles. Analysis of plasma samples for glesatinib, erlotinib, and docetaxel concentrations were performed using validated methods.

2.3 Statistical analysis

For the phase I dose escalation, enrollment of approximately 60–90 patients was planned for the glesatinib + erlotinib

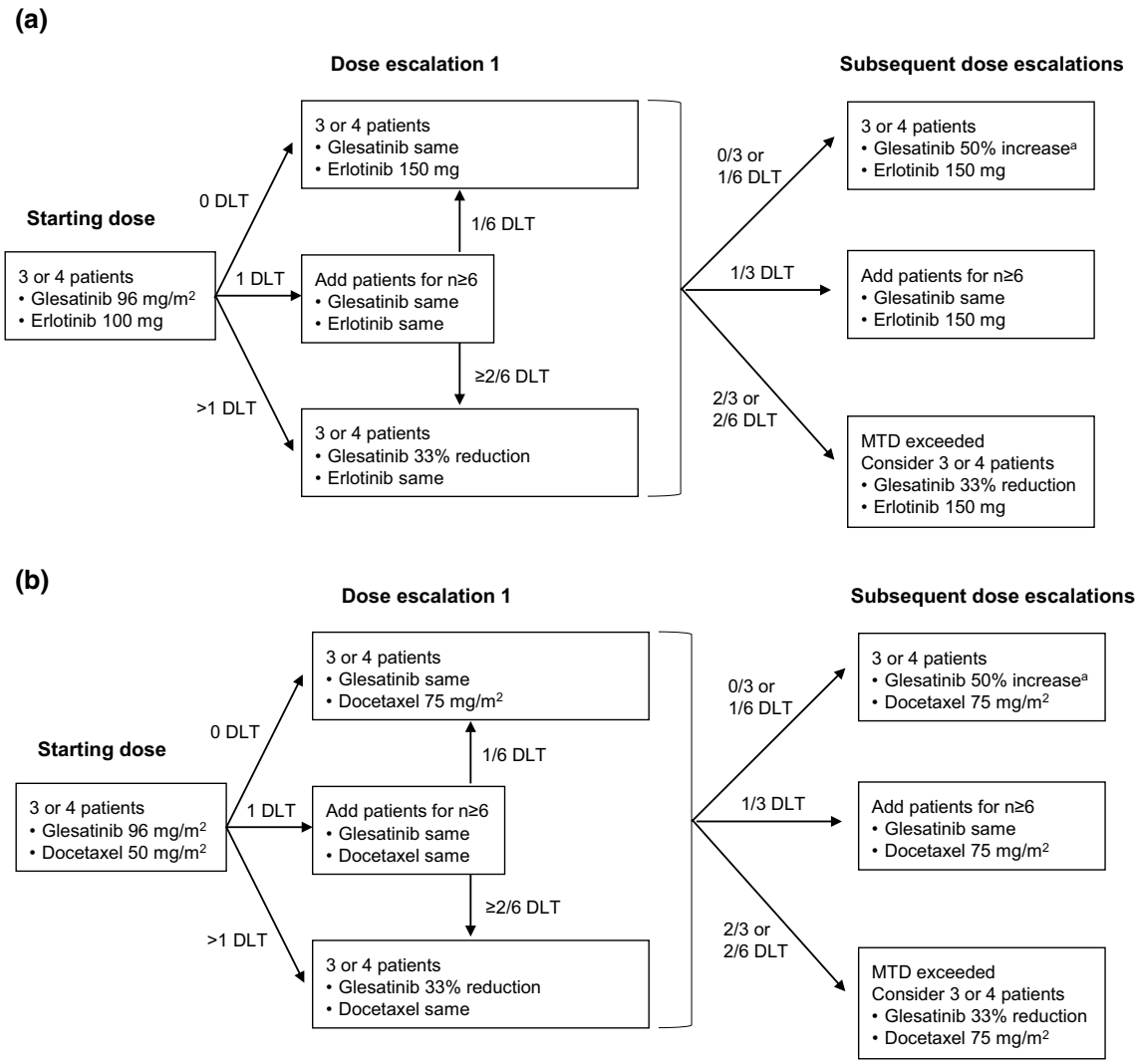

Fig. 1 Dose escalation schemes. **a** Glesatinib plus erlotinib; **b** glesatinib plus docetaxel. [a]If no Grade 2 or higher treatment-related adverse events had occurred at that dose level or at any prior dose level, the glesatinib dose could be increased by more than 50% (but not > 100%) following agreement by the study investigators and sponsor. *DLT* dose-limiting toxicity, *MTD* maximum tolerated dose

arm. Approximately 60–90 patients were also planned for the glesatinib + docetaxel arm.

Data were summarized using descriptive statistics. Safety was evaluated in all patients who received one or more doses of any study drug. DLTs were evaluated in patients who received ≥ 70% of the planned glesatinib dose and either ≥ 70% of the planned erlotinib dose or the single planned intravenous administration of docetaxel during Cycle 1 and who were evaluable for toxicity throughout Cycle 1 or experienced a DLT. Efficacy is presented for patients who received one or more doses of glesatinib and erlotinib/docetaxel and had one or more on-study disease assessments. PK were assessed in all patients with sufficient concentration–time data and analyzed by noncompartmental methods using Phoenix WinNonlin v6.2.1 (Pharsight Corporation, St Louis, MO, USA).

