Phase Ib/II Study (NCT02488408 / BGBC003) of Bemcentinib Monotherapy or in Combination With Cytarabine or Decitabine in Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS): FINAL RESULTS

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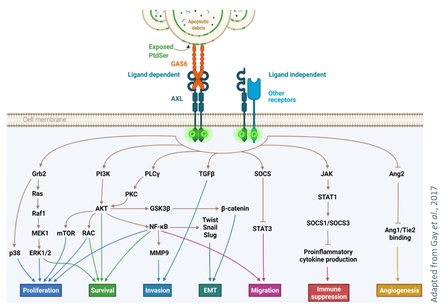
Introduction

The standard of care (SOC) in newly-diagnosed (ND) AML patients (pts) unfit for intensive chemotherapy (IC) has changed recently with the introduction of venetoclax and hypomethylating agents, yielding a median overall survival (mOS) of 14.7 months. However, beyond first line, the prognosis of both relapsed/refractory (R/R) AML is only 2.3 months[1] (~5 months in the pre-venetoclax era[2]) and new treatment options are needed.

AXL, a member of the TAM (TYRO3, AXL, MER) receptor tyrosine kinase family, is overexpressed in AML and represents an independent predictor of poor prognosis, resistance to chemotherapy and decreased antitumor immune response. The activation of the biological target pAXL is implicated in several tumorigenic downstream pathways (Figure 1).



Adapted from Gay et al., 2017

Figure 1: AXL activation is involved in a number of tumorigenic downstream signaling pathways

Bemcentinib (BEM) is a first-in-class highly selective, potent, oral once-a-day AXL inhibitor, which in preclinical studies inhibits AXL-mediated pro-tumour signalling, reverses AXL-dependent innate immune suppression and reduces AML cell survival, sensitizing AML blasts to low- dose cytarabine LDAC.

Bemcentinib MoA:

- AXL signalling in M2 macrophages and NK cells leads to suppression of immune activity towards tumor cells
- Blockade of the GAS6/AXL signalling axis by BEM leads to:
  - re-sensitization of AML blasts to LDAC and apoptosis
  - innate immune cell antigen presentation and T-cell activation
  - NK activation

Study Objectives

- Safety and efficacy of BEM as monotherapy in AML (cohort B1) and MDS (cohort B4), in combination with decitabine (cohort B3) or LDAC (cohorts B2 and B5) in ND and relapsed/refractory (R/R) AML pts unfit for IC.
- Pharmacokinetic/pharmacodynamic (PK/PD) analysis was conducted in pts treated with BEM monotherapy in the safety run-in phase (part A). Here, we present final efficacy and safety data, as well as PK/PD analysis from part A.

Methods

In part A, 36 pts received BEM monotherapy in a dose escalation manner. In part B (cohorts B1-B5), pts received 3 loading doses at daily 400 mg BEM followed by 200 mg BEM daily. Study endpoints included OS, objective response rate (ORR), clinical benefit rate (CBR) (ORR+unchanged [UC]). Plasma and peripheral blood (PB) samples were used for PK and phospho-AXL (pAXL) analyses. (Figure 2)

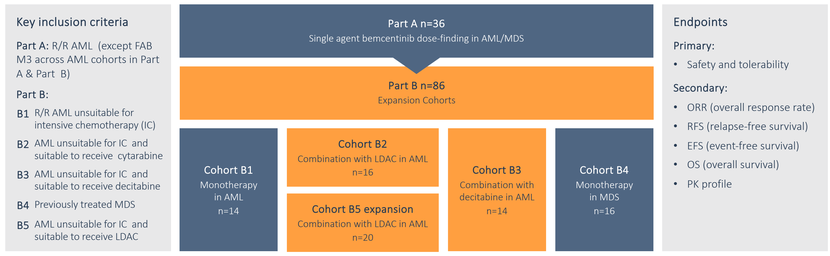


Figure 2: BGBC003 study Schema

Key Patient Demographics

		Part A	Part B
Median Age (years)		74.5	76.0
Gender (n [%])	Male	22 (61.1%)	56 (65.1%)
Race n (%)	White	35 (97.2%)	84 (9.7%)
ECOG Performance Status: n (%)	0	7 (19.4%)	35 (40.7%)
	1	19 (52.8%)	42 (48.8%)
	2	10 (28.8%)	9 (10.5%)

ECOG = Eastern Cooperative Oncology Group, STD = standard deviation. Notes: [1] Data presented are from screening visit [2] Multiple Races may be selected by a single subject [3] Percentages are based on the number of subjects in the Safety Population in each group. Database Lock Date: 12 September 2022. References: Table 14.1.2.1, Listing 16.2.4.1.

