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Phase I dose-escalation study to examine the safety and tolerability of LY2603618, a checkpoint 1 kinase inhibitor, administered 1 day after pemetrexed 500 mg/m² every 21 days in patients with cancer

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Summary

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The results of this study have been reported at the 22nd EORTC-NCI-AACR symposium on “Molecular Targets and Cancer Therapeutics”; Berlin, Germany; November 16–19, 2010.

Conflicts of interest GJ Weiss is a consultant/advisory board member of Merrimack Pharmaceuticals, Cephalon, Inc., Eli Lilly and Genzyme Corporation.

Purpose—This phase I study aims at assessing the safety and tolerability of LY2603618, a selective inhibitor of Checkpoint Kinase 1, in combination with pemetrexed and determining the maximum tolerable dose and the pharmacokinetic parameters.

Experimental design—This was an open-label, multicenter, dose-escalation study in patients with advanced solid tumors. Increasing doses of LY2603618 (40–195 mg/m²) were combined with 500 mg/m² of pemetrexed. LY2603618 was administered on Days 1 and 9 and pemetrexed on Day 8 in a 28-day cycle. For all subsequent 21-day cycles, pemetrexed was administered on Day 1 and LY2603618 on Day 2. Anti-tumor activity was evaluated as per Response Evaluation Criteria in Solid Tumors 1.0.

Results—A total of 31 patients were enrolled into six cohorts (three at 40 mg/m² over 4.5-hour infusion, 1-hour infusion in subsequent cohorts; three each at 40 mg/m², 70 mg/m², and 195 mg/m²; 13 at 105 mg/m²; six at 150 mg/m²). Four patients experienced a dose-limiting toxicity: diarrhea (105 mg/m²); reversible infusion-related reaction (150 mg/m²); thrombocytopenia (195 mg/m²); and fatigue (195 mg/m²). The maximum tolerated dose was defined as 150 mg/m². The pharmacokinetic data demonstrated that the exposure of LY2603618 increased in a dose-dependent manner, displayed a suitable half-life for maintaining required human exposures while minimizing the intra- and inter-cycle accumulation, and was unaffected by the pemetrexed administration. The pharmacokinetic-defined biologically efficacious dose was achieved at doses 105 mg/m².

Conclusion—LY2603618 administered approximately 24 h after pemetrexed showed acceptable safety and pharmacokinetic profiles.

Keywords

LY2603618; Pemetrexed; Checkpoint kinase; inhibitor; Cancer

Introduction

Checkpoint kinase1 (Chk1), a protein kinase activated by diverse stimuli, encodes a serine/threonine protein kinase with a highly conserved amino-terminal as the catalytic domain and the carboxyl terminal as a regulatory domain [1]. Chk1 plays a key role in the DNA-damage checkpoint signal transduction pathway [2]. In mammalian cells, Chk1 is activated in response to disruption or halting of DNA replication by chemotherapeutics such as hydroxyurea, pemetrexed, and gemcitabine; and also by ionization and ultraviolet radiation [3–6].

Inhibition of Chk1 has been shown to sensitize tumor cells to DNA-damaging agents, leading to the induction of apoptosis and cell death even at lower concentrations of the agent [7–11]. LY2603618 is an adenosine triphosphate-competitive inhibitor of Chk1, with a half-maximal inhibitory concentration (IC₅₀) of 7 nM with more than 50-fold selectivity for Chk1 inhibition as compared across a 100-member protein-kinase panel [12]. In vivo xenograft studies have demonstrated that LY2603618 in combination with pemetrexed or gemcitabine results in an increase in the antitumor effect compared to that observed in the respective chemotherapeutic agents when administered alone (unpublished data).

Pemetrexed is classified as an antimetabolite, and has been reported to cause DNA damage as well as activation of DNA damage checkpoints [13, 14]. When Chk1 is inhibited by LY2603618, cells containing damaged DNA are programmed to progress into mitosis without repairing the DNA, leading to cell death [15]. Chk1 inhibitor, LY2603618, combines synergistically with pemetrexed in vitro resulting in enhanced reduction of DNA synthesis, increased DNA damage, and cell cycle arrest compared to pemetrexed alone [15]. In NSCLC tumor xenografts, LY2603618 administered 24 h following pemetrexed

potentiated the anti-tumor activity of pemetrexed compared to concurrent administration [15]. Thus, the mechanism of action of LY2603618 and the studies using nonclinical efficacy models point out the usefulness of LY2603618 for its efficacy in combination when administered 24 h after the chemotherapeutic agent.

