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A phase Ib trial of LY2584702 tosylate, a p70 S6 inhibitor, in combination with erlotinib or everolimus in patients with solid tumours ☆,☆☆

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KEYWORDS
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Abstract ***Background:*** LY2584702 tosylate (hereafter referred to as LY2584702) is an oral, selective ATP competitive inhibitor of p70 S6 kinase. Preclinical studies with LY2584702 demonstrated significant synergistic activity with erlotinib and everolimus. The primary objective was to determine a phase II dose and schedule. Secondary objectives included evaluation of safety, toxicity and pharmacokinetics of LY2584702 in combination with erlotinib or everolimus.

Methods: Patients with advanced solid tumours were treated with a total daily dose of 50–200 mg of LY2584702 in combination with erlotinib 150 mg once daily (Arm A) or everolimus 10 mg once daily (Arm B). Dose escalation was based on 3+3 design and used the Common Terminology Criteria for Adverse Events Version 4.0.

Results: Twenty-nine patients were enrolled, 17 in Arm A and 12 in Arm B. Dose limiting toxicities (DLTs) in cycle 1 were observed in Arm A in four patients and consisted of Grade 3 vomiting, hypophosphataemia, pulmonary embolism and decreased clotting factor V. No DLTs were observed in Arm B at cycle 1, and the most frequent treatment-emergent adverse events related to study drug were: fatigue, anorexia, diarrhoea, nausea and vomiting. Seven

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patients received ⩾4 cycles (3 in A, 4 in B). Best overall response was stable disease. Exposure accumulation of LY2584702 occurred with BID (twice daily) dosing. Exposure of erlotinib increased when administered in combination with LY2584702.

Conclusion: LY2584702 was not well tolerated when administered with erlotinib, therefore this combination is not feasible. The combination with everolimus was better tolerated but yielded very limited clinical benefit.

1. Introduction

The mammalian target of rapamycin (mTOR) is a component of the phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR signalling pathway, which regulates cell growth and survival and is often mutated in human cancers. Akt, via the mTORC1 complex [1], activates the serine/threonine p70 S6 kinase (S6K1). S6K1 together with the elongation initiation factor 4E-binding protein (4EBP1) promotes translation initiation for protein synthesis [2–6]. S6K1 activates the ribosomal protein S6 (S6), a component of the 40S ribosomal subunit, and the elongation initiation factor 4B (eIF4B) [7,8]. Both S6 and eIF4B promote protein synthesis via ribosome biosynthesis and cap-dependent translation initiation, respectively. Suppressing S6K1 activity is predicted to inhibit ribosome biogenesis, synthesis of angiogenic proteins [vascular endothelial growth factor (VEGF)] [8] and cell cycle regulatory proteins.

A small molecule inhibitor of S6K1, LY2584702 tosylate (hereafter referred to as LY2584702) was analysed in a monotherapy phase I clinical trial that enrolled 34 patients treated with LY2584702 on a QD (once daily) or BID (twice daily) dosing schedule ranging from 25 to 300 mg [9]. Five patients experienced dose limiting toxicity (DLT). All were grade 3 and included: vomiting, lipase, nausea, hypophosphataemia, fatigue and pancreatitis. The maximum tolerated dose (MTD) was determined to be 75 mg BID or 100 mg QD.

Preclinical data suggest that LY2584702 has significant synergistic effects when combined with the epidermal growth factor receptor (EGFR) inhibitor erlotinib or with the mTOR inhibitor everolimus. The objective of this phase Ib clinical trial was to determine the recommended phase II dose and schedule of LY2584702 when administered in combination with erlotinib or everolimus. Secondary objectives included safety and toxicity profile analysis and analysis of pharmacokinetic (PK) parameters of LY2584702, erlotinib and everolimus.