3 Results

3.1 Patient Characteristics and Disposition

In total, 126 patients were recruited into the Phase I portion of the study between 15 August 2009 and 15 July 2013, with $n = 69$ and $n = 57$, respectively, for the combinations of glesatinib + erlotinib and glesatinib + docetaxel. The study was closed prematurely prior to enrollment of the phase I dose expansion and the phase II

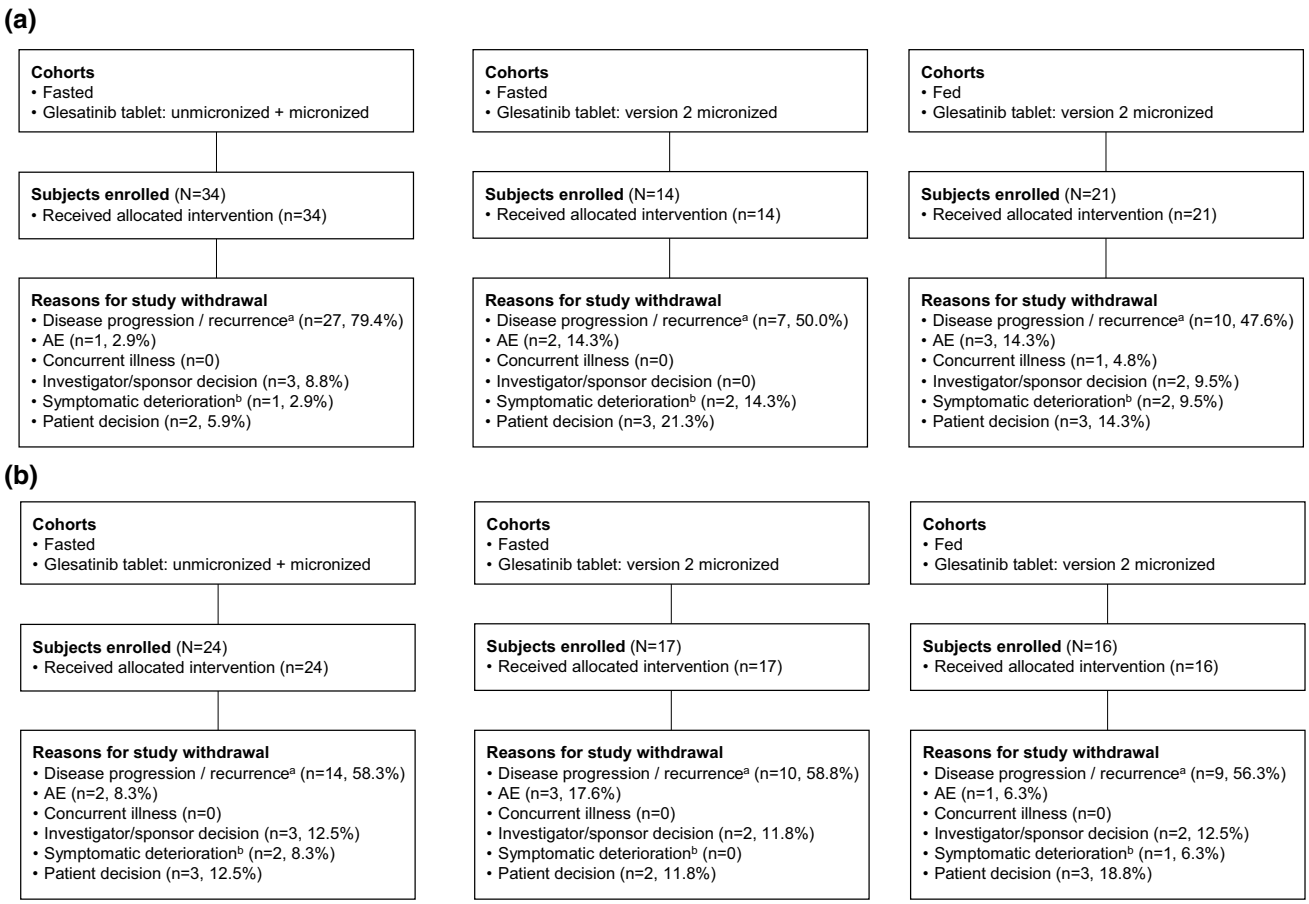

Fig. 2 Patient disposition. **a** Glesatinib plus erlotinib; **b** glesatinib plus docetaxel. [a]Per RECIST version 1.1 (patients with prior response or stable disease recorded in efficacy evaluations may discontinue due to disease progression reported at a later timepoint). [b]Global deterioration in health status without objective evidence of disease progression per RECIST version 1.1. *AE* adverse event, *RECIST* Response Evaluation Criteria in Solid Tumors

randomized portions of this study due to the planned reformulation of glesatinib. Most patients discontinued due to disease progression (glesatinib + erlotinib, $n = 44$ [63.8%]; glesatinib + docetaxel, $n = 33$ [57.9%]) and few discontinued due to AEs ($n = 6$ [8.7%]; $n = 6$ [10.5%]) (Fig. 2).

Baseline demographic and disease characteristics were similar across the two phase I cohorts (Table 1). Median age was 61.9 and 61.6 years in the glesatinib + erlotinib and glesatinib + docetaxel cohorts, respectively. Approximately half the patients were never smokers and had an ECOG performance status of 1. Nearly all patients had received prior chemotherapy and approximately half had received radiotherapy. The most frequent cancer diagnoses were NSCLC, colon cancer, pancreatic cancer, and gastric cancer (Table 1).

3.2 Dose Escalation and Dose-Limiting Toxicities

In each study arm, 14 dosing cohorts were investigated based on the formulation (unmicronized, micronized, or micronized V2 tablets), dose and frequency of glesatinib administration, erlotinib/docetaxel dose, and whether study treatment was administered in a fasted or fed state (Table 2).

