# Ph II trial with selective oral AXL inhibitor bemcentinib (BGB324) in relapsed/refractory AML and MDS: Identification of predictive and pharmacodynamic biomarker candidates associated with patient benefit

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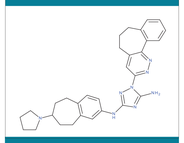
abstract #: PS981

## Ph I/II trial in R/R AML and MDS to evaluate safety and efficacy of bemcentinib (BGB324)

### Bemcentinib, first-in-class, highly selective orally bioavilable AXL inhibitor in phase II

**bemcentinib (BGB324)**



**Selectivity Profile**

| | nM | Fold |
|---|---|---|
| AXL | 0.4 | 1 |
| Mer | 100 | 250 |
| Tyro | >1000 | >1000 |

#### Background

Bemcentinib (BGB324) is a first-in-class, oral selective inhibitor of the RTK AXL currently in ph II clinical development across several cancer types. AXL overexpression has been established as an independent negative prognostic factor in AML. AXL inhibition via bemcentinib has shown anti-leukaemic activity and immune activation in pre-clinical models of AML and other cancers.

#### Bemcentinib clinical development

Bemcentinib is being explored as a mono-therapy and in combination with immune-, targeted and chemo-therapy in AML/MDS, NSCLC, TNBC and melanoma across six phase II clinical trials.

**AML or high & int-2 risk MDS / pre-viously treated MDS**
dose escalation (complete)

- up to 75 patients
- AML unsuitable for int. chemo
- prev. treated MDS, exc del(5q)
- High/Int-2 risk MDS

AML: Single agent; bemcentinib + cytarabine; bemcentinib + decitabine
MDS: Single agent

- Safety
- ORR
- PFS
- OS

**BGBC003 (NCT02488408): Phase I/II trial in R/R AML and MDS**

AML or MDS (interm-2 and high-risk) patients received bemcentinib monotherapy in this two part 3+3 dose escalation and cohort expansion study.

### BGBC003 demographics

**Age (yrs)**

| | |
|---|---|
| Median | 74 |
| Range | 51 - 85 |

**Type of cancer**

| | |
|---|---|
| R/R AML | 32 |
| MDS | 5 |

**Gender**

| | |
|---|---|
| Male | 22 |
| Female | 15 |

**# Prior therapies**

| | |
|---|---|
| Median | 2 |
| Range | 0 - 6 |

**Ethnicity**

| | |
|---|---|
| Caucasian | 36 |
| African American | 1 |

### Safety: Treatment-related AEs experienced by > 1 patient

| Treatment-related AEs | All grades (n=24) | Grade 3 (n=24) |
|---|---|---|
| **Total number of treatment-related AEs** | **34** | **12** |
| **Total number of subjects with AEs** | **13** | **7** |
| Gastrointestinal disorders | 17 | 6 |
| Investigations | 4 | 2 |
| Blood and lymphatic disorders | 3 | 2 |
| Nervous system disorders | 3 | 1 |
| Fatigue | 2 | 1 |
| Metabolism and nutrition | 2 | 0 |
| Cardiac disorders | 1 | 1 |
| Eye disorders | 1 | 0 |
| Skin disorders | 1 | 0 |

Dose expansion cohort, all doses. No grade 4 or 5 events.