2. Patients and methods

2.1. Patients

Eligible patients were male and female, age ⩾18 years, with histologically confirmed solid tumours refractory to standard therapy. Patients discontinued all previous chemotherapy, radiotherapy, or immunotherapy ⩾2 weeks (3 weeks for myelosuppressive agents) prior to enrolment and had a performance status of ⩽1 on the Eastern Cooperative Oncology Group (ECOG) scale. Required laboratory tests included adequate hematopoietic function defined as: absolute neutrophil count $\geqslant 1.5 \times 10^9$/L; platelets $\geqslant 100 \times 10^9$/L; haemoglobin ⩾8 g/dL; serum creatinine ⩽1.5 × upper limits of normal (ULN) or calculated creatinine clearance ⩾45 mL/min; bilirubin ⩽1.5 × ULN; alanine transaminase and aspartate transaminase ⩽2.5 × ULN (⩽5 × ULN for patients with liver tumour). Patients with bone metastases were enrolled with alkaline phosphatase values ⩽5 × ULN. Inclusion in Arm A required patients with advanced or metastatic non-small cell lung cancer (NSCLC) after failure of 1 prior chemotherapy regimen. Arm B required patients with advanced neuroendocrine tumours or advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. For dose confirmation, patients had measurable disease and had not previously received erlotinib or everolimus. Patients were excluded for any of the following reasons: symptomatic central nervous system malignancy or metastasis; concomitant treatment by strong CYP3A4 inhibitors or inducers; acute or chronic leukaemia; received autologous or allogeneic stem-cell transplant within 75 days of initial dose of study drug; use of immunosuppressive therapy within 24 h of initial dose of study drug; >Grade 1 acute graft-versus-host disease; pregnancy; lactation; or bleeding diathesis.

2.2. Study design

This was a multi-centric, non-randomised, open-label, phase Ib trial of LY2584702 in combination with either erlotinib (Arm A) or everolimus (Arm B). Eligible patients received LY2584702 either QD or BID on a 28-day cycle when administered in combination with either erlotinib (150 mg/day QD) or everolimus (10 mg/day QD). Study drug was administered during or within 30 min of a meal. A flat dosing scheme was used for LY2584702 with total daily dose ranging from 50 to 300 mg starting at 50 mg QD. A BID dose schedule was implemented in both arms based on patient toxicity and PK/pharmacodynamic data from all completed QD cohorts. Dose escalation proceeded in a 3+3 design with escalation to the MTD. Patients received 2 cycles of

Table 1
Baseline patient characteristics.

	Patients $N = 29$	
	Arm A LY + erlotinib	Arm B LY + everolimus
Characteristic	N = 17	N = 12
Sex		
Male	9	5
Female	8	7
Age, years		
Median	60	48
Range	41-74	32-73
Ethnic origin		
Caucasian	15	9
African American	0	1
Asian	0	1
Did not indicate	2	1
ECOG performance status		
0	3	4
1	14	8
Tumour type		
Colorectal	3	2
Breast	2	1
Cervix (SCC and ADC)	2	1
Sarcoma	1	2
Melanoma	0	2
Other	9	4
No. of prior chemotherapies		
1	1	1
2	3	2
⩾3	13	9
Prior radiotherapy	12	5
Prior surgery	13	11

Abbreviations: ADC, adenocarcinoma; SCC, squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; LY, LY2584702.

LY2584702 unless criteria for discontinuation were met. This study was conducted in accordance with applicable laws and regulations, Good Clinical Practices and the ethical principles that have their origin in the Declaration of Helsinki.

Dose escalation was guided by toxicity assessments during cycle 1 using the Common Terminology Criteria for Adverse Events (CTCAE v4.0) along with PK/pharmacodynamic data when available as a secondary consideration. Any adverse events (AE) possibly related to the treatment with LY2584702 were considered toxicities. DLT was defined as an AE occurring during cycle 1 criteria: ⩾Grade 3 thrombocytopenia with bleeding, Grade 4 haematological toxicity of >5 days duration excluding lymphopaenia, febrile neutropenia, and ⩾Grade 3 non-haematological toxicity except nausea/vomiting/diarrhoea, Grade 3 rash, or Grade 3 hyperglycaemia/hypertriglyceridaemia/hyperlipidaemia when responsive to medical treatment. If a single patient experienced DLT within the first cycle of LY2584702, three additional patients were enrolled at that dose level. If a DLT was observed in two or more patients at any dose level, escalation ceased and the previous dose was declared the MTD.

2.3. Drug supply

LY2584702 was provided by Eli Lilly & Company (Indianapolis, IN) as capsules containing 25 or 100 mg of active drug. Erlotinib was supplied as 25, 100 or 150 mg tablets. Everolimus was supplied as 5 or 10 mg tablets.