In the glesatinib + erlotinib arm, dose escalation proceeded through 10 dose levels of glesatinib across the three formulations. As one of three patients experienced a DLT of Grade 3 diarrhea (probably related to glesatinib and erlotinib) in the first cohort of glesatinib 96 mg/m^2 once daily (unmicronized), this was expanded to six evaluable patients and no further DLTs were observed. Acneiform rash and fatigue (both Grade 3 and considered related to glesatinib and erlotinib) were observed in two patients enrolled in the glesatinib 144 mg/m^2 once daily (micronized) cohort; the cohort was expanded with no further DLTs reported. DLTs were also seen with glesatinib micronized V2 tablets 108 mg/m^2 twice daily (Grade 3 diarrhea, related to glesatinib and erlotinib) and 162 mg/m^2 twice daily (diarrhea and rhabdomyolysis; both Grade 3 and related to glesatinib and erlotinib). No DLTs were observed with fixed doses of glesatinib (V2 micronized) 250 mg once daily, 500 mg once daily, or 500 mg twice daily + erlotinib. The final dose level

Table 1 Baseline demographic and disease characteristics (safety population)

	Glesatinib + erlotinib [*N* = 69]	Glesatinib + docetaxel [*N* = 57]
Age, years [median (range)]	61.9 (32.6–84.1)	61.6 (46.2–81.4)
Male	39 (56.5)	32 (56.1)
ECOG performance status		
0	31 (44.9)	29 (50.9)
1	38 (55.1)	28 (49.1)
Never smoker	38 (55.1)	23 (40.4)
Cancer diagnosis[a]		
NSCLC	10 (14.5)	16 (28.1)
Colon cancer	14 (20.3)	0
Pancreatic carcinoma	3 (4.3)	7 (12.3)
Gastric cancer	5 (7.2)	2 (3.5)
Pancreatic adenocarcinoma	6 (8.7)	0
Esophageal adenocarcinoma	4 (5.8)	2 (3.5)
Rectal cancer	5 (7.2)	0
Liver cancer	4 (5.8)	0
Prostate cancer	0	4 (7.0)
Bladder cancer	1 (1.4)	2 (3.5)
Transitional cell carcinoma	0	3 (5.3)
Prior cancer treatment		
Chemotherapy	66 (95.7)	51 (89.5)
Surgery	40 (58.0)	30 (52.6)
Radiation	38 (55.1)	30 (52.6)
Hormonal therapy	0	4 (7.0)
Other	15 (21.7)	18 (31.6)
Months from cancer diagnosis to first dose of study medication [mean (SD)]	44.3 (47.7)	36.3 (31.1)
Months from the most recent recurrence/relapse to first dose of study medication [mean (SD)]	14.3 (16.5)	12.6 (17.3)

Data are expressed as *n* (%) unless otherwise specified

ECOG Eastern Cooperative Oncology Group, *NSCLC* non-small cell lung cancer, *SD* standard deviation

[a]Reported for three or more patients

and MAD in this treatment arm was glesatinib 700 mg (V2 micronized) twice daily with food + erlotinib 150 mg once daily, at which two of five DLT-evaluable patients experienced DLTs of Grade 3 diarrhea (both considered related to glesatinib and erlotinib) (Table 2).

Dose escalation of glesatinib + docetaxel also proceeded through 10 glesatinib dose levels across the three formulations. No DLTs were observed with glesatinib (unmicronized and micronized formulations) at doses up to 144 mg once daily in combination with docetaxel. Following DLTs of Grade 3 diarrhea (related to glesatinib and docetaxel) and Grade 3 elevated lipase (related to glesatinib) in the first patient who received glesatinib 96 mg/m^2 twice daily (micronized) + docetaxel 75 mg/m^2 every 3 weeks, and a DLT of Grade 3 fatigue in the second patient in this cohort, the MTD of micronized glesatinib (micronized) + docetaxel was considered exceeded. With glesatinib micronized V2 tablets, no DLTs were observed at doses of 48–170 mg/m^2 twice daily or a 300 mg twice-daily fixed dose. A DLT of elevated aspartate aminotransferase (AST; considered related to docetaxel) was observed in one of six patients in the glesatinib 450 mg twice daily cohort, and at the MAD of glesatinib 700 mg twice daily (V2 micronized) + docetaxel 75 mg/m^2 every 3 weeks, two of six DLT-evaluable patients experienced DLTs: Grade 2 acute pancreatitis (considered related to glesatinib and unrelated to docetaxel) and Grade 3 elevated AST (considered related to glesatinib and docetaxel) (Table 2).

While the MADs of glesatinib (V2 micronized) 700 mg twice daily in combination with erlotinib 150 mg once daily or docetaxel 75 mg/m^2 every 3 weeks exceeded the MTD in both study arms, evaluation of MTD did not proceed due to termination of the study (further MTD