Accordingly, the primary objective of this study was to examine the safety and tolerability of LY2603618, including the determination of the maximum tolerated dose (MTD), when administered after pemetrexed. Secondary objectives included the characterization of its pharmacokinetics and also documentation of any antitumor activity when LY2603618 was administered after pemetrexed.

Materials and methods

Patient selection

Patients with a histologically or cytologically confirmed advanced solid malignancy that had progressed or relapsed after a minimum of 1 systemic therapy and no other approved therapies available to treat their disease were included. Patients must have had at least 1 lesion that could be evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST 1.0). Patients were required to have a life expectancy of at least 3 months and have an Eastern Cooperative Oncology Group (ECOG) performance status of 1. The patient must not have received drugs like mitomycin C and/or carmustine (BiCNU) or any others belonging to the nitrosourea class within 42 days prior to Cycle 1. A written informed consent was obtained at Visit 0 (screening). The protocol was approved by the Western Institutional Review Board (WIRB). This study was conducted in accordance with the approved protocol and ethical principles stated in the 1996 version of the Declaration of Helsinki or the applicable guidelines on Good Clinical Practice, and all applicable federal, state and local laws, rules, and regulations.

Study design

This was a Phase I, open-label, dose-escalation study aimed at examining the safety and tolerability of increasing doses of LY2603618 administered approximately 24 h after pemetrexed 500 mg/m², during all the 21-day treatment cycles. Six cohorts were enrolled; LY2603618 was initially administered over 4.5 h (that is, 30-minute bolus dose during which 25% of the total dose was delivered followed by a 4-hour infusion during which 75% of the total dose was delivered) in Cohort 1. Based on the pharmacokinetic data from the first cohort, the infusion duration was reduced to 1 h in Cohort 2 and all subsequent cohorts. During Cycle 1, a 28-day cycle, LY2603618 was administered on Days 1 and 9 and pemetrexed on Day 8. For all the subsequent 21-day cycles, pemetrexed was administered on Day 1 followed by LY2603618 on Day 2.

Treatment

LY2603618 and pemetrexed (500 mg/m²) were administered through IV infusion. Initial cohort with 40 mg/m² of LY2603618 was administered over 4.5-hour infusion, followed by escalating doses from 40 to 195 mg/m² over a 1-hour period (± 10 min). Patients received vitamin supplementation with folic acid and vitamin B12. Corticosteroids such as dexamethasone and prednisone were also administered.

Dose-limiting toxicities and maximum tolerated dose

Assessment of dose-limiting toxicities (DLTs) for the determination of the maximum tolerated dose (MTD) were made during Cycle 1 of each cohort in terms of (a) absolute neutrophil count < 500 cells/mm³; (b) platelet count $< 25,000$ cells/mm³; (c) Grade 4 hematologic toxicity; (d) Grade 3 or 4 non-hematologic adverse event (AE) (National

Cancer Institute Common Terminology Criteria for AEs version 3; NCI CTCAEv3) related to LY2603618, except for adequately controlled nausea and vomiting; (e) any drug-related AE requiring more than a 14-day dose delay for recovery.

Dose-escalation procedure

Following the initial starting dose of 40 mg/m² of LY2603618 with three patients per cohort (Cohorts 1 and 2), the subsequent dose was increased by a factor of 1.75, 1.5, 1.4, and 1.3; respectively. If one patient experienced a DLT, the cohort was expanded to six patients. If DLT was observed in 2 or more patients at any given dose, dose escalation was stopped and the MTD was defined as the previous dose level. An expansion cohort of 10 additional patients was planned, to define the recommended Phase II dose (RP2D) at a pharmacokinetically defined biological effective dose (BED). The BED was defined as 1) achieving an area under the plasma concentration versus time curve (AUC_{0-∞}) 21,000 ng*h/mL, and 2) achieving a maximum plasma concentration (C_{max}) 2000 ng/mL.

