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A Phase I/II, First in Human Trial of the Bruton's Tyrosine Kinase Inhibitor M7583 in Patients with B-Cell Malignancies

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INTRODUCTION

- Bruton's tyrosine kinase (BTK) plays a key role in B-cell receptor-mediated pathways implicated in the pathogenesis of several B-cell malignancies, and its inhibition blocks several B-cell functions.[1]
- M7583 is a potent, highly selective BTK inhibitor (BTKi) that has shown *in vitro* and *in vivo* activity against several B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL).[2]
- M7583 has been investigated in a phase I/II trial (NCT02825836) in patients with refractory/resistant B-cell malignancies; final dose-escalation data are presented.

OBJECTIVES

- Primary objective: determine the recommended dose of single-agent M7583 for further investigation.
- Secondary objectives: included evaluation of preliminary efficacy (best overall response, duration of response, progression-free survival) and safety/tolerability.

METHODS

Study design

- Study conducted in patients with refractory/resistant B-cell malignancies who had failed 1–3 lines of prior therapy.
- M7583 given once daily (QD) in 28-day cycles in ascending dose cohorts until disease progression, withdrawal of consent, or early discontinuation from the study.
  - Starting dose was 80 mg QD for 3 days followed by 160 mg QD, then doses increased sequentially according to an adaptive Bayesian design up to 900 mg QD (n=3-6 patients per dosing cohort).

Key eligibility criteria

- Adults with pathologically confirmed DLBCL, CLL, small lymphocytic lymphoma, follicular lymphoma, MCL, or Waldenström's macroglobulinemia (WM) who had received 1–3 lines of prior therapy.
  - Other inclusion criteria included: life expectancy >4 months from first dose, Eastern Cooperative Oncology Group performance status ≤2, and adequate hematological, hepatic and renal function.
- Patients were excluded if they had had anticancer therapy within 28 days prior to trial drug treatment or any prior BTKi exposure, central nervous system lymphoma or leukemia, or significant cardiac conduction abnormalities or a history of Richter's transformation, prolymphocytic leukemia or cardiovascular/cerebrovascular disease.

Assessments

- DLTs were assessed during cycle 1 (primary endpoint) using NCI-CTCAE version 4.03 and defined as:
  - Treatment-related hepatocellular injury or treatment-related grade ≥3 non-hematological treatment-emergent adverse events (TEAEs) except: diarrhea or nausea/vomiting <3 days duration; asymptomatic grade 3 increase in liver function tests that resolve within 7 days; grade 3 skin toxicity that resolves to grade ≤2 within 7 days; grade 3 hyperglycemia (in patients with diabetes or decreased glucose tolerance) that resolves in <5 days; fatigue/headache of <7 days duration; or single laboratory values out of the normal range that resolve in ≤5 days.
  - Treatment-related grade 4 neutropenia of >5 days duration, grade ≥3 febrile neutropenia or grade 4 hemoglobin decrease, grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding, or any treatment-related TEAE causing the patient to miss ≥6 consecutive days of treatment in Cycle 1.
- Best overall response was assessed by investigators according to the revised International Working Group Criteria for Non-Hodgkin's lymphoma, and Owen criteria for WM.
- Incidence and severity of TEAEs were reported using NCI-CTCAE version 4.03.

RESULTS

Baseline Characteristics

- At the time of analysis (data cut-off, 20 May 2018), 25 patients had been screened and 18 had received M7583 treatment in five dose cohorts (**Table 1**)
  - Eleven patients were still on treatment; 3 patients had completed treatment and 4 had discontinued due to TEAEs (n=2), complete remission - stem cell transplant (n=1) and investigator's decision (n=1)
- Patients were white, predominantly male (aged 49 to 80 years).

Table 1. Baseline Demographics and Disease Characteristics

	M7583 dose					Total (N=18)
	80/160 mg QD (n=3)	300 mg QD (n=3)	600 mg QD (n=5)	300 mg BID (n=3)	900 mg QD (n=4)	
Age, median years (range)	68 (57, 80)	66 (59, 74)	55 (49, 63)	63 (62, 73)	59 (43, 70)	63 (43, 80)
Male, n (%)	2 (66.7)	2 (66.7)	4 (80.0)	2 (66.7)	3 (75.0)	13 (72.2)
B cell malignancy, n (%)						
DLBCL	0 (0)	0 (0)	1 (20.0)	0 (0)	2 (50.0)	3 (16.7)
WM	1 (33.3)	2 (66.7)	1 (20.0)	0 (0)	0 (0)	4 (22.2)
MCL	1 (33.3)	0 (0)	3 (60.0)	2 (66.7)	2 (50.0)	8 (44.4)
SLL	0 (0)	0 (0)	0 (0)	1 (33.3)	0 (0)	1 (5.6)
MZL	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0 (0)	2 (11.1)

BID, twice daily; **DLBCL**, diffuse large B-cell lymphoma; **MCL**, mantle cell lymphoma; **MZL**, marginal zone lymphoma; **QD**, once daily; **SLL**, small lymphocytic lymphoma; **WM**, Waldenström's macroglobulinemia.