Table 2 Dose-limiting toxicities across the glesatinib dosing cohorts

Cohort	Glesatinib dose and formulation	Fed or fasting	Received study medication (DLT evaluable), *n*	Observed DLTs[a] *Relationship to study medication*
Glesatinib glycolate + erlotinib (100 mg qd in Cohort 1 and 150 mg qd in Cohorts 2–14)				
1	96 mg/m^2 qd Unmicronized	Fasting	8 (6)	Diarrhea (Grade 3, $n = 1$) *Related to glesatinib and erlotinib*
2	96 mg/m^2 qd Unmicronized	Fasting	6 (4)	0
3	96 mg/m^2 qd Micronized	Fasting	4 (3)	0
4	144 mg/m^2 qd Micronized	Fasting	9 (9)	Acneiform rash (Grade 3, $n = 1$) *Related to glesatinib and erlotinib* Fatigue (Grade 3, $n = 1$) *Related to glesatinib and erlotinib*
5	72 mg/m^2 bid Unmicronized	Fasting	4 (4)	0
6	108 mg/m^2 bid Unmicronized	Fasting	3 (3)	0
7	72 mg/m^2 bid Micronized V2	Fasting	3 (3)	0
8	108 mg/m^2 bid Micronized V2	Fasting	4 (4)	Diarrhea (Grade 3, $n = 1$) *Related to glesatinib and erlotinib*
9	162 mg/m^2 bid Micronized V2	Fasting	7 (4)	Diarrhea (Grade 3, $n = 1$) *Related to glesatinib and erlotinib* Rhabdomyolysis (Grade 3, $n = 1$) *Related to glesatinib and erlotinib*
10	75 mg/m^2 qd Micronized V2	Fed	3 (3)	0
11	250 mg qd Micronized V2	Fed	4 (3)	0
12	500 mg qd Micronized V2	Fed	3 (3)	0
13	500 mg bid Micronized V2	Fed	4 (4)	0
14	700 mg bid Micronized V2	Fed	7 (5)	Diarrhea (Grade 3, $n = 2$) *Related to glesatinib and erlotinib (both events)*
Glesatinib glycolate + docetaxel (50 mg/m^2 q3w in Cohort 1 and 75 mg/m^2 q3w in Cohorts 2–14)				
1	96 mg/m^2 qd Unmicronized	Fasting	3 (3)	0
2	96 mg/m^2 qd Unmicronized	Fasting	4 (3)	0
3	144 mg/m^2 qd Unmicronized	Fasting	4 (3)	0
4	144 mg/m^2 qd Micronized	Fasting	4 (4)	0
5	96 mg/m^2 bid Micronized	Fasting	2 (2)	Fatigue (Grade 3, $n = 1$) *Related to glesatinib and docetaxel* Diarrhea (Grade 3, $n = 1$)[b] *Related to glesatinib and docetaxel* Lipase increased (Grade 3, $n = 1$)[b] *Related to glesatinib*
6	72 mg/m^2 bid Unmicronized	Fasting	7 (7)	Lipase increased (Grade 3, $n = 1$) *Related to glesatinib*
7	48 mg/m^2 bid Micronized V2	Fasting	3 (3)	0
8	72 mg/m^2 bid Micronized V2	Fasting	3 (3)	0

Table 2 (continued)

Cohort		Glesatinib dose and formulation	Fed or fasting	Received study medication (DLT evaluable), *n*	Observed DLTs[a] *Relationship to study medication*
9	96 mg/m^2 bid Micronized V2		Fasting	4 (3)	0
10	128 mg/m^2 bid Micronized V2		Fasting	3 (3)	0
11	170 mg/m^2 bid Micronized V2		Fasting	4 (4)	0
12	300 mg bid Micronized V2		Fed	4 (4)	0
13	450 mg bid Micronized V2		Fed	6 (6)	AST increased (Grade 3, $n = 1$) *Related to docetaxel*
14	700 mg bid Micronized V2		Fed	6 (6)	AST increased (Grade 3, $n = 1$) *Unrelated to glesatinib and docetaxel* Acute pancreatitis (Grade 2, $n = 1$)[c] *Related to glesatinib*

AST aspartate aminotransferase, *bid* twice daily, *DLT* dose-limiting toxicity, *qd* once daily, *q3w* once every 3 weeks, *V2* version 2 formulation (contained sodium lauryl sulphate), *NCI-CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events

[a]NCI-CTCAE grade; 'related' includes 'definitely', 'probably', and 'possibly' related to study treatment per investigator assessment

[b]Observed in the same patient

[c]Event resulted in study discontinuation and was determined as a DLT by the investigator, in consultation with the sponsor

evaluations were planned using reformulated glesatinib, as described below).

3.3 Safety

Median (range) duration of study treatment was 1.3 months (0 days to 28.0 months) and 1.3 months (1 day to 18.1 months) in the glesatinib + erlotinib and glesatinib + docetaxel groups, respectively, with approximately half of the patients (50.7% and 52.6%, respectively) completing only one cycle of treatment. The mean (standard deviation) relative dose intensity of glesatinib was 90.7% (16.7%) and 89.6% (16.9%) in the glesatinib + erlotinib and glesatinib + docetaxel groups, respectively.

The most frequent treatment-emergent AEs were diarrhea (glesatinib + erlotinib: 80.7% [$n = 60$]; glesatinib + docetaxel: 49.1% [$n = 28$]), fatigue (59.4% [$n = 41$]; 75.4% [$n = 43$]), neutropenia (0; 64.9% [$n = 37$]), alopecia (0; 49.1% [$n = 28$]), and nausea (40.6% [$n = 28$]; 40.4% [$n = 23$]). These AEs were frequently considered related to study treatment (Table 3). Across the study, 42 patients experienced 64 treatment-emergent serious AEs (SAEs), of which disease progression was most frequent (glesatinib + erlotinib: 11.6% [$n = 8$]; glesatinib + docetaxel: 5.3% [$n = 3$]). Other treatment-emergent SAEs occurring in two or more patients were gastrointestinal hemorrhage, pneumonia, and pulmonary embolism (glesatinib + erlotinib, each $n = 2$ [2.9%]) and febrile neutropenia (glesatinib + docetaxel: $n = 2$ [3.5%]). Laboratory results were unremarkable. Increased QTc (≥30 msec from baseline) was observed in eight patients (14.0%) receiving glesatinib + docetaxel, ranging from 30.8 to 38.6 msec, and was not considered clinically significant. Left ventricular ejection fraction decline was observed in two patients (2.9%) receiving glesatinib + erlotinib (screening to study end: 55 to 36% [reported as a treatment-related SAE in an individual with a history of coronary disease] and 57 to 41% [not reported as an AE]). Thirteen patients (10.3%) died within 28 days of receiving the last dose of study medication: 12 deaths were considered unrelated to study medication ($n = 11$ disease progression, $n = 1$ cardiorespiratory arrest), while one death due to pneumonitis was considered possibly related to study medication and occurred in a patient with NSCLC receiving glesatinib + docetaxel (1.8%) who had dyspnea and decreased right lung breath sounds, ongoing since study enrollment.