Safety assessments

Safety evaluations included assessments of AEs, DLTs, physical examination findings, vital sign measures, electrocardiogram tracings, and results of laboratory analyses (hematology, serum chemistry, coagulation, and urine analysis). Severity was graded as per the NCI CTCAEv3.

Pharmacokinetics

Pharmacokinetic assessments were performed for LY2603618 administration on Cycle 1-Day 1 and Cycle 1-Day 9. Samples were collected within 10 min before infusion, within 30 min during infusion, prior to the end of infusion, and at 1, 3, 5, 7, 24, 48, and 72 h after the end of infusion. Pharmacokinetic assessments were performed for the first pemetrexed dose on Cycle 1-Day 8; the samples were collected at 9.5 min during infusions and at 1, 2, 6, and 24 h after infusion. Pharmacokinetic analyses were performed for individual patients who received at least 1 dose of the study drug. Pharmacokinetic parameters for LY2603618 and pemetrexed were computed by standard non-compartmental methods of analysis using WinNonlin® Enterprise Version 5.3. The C_{max} and the area under the plasma concentration-time curve (AUC_{0-∞}) on Day 1 and Day 9 of Cycle 1 were calculated to assess intra-cycle exposure variability and the potential effect of pemetrexed on the pharmacokinetics of LY2603618. The clearance (CL), volume of distribution (V_{ss}), and terminal half-life (t_{1/2}) were estimated from the plasma concentration versus time data of LY2603618 and pemetrexed. The pharmacokinetic parameter estimates of C_{max} and AUC_{0-∞} were used for an exploratory assessment of dose proportionality. Log-transformed C_{max} and AUC_{0-∞} estimates were evaluated and used to estimate ratios of geometric means and the corresponding 90% confidence intervals. For analysis purposes, pemetrexed concentration data were dose-normalized to a 500 mg/m² dose prior to analysis. For estimation of the pemetrexed t_{1/2}, plasma concentrations residing primarily within 6 to 24 h after initiation of the pemetrexed infusion were selected to maintain consistency with previous pemetrexed pharmacokinetic analyses conducted by Eli Lilly and Company.

Efficacy assessment

Tumor response assessments were conducted according to RECIST 1.0. Assessments were carried out after 2 completed cycles (Cycle 3-Day 1) and on the first day of alternating cycles thereafter (Cycle 5-Day 1, Cycle 7-Day 1, etc.). If a response was observed at any assessment, a follow-up assessment to confirm the response was performed 28 days later.

Statistical measures

Patients, in this open-label, dose-escalation Phase I study, were enrolled into cohorts sequentially without randomization to dose. The total sample size was determined by DLTs (up to six patients per dose group prior to establishment of the MTD). Data analyses for the study were based on descriptive statistics for the different dose groups; no p-values were calculated. All continuous endpoints were summarized using the following descriptive statistics: number of patients, mean, standard deviation, standard error, median, minimum, and maximum. Categorical endpoints were summarized using the number of patients, frequency, percentages, and their standard errors. Missing data were not imputed.

Results

Patient disposition

All the 31 patients (16 men and 15 women) enrolled in the present study had an average of 5 prior chemotherapy regimens (minimum 1; maximum 15). Twenty-four (24) of them had surgery and 18 of them had radiotherapy. Breast cancer had been diagnosed in 19.4% of the patients; 3.2% had been diagnosed as non-small cell lung cancer (NSCLC) patients; and 19.4% as pancreatic cancer patients. The majority of patients were enrolled with tumors of 'Other' types (58.1 %) (Table 1). Tumor types in this "other" category included colon, ovarian, rectal, gastroesophageal carcinoma, cervical, salivary gland, small bowel, unknown primary, papillary renal carcinoma, and adenocarcinoma with bronchioloalveolar features. All the 31 patients who were registered into the study received at least 1 dose of LY2603618. Thirty patients had discontinued from the study at the time of the final data lock for the primary analysis on 25 May 2010. The most common reasons for discontinuation were related to the patients' cancer: Nineteen patients (61.3%) were withdrawn due to disease progression; 6 patients (19.4%) due to symptomatic deterioration; 2 patients (6.5%) due to an AE; 2 patients (6.5%) due to death; and 1 patient (3.2%) discontinued by personal choice. One patient remained on study treatment beyond the database lock date of 25 May 2010 and came off study later in 2010 for disease progression.

