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Clinical Trial

A phase II trial to evaluate the efficacy of fostamatinib in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

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Abstract ***Purpose:*** To assess the safety and efficacy of fostamatinib in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).
Experimental design: Relapsed or refractory DLBCL patients originally received the oral spleen tyrosine kinase inhibitor, fostamatinib in a two-arm, randomised, double-blinded manner at either 100 mg twice a day (BID) or 200 mg BID until disease progression or unacceptable toxicity. The primary objective was to assess the overall response rate (ORR). Preliminary analysis showed limited efficacy and all subsequent patients were treated at 200 mg BID. Previously randomised patients were unblinded and given the opportunity to receive 200 mg BID.

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Results: Sixty-eight patients were treated (47 at 200 mg BID, 21 at 100 mg BID). Cell of origin analysis showed 58% germinal B-cell (GCB) origin, 30% activated B-cell (ABC) origin and 12% with an intermediate cell of origin signature. The most common treatment-related adverse events of all patients were diarrhoea (21% total, 6% grade 3/4), nausea (19% total, 3% grade 3/4), and, fatigue (18% total, 9% grade 3/4). The ORR rate was 3% across both arms and clinical benefit (≥stable disease) was achieved for 13% of all patients. The cell of origin for patients with clinical benefit was GCB (4 patients), intermediate (4 patients) or unknown (1 patient). None of the patients with clinical benefit had ABC genotype.
Conclusions: While fostamatinib was generally well tolerated in this patient population, efficacy at these doses and schedule was poor. Unlike data with other B-cell antigen receptor pathway inhibitors, responses were not observed in the ABC genotype.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is a fast-growing and aggressive form of non-Hodgkin lymphoma. While between 50–60% of all patients can be cured with combination chemoimmunotherapy such as rituximab/cyclophosphamide/doxorubicin hydrochloride/vincristine sulfate/prednisone [1], many patients either do not fully respond to initial treatment (refractory disease), or relapse following initial remission. New therapies are especially important in refractory DLBCL, in which outcomes are extremely poor.

DLBCL is a markedly heterogeneous group of tumours and several approaches have been employed to help define distinct, molecular subsets of the disease. One such approach has focused on the cell of origin of DLBCL, leading to patient classification into primary mediastinal, activated B-cell (ABC), and germinal-center B-cell (GCB) lymphomas as defined by gene expression profiling (GEP) [2].

The tumours of many DLBCL patients exhibit overexpression of components of the B-cell receptor signaling cascade such as spleen tyrosine kinase (Syk) [3], and some DLBCL subsets are particularly reliant on tonic signalling through the B-cell receptor. Emerging data on DLBCL [3] implicates chronic activation of malignant B-cells through Syk-dependent pathways as a mechanism of lymphomagenesis. Syk, a non-receptor SH2-domain-containing tyrosine kinase is involved in key regulatory pathways downstream of several immunoreceptors, including the B-cell antigen receptor (BCR) [4]. Dependence on BCR-mediated survival signals is exhibited by most B-cell lymphomas: they rarely lose BCR expression despite ongoing somatic hypermutation, and treatment with anti-idiotypic antibodies does not induce the emergence of BCR-negative lymphoma variants [5].

Fostamatinib is an orally administered Syk inhibitor studied in patients with rheumatoid arthritis, immune thrombocytopenic purpura, solid tumours, and B-cell malignancies [6–9]. It is hypothesised to inhibit and eliminate tumour cells addicted to the B-cell receptor pathway and recent clinical trials evaluating agents targeted against BCR signaling components (Syk/fostamatinib [9], and Bruton's tyrosine kinase/ibrutinib [10]) demonstrated clinical responses, underscoring the importance of the BCR signalling pathway in the progression of malignant B-cell diseases, such as DLBCL.

In a phase I/II study of fostamatinib in patients with refractory B-cell lymphomas [9], the overall response rate (ORR) among patients with DLBCL (n = 23) in the phase II part was 21%; and 5 had responses (one complete response [CR] and four partial responses [PRs]) [9]. Median progression-free survival (PFS) for the phase II patients was 4.1 months, and for DLBCL patients, median PFS was 2.7 months [9].

Based on these data, we conducted a phase II trial to examine the safety and efficacy of fostamatinib in patients with relapsed/refractory DLBCL.

2. Methods

2.1. Patients and eligibility criteria

This study (ClinicalTrials.gov: NCT01499303; **EudraCT Number:**2011-005371-16) investigated the efficacy of fostamatinib in the treatment of patients with relapsed or refractory DLBCL. The study was conducted within applicable regulatory guidelines, International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki. Institutional review boards at all participating sites approved the study, and all patients provided written informed consent.

Eligible patients had measurable relapsed or refractory DLBCL, had previously received chemoimmunotherapy, and had received, or were ineligible for, high-dose chemotherapy with stem-cell rescue. Patients were required to provide previously obtained archival tumour biopsy tissue, previous fresh frozen