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Original Research

A first-in-human phase I study of the oral Notch inhibitor, LY900009, in patients with advanced cancer

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Abstract ***Background:*** Notch signalling regulates stem cell development and survival and is deregulated in multiple malignancies. LY900009 is a small molecule inhibitor of Notch signalling via selective inhibition of the γ-secretase protein. We report the first-in-human phase I trial of LY900009.

Methods: Dose escalation (Part A) was performed in cohorts of three advanced cancer patients using a modified continual reassessment method and dose confirmation (Part B) was performed in ovarian cancer patients. LY900009 was taken orally thrice weekly (every Monday, Wednesday, and Friday) during a 28-d cycle. The primary objective determined the maximum tolerated dose (MTD); secondary end-points included toxicity, pharmacokinetics, pharmacodynamics, and antitumour activity.

Results: Thirty-five patients received LY900009 at dose levels ranging from 2–60 mg. Study drug-related adverse events were diarrhoea (46%), vomiting (34%), anorexia (31%), nausea (31%), and fatigue (23%). At 30 mg, a dose-limiting toxicity (grade III mucosal inflammation) was observed. LY900009 absorption was rapid, with median tmax at 1–4 h post-dose. LY900009 inhibited plasma levels of amyloid-β peptide in a dose-dependent manner with 80–90% inhibition observed in the 30- to 60-mg cohorts. No responses were seen, but five

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patients had stable disease. Two patients (5.7%) with leiomyosarcoma and ovarian cancer received four cycles of therapy. One patient (15 mg) showed markedly increased glandular mucin consistent with pharmacologic inhibition of the Notch pathway.
Conclusions: The recommended MTD schedule for future studies was 30 mg thrice weekly, which exceeds the target inhibition level observed in preclinical models to promote tumour regression in humans.

1. Introduction

The Notch signalling pathway is involved in stem cell development and maintenance, both key components of cancer cell survival and metastasis [1,2]. Notch signalling regulates expression of receptor tyrosine kinases, including the pro-angiogenic vascular endothelial growth factor receptor-1 [3] and the pro-growth epidermal growth factor receptor [4,5]. Also, Notch signalling is a component of stem cell fate and differentiation in a variety of tissues [6].

Notch cell surface receptors 1–4 are heterodimeric proteins composed of extracellular and intracellular domains [7]. The extracellular domain contains conserved epidermal growth factor-like repeat domains involved in ligand binding [7]. Notch is activated by its ligands, which are Delta/Serrate/*lag-2* (DSL) proteins in Drosophila (Delta-like and Jagged proteins in vertebrates). Upon activation, the Notch receptor undergoes proteolytic cleavages that release the Notch intracellular domain (NICD) which translocates to the nucleus and functions as a transcriptional regulator. The NICD interacts with a CBF-1/RBPjk/Su(H)/Lag-1 (CSL) protein which binds DNA and directs NICD to target genes. This complex recruits transcriptional coactivator MasterMind/Lag-3 and regulates protein expression involved in proliferation, differentiation, and apoptosis [8].

Aberrant expression of Notch signalling components correlates with breast cancer growth, metastasis, and poor prognosis [1,9–11]. Evidence suggests that deregulated Notch 1–4 signalling is also implicated in numerous malignancies [7,9,10,12]. In serous ovarian cancer, Notch signalling pathway is altered in 22% of cases [12]. Notch3 overexpression in ovarian cancer cells also results in expansion of cancer stem cells and increased platinum chemoresistance [13]. Therefore, inhibition of Notch signalling via γ-secretase may be an attractive cancer therapy target.

LY900009, a selective inhibitor of the γ-secretase protein, inhibits cleavage of NICD. LY900009 inhibited Notch signalling in tumour cell lines and endothelial cells (half maximal inhibitory concentration [IC_{50}] range: 0.005–20 nM) [14]. In a xenograft tumour model, LY900009 dose dependently inhibited Notch cleavage and induced apoptosis 24 h after a single 3 mg/kg oral dose. Animal tumours treated with LY900009 also revealed inhibition of angiogenesis through formation of leaky vasculature, which may possibly contribute to antitumour activity. Furthermore, LY900009 produced tumour regression in Notch-dependent tumour models [15].

Here, we report the first-in-human phase I trial of LY900009 designed to evaluate the safety and tolerability of LY900009. Secondary objectives included pharmacokinetics (PK), pharmacodynamics (PD), preliminary antitumour activity, and establishing a recommended dose of LY900009.

2. Patients and methods

2.1. Study objectives

The primary objective was to evaluate the safety and tolerability of LY900009 when administered orally to patients with advanced cancer. The secondary objectives were to determine the PK of LY900009, evaluate PD and predictive biomarkers, establish a recommended dose range of LY900009 in the absence of corticosteroid therapy, and explore antitumour activity of LY90009.

2.2. Patient eligibility

Eligible patients (≥18 years) had disease refractory to standard therapy (or no available standard therapy) and a ≥12-week expectancy. In Part A (dose escalation), patients had non-measurable or measurable advanced and/or metastatic solid tumour or lymphoma. In Part B (dose confirmation), patients had measurable advanced or metastatic ovarian cancer. Measurable disease was defined by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 [16] or the Revised Response Criteria for Malignant Lymphoma [17]. Patients discontinued all treatments up to 21 d prior to enrolment, except for patients with breast or prostate cancers progressing on endocrine therapies who may have continued treatment. Patients had a performance status of ≤1 (Part A) and ≤2 (Part B) on the Eastern Cooperative Oncology Group scale. Adequate haematopoietic, renal, and hepatic functions