Dose-limiting toxicities and maximum tolerated dose

Four patients (13.3%) experienced a total of five types of DLTs and in each case the DLTs were reported as serious AEs. One patient developed severe diarrhea lasting more than 5 days after starting treatment with pemetrexed and LY2603618 at the 105 mg/m² dose level. At the 195 mg/m² dose level, one patient experienced Grade 4 platelet toxicity (Table 2) and another experienced a Grade 3 and 4 platelet toxicity and severe fatigue. One patient at the 150 mg/m² level experienced a reversible, but life-threatening allergic infusion reaction with tachypnea, dyspnea without wheezing, tachycardia, and elevated blood pressure that was solely attributed to LY2603618. The patient was given 40 mg of IV prednisolone which provided immediate relief and the patient recovered without being hospitalized. Based on these results, the MTD was determined to be 150 mg/m². Beginning with the completion of Cohort 4 (105 mg/m²), a 10-patient expansion was enrolled to evaluate the pharmacokinetics at this BED (see Pharmacokinetic section below). Fewer than 3 DLTs were observed for the expanded dose cohort at 105 mg/m² (13 patients).

Safety evaluation

Common treatment-emergent adverse events (TEAEs) reported were fatigue (61.3%), nausea (51.6%), vomiting (38.7%), diarrhea (35.5%), dyspnea (35.5%), and neutrophils/granulocyte count decrease (32.3%) (Table 3). Most TEAEs were of mild to moderate severity; there was no correlation between the incidence of TEAEs and the dose increase of LY2603618. Serious adverse events (SAEs) related to both the study drugs included Grade 3

hemoglobin decrease, pneumonia, diarrhea, blood/bone marrow events and Grade 2 fatigue and fever. SAEs related to pemetrexed included Grade 3 hemoglobin decrease, leukocytes, and neutrophils/granulocyte count decrease. One SAE, a Grade 4 allergic reaction/hypersensitivity (including drug fever), was considered to be related only to LY2603618. Multiple reported SAEs included hemoglobin decrease ($n=3$; 9.7%), bone marrow suppression ($n=2$; 6.5%), and fever ($n=2$; 6.5%) and these occurred at LY2603618 doses at or beyond 105 mg/m².

Pharmacokinetics

The pharmacokinetic characteristics have been analyzed for LY2603618 and pemetrexed.

LY2603618

The first 3 patients enrolled in this study received a starting dose of 40 mg/m² as a 4.5-hour infusion (that is, 30-minute bolus dose during which 25% of the total dose was delivered followed by a 4-hour infusion during which 75% of the total dose was delivered). The mean pharmacokinetic parameters after a 4.5-hour infusion of 40 mg/m² were consistent with the reported pharmacokinetic parameters in patients who received a 1-hour infusion of the same dose (data not shown). The mean LY2603618 plasma concentration versus time profiles covering a time period of 72 h demonstrate a biexponential nature (Fig. 1A, B), with a consistent rate of elimination for all the doses investigated on both Days 1 and 9 of Cycle 1. LY2603618 showed dose-dependent increases in AUC_{0-∞} and C_{max} after its administration on Day 1 and Day 9 of Cycle 1 across the dose range of 40–195 mg/m² (Table 4). The CL of LY2603618 appeared to be relatively dose-independent, indicative of a linear pharmacokinetic behavior. The mean t_{1/2} of LY2603618 varied across the dose range investigated, with an average ranging from 5.09 to 25.2 h on Day 1 and from 6.19 to 19.9 h on Day 9 (24 h after pemetrexed administration) (Table 4). Overall, there was only a relatively minor amount of intra-cycle accumulation of LY2603618 on Day 1 and Day 9 of Cycle 1, with an accumulation ratio of approximately 0.98 across cohorts. Furthermore, the administration of pemetrexed (500 mg/m²) approximately 24 h before LY2603618 did not appear to alter the pharmacokinetics of LY2603618 (Figs. 1B and 2A, B). The LY2603618 pharmacokinetic targets that correlate with the maximal pharmacodynamic effect observed in preclinical xenograft models and define the BED for LY2603618 in combination with pemetrexed are: 1) achieving an AUC_{0-∞} 21,000 ng·h/mL, and 2) achieving a C_{max} 2000 ng/mL. Both of these pharmacokinetic exposure endpoints were achieved based on the cohort geometric mean values for each parameter at doses 105 mg/m² (Table 4 and Fig. 2A, B). In addition, the calculated average plasma concentrations (C_{av}) for doses 105 mg/m² were at or near 2000 ng/mL (Table 4). The MTD was established at a dose of 150 mg/m², corresponding to a geometric mean AUC_{0-∞} of 49,200 and 44,700 ng·h/mL on Days 1 and 9, respectively (Fig. 2A; Table 4), with corresponding geometric mean C_{max} of 4040 ng/mL and 3330 ng/mL (Fig. 2B; Table 4).

