blood

624. LYMPHOMA: THERAPY WITH BIOLOGIC AGENTS, EXCLUDING PRE-CLINICAL MODELS: POSTER III | NOVEMBER 15, 2013

A Phase I Study Of The Oral Btk Inhibitor ONO-4059 In Patients With Relapsed/Refractory B-Cell Lymphoma

Simon Rule, MD,[*,1] Nimish Shah, MD,[*,1] Gilles Andre Salles, MD, PhD,[2] Lionel Karlin, MD,[*,3] Franck Morschhauser, MD, PhD,[*,4] Louis Terriou, MD,[*,5] Martin JS Dyer, MA, DPhil, FRCP, FRCPath,[6] Claire Hutchinson, BMedSci, MRCP, FRCPath,[*,7] Chris Fegan, MBBS,[*,8] Guillaume Cartron, MD, PhD,[*,9] Tomasz Knurowski, MD,[*,10] James G Wright, PhD,[*,11] Andrew J Saunders, MD,[*,12] Hideyuki Honda, Bsc,[*,13] Andrew Mazur,[*,13] Toshio Yoshizawa, PhD,[*,14] Kazuhito Kawabata, PhD,[*,15] Joseph TP Birkett, PhD[*,16]

[1]Department of Haematology, Derriford Hospital, Plymouth, United Kingdom,

[2]Hospices Civils de Lyon; Université Claude Bernard Lyon 1, Lyon, France,

[3]Centre Hospitalier Lyon Sud/Hospices Civils de Lyon, Pierre-Bénite, France,

[4]Service Maladies du Sang, CHRU - Hôpital Claude Huriez, Lille, France,

[5]Hôpital Claude Huriez, Lille, France,

[6]Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester, United Kingdom,

[7]Department Cancer Studies and Molecular Medicine, University of Leicester, Leicester, United Kingdom,

[8]Department of Haematology, Cardiff University, Cardiff, United Kingdom,

[9]Département d'Hématologie Clinique, CHU Montpellier, Monpellier, France,

[10]Orion Clinical Services, Slough, United Kingdom,

[11]Wright Dose Limited, Manchester, United Kingdom,

[12]Linden Oncology, Edinburgh, United Kingdom,

[13]ONO Pharma UK LTD, London, United Kingdom,

[14]Ono Pharmaceutical CO., LTD, Osaka, Japan,

[15]Ono Pharmaceutical Co., Ltd., Osaka, Japan,

[16]Clinical Science Oncology, Ono Pharma UK Ltd., London, United Kingdom

Blood **(2013) 122 (21) : 4397.**

http://doi.org/10.1182/blood.V122.21.4397.4397

Abstract

Introduction

The B-cell receptor (BCR) pathway plays a central role in signal transduction pathways that regulate survival, activation, proliferation and differentiation of B-lineage lymphoid cells. Bruton's tyrosine kinase (Btk) is a critical kinase in BCR signal transduction and recent studies support that targeting Btk is effective in the treatment of B-cell malignancies. ONO-4059 is a highly potent and selective oral Btk inhibitor with an IC50 in the sub-nmol/L range that has demonstrated anti-tumour activity in several pre-clinical models (Yasuhiro T et al, AACR 2013).

Methods

This Phase I study was initiated to determine the safety, tolerability, dose-limiting toxicity (DLT), pharmacokinetics and pharmacodynamics of ONO-4059 given as monotherapy to patients with relapsed/ refractory NHL for whom no therapy of higher priority was available. In this safety-driven, dose-escalating 3+3 design, ONO-4059 was administered as an oral, daily dose (flat dose) given continuously initially for up to 6 months, with the option of additional dosing up to 2 years. We present the safety and efficacy data on 14 evaluable patients (mantle cell lymphoma n=7, follicular lymphoma n=3, plasmablastic DLBCL n=1, ABC-DLBCL n=1, small lymphocytic lymphoma n=1 and Waldenstrom's macroglobulinaemia n=1), with a median age 64 yrs (range 48-88), median baseline tumour burden 5,668 mm^2 [1,582-19,509]. Patients received a median of 3 prior therapies [range 2-8], with all patients having prior exposure to a rituximab-containing regimen 93% (13/14) and 29% of patients (4/14) had prior ASCT. Patients received ONO-4059 at doses ranging from 20mg-160mg (cohorts 1-4) and the study is currently ongoing with additional dose escalation cohorts to be completed.

Results

ONO-4059 was found to be well tolerated, with no dose limiting toxicities (DLTs). A total of 18 ONO-4059-related adverse events were reported in 6 out of 14 patients; CTCAE-V4.0 G1 (n=10 [n=6 in 1 patient]) and G2 (n=5). Three ONO-4059-related G3 haematological toxicities were reported in 2 patients; thrombocytopenia (x2) and anemia. No ONO-4059-related G4 events, or related SAEs or infections were reported. The pharmacokinetics of ONO-4059 reflects rapid absorption and elimination, a half-life of ~6 hours, a dose dependent increase in exposure with no accumulation of ONO-4059 exposure and low inter- or intra-patient variability; with Btk occupancy in peripheral blood (as measured by phosphorylated Btk) being maintained for at least 24 hours across all dose levels. Responses have occurred at doses of 40, 80 and 160mg, with a best overall response rate of 42% [based on CT-scan and physical examination for 5/12 evaluable patients]; with 5 PR, 4 SD, 2 PD (both MCL) and one ABC-DLBCL patient was withdrawn due to non-related SAE during Cycle 1. Of the 6 evaluable MCL patients, 3 have achieved PR resulting in a best ORR of 50% (median reduction of lymph nodes was 73% [45%-84%]). Almost all

patients experienced clinically meaningful rapid reductions in lymphadenopathy observed within the first cycle. Ten of the fourteen patients are currently still on study with a median progression-free survival of 93.5 days [Range 8-268]. In conclusion, ONO-4059 is a highly potent and selective oral Btk inhibitor that shows a favourable safety profile along with promising efficacy in this difficult-to-treat patient population.

Disclosures:

Salles: *Janssen:* Honoraria; *Gilead:* Honoraria; *Celgene:* Honoraria. **Karlin:** *Janssen:* Honoraria; *Celgene:* Honoraria. **Morschhauser:** *ONO Pharma:* Honoraria; *Roche:* Honoraria; *Celgene:* Honoraria; *Mundipharma:* Honoraria. **Dyer:** *Ono Pharma:* Honoraria, Research Funding. **Hutchinson:** *Ono Pharma:* Research Funding. **Fegan:** *ONO Pharma:* Honoraria. **Cartron:** *ONO Pharma:* Honoraria. **Knurowski:** *ONO Pharma:* Consultancy. **Wright:** *ONO Pharma:* Consultancy. **Saunders:** *ONO Pharma:* Consultancy; *Pharmacyclics:* Consultancy. **Honda:** *ONO Pharma:* Employment. **Mazur:** *ONO Pharma:* Consultancy. **Yoshizawa:** *Ono Pharma:* Employment. **Kawabata:** *Ono Pharmaceutical Co., Ltd.:* Employment. **Birkett:** *Ono Pharma UK:* Employment.

Author notes

* Asterisk with author names denotes non-ASH members.