UPDATED SAFETY AND EFFICACY DATA IN A PHASE 1/2 TRIAL OF PATIENTS WITH WALDENSTRÖM MACROGLOBULINAEMIA (WM) TREATED WITH THE BRUTON TYROSINE KINASE (BTK) INHIBITOR ZANUBRUTINIB (BGB-3111)

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Aims

To present updated zanubrutinib safety and efficacy data in patients (pts) with WM.

Methods

This is a global, open-label, multicenter, phase 1/2 study in pts with B-cell malignancies with indication-specific expansion cohorts. Pts received doses of zanubrutinib ranging from 40 mg once daily to the final recommended phase 2 dose of 160 mg twice daily or 320 mg once daily until disease progression (PD) or unacceptable toxicity. We report here on the 77 WM pts from the cohorts who had no prior BTK therapy. The primary endpoint is safety/tolerability. Secondary endpoints include response rate and PFS assessed by IRC.

Results

As of September 16th, 2018, 77 pts with WM received zanubrutinib (Table). The most common (>15%) adverse events (AEs) of any grade were upper respiratory tract infection (46%), contusion (30%), cough (20%), headache (18%), back pain (17%), diarrhea (17%), urinary tract infection (16%), and constipation (16%). Grade ≥3 AEs in ≥5% of pts were neutropenia (10%) anemia (8%), hypertension (5%), and basal cell carcinoma (5%). The most common serious AEs were cellulitis (5%), pneumonia (4%), pyrexia (3%), febrile neutropenia (3%), and atrial fibrillation (3%). Sixteen pts discontinued treatment, 8 due to AE, 4 due to PD, 1 due to investigator decision, and 3 others (radiation therapy [n=1], not compliant with taking drug [n=2]). Five fatal AEs occurred: abdominal sepsis, septic arthritis, scedosporium infection, bronchiectasis, and gastric adenocarcinoma, of which one was considered related to treatment (septic arthritis) Regarding AEs of special interest with BTK inhibitor therapy, 2 pts (3%) had major haemorrhage (1 with melaena and hemothorax, 1 with haemorrhagic cystitis) and 4 pts (5%) experienced atrial fibrillation or flutter, 1 of which was grade 3. Two pts (3%) had grade 3 diarrhea. Of the 73 efficacy evaluable pts (4 pts non-evaluable due to having <5g/L IgM levels at baseline), 24 were treatment-naïve and 49 were relapsed/refractory (Table; median follow-up 23.9 mo [range, 4.4-45.7]). Based on modified IWWM-6 (Owen) as assessed by IRC, the overall response rate (ORR; minor response [MR] or better) was 92% (67/73 pts), major response rate (MRR; partial response [PR] or better) 82%, and rate of very good PR (VGPR, ≥90% IgM reduction) or complete response (CR) was 42%. Consistent with prior reports of BTK inhibitors in WM, 26/57 pts (46%) with $MYD88^{L265P}$ achieved VGPR or CR. Of the pts with known $MYD88^{WT}$ WM, 7/8 (88%) responded to zanubrutinib, including 1 CR, 1 VGPR, 3 PR, and 2 MR. Median PFS has not been reached; PFS rate at 12 months was 90% (95% CI [80, 95]) and at 24 months was 81% (95% CI [68, 89]). 60 of 67 responding patients (MR or better) remained in response at 12 months and 58 of 67 pts at 24 months.

Baseline Pt Characteristics	N = 77
Median (range) age, years	67 (40–87)
Eastern Cooperative Oncology Group performance status, n (%)	
0	27 (35.1)
1-2	50 (64.9)
Treatment-naïve, n (%)	24 (31)
Relapsed/refractory, n (%)	53 (69)
Median (range) no. prior therapies	2 (1–8)
Adverse events, n (%)	**N = 77**
Any	77 (100)
Grade ≥3	40 (51.9)
Serious	36 (46.8)
Leading to discontinuation	8 (10.4)
Leading to death	5 (6.5)

Best response (n = 73*)	Modified IWWM-6 (Owen) by IRC			NCCN	
	T/N (n = 24)	R/R (n = 49)	Overall (n = 73)	IRC (n = 73)	Investigator (n = 73)
ORR, n (%) [95% CI]	23 (96) [79, 100]	44 (90) [78, 97]	67 (92) [83, 97]	67 (92) [83, 97]	67 (92) [83, 97]
MRR, n (%) [95% CI]	21 (88) [68, 97]	39 (80) [66, 90]	60 (82) [72, 90]	52 (71) [59, 81]	60 (82) [72, 90]
CR, n (%)	0 (0)	1 (2)	1 (1)	1 (1)	1 (1)
VGPR, n (%)	7 (29)	23 (47)	30 (41)	27 (37)	29 (40)
PR, n (%)	14 (58)	15 (31)	29 (40)	24 (33)	30 (41)
MR, n (%)	2 (8)	5 (10)	7 (10)	15 (21)	7 (10)
SD, n (%)	1 (4)	4 (8)	5 (7)	5 (7)	5 (7)
PD, n (%)	0	1 (20	1 (1)	1 (1)	1 (1)
Median follow up in month (range)	12.3 (5.9, 28.0)	24.8 (4.4, 45.7)	23.9 (4.4, 45.7)	23.9 (4.4, 45.7)	23.9 (4.4, 45.7)

Best response based on mutation status assessed Modified IWWM-6 (Owen) by IRC, n (%)	*MYD88*^{L265P} (n=57)	*MYD88*^{WT} (n=8)	Unavailable (n=8)	Overall (N=73*)
VGPR or CR	26 (46)	2 (25)	3 (38)	31 (42)
MRR (PR or better)	49 (86)	5 (63)	6 (75)	60 (82)
ORR (MR or better)	52 (91)	7 (88)	8 (100)	67 (92)
Median follow up in month (range)	21.8 (4.4, 45.7)	24.1 (6.6, 45.5)	33.2 (11.0, 35.8)	23.9 (4.4, 45.7)

*73 pts evaluable for efficacy (4 nonevaluable due to <5 g/L IgM levels at baseline).
Modified IWWM-6 (Owen et al, 2013) to include IgM decreases only, and not extramedullary disease.

Conclusion

These data demonstrate that zanubrutinib monotherapy is well tolerated and highly effective in the treatment of pts with WM. The notable CR/VGPR and 2 year PFS rates confirm this BTK inhibitor achieves both deep and durable responses. The results of a phase 3 study comparing zanubrutinib with ibrutinib are awaited.

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