As demonstrated by the percent coefficient of variation (CV%) associated with the LY2603618 pharmacokinetic parameters (Table 4) and the standard deviation associated with the LY2603618 exposure (C_{max}, AUC_{0-∞}) observed on Day 1 and Day 9 (Fig. 2A, B), there appears to be a relatively moderate to large degree of interpatient pharmacokinetic variability associated with LY2603618 after IV administration across the dose range of 40 to 195 mg/m² in Cycle 1.

Pemetrexed

The dose normalized noncompartmental pharmacokinetic parameters of pemetrexed (500 mg/m²) were calculated in 27 patients on Day 8 of cycle 1 (Table 4). The results demonstrate the administration of LY2603618 across the dose range of 40 to 195 mg/m²

does not appear to affect the pharmacokinetics of pemetrexed (Fig. 3; Table 4). As indicated by the mean plasma concentration versus time profiles (Fig. 3), the overall pemetrexed exposure was essentially the same in the presence of increasing doses of LY2603618, and was similar to a previous historical Phase Ib study [16] conducted with pemetrexed (500 mg/m²). The estimated pemetrexed pharmacokinetic parameters (Table 4) are also similar to those reported in the pemetrexed package insert, with reported clearance of 91.8 mL/min (3.06 L/h/m² for a patient with body surface area (BSA) of 1.8 m²), V_{ss} of 16.1 L (8.9 L/m² for a patient with BSA 1.8 m²), and t_{1/2} of 3.5 h.

Efficacy

Of the 31 treated patients, 23 were considered evaluable for best tumor response; remaining 8 patients are described in the notes for Fig. 4. The changes in tumor size from baseline with different doses of drug administration are depicted in Fig. 4. One partial response (50% decreases in sum of longest diameters of lesions) was observed in a patient with adenocarcinoma of the pancreas dosed on the 105 mg/m² cohort (Fig. 4). Nine patients (39.1%) showed the best response of stable disease and 13 (56.5%) exhibited progressive disease.

Discussion

In this Phase I study, the MTD of LY2603618, when dosed in combination with 500 mg/m² pemetrexed on a 21 day schedule, was established at 150 mg/m². The toxicity profile of LY2603618 in combination with pemetrexed is similar to that seen for single-agent pemetrexed use and is consistent with its non-clinical toxicology profile. The pharmacokinetic targets (i.e., C_{max} 2000 ng/mL and AUC_{0-∞} 21,000 ng·h/mL) that correlate with the maximal pharmacodynamic effect observed in preclinical models and define the human BED were achieved at doses of 105 mg/m² (Fig. 2A and B). In addition, the majority of the calculated t_{1/2}'s at doses >105 mg/m² (including the MTD of 150 mg/m²) are consistent with a t_{1/2} (i.e., >10 h and <24 h) suitable for achieving and maintaining acceptable human exposures (i.e., AUC_{0-∞}, C_{max}) while minimizing the intra-cycle accumulation of LY2603618 when given in combination with pemetrexed (Figs. 1 and 2). This is further illustrated by the fact that the C_{av} for patients who received doses 105 mg/m² were at or near 2000 ng/mL (Table 4), indicating that LY2603618 plasma concentration remains close to target levels for at least 72 h after dosing (i.e., since pharmacokinetic sampling occurs out to 72 h).