2.4. Pharmacokinetic studies

PK analyses of LY2584702 were performed on all patients using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method. Whole blood samples were collected on day 1, and 7 or 8 for PK evaluation, the measurement of the desmethyl metabolite and for the assessment of erlotinib and everolimus. PK parameters were derived from the concentration–time profiles using non-compartmental analysis method. PK parameters following a single dose of LY2584702 included: area under the plasma concentration–time curve (AUC) to the last measure time point

Table 2
Dose-escalation and dose limiting toxicity (DLT) ⩾ Grade 3.

Cohort	Dose	No. of patients	No. of patients with DLT	Event
Arm A				
1	50 mg QD + erlotinib 150 mg QD	4	0	
2	50 mg BID + erlotinib 150 mg QD	5	0	
3	100 mg BID + erlotinib 150 mg QD	3	1	Gr 3 vomiting
			1	Gr 3 hypophosphataemia
4	75 mg BID + erlotinib 150 mg QD	5	1	Gr 3 thromboembolic event
			1	Gr 3 coagulation Factor V levels decreased
Arm B				
1	50 mg QD + everolimus 10 mg QD	3	0	
2	100 mg QD + everolimus 10 mg QD	3	0	
3	50 mg BID + everolimus 10 mg QD	6	0	

Abbreviations: No., number; QD, once daily; BID, twice daily; Gr, Grade.

Table 3
Treatment emergent adverse events (all grades[a] that occurred in ⩾10% of patients).

Adverse event	All grades, *n* (%) (*n* = 29)	Grade 3/4, *n*	Arm A LY + erlotinib (*n* = 17)	Arm B LY + everolimus (*n* = 12)
Fatigue	25 (86)	3	15 (88)	10 (83)
Anorexia	20 (69)	4	12 (71)	8 (67)
Diarrhea	17 (59)	0	11 (65)	6 (50)
Nausea	16 (55)	3	9 (53)	7 (58)
Vomiting	12 (41)	2	7 (41)	5 (42)
Oral mucositis	9 (31)	0	3 (18)	6 (50)
Rash acneiform	9 (31)	0	9 (53)	0
Dry skin	8 (28)	0	6 (35)	2 (17)
Cutaneous toxicity	5 (17)	0	5 (29)	0
Pruritus	4 (14)	0	2 (12)	2 (17)
Weight loss	4 (14)	0	1 (6)	3 (25)

[a] Grades are according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Summaries are for both QD and BID dosing.

[$AUC_{(0-t)}$] where t is the last quantifiable time point above the lower limit of quantification, and $AUC_{(0-\infty)}$ (0 to infinity), peak observed concentration (C_{max}), time to C_{max} (t_{max}), half-life ($t_{½}$) clearance (CL/F), apparent volume of distribution (V/F).

2.5. Pharmacodynamic studies

Three biomarkers were measured in peripheral blood mononuclear cells: proline rich Akt substrate 40 kDa (PRAS40), Akt, and phospho-S6 ribosomal protein (pS6), which were normalised to total protein. Levels of pS6 protein were examined using quantitative immunohistochemistry (IHC) using two scoring schemes: (1) expression in the entire epidermis, and (2) expression in the epidermis minus the stratum granulosum (epidermis-SG).

2.6. Antitumour activity

Patients were assessed at baseline, the end of cycle 2 and every other cycle thereafter by one or more of the following radiologic test for tumour measurement: computerised tomography (CT) scan, magnetic resonance imaging (MRI), chest X-ray. The extent of each patient's response was analysed using the following procedures: tumour measurement of palpable or visible lesions for patients with solid tumours (RECIST v1.1 guidelines) [12] or the Revised Response Criteria for Malignant Lymphoma [13] for patients with Non-Hodgkin's Lymphoma.

3. Results

Twenty-nine patients were enrolled into this study, 17 in Arm A and 12 in Arm B. Patient characteristics and dose escalation are summarised in Tables 1 and 2. The median number of treatments was 1.0 cycle (range 1–6) for Arm A and 1.5 cycles (range 0–6) for Arm B. In Arm A, nine patients completed 1 cycle, five patients completed 2 cycles and one patient completed 6 cycles. Five patients completed 1 cycle, two patients each completed 2, 4 and 6 cycles in Arm B.