3.4 Efficacy

Of the patients who received glesatinib + erlotinib, ORR was 1.8%. One PR (duration of 6 months with fasted glesatinib 72 mg/m^2 twice daily + erlotinib 150 mg in an individual with NSCLC) was reported among the 50 patients with measurable disease at baseline (there were no responses in the seven patients with non-measurable disease at baseline). Stable disease (SD) was observed in 27 patients (47.4%), while 22 patients (38.6%) had disease progression (PD). Of the patients who received glesatinib + docetaxel, ORR was 12.0%. PRs were observed in 6 of 49 patients with measurable disease at baseline (NSCLC, $n = 2$; urothelial cancer,

Table 3 AEs (NCI-CTCAE grade) considered related to study treatment (any AE considered 'unknown', 'possibly', 'probably' or 'definitely' related to any study drug) occurring in ≥10% of patients (safety population)

MedDRA preferred term	Glesatinib + erlotinib [*N* = 69]		Glesatinib + docetaxel [*N* = 57]	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Diarrhea	58 (84.1)	12 (17.4)	26 (45.6)	4 (7.0)
Fatigue	32 (46.4)	1 (1.4)	40 (70.2)	1 (1.8)
Nausea	21 (30.4)	0	20 (35.1)	0
Rash	30 (43.5)	1 (1.4)	8 (14.0)	0
Neutropenia	0	0	37 (64.9)	37 (64.9)
Anorexia	20 (29.0)	0	16 (28.1)	0
Alopecia	0	0	28 (49.1)	0
Vomiting	9 (13.0)	0	13 (22.8)	0
Dysgeusia	8 (11.6)	0	13 (22.8)	0
Mucosal inflammation	6 (8.7)	0	10 (17.5)	0
Hypokalemia	10 (14.5)	4 (5.8)	5 (8.8)	2 (3.5)
Dermatitis acneiform	14 (20.3)	1 (1.4)	0	0
Dry skin	10 (14.5)	0	4 (7.0)	0

Data are expressed as *n* (%)

AEs adverse events, *MedDRA* Medical Dictionary for Regulatory Activities, *NCI-CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events

nasopharyngeal cancer, prostate cancer, endometrial cancer, $n = 1$ each; median [range] duration of response was 2.8 months [1 day to 10.6 months]; there was no response in one patient with non-measurable disease). SD was reported in 24 patients (48.0%) and PD in 19 patients (38.0%). Median (95% confidence interval) PFS was 2.5 months (1.4–3.7) and 3.1 months (1.5–4.4) for the glesatinib + erlotinib and glesatinib + docetaxel groups, respectively.

3.5 Pharmacokinetics

Following multiple doses of glesatinib with docetaxel or erlotinib under fasted or fed conditions, after reaching maximum plasma concentration (C_{max}), plasma glesatinib concentration declined slowly. The median time to reach C_{max} (t_{max}) was observed 1–11 h postdose, and mean peak-to-trough ratios were approximately 0.9–3.4 across all cohorts under fasted conditions. Bioavailability was limited, with systemic exposure to glesatinib tending to increase in a less than dose proportional manner at higher doses, and there was no evidence to suggest improved absorption or bioavailability was associated with a particular formulation of glesatinib. Food did not appear to impact the PK parameters of glesatinib: C_{max} and area under the plasma concentration–time curve from time zero to 12 h (AUC_{12}) values were comparable in fed and fasted cohorts receiving glesatinib V2 tablets twice daily (with erlotinib or docetaxel). While high interpatient variability was observed, there was no evidence that increasing the dose of erlotinib or docetaxel impacted glesatinib PK parameters, or *vice versa*. Plasma PK parameters for glesatinib in combination with erlotinib and docetaxel are summarized Tables 4 and 5, respectively.

4 Discussion

This study examined the potential utility of combining glesatinib, an investigational TKI of MET and AXL at clinically relevant doses, with erlotinib and separately with docetaxel. Glesatinib was evaluated across different glycolate formulations (unmicronized, micronized, and micronized V2 tablets) and at differing dose levels.

The tolerability of glesatinib in combination with erlotinib or docetaxel was acceptable and no safety concerns were identified that were considered likely to impact further clinical development. Across the treatment cohorts, diarrhea (glesatinib + erlotinib: 84.1%; glesatinib + docetaxel: 45.6%), fatigue (46.4%; 70.4%), nausea (30.4%; 35.1%), and rash (43.5%; 14.0%) were the most frequent AEs considered related to any study treatment, broadly in line with the anticipated safety profile of these treatment combinations. PK data revealed glesatinib concentrations were comparable between the fed and fasted cohorts receiving glesatinib micronized V2, indicating a lack of food effect, facilitating convenient timing for twice-daily dosing. Furthermore, there was no evidence of drug–drug interactions with glesatinib and erlotinib or docetaxel, suggesting glesatinib may have the potential to be combined with other cytotoxic agents.