The CL of LY2603618 appeared to be relatively dose-independent across the dose range of 40 to 195 mg/m², indicative of linear pharmacokinetic behavior and was unchanged by the administration of pemetrexed (500 mg/m²) approximately 24 h before LY2603618. Though the present study was not powered to determine dose proportionality, the exploratory dose proportionality analysis for LY2603618 indicated that increases in AUC_{0-∞}, and C_{max} did not appear to be strictly dose proportional (data not shown).

Since LY2603618 is administered 24 h after pemetrexed (t_{1/2} of 3.5 h; pemetrexed package insert), and because pemetrexed is eliminated as parent drug or metabolite in the urine, with 70% to 90% of the dose recovered during the 24 h after dosing (pemetrexed package insert), whereas LY2603618 is partially metabolized and eliminated through the biliary system in both rats and dogs (unpublished data), it is unlikely that drug interactions will occur between LY2603618 or pemetrexed. Administration of pemetrexed (500 mg/m²) approximately 24 h prior to 105 mg/m² of LY2603618 in the present study demonstrated the following values for pemetrexed: C_{max} (85.7 µg/mL), AUC_{0-∞} (179 µg·h/mL), and t_{1/2} (2.75 h) (Table 4). These values are consistent with those reported in the pemetrexed package insert, indicating that administration of LY2603618 at the BED approximately 24 h after pemetrexed

administration does not alter the pharmacokinetic profile of pemetrexed. In addition, the plasma clearance of pemetrexed in combination with LY2603618 (Table 4) remained unaltered compared to that observed when administered alone in other studies [17].

As previously described, there is a relatively moderate to large degree of pharmacokinetic variability associated with LY2603618 after IV administration. As a result, a population-based pharmacokinetic analysis incorporating intense and sparse pharmacokinetic sampling from ongoing and completed Phase I and II studies with LY2603618 is planned, in order to more accurately characterize (quantify) and identify the sources of intra- and interpatient pharmacokinetic LY2603618 variability.

Disruptions of Chk1 by inhibitors may lead to anemia [18] as reported from a Phase I study of UCN-01 where all patients developed Grade 3 hyperglycemia and the observed DLTs were hyphosphatemia and anemia [19]. However, the present study with the administration of LY2603618 in combination with pemetrexed showed neither anemia nor hyphosphatemia as DLT, but a Grade 3 diarrhea was observed in one patient at 105 mg/m², a Grade 3 fatigue in one patient at 195 mg/m², a Grade 4 allergic reaction/hypersensitivity was observed in one patient at 150 mg/m², and Grade 4 thrombocytopenia in two patients at 195 mg/m². Grade 3 lower GI hemorrhage was observed in one patient but was not related to LY2603618. Grade 3 fatigue and occurrence of treatment-related neutropenia are the known pemetrexed drug-related toxicities [20, 21]. The mean LY2603618 exposures (Table 4) achieved after 105 and 150 mg/m² doses of LY2603618 exceed the exposures required for maximum biological effect in non-clinical models. In conclusion, LY2603618 administered approximately 24 h after pemetrexed showed an acceptable safety profile with pharmacokinetic properties remaining unchanged for both agents administered in combination at the doses evaluated in this study. The RP2D of the combination of pemetrexed 500 mg/m² and LY2603618 150 mg/m² is currently under evaluation in Phase II NSCLC (NCT00988858).

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Fig. 1.