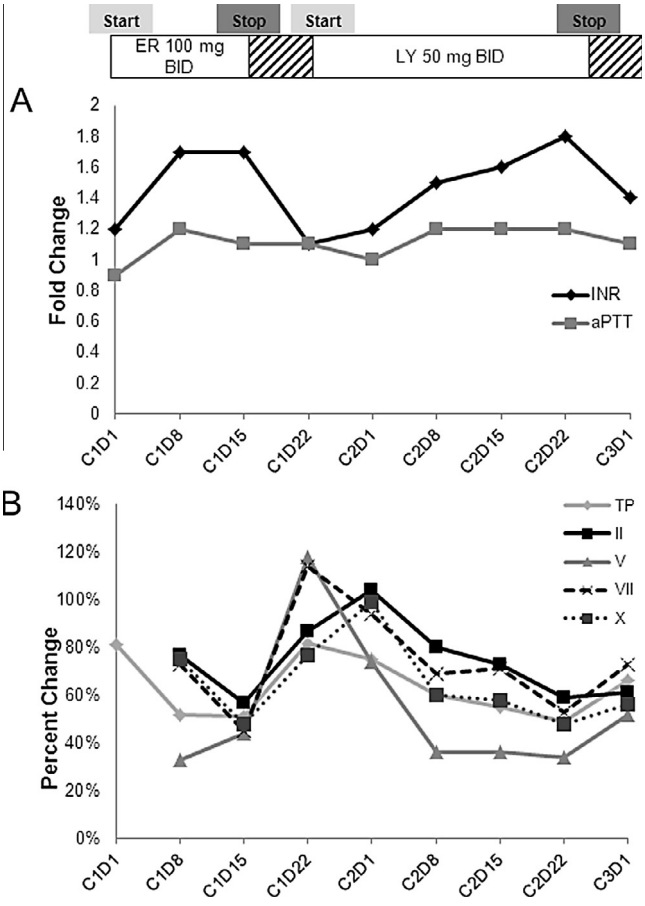

Fig. 1. Analysis of coagulation factors in a patient treated with LY2584702 and erlotinib. A single patient treated with LY2584702 100 mg BID with erlotinib 50 mg BID (Cohort 2 Arm A) exhibited coagulation disorders during treatment. Graphical report of (A) international normalised ratio (INR) and activated partial thromboplastin time (aPTT) levels during cycles 1–3 and of (B) Clotting factors II, V, VII, X and thromboplastin (TP) during cycle 1–2.

3.1. Toxicity

Twenty-nine patients enrolled, and four had DLTs ⩾Grade 3: one case each of hypophosphataemia, vomiting, thromboembolic event and decreased levels of coagulation factor V (Table 2). In Arm A, eight patients (47%) experienced serious adverse events (SAEs), and six patients (50%) experienced SAEs in Arm B. SAE possibly related to study drug included: Grade 3 nausea, Grade 3 vomiting, Grade 3 anorexia, Grade 3 gastritis, grade 3 pulmonary embolism, Grade 3 increased international normalised ratio (INR), Grade 2 interstitial lung disease, Grade 2 deep vein thrombosis. Three patients (17.6%, $n = 17$) in Arm A and two patients (16.7%, $n = 12$) in Arm B discontinued treatment due to AEs. The most common drug related treatment-emergent adverse events (TEAE) were fatigue (88%), anorexia (71%), diarrhoea (65%), nausea (53%), rash acneiform (53%) and vomiting (41%) in Arm A; and fatigue (83%), anorexia (67%), nausea (58%), diarrhoea (50%) and oral mucositis (50%) in Arm B (Table 3). Eleven patients in Arm A ($n = 17$) and eight patients in Arm B ($n = 12$) experienced Grade 3/4 TEAE.

