European Journal of Cancer (2014) 50, 867–875

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# A phase I trial of LY2584702 tosylate, a p70 S6 kinase inhibitor, in patients with advanced solid tumours

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Received 11 September 2013; received in revised form 6 November 2013; accepted 9 November 2013
Available online 15 January 2014

**KEYWORDS**
Cancer
p70 S6 kinase (p70S6K)
LY2584702 tosylate
PI3 kinase

**Abstract** ***Background:*** LY2584702 tosylate (hereafter referred to as LY2584702) is a potent, highly selective adenosine triphosphate (ATP) competitive inhibitor against p70 S6 kinase, a downstream component of the phosphatidylinositol-3-kinase signalling pathway which regulates cell proliferation and survival. LY2584702 exhibited anti-tumour activity in preclinical analysis.

***Methods:*** Patients with advanced solid tumours were treated with LY2584702 orally on a 28-day cycle until the criteria for maximum tolerated dose (MTD) were met. Skin biopsies were collected for pharmacodynamic analysis, and levels of phospho-S6 protein were examined. The primary objective was to determine a phase II dose and schedule with secondary objectives of observing safety and tolerability. Dose escalation was based upon Common Terminology Criteria for Adverse Events Version 3.0.

***Results:*** Thirty-four patients were enrolled onto this phase I study and treated with LY2584702 on a QD (once-daily) or BID (twice-daily) dosing schedule. Part A dose escalation ($n = 22$) began with 300 mg BID ($n = 2$). Due to toxicity, this was scaled back to doses of 25 mg ($n = 3$), 50 mg ($n = 8$), 100 mg ($n = 3$), and 200 mg ($n = 6$) QD. Part B dose escalation

Research support: The study was sponsored by Eli Lilly and Company.Clinical Trial No. NCT01394003.
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http://dx.doi.org/10.1016/j.ejca.2013.11.039

($n = 12$) included 50 mg ($n = 3$), 75 mg ($n = 3$), and 100 mg ($n = 6$) BID. Seven patients experienced dose-limiting toxicity (DLT). All DLTs were Grade 3 and included vomiting, increased lipase, nausea, hypophosphataemia, fatigue and pancreatitis.

***Conclusion:*** The MTD was determined to be 75 mg BID or 100 mg QD. No responses were observed at these levels. Pharmacokinetic analysis revealed substantial variability in exposure and determined that LY2584702 treatment was not dose proportional with increasing dose.



## 1. Introduction

The phosphatidylinositol-3-kinase (PI3K) is a component of the PI3K/Protein Kinase B (PKB, Akt)/mammalian target of rapamycin (mTOR) signalling pathway, which is a key regulator of cell division and survival. The PI3K/Akt/mTOR signalling pathway is one of the most frequently mutated pathways [1–3], thus making it a target of therapeutic agents. Activation of Akt results in activated mTOR, which functions in the multiprotein complex mTOR complex 1 [4]. This complex activates the serine/threonine protein kinase p70 S6 kinase (p70S6K) and the elongation initiation factor 4E-binding protein (4EBP1), which promote translation initiation during protein synthesis (Fig. 1) [5–9]. p70S6K phosphorylates and activates ribosomal protein S6 (S6), a component of the 40S ribosomal subunit [10], and phosphorylates the eukaryotic initiation factor 4B (eIF4B), a regulator of protein synthesis including the vascular endothelial growth factor (VEGF) [11,12].

The antitumour activity of rapamycin and its analogues is evidence that inhibition of the p70S6K pathway may be an appropriate strategy for cancer therapy. Research efforts identified LY2584702, a selective adenosine triphosphate (ATP) competitive inhibitor of p70S6K with an inhibitory concentration 50% (IC50) of 0.004 μM. LY2584702 inhibits phosphorylation of the S6 ribosomal protein (pS6) in HCT116 colon cancer cells with an IC50 of 0.1–0.24 μM and is selective against 83 other kinases as determined by a ubiquitin kinase panel, and 45 cell surface markers as determined by a CEREP mini panel. LY2584702 demonstrated significant single-agent efficacy in both U87MG glioblastoma and HCT116 colon carcinoma xenograft models at two dose levels of 2.5 mg/kg twice daily (BID) and 12.5 mg/kg BID. LY2584702 demonstrated statistically significant tumour growth reduction at TMED50 (threshold minimum effective dose 50%) (2.3 mg/kg) and TMED90 (10 mg/kg) in the HCT116 colon carcinoma xenograft model.

Suppressing the activity of p70S6K is predicted to inhibit ribosome biogenesis and synthesis of angiogenic and cell-cycle regulatory proteins. We report the first-in-human phase I trial results of LY2584702 with the primary objective of determining a phase II dose and schedule, and the secondary objectives to analyse the safety and toxicity profile of LY2584702.

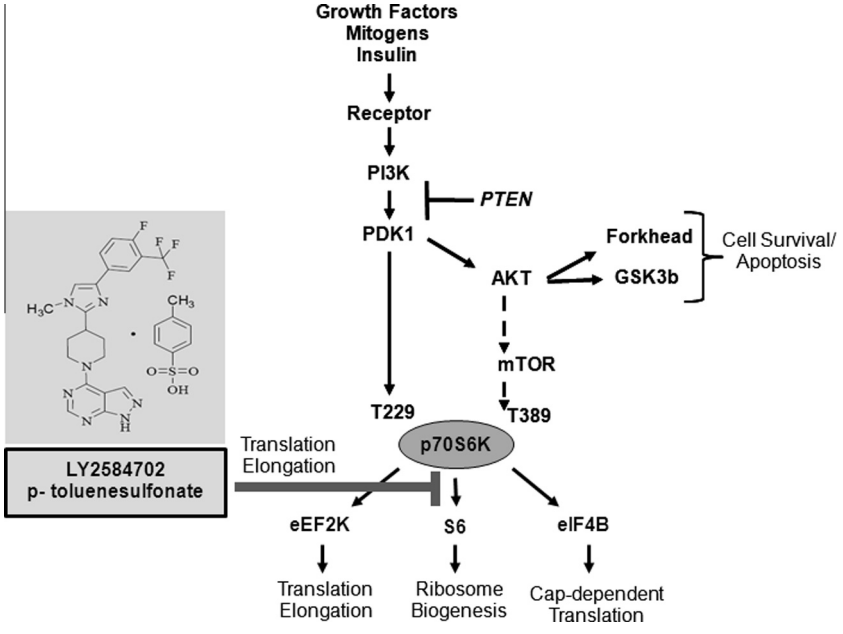


Fig. 1. The S6K1 pathway. Key regulators of the S6K1 pathway and downstream targets are shown. The molecular model of LY2584702 is depicted, which inhibits the phosphorylation of S6 via p70S6K.