Table 4 Pharmacokinetic parameters for glesatinib in combination with erlotinib (erlotinib dose was 100 mg qd in cohort 1 and 150 mg qd in cohorts 2–14) during cycle 2, day 1

Cohort	Glesatinib dose and formulation	Statistic	C_{max} (ng/mL)	t_{max} [a] (h)	AUC_{12} [b] (ng·h/mL)	CL_{ss}/F (L/h)	C_{max}/C_{trough} ratio
Glesatinib qd under fasted conditions							
1	96 mg/m^2 qd	Mean	59.3	4.0	1080	208	2.56
	Unmicronized	SD	25.5	(3.0–10.0)	443	74.7	1.36
		n	6	6	6	6	6
2	96 mg/m^2 qd	Mean	58.4	7.5	1143	207	3.38
	Unmicronized	SD	34.6	(5.0–24.0)	792	126	3.86
		n	4	4	4	4	4
3	96 mg/m^2 qd	Mean	56.8	3.0	1160	212	1.49
	Micronized	SD	26.9	(3.0–5.0)	529	123	0.116
		n	4	4	4	4	4
4	144 mg/m^2 qd	Mean	51.8	5.0	975	358	1.75
	Micronized	SD	21.8	(1.0–5.0)	488	144	0.502
		n	7	7	7	7	7
Glesatinib bid under fasted conditions							
5	72 mg/m^2 bid	Mean	48.0	2.0	529	500	1.00
	Unmicronized	SD	38.0	(1.0–10.0)	416	449	0.068
		n	4	4	4	4	4
6	108 mg/m^2 bid	Mean	60.5	5.5	690	513	0.937
	Unmicronized	SD	NC	(1.0–10.0)	NC	NC	NC
		n	2	2	2	2	2
7	72 mg/m^2 bid	Mean	62.0	5.0	629	253	1.28
	Micronized V2	SD	21.2	(3.0–12.0)	177	78.6	0.417
		n	3	3	3	3	3
8	108 mg/m^2 bid	Mean	59.3	5.0	452	485	1.09
	Micronized V2	SD	32.2	(1.0–10.0)	NC	NC	0.077
		n	3	3	2	2	3
9	162 mg/m^2 bid	Mean	90.6	1.0	937	389	0.99
	Micronized V2	SD	41.3	(1.0–3.0)	422	232	0.241
		n	3	3	3	3	3
Glesatinib qd under fed conditions							
10	75 mg/m^2 qd	Mean	50.8	24.0	1018	131	1.36
	Micronized V2	SD	3.64	(5.0–24.0)	72.7	56.3	0.361
		n	3	3	3	3	3
11	250 mg qd	Mean	39.0	9.0	846	403	1.22
	Micronized V2	SD	24.6	(1.0–12.0)	538	272	0.356
		n	3	3	3	3	3
12	500 mg qd	Mean	94.4	12.0	1935	265	1.34
	Micronized V2	SD	14.5	(10.0–24.0)	393	53.0	0.114
		n	3	3	3	3	3
Glesatinib bid under fed conditions							
13	500 mg bid	Mean	183	7.5	1916	269	1.15
	Micronized V2	SD	51.5	(5.0–10.0)	412	53.3	0.044
		n	4	4	4	4	4
14	700 mg bid	Mean	111	5.0	1290	543	1.18
	Micronized V2	SD	NC	(5.0–5.0)	NC	NC	NC
		n	1	1	1	1	1

$AUC_{12/24}$ area under the plasma concentration–time curve from time zero to 12 or 24 h after dosing, *bid* twice daily, *CL_{ss}/F* apparent clearance after multiple oral administrations, *C_{max}* maximum plasma concentration, *C_{trough}* predose plasma concentration, *NC* not calculated, *qd* once daily, *SD* standard deviation, *t_{max}* time to maximum observed plasma concentration

[a]Median and range reported for t_{max}

[b]AUC_{24} reported for cohorts 1–4 and cohorts 10–12

Table 5 Pharmacokinetic parameters for glesatinib in combination with docetaxel (docetaxel dose was 50 mg/m^2 q3w in cohort 1 and 75 mg/m^2 q3w in cohorts 2–14) during cycle 2, day 1