Three patients in Arm A and one patient in Arm B exhibited coagulation abnormalities. One patient in Arm A experienced thromboembolic event (pulmonary embolism), and one patient in Arm B experienced a possibly related SAE of deep venous thrombosis. A third patient experienced decreased coagulation Factor V, which changed from 60% (day 1) to 24% (day 8) then recovered to 85% (day 15) and again declined to 35% (day 22) all in cycle 1. There were no clinically significant changes in intrinsic coagulation pathway factors IX, XI, XII and thromboplastin (TP). A fourth patient in Arm A experienced DLT of hypophosphataemia accompanied with increased INR along with decreases in clotting factors II, V, VII and X (Fig. 1). The changes observed were induced by treatment and improved after treatment discontinuation. Several patients in both arms experienced weight loss while on treatment and ranged from 3% to 10% in Arm A and 4–11% in Arm B. Three patients (18%) in Arm A and six patients (50%) in Arm B experienced weight loss ⩾10% of baseline (Fig. 2). Dose escalation stopped in arm B after occurrence of thromboembolic events in Arm A and B and observance of other toxicities (fatigue and weight loss).

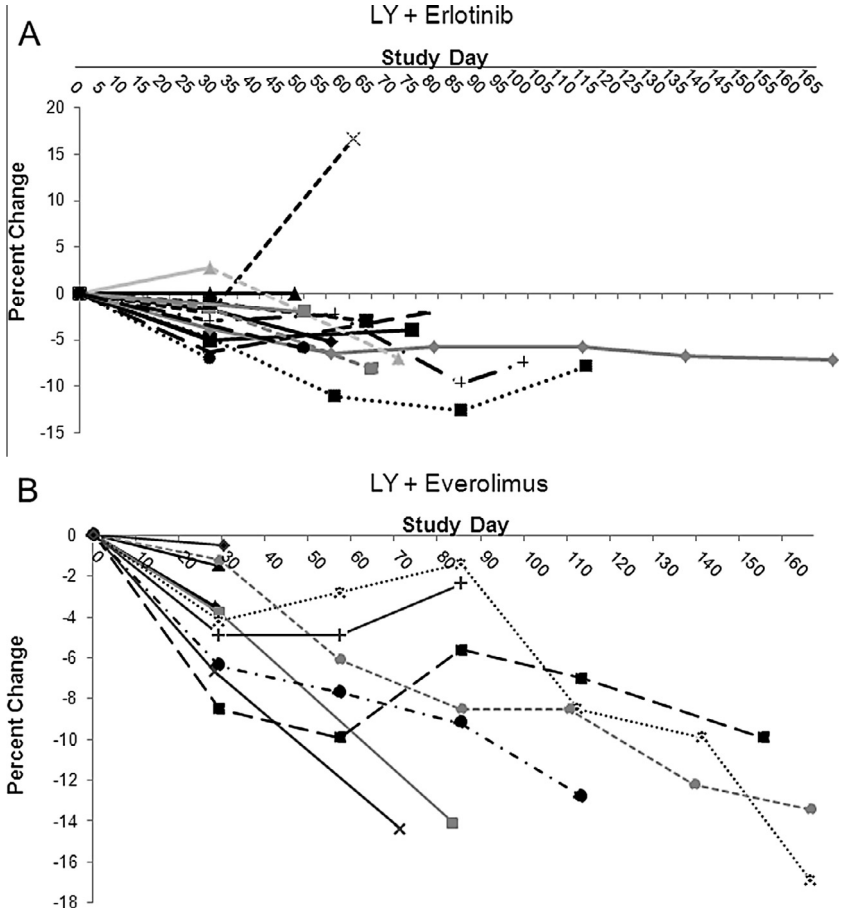

Fig. 2. Weight change from baseline. The percent weight change from baseline was calculated for patients treated with LY2584702 and (A) erlotinib and (B) everolimus. Each line represents a single patient.

Table 4
LY2584702 PK Parameters, Mean (CV%).