Table 1: Patient Demographics

Disease Status

		AML					Overall
		B1: BEM Single agent (n = 14)	B2: BEM + Cytarabine (n = 16)	B3: BEM + Decitabine (n = 18)	B5: BEM + Cytarabine (n = 20)	B2 & B5: BEM + Cytarabine (n = 36)	(n = 86)
AML Disease Status: n (%)	Relapsed	7 (50.0)	5 (31.3)	4 (22.2)	16 (80.0)	21 (58.3)	32 (37.2)
	Refractory	7 (50.0)	4 (25.0)	3 (16.7)	4 (20.0)	8 (22.2)	18 (26.5)
AML Disease Type: n (%)	Primary	6 (42.9)	10 (62.5)	9 (50.0)	14 (70.0)	24 (66.7)	39 (45.3)
	Secondary	8 (57.1)	6 (37.5)	9 (50.0)	6 (30.0)	12 (33.3)	29 (42.6)
AML Disease Cytogenetic Profile n(%)	Favorable	1 (7.1)	3 (18.8)	3 (16.7)	4 (20.0)	7 (19.4)	11 (12.8)
	Intermediate	5 (35.7)	7 (43.8)	8 (44.4)	6 (30.0)	13 (36.1)	26 (38.2)
	Adverse	7 (50.0)	6 (37.5)	6 (33.3)	8 (40.0)	14 (38.9)	27 (39.7)
	Not done	1 (7.1)	0	1 (5.6)	2 (10.0)	2 (5.6)	4 (5.9)

French-American-British (FAB) Classification.

Table 2: Disease Status at Study Entry

Clinical Results

Overall Response Rate

	AML			MDS
	B1: BEM Single agent (n = 11)	B3: BEM + Decitabine (n = 13)	B2 & B5: BEM+ LDAC (n = 32)	B4: BEM (n = 16)
ORR	18%	0%	25%	19%
CBR	45%	31%	31%	56%
mOS (months)	18	6.4	8.0	9.2
mOS (months) ND			16.5	
R/R			7.8	

n = number of subjects with available response information; CBR : clinical benefit rate (ORR + unchanged). ORR: Objective Response: for subjects with AML= BOR as CR, CRi, CRp, MLFS or PR ; for subjects with MDS=BOR as CR, PR, MR or PMR.

Table 3: Overall Response Rate

Overall Survival

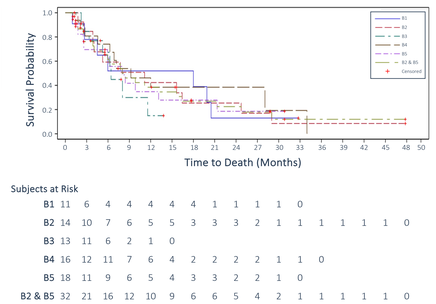


Figure 3: Overall Survival - Kaplan-Meier Survival Curves - Part B (Efficacy Population) for Protocol BGBC003

PK/PD Results

- BEM inhibited pAXL its downstream targets (pAKT, pERK, pS6 and pSTAT1/5) in longitudinal peripheral blood from patients in cohort A in a dose concentration manner generating EC_{50} values in a plasma concentration range of 89-162 ng/mL (Table 4)
- pAXL EC_{50} of 103ng/mL equivalent to free BEM concentration of 20nM, which is similar to concentration needed to occupy 80-90% of AXL receptors (based on K_i value for BEM)
- Mean C_{trough} values at steady state following a maintenance dose of 200mg of BEM daily in cohorts B2 and B5 were 188 ± 134 ng/mL and 214 ± 97.1 ng/mL, respectively

PD marker	EC_{50} (ng/mL)
pAXL	103***
pAKT	141***
pERK1, 2	87***
pSTAT1	70***
pSTAT5	91***
p38	121***
pS6 (mTOR)	119***

*** p<0.001

Table 4: Bemcentinib inhibits pAXL and downstream targets in a dose concentration manner

Conclusions

BEM demonstrated on-target effect by inhibition of pAXL and downstream signalling in a concentration-dependant manner

BEM monotherapy and in combination was well tolerated across all cohorts

A survival benefit (mOS 16.5 months) was observed with BEM+LDAC in ND AML pts, which would warrant further validation

The overall efficacy observed is comparable with historical data in 2L AML and MDS

However, the shift in 1L SOC in AML for pts unfit for IC during the study limits adequate comparisons

Keywords: Acute myeloid leukemia, Clinical trial, Receptor tyrosine kinase,

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