Cohort	Glesatinib dose and formulation	Statistic	C_{max} (ng/mL)	t_{max} [a] (h)	AUC_{12} [b] (ng·h/mL)	CL_{ss}/F (L/h)	C_{max}/C_{trough} ratio
Glesatinib qd under fasted conditions							
1	96 mg/m^2 qd	Mean	83.5	3.0	1574	128	1.74
	Unmicronized	SD	11.9	(2.0–5.0)	137	11.1	0.475
		n	3	3	3	3	3
2	96 mg/m^2 qd	Mean	74.7	5.0	1207	157	2.51
	Unmicronized	SD	30.8	(3.0–5.0)	443	85.2	0.799
		n	3	3	3	3	3
3	144 mg/m^2 qd	Mean	67.3	7.0	1120	407	2.37
	Unmicronized	SD	58.5	(3.0–7.0)	928	355	0.860
		n	3	3	3	3	3
4	144 mg/m^2 qd	Mean	99.7	2.0	1643	182	1.56
	Micronized	SD	41.7	(2.0–24.0)	861	57.3	0.465
		n	3	3	3	3	3
Glesatinib bid under fasted conditions							
5	96 mg/m^2 bid	Mean	64.7	11.0	488	410	120
	Micronized	SD	NC	(11.0–11.0)	NC	NC	NC
		n	1	1	1	1	1
6	72 mg/m^2 bid	Mean	84.2	4.0	828	241	1.43
	Unmicronized	SD	45.8	(2.0–5.0)	430	226	0.302
		n	6	6	6	6	6
7	48 mg/m^2 bid	Mean	58.9	2.0	602	184	1.12
	Micronized V2	SD	24.3	(2.0–2.0)	246	66.8	0.098
		n	3	3	3	3	3
8	72 mg/m^2 bid	Mean	96.3	1.0	854	138	1.19
	Micronized V2	SD	23.8	(1.0–2.0)	162	27.1	0.058
		n	3	3	3	3	3
9	96 mg/m^2 bid	Mean	62.6	7.0	578	546	1.24
	Micronized V2	SD	48.0	(2.0–12.0)	394	528	NC
		n	3	3	3	3	2
10	128 mg/m^2 bid	Mean	93.3	2.0	922	403	1.23
	Micronized V2	SD	NC	(1.0–3.0)	NC	NC	NC
		n	2	2	2	2	2
11	170 mg/m^2 bid	Mean	119	2.0	1122	330	1.30
	Micronized V2	SD	48.5	(1.0–5.0)	441	148	0.363
		n	4	4	4	4	4
Glesatinib bid under fed conditions							
12	300 mg bid	Mean	205	2.0	2105	162	1.14
	Micronized V2	SD	77.2	(1.0–12.0)	800	72.2	0.164
		n	4	4	4	4	4
13	450 mg bid	Mean	132	5.0	1190	503	21.2
	Micronized V2	SD	74.6	(1.0–12.0)	824	255	37.9
		n	5	5	5	5	5
14	700 mg bid	Mean	141	6.0	1547	528	1.11
	Micronized V2	SD	53.0	(2.0–7.0)	554	284	0.433
		n	4	4	4	4	4

$AUC_{12/24}$ area under the plasma concentration–time curve from time zero to 12 or 24 h after dosing, *bid* twice daily, *CL_{ss}/F* apparent clearance after multiple oral administrations, *C_{max}* maximum plasma concentration, *C_{trough}* predose plasma concentration, *NC* not calculated, *q3w* once every 3 weeks, *qd* once daily, *SD* standard deviation, *t_{max}* time to maximum observed plasma concentration

[a] Median and range reported for t_{max}

[b] AUC_{24} reported for cohorts 1–4

Despite activating *MET* alterations or AXL overexpression not being inclusion criteria for this phase I study that focused on safety, modest signals of efficacy were observed, with PRs of 1.8% and 12.0% in the glesatinib + erlotinib and glesatinib + docetaxel cohorts, respectively. While exposure to study medication was acceptable (mean relative dose intensity of glesatinib was 90.7% and 89.6% in the erlotinib and docetaxel groups, respectively) and the adverse effect profile of both treatment combinations was suggestive of biological activity, it is likely that lack of genetic selection impacted efficacy findings. Indeed, selection for MET and AXL was planned for further cohorts in this study, which did not proceed due to early termination. These included planned phase I expansion cohorts at the MTD or MAD in each study arm, and a phase II randomized portion investigating glesatinib plus erlotinib versus glesatinib plus docetaxel in patients with stage 3b/4 NSCLC and MET-positive disease and/or AXL overexpression or translocation.

In the dose-escalation portion of this study, the MAD of glesatinib (micronized V2) was 700 mg twice daily in combination with erlotinib 150 mg once daily, or with docetaxel 75 mg/m^2 every 3 weeks. Two of five evaluable patients experienced DLTs of Grade 3 diarrhea at the glesatinib + erlotinib MAD, and two of six evaluable patients experienced DLTs of Grade 2 acute pancreatitis (which resulted in study discontinuation) and Grade 3 elevated AST at the glesatinib + docetaxel MAD. While the MTD of glesatinib with either erlotinib or docetaxel was not formally established, the numbers of DLTs observed at the MAD of both treatment combinations suggests glesatinib (V2 micronized) 700 mg twice daily in combination with erlotinib or docetaxel exceeded the MTD by a small margin.

The MTD of the glesatinib treatment combinations was not established because the study was terminated early due to challenges with the consistency of particle size and bioavailability of glesatinib necessitating further refinement of the tablet formulation. Indeed, the levels of exposure achieved at the MAD of glesatinib (V2 micronized) 700 mg twice daily administered with either erlotinib or docetaxel were considered suboptimal to achieve complete inhibition of MET or AXL, based on preclinical data. Following preliminary observations of a lack of increased exposure at glesatinib with the initial unmicronized formulation assessed at doses > 96 mg/m^2, attempts were made to improve drug absorption during the course of this study. These included micronization and a micronized formulation of glesatinib containing sodium lauryl sulphate (V2 tablets) in order to reduce particle size and increase the rates of dissolution and solid dispersion [22]. However, PK data comparing the different formulations of glesatinib were variable and inconclusive, likely due in part to small numbers of patients in each cohort and high interpatient variability. Systemic exposure to glesatinib increased in a less than dose proportional manner, with no clinically meaningful differences in exposure or bioavailability between the tested formulations. Suboptimal drug formulation, including poor solubility, stability and/or biodistribution, is an inherent challenge of developing novel agents, due in part to limitations in the prediction of drug bioavailability in humans [23]. This underscores the need to improve preclinical evaluations, to effectively predict PK parameters in the clinic, and physiochemical studies, to inform particle size specification and optimize manufacturing consistency, thereby guiding the refinement of novel drug formulations. Findings from another phase I study, investigating other formulations of glesatinib as monotherapy, impacted the present study (results to be reported separately). Rather than glesatinib glycolate as investigated in this study, this resulted in further assessments of glesatinib, including MTD, being focused on free-base formulations: glesatinib FBS capsule (glesatinib free base suspended in Miglycol®) and glesatinib SDD tablet (spray-dried dispersion tablet comprising amorphous solid dispersion of glesatinib free base in a polymer matrix).