	Arm A: LY2584702 + erlotinib ($n = 17$)								Arm B: LY2584702 + everolimus ($n = 12$)					
	50 mg QD + ER 150 mg QD $n = 4$		50 mg BID + ER 150 mg QD $n = 5$		75 mg BID + ER 150 mg QD $n = 5$		100 mg BID + ER 150 mg QD $n = 3$		50 mg QD + EV 10 mg QD $n = 3$		100 mg QD + EV 10 mg QD $n = 3$		50 mg BID + EV 10 mg QD $n = 6$	
	Day 1	Day 7/8/9	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8	Day 1	Day 7/8/9	Day 1	Day 7/8/9	Day 1	Day 8
N	3[b]	4	3[c]	4[d]	5	4[d]	3	3	3	3	2[f]	3	3[e]	6
t_{max} (h[a])	5.03 (3.00–5.08)	5.00 (3.17–5.12)	2.95 (2.00–6.17)	3.29 (1.92–7.92)	3.00 (2.03–8.08)	4.98 (3.00–26.83)	3.00 (1.92–5.00)	5.00 (2.94–17.48)	5.00 (3.05–5.00)	5.00 (2.02–5.00)	3.00 (2.97–3.03)	3.08 (3.00–5.05)	3.00 (2.00–3.00)	2.42 (1.17–5.00)
$C_{max,}$ (ng/mL)	918.24 (42.9)	1125.46 (64.6)	999.54 (68.3)	1636.71 (52.6)	1768.59 (50.3)	1967.04 (24.8)	2421.64 (35.1)	2709.61 (50.7)	1192.46 (31.5)	1169.95 (25.2)	2286.22 (7.3)	2260.71 (34.8)	1569.24 (28.6)	2109.62 (44.1)
$AUC_{(0–8)}$ (h·ng/mL)	4436.60 (50.6)	5395.96 (70.7)	4308.98 (79.8)	7948.43 (50.4)	8091.93 (47.8)	13959.74 (45.6)	8610.54 (49.4)	15225.08 (44.1)	5699.87 (31.9)	5460.80 (23.3)	11410.18 (3.9)	11324.33 (34.7)	6097.44 (15.9)	10527.68 (44.1)
$AUC_{(0–\infty)}$ (h·ng/mL)	8699.54 (38.0)		7627.50 (37.9)		16254.07 (20.3)		20813.83 (25.0)		11386.03 (34.8)		22343.07 (210843.93–23602.20)		8764.13 (14.1)	
CL (L/h)	6.29 (30.9)		7.06 (37.9)		4.79 (23.7)		5.00 (23.1)		4.73 (31.0)		4.49 (4.74–4.24)		5.79 (14.7)	
$t_{1/2}$ (h)	5.13 (14.5)		3.93 (49.5)		5.73 (62.1)		5.57 (42.5)		5.71 (6.9)		6.06 (5.08-7.05)		3.73 (28.0)	

Abbreviations: $AUC_{(0–8)}$, area under the concentration time curve from zero to 8 h; $AUC_{(0–\infty)}$, area under the concentration time curve from zero to infinity; BID, twice daily; CL/F, apparent total body clearance; C_{max}, maximum observed concentration; CV%, percent coefficient of variation; ER, erlotinib; EV, everolimus; h, hours; PK, pharmacokinetics; QD, once daily; *N*, number of patients; NC, not calculated; $t_{1/2}$, elimination half life; t_{max}, time to C_{max}.

[a] t_{max} reported as median and range.

[b] Insufficient data for a single patient on Day 1, therefore $n = 3$.

[c] Insufficient data for two patients on Day 1, therefore $n = 3$.

[d] Insufficient data for a single patient at steady state, therefore $n = 4$.

[e] Insufficient data for three patients on Day 1, therefore $n = 3$.

[f] Outlier for a single patient on Day 1, therefore $n = 2$.

3.2. Pharmacokinetics

PK parameters for LY2584702 were analysed and are summarised in (Table 4). LY2584702 exposure increased dose-proportionally when concomitantly administered with erlotinib, and the dose-normalised AUC for 50 mg QD and 50 mg BID were 88.73 ng h/mL/mg and 86.16 ng h/mL/mg, respectively. The AUC increased slightly at 75 mg BID (107.89 ng h/mL/mg) but decreased at 100 mg BID (86.11 ng h/mL/mg). The LY2584702 exposure increased dose-proportionally when administered concomitantly with everolimus. The dose-normalised AUC values were 121.95, 114.00 and 114.10 ng h/mL/mg for 50 mg BID, 50 mg QD and 100 QD, respectively. For dosing with erlotinib and everolimus, the median accumulation ratio for QD dosing was 1.09 and 1.07 (range, 0.98–1.16) and 2.16 and 1.98 (range, 1.85–3.41) for BID dosing. There was a significant difference ($p = 0.0145$, t-test) in LY2584702 exposure between QD and BID dosing with accumulation ratios of 1.08 and 2.46, respectively. Over all the dose groups, V/F exhibited high variability 34.52 L (47% CV).