Treatment Exposure

- Maximum treatment duration with M7583 was 20.1 months (**Table 2**).

Table 2. Duration of M7583 Treatment

Treatment duration, months	M7583 dose					Total (N=18)
	80/160 mg QD (n=3)	300 mg QD (n=3)	600 mg QD (n=5)	300 mg BID (n=3)	900 mg QD (n=4)	
n (%)						
≥0−6	0 (0)	0 (0)	2 (40.0)	0 (0)	3 (75.0)	5 (27.8)
>6−12	1 (33.3)	0 (0)	3 (60.0)	3 (100)	1 (25.0)	8 (44.4)
>12−18	0 (0)	3 (100)	0 (0)	0 (0)	0 (0)	3 (16.7)
>18−24	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11.1)
Median (range)	19.5 (12.0, 20.1)	14.2 (14.0, 15.8)	6.2 (0.5, 11.9)	7.8 (7.7, 8.0)	2.8 (0.8, 6.6)	7.9 (0.5, 20.1)

BID, twice daily; **QD**, once daily.

Safety

- No DLTs were reported.
- Overall, 89% of patients reported ≥1 TEAE of any grade (**Table 3**).
- Ten (56%) patients reported grade ≥3 TEAEs, three (17%) had TEAEs considered to be related to treatment (**Table 3**), which were neutropenia, febrile neutropenia and pneumonia.
- Four (22%) patients had grade ≥4 TEAEs, considered to be treatment-related in one (6%) patient (neutropenia).
- Six patients (33%) had serious TEAEs, two (11%) patients had treatment-related serious TEAEs (**Table 3**), which were febrile neutropenia and pneumonia.
- Two deaths due to TEAEs (disease progression), neither related to treatment (**Table 3**).
- Most common TEAEs were diarrhea, fatigue and vomiting (**Table 4**).

Table 3. Summary of TEAEs

Patients, n (%), with any	M7583 dose					Total (N=18)
	80/160 mg QD (n=3)	300 mg QD (n=3)	600 mg QD (n=5)	300 mg BID (n=3)	900 mg QD (n=4)	
TEAE	3 (100)	3 (100)	4 (80.0)	2 (66.7)	4 (100)	16 (88.9)
M7583-related TEAE	3 (100)	2 (66.7)	3 (60.0)	2 (66.7)	4 (100)	14 (77.8)
Serious TEAE	0 (0)	0 (0)	2 (40.0)	0 (0)	4 (100)	6 (33.3)
Serious M7583-related TEAE	0 (0)	0 (0)	0 (0)	0 (0)	2 (50)	2 (11.1)
Grade ≥3 TEAE	3 (100)	0 (0)	3 (60.0)	0 (0)	4 (100)	10 (55.6)
Grade ≥3 M7583-related TEAE	1 (33.3)	0 (0)	0 (0)	0 (0)	2 (50)	3 (16.7)
Grade ≥4 TEAE	1 (33.3)	0 (0)	1 (20.0)	0 (0)	2 (50)	4 (22.2)
Grade ≥4 M7583-related TEAE	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.6)
TEAE leading to death	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25)	2 (11.1)

BID, twice daily; **QD**, once daily; **TEAE**, treatment-emergent adverse event.

Table 4. Most common TEAEs (Occurring in ≥2 Patients)

Patients with TEAEs, n (%)	M7583 dose					Total (N=18)
	80/160 mg QD (n=3)	300 mg QD (n=3)	600 mg QD (n=5)	300 mg BID (n=3)	900 mg QD (n=4)	
Diarrhea*	1 (33.3)	1 (33.3)	2 (40.0)	0 (0)	2 (50.0)	6 (33.3)
Fatigue	0 (0)	1 (33.3)	1 (20.0)	0 (0)	2 (50.0)	4 (22.2)
Vomiting*	0 (0)	0 (0)	2 (40.0)	0 (0)	1 (25.0)	3 (16.7)
Neutropenia*	1 (33.3)	0 (0)	0 (0)	0 (0)	1 (25.0)	2 (11.1)
Upper abdominal pain*	1 (33.3)	0 (0)	0 (0)	0 (0)	1 (25.0)	2 (11.1)
Gastro-esophageal reflux disease*	1 (33.3)	0 (0)	0 (0)	0 (0)	1 (25.0)	2 (11.1)
Nausea*	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25.0)	2 (11.1)
Disease progression	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25.0)	2 (11.1)
Peripheral edema	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25.0)	2 (11.1)
Pyrexia	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25.0)	2 (11.1)
Conjunctivitis	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0 (0)	2 (11.1)
Nasopharyngitis	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11.1)
Dizziness	0 (0)	0 (0)	1 (20.0)	1 (33.3)	0 (0)	2 (11.1)
Rhinitis	1 (33.3)	0 (0)	0 (0)	0 (0)	1 (25.0)	2 (11.1)
Dyspnea	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25.0)	2 (11.1)
Dry skin	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0 (0)	2 (11.1)
Pruritus*	0 (0)	0 (0)	2 (40.0)	0 (0)	0 (0)	2 (11.1)