5 Conclusion

The safety profile of glesatinib glycolate formulations in combination with erlotinib and docetaxel was acceptable and no PK interactions were identified. Modest signals of efficacy with these treatment combinations were also observed in patients with genetically unselected, advanced solid tumors. Based on other emerging phase I data, further investigation of glesatinib focused on alternate free-base formulations that aimed to improve drug bioavailability and centered on patients with activating *MET* alterations (ClinicalTrials.gov identifier: NCT02544633; data to be reported separately). While the data from the present study could guide dose selection for future combination trials of reformulated glesatinib, clinical development of glesatinib was ultimately terminated because bioavailability challenges impacted the ability to achieve exposure levels required for optimal efficacy.

Acknowledgments The authors thank the patients and their families who participated in this study. They also thank Josée Morin (Excelsus Statistics Inc.) for critical review of the manuscript draft and Michel Drouin (formally of Methylgene Inc.) for contribution to the study design. Medical writing services were provided by Siân Marshall (SIANTIFIX, Cambridge, UK) in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3) and funded by Mirati Therapeutics, Inc.

Declarations

Author contributions Study conception and design: MT, RC, VT. Data acquisition: AP, SG, KPP, DWR, NBH, PJO. Data analysis and interpretation: All authors. Manuscript reviewing and editing: All

authors. Manuscript original draft: No authors, see medical writing acknowledgment. All authors reviewed and approved the final draft of the manuscript for publication and agree to be accountable for all aspects of this work.

Funding This study (NCT00975767) was supported by Mirati Therapeutics Inc. Funding for a professional medical writer with access to the data was provided by Mirati Therapeutics Inc.

Conflict of interest Amita Patnaik reports honoraria from the Texas Society of Clinical Oncology; consulting fees (personal) from Bayer, Daiichi Sankyo, Gilead Sciences, HalioDx, Merck, Novartis, Seattle Genetics, Shenzhen IONOVA Life Sciences, and Silverback Therapeutics; consulting fees (to an immediate family member) from Bristol Meyers Squibb, Genentech/Roche, and Merck; and research funding from Abbvie, Arcus Ventures, Astellas Pharma, Bolt Biotherapeutics, Corvus Pharmaceuticals, Daiichi-Sankyo, Exelixis, Fochon Pharmaceuticals, Five Prime Therapeutics, FortySeven, Gilead Sciences, Infinity Pharmaceuticals, Inova, Klus Pharma, Lilly, Livzon, Merck, Pfizer, Pieris Pharmaceuticals, Plexxikon, Sanofi, Seattle Genetics, Surface Oncology, Symphogen, Syndax, Tesaro, Upsher-Smith, and Viego Therapeutics. Shirish Gadgeel reports consulting fees or honorarium from AstraZeneca, Blueprint Medicines, Bristol Meyers Squibb, Eli Lilly, Genentech-Roche, Janssen, Mirati Therapeutics, Novartis, and Pfizer; support for travel to meetings for study manuscript preparation from Genetech-Roche and Merck; fees for participating in review activities from AstraZeneca; and provision of writing assistance from Genentech-Roche and Pfizer. Kyriakos Papadopoulos reports consulting fees from Bicycle Therapeutics and Turning Point Therapeutics; fees for review activities from Basilea Pharmaceutica; and funding for clinical trial conduct from Abbvie, ADC Therapeutics, Amgen, Bayer, Clithera Biosciences, Daiichi Sankyo, EMD Serono, F-star Therapeutics, Incyte, Jounce Therapeutics, Linnaeus Therapeutics, Loxo Oncology, MabSpace Biosciences, 3D Medicines, MedImmune, Merck, Mersana Therapeutics, Mirati Therapeutics, Pfizer, Peloton Therapeutics, Regeneron Pharmaceuticals, Syros Pharmaceuticals, Tempest Therapeutics, and Treadwell. Drew Rasco reports research funding from Mirati Therapeutics. Naomi Haas has no potential conflicts of interest to disclose. Peter O'Dwyer reports research support from Array Biopharma, AstraZeneca, BBI, Bristol Meyers Squibb, Celgene, Five Prime Therapeutics, FortySeven, Genentech, GSK, H3 Biomedicine, Incyte, Lilly (Imclone), Merck, Minneamrita Therapeutics, Mirati Therapeutics, Novartis, Pfizer, Pharmacyclics (AbbVie), Syndax Pharmaceuticals, and Taiho Pharma; consulting fees from Array Biopharma and Genentech; and expert testimonial fees from Bayer and Lilly. Richard Chao, Hirak Der-Torossian, and Vanessa Tassell report employment and stock ownership for Mirati Therapeutics. Diane Potvin reports employment for Mirati Therapeutics. Demiana Faltaos reports prior employment and stock ownership for Mirati Therapeutics. Manal Tawashi reports prior employment for Mirati Therapeutics.

Data availability Requests for data underlying the findings described in this article are available following reasonable request to the corresponding author.

Code availability Not applicable.

Ethics approval This study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, and local regulatory requirements. The study protocol was approved by the Institutional Review Boards at each participating study site.

Consent to participate Patients provided written, informed consent

Consent for publication All authors gave final approval of the version to be published.

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