3.3. Pharmacodynamics

Three biomarkers were analysed for LY2584702 effect: PRAS40, Akt and pS6 (Fig. 3). There was an overall decrease in these targets at steady state suggesting a biologically effective dose range. This was further supported by the decrease in cholesterol, which was observed in 14 patients. Limited samples of skin biopsies were available for pS6 IHC assessment. Among the samples available from three patients (1 in the 50 mg BID cohort, 2 in the 75 mg BID cohort), one patient showed complete pS6 inhibition in skin (75 mg BID cohort).

3.4. Antitumour activity

There were no patients with partial or complete response. Eight patients (28%) had stable disease as best overall response, four patients in each the erlotinib the everolimus arms. Patient response and duration of treatment are summarised in Supplemental Table 1.

4. Discussion

The combination of LY2584702 with erlotinib or everolimus resulted in unexpected treatment emergent coagulation disorders, which consisted of an increase of INR, a decrease of extrinsic coagulation pathway factors (Factors II, V, VII and X and TP), and a decrease of fibrinogen. These changes did not correlate with signs of liver toxicity. There were no clinically significant changes in intrinsic coagulation pathway factors IX,

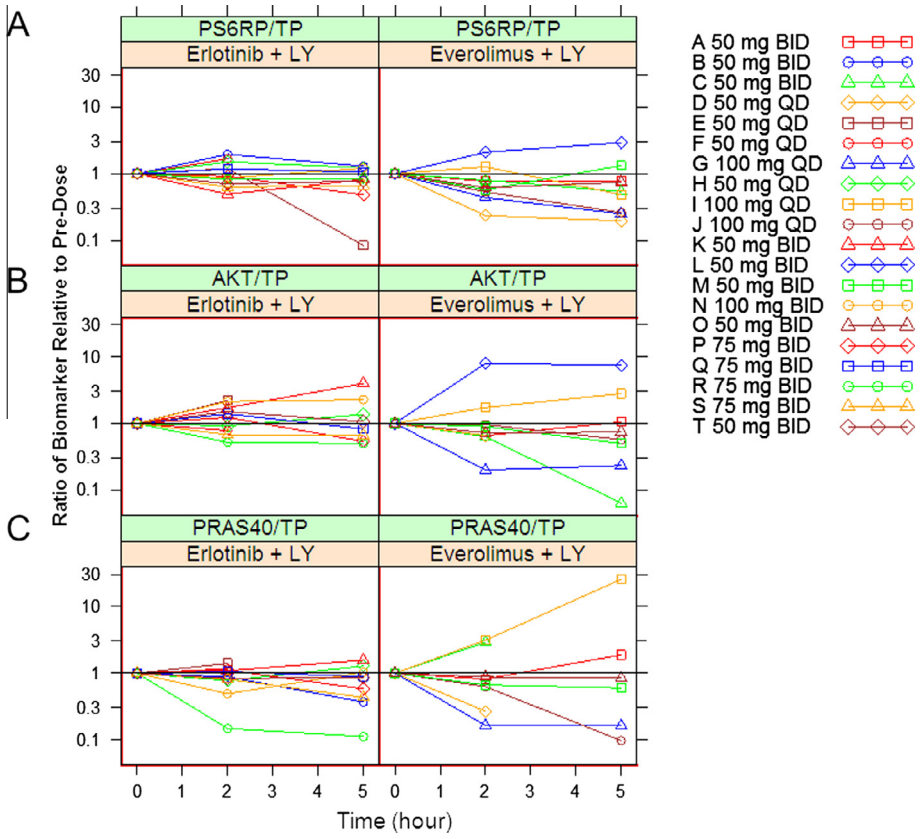

Fig. 3. Biomarker analysis of PRAS40, Akt and pS6. Biomarkers were analysed pre-dose to day 2 of patients (A–T) administered LY2584702 (LY) and erlotinib (left column) and everolimus (right column). Markers analysed included (A) PRAS40, (B) Akt, and (C) pS6 as compared to total protein (TP). Abbreviations: QD = once daily; BID = twice daily.