Mean LY2603618 plasma concentrations versus time profiles after one-hour infusion of LY2603618 Day 1 and Day 9 of Cycle 1. Mean LY2603618 plasma concentration versus time profiles across dose range of 40–195 mg/m² following a 1-hour IV infusion of LY2603618 on Day 1 (alone: Panel A) and Day 9 (24 h after 500 mg/m² of pemetrexed: Panel B) of Cycle 1

Fig. 2. Dose-dependent changes (Mean±SD) in LY2603618 AUC_{0-∞} (Panel **A**) and C_{max} (Panel **B**) between Day 1 and Day 9 of Cycle 1. Dashed lines represent AUC_{0-∞} (Panel **A**) and C_{max} (Panel **B**) that correlate to the maximal pharmacodynamic effect observed in preclinical models and define the human BED

Fig. 3.
Mean dose-normalized pemetrexed plasma concentration versus time profile by LY2603618 dose with mean pemetrexed PK profile from historical study conducted with enzastaurin (ENZ)

Fig. 4. Change in Tumor Size at Best Response by Dose is presented as waterfall plot of dose-dependent mean change in tumor size at best response. The waterfall plot uses target lesion measurements only. †Three patients with response data are not included in the waterfall plot due to incomplete lesion assessments at post baseline visits. Patient 2 in LY 40 mg/m² cohort, patient 1 in the LY 70 mg/m² cohort, and patients 3, 4, and 5 in LY 105 mg/m² cohort had progressive disease due to the appearance of non-target lesions. Numbers of days on study are indicated above/below each bar

Table 1
Baseline patient and disease characteristics

Characteristic	N (%)
Gender, male: female	16 (51.6): 15 (48.4)
Median Age{range}, years	60 {30–77}
ECOG performance status 0/1	8 (25.8)/23 (74.2)
Tumor type	
Breast	6 (19.4)
Non-small cell lung	1 (3.2)
Pancreatic	6 (19.4)
Other	18 (58.1)
Prior chemotherapy	31 (100)
Prior surgery	24 (77.4)
Prior radiotherapy	18 (58.1)

Table 2
DLTs and MTD

Cohort	N	LY2603618 dose (mg/m ²)	DLTs (n)
1	3	40 ^a	0
2	3	40 ^b	0
3	3	70	0
4	13 ^c	105	G3 diarrhea (1)
5	6	150	G4 allergic reaction/hypersensitivity (1)
6	3	195	G3 lower GI hemorrhage (1) ^d , G3 fatigue (1); G4 thrombocytopenia (2) ^e

^a Cohort 1 received 40 mg/m² over a 4.5-hour period, based on PK modeling of preclinical data determining the BED

^b Cohort 2 received 40 mg/m² over a 1-hour period, a duration selected based on PK exposure data for Cohort 1

^c Study was amended to expand patient accrual to the 105 mg/m² dose to evaluate the PK parameters and to provide guidance on the determination of a biological dose relative to the MTD

^d Later determined to be unrelated to LY2603618

^e Platelet count <25,000 cells/m²

Table 3

LY2603618 or Pemetrexed-related Grade 3 and 4 Toxicities

Toxicity	No. patients				
	LY2603618 dose (mg/m ²)				
	40 ^a (n=6)	70 ^b (n=3)	105 (n=13 ^c)	150 (n=6)	195 (n=3)
Neutropenia	0	0	4 ^f	2 ^f	1 ^f
Anemia	0	1 ^f	1 ^f	1 ^f	1 ^f
Thrombocytopenia	0	1 ^f	1 ^g	0	2 ^{eg}
Lymphopenia	1 ^f	0	0	0	0
Leukopenia	0	0	1 ^f	0	0
Blood/bone Marrow-other	0	0	0	0	2 ^f
Lung infection	1 ^f	0	0	0	0
Constitutional Symptoms-other	1 ^f	0	0	0	0
Nausea	0	1 ^f	0	0	0
Allergic reaction/hypersensitivity	0	0	0	1 ^g	0
Hypertension	0	0	0	1 ^g	0
Diarrhea	0	0	2 ^f	0	0
Dyspnea	0	0	0	1 ^g	0
Fatigue	0	0	0	2 ^f	1 ^f
Lower GI hemorrhage	0	0	0	0	1 ^{fd}

^aCohort 1 received 40 mg/m² over a 4.5-hour period based on pharmacokinetic modeling of preclinical data

^bCohort 2 received 40 mg/m² over a 1-hour period, a duration selected based on PK exposure data for Cohort 1.