BID, twice daily; **QD**, once daily; **TEAE**, treatment-emergent adverse event.
*TEAE was considered treatment-related in ≥2 patients

Efficacy

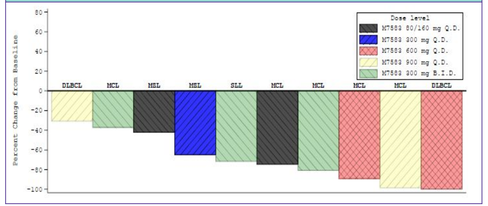
- Objective response rate was 50% and disease control rate was 78% (**Table 5**).
- Two patients achieved complete response (**Table 5**)
  - One reached complete response after 4 months of treatment and complete remission after 6 months of treatment, and then went on to receive stem cell transplantation
  - the second attained a complete response following 2 months of treatment.

Table 5. Best Overall Response to M7583

Response, n (%)	M7583 dose					Total (n=18)
	80/160 mg QD (n=3)	300 mg QD (n=3)	600 mg QD (n=5)	300 mg BID (n=3)	900 mg QD (n=4)	
Best overall response						
Complete response	0 (0)	0 (0)	1 (20.0)	0 (0)	1 (25.0)	2 (11.1)
Partial response	1 (33.3)	2 (66.7)	2 (40.0)	2 (66.7)	0 (0)	7 (38.9)
Minor response	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	1 (5.6)
Stable disease	2 (66.7)	0 (0)	0 (0)	1 (33.3)	1 (25.0)	4 (22.2)
Not evaluable	0 (0)	0 (0)	2 (40.0)	0 (0)	1 (25.0)	3 (16.7)
Objective response rate	1 (33.3)	2 (66.7)	3 (60.0)	2 (66.7)	1 (25.0)	9 (50.0)
Disease control rate	3 (100.0)	3 (100.0)	3 (60.0)	3 (100.0)	2 (50.0)	14 (77.8)

- Median time to the observed responses was 7.1 weeks (range, 7.1, 50.0 weeks).
- Decreases in tumor burden were observed across dose levels and tumor types: 10 patients had a decrease in tumor burden of ≥30% (**Figure 1**).

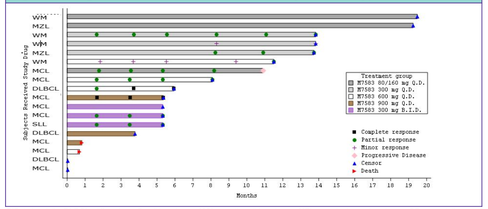
Figure 1. Change (%) in Tumor Burden* by Disease and Dose



BID, twice daily; **DLBCL**, diffuse large B-cell lymphoma; **MCL**, mantle cell lymphoma; **MZL**, marginal zone lymphoma; **QD**, once daily; **SLL**, small lymphocytic lymphoma. *Maximum relative decrease in the sum of the products of the target tumor diameters (SPD) from baseline. Patients with WM are excluded along with patients who were not evaluable due to missing baseline or post-baseline assessments.

- At 12 months, 75% of patients were progression free (Kaplan-Meier estimate).
- The progression-free survival observed in individual patients is shown in **Figure 2**.

Figure 2. Progression Free Survival in Patients by Disease Type



BID, twice daily; **DLBCL**, diffuse large B-cell lymphoma; **MCL**, mantle cell lymphoma; **MZL**, marginal zone lymphoma; **QD**, once daily; **SLL**, small lymphocytic lymphoma; **WM**, Waldenström's macroglobulinemia.

CONCLUSIONS

- **In this dose-escalation study, M7583 was well tolerated at all the doses investigated (80/160 mg QD, 300 mg QD, 600 mg QD, 300 mg BID, and 900 mg QD)**
  - **No DLTs were observed**
- **There was evidence of clinical benefit at all of the doses investigated and across the tumor types**
  - **positive tumor response observed at the lowest dose investigated (80/160mg QD)**
  - **Three quarters of patients were still progression free after 12 months of treatment; however, PFS data are not yet mature**
- **M7583 appears, therefore, to have a favorable benefit:risk profile**
- **The recommended dose for further investigation is 300 mg BID, with 900 mg QD as a supporting daily dose**

REFERENCES

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2. Goodstal SM, et al. *Blood* 2017;130 (Suppl 1):Abstract #3845.

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DISCLOSURES

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WT has received consultancy honoraria from Roche and Gilead.

DT declares no conflict of interest.

BS and JS are employees of Merck KGaA.

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PLZ has received honoraria from and served on advisory boards for Roche, Celgene, Gilead, J&J, BMS, Karyopharma, Millennium Pharmaceuticals, Bayer, Verastem, Merck, and Servier.

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