XI, XII and TP. The coagulation disorders described were likely related to activation of tissue factor and the extrinsic coagulation pathway, but the mechanism of activation is not clear. It was reported that co-stimulatory effect of rapamycin and local VEGF secretion by tumours resulted in excessive endothelial transcription factor expression and tumour vessel thrombosis. This may occur through inhibition of mTOR with rapamycin and loss of p70S6 kinase-mediated negative regulation [10].

An opposing effect on endothelial tissue factor regulation between mTOR and S6K1 was previously reported. Knocking-down mTOR enhanced thrombin-induced tissue factor mRNA and protein levels, whereas silencing S6K1 mitigated up-regulation of tissue factor protein but not tissue factor mRNA level [11]. S6K1 regulation occurs in concert with other pathways [11]. Inhibition of S6K1 concomitantly to EGFR or mTOR inhibition may have caused the increase of coagulation pathway factors and tissue factor activation. Treatment with LY2584702 alone did not demonstrate coagulation toxicities when administered to patients with advanced cancer [9].

PK analyses indicated differences in LY2584702 exposure between the two arms. Data suggest that LY2584702 exposure accumulated under BID dosing, with accumulation ratios of 1.08 (range, 0.98–1.16) and 2.46 (range, 1.85–3.41) for QD and BID dosing, respectively ($p = 0.0145$, t-test). Because this study was an unpaired comparison, no conclusions can be made between the two arms. Terminal slopes of the curves for the 50–100 mg doses are parallel, suggesting that lack of dose proportionality is likely due to variability in the absorption caused by limited solubility and saturation of absorption. Clearance and volume distribution were not significantly different for LY2584702 between everolimus and erlotinib.

Erlotinib exposure increased when administered with LY2584702 as compared to previous studies. The mean value of $AUC_{(0\text{-}\infty)}$ for a single dose of erlotinib across all cohorts higher than the previously reported mean (30390.67 ng h/mL) [12–14]. The mean AUC for erlotinib across all LY2584702 dose groups at steady state was more than 2-fold the previously reported mean value [12,15,16]. The mean clearance for the erlotinib cohorts was higher than previously published values of 3.92 and 5.11 L/h [13,17]. However, the half-life is significantly longer than previously reported with a value of 60.122 h [13,17,18]. The increase in erlotinib exposure at steady state in the 50 and 100 mg BID cohorts suggests inhibition by LY2584702 of the CYP3A4 enzymes, which are important for drug metabolism and cholesterol synthesis.

In contrast, exposure of everolimus was lower than expected when combined with LY2584702. The mean normalised AUC for everolimus was lower compared to previously published values [19,20]. The mean C_{max} was similar to previously published values. Analyses of the $AUC_{(0-\infty)}$ determined that there was not a LY2584702 dose-dependent decrease in exposure for everolimus.

This phase Ib study exhibited less variability than the previous phase I study of LY2584702 [9]. There was a significant difference between the two studies with values of 11.46 L/h (75.1% CV) and 94.24 L (88.9% CV) for CL/F and V/F ($p < 0.001$). This could be due to possible drug–drug interactions in the phase Ib study. These differences could also be attributed to the short concentration curve used for the phase Ib analysis.

This phase Ib study determined that LY2584702 was not well tolerated when administered with erlotinib or everolimus. A recommended phase II dose was not determined for LY2584702. The increase in erlotinib exposure at steady state in the 50 and 100 mg BID cohorts suggests inhibition of the CYP3A4 enzymes by LY2584702. The dual treatment is not feasible due to resulting toxicities of coagulation disorders, fatigue and weight loss. Although in pre-clinical studies the combination of LY2584702 with erlotinib and everolimus was synergistic, clinically there was no evidence of tumour response. Any future studies with compounds which target S6K1 should include coagulation monitoring.

Conflict of interest statement

A.H., N.H., C.M. and A.I. have no COI to report; E.E.W.C. honorarium Eli Lilly and Company in 2011; P.W., W.B., J.M., L.H.B., K.B. are all employees of Eli Lilly and Company; J.C.S. honorarium Eli Lilly and Company.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2013.12.006.

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