^cStudy was amended to expand patient accrual to the 105 mg/m² dose to evaluate pharmacokinetic parameters and to provide guidance on the determination of a biological dose relative to the MTD

^dLater determined to be unrelated to LY2603618

^ePlatelet count <25,000 cells/mm³

$f_{\text{Grade 3}}$
 $g_{\text{Grade 4}}$

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Table 4

Pharmacokinetic parameters

Group	LY ^a (mg/m2) dose (N)	Geometric mean (CV%)					t _{1/2} (h)	AUC _{0-∞} (ng ^a h/mL)	CL (L/h)	V _{ss} (L)	R _a
		C _{max} (ng/mL)	C _{av} (ng/mL)	t _{max} ^b (h)	C _L (ng/mL)						
LY2603618 Day 1 (alone)	40 (3)	1530 (22)	418 (30)	1.02 (0.83–1.02)	11.9 (23)	10000 (30)	7.90 (35)	105 (18)	NC		
	70 (3)	2060 (65)	351 (68)	0.98 (0.50–1.07)	5.09 (64)	8420 (68)	15.1 (54)	83.5 (51)	NC		
	105 (13)	4010 (35)	2430 (84)	0.97 (0.33–1.08)	20.3 (34)	58300 (84)	3.80 (94)	100 (67)	NC		
	150 (6)	4040 (35)	2050 (79)	0.98 (0.95–1.00)	16.6 (59)	49200 (79)	6.04 (82)	115 (31)	NC		
	195 (3)	6800 (13)	4860 (36)	0.97 (0.95–0.97)	25.2 (21)	117000 (36)	3.13 (37)	85.2 (10)	NC		
LY2603618 Day 9	40 (3)	1960 (28)	450 (23)	1.03 (0.98–1.08)	16.2 (44)	10800 (23)	7.21 (26)	109 (7)	1.08 (12)		
	70 (3)	2390 (43)	399 (73)	0.98 (0.88–1.00)	6.19 (54)	9570 (73)	13.3 (59)	80.7 (31)	1.14 (9)		
	105 (12)	4070 (52)	1820 (67)	0.98 (0.42–1.05)	15.9 (34)	43600 (67)	4.7 (82)	94.6 (57)	0.80 (25)		
	150 (5)	3330 (44)	1860 (75)	0.98 (0.92–1.00)	12.8 (52)	44700 (75)	6.25 (83)	105 (61)	0.89 (14)		
	195 (3)	7510 (17)	4840 (27)	1.07 (0.92–1.13)	19.9 (39)	116000 (27)	3.79 (19)	101 (16)	1.00 (38)		
Pemetrexed	mg/m ²	μg/mL	NC	(h)	(h)	μg ^a h/mL	L/h/m ²	L/m ²	NC		
	40 (3)	89.0 (34)	NC	0.23 (0.17–1.20)	2.43 (34)	179 (18)	2.8 (18)	8.58 (19)	NC		
	70 (3)	67.6 (75)	NC	0.17 (0.15–1.17)	2.86 (21)	144 (13)	3.48 (13)	11.6 (47)	NC		
	105 (12)	85.7 (59)	NC	0.16 (0.15–1.17)	2.75 (18)	179 (34)	2.79 (34)	9.10 (42)	NC		
	150 (6)	88.2 (27)	NC	0.16 (0.15–0.47)	3.14 (38)	204 (74)	2.45 (74)	8.92 (20)	NC		
	195 (3)	114 (3)	NC	0.15 (0.07–0.18)	3.36 (21)	255 (37)	1.96 (37)	7.64 (15)	NC		

LY2603618; CV% percent coefficient of variation; C_{max} maximum observed drug concentration; C_{av} average plasma concentrations; t_{max} time of maximum observed drug concentration; t_{1/2} half-life associated with the terminal rate constant (λ_z) in noncompartmental analysis; V_{ss} volume of distribution at steady state after IV administration; AUC_{0-∞} area under the concentration versus time curve from zero to infinity; CL total body clearance of drug calculated after intravenous administration; R_a Intracycle accumulation ratio: Day 9 AUC_{0-∞}/day 1 AUC_{0-∞}; NC not calculated

^a 1-h IV infusion of LY2603618

^b Median (Min-Max)