1014PD Phase I/II, first in human trial with M7583, a Bruton's tyrosine kinase inhibitor (BTKi), in patients with B cell malignancies

W. Jurczak[1], S. Rule[2], W. Townsend[3], D. Tucker[4], B. Sarholz[5], J. Scheele[6], J. Gribben[7], P.L. Zinzani[8]

[1]Department of Haematology, Jagiellonian University, Krakow, Poland, [2]Department of Haematology, Plymouth University Medical School, Plymouth, UK, [3]Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK, [4]Department of Haematology, Torbay and South Devon NHS Trust, Torquay, UK, [5]R&D Global Biostatistics & Epidemiology, Merck KGaA, Darmstadt, Germany, [6]Global Clinical Development, Merck KGaA, Darmstadt, Germany, [7]Department of Haematology, Barts Cancer Institute, Queen Mary University of London, London, UK, [8]Institute of Hematology "L.e A. Seragnoli", University of Bologna, Bologna, Italy

Background: BTK is a key regulator in B-cell receptor-mediated signaling and its inhibition blocks several B-cell functions. Small molecule BTKi have been approved for the treatment of B-cell malignancies, such as resistant/refractory chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and Waldenström's macroglobulinemia (WM). M7583 is a potent, highly selective BTKi, under investigation in a two-part, phase I/II trial (NCT02825836) in patients (pts) with refractory/resistant B cell malignancies.

Methods: In Part 1 (dose escalation), pts with refractory/resistant B cell malignancies received 28-day cycles of once-daily (QD) M7583, starting at 80 mg for 3 days followed by 160 mg with doses increasing according to an adaptive Bayesian design. Part 2 (dose expansion) will be in pts with diffuse large B cell lymphoma (DLBCL; activated B-cell subtype) or MCL who have failed 1–3 lines of therapy. Safety and tumor response (investigator's assessment according to Cheson/CLL/Owen criteria) are presented.

Results: As of 27/02/18, in Part 1, 14 pts have been enrolled into the first 4 dose levels (80/160 mg, 300 mg and 600 mg QD and 300 mg twice daily [BID]): 10 men, 4 women; age, 49–80 years; WM (n = 4), MCL (n = 6), marginal zone lymphoma (n = 2), CLL (n = 1), or DLBCL (n = 1). Treatment-emergent adverse events (TEAEs) were mainly mild to moderate in intensity with no dose-limiting toxicities reported. Six pts have had a total of 8 grade $\geq$3 TEAEs; only 1 TEAE was considered related to treatment (grade 4 neutropenia). One pt had 2 serious TEAEs (chest pain and fever) and 1 pt died (extensive progressive disease, cycle 1). Clinical benefit (stable disease [SD], complete [CR], minor [MR] or partial response [PR]) was observed in 12/14 pts: 6/6 pts who received 160 mg or 300 mg QD (3 PR, 1 MR, 2 SD), 3/5 pts treated with 600 mg QD (1 CR, 1 PR, 1 MR) and 3/3 pts on 300 mg BID (2 PR, 1 SD). Study is ongoing.

Conclusions: M7583 has been well tolerated with evidence of clinical benefit at all the doses investigated. M7583 appears to have a favorable benefit: risk profile.

Clinical trial identification: NCT02825836.

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