### AXL receptor tyrosine kinase drives tumour survival and is negatively regulated by receptor shedding

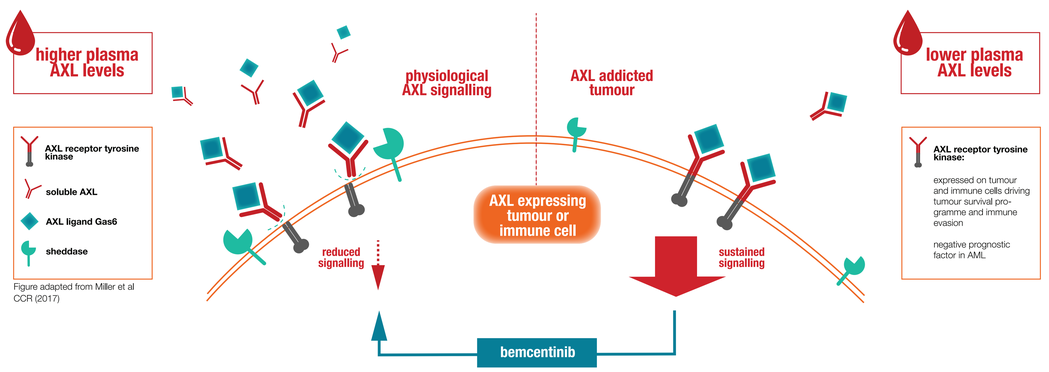
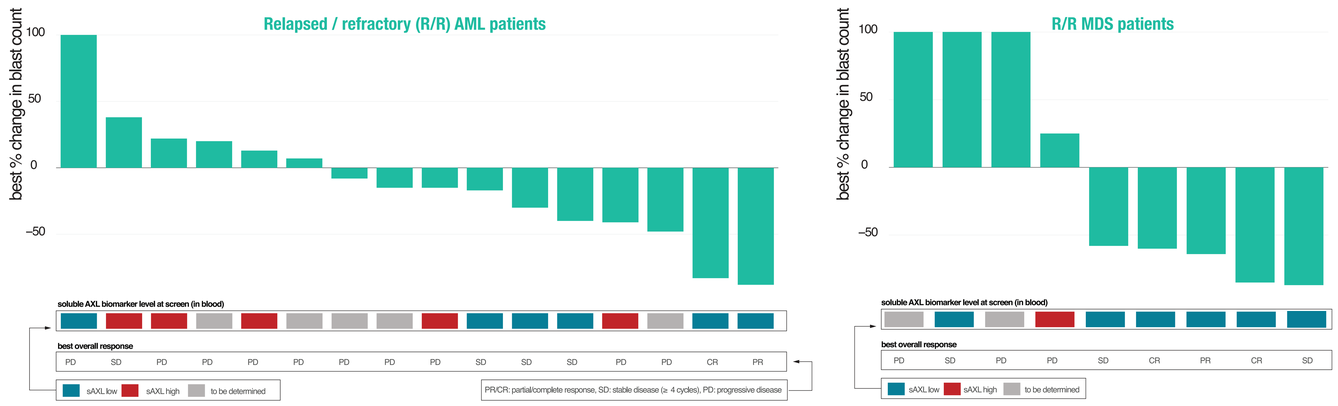



Figure adapted from Miller et al CCR (2017)

## Blood and bone marrow plasma levels of AXL correlate with patient benefit

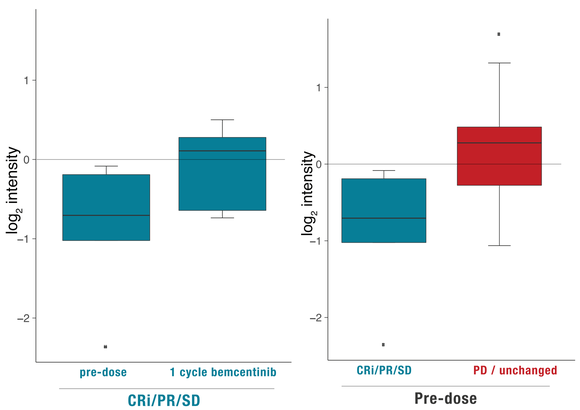
### Bemcentinib is active as a monotherapy in relapsed and refractory AML and high risk MDS, particularly in patients with low screen serum AXL levels



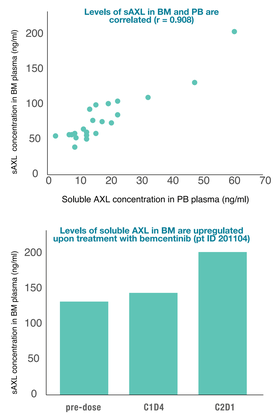

### Response assessment per soluble AXL biomarker (measured at screen in plasma)

| | | PD | SD | PR | CR | N | ORR (%) | CBR (%) |
|---|---|---|---|---|---|---|---|---|
| AML+ MDS | sAXL high | 6 | 1 | | | 7 | 0 | 17 |
| | sAXL low | 1 | 6 | 3 | 3 | 13 | 46 | 92 |
| AML | sAXL high | 5 | 1 | | | 6 | 0 | 17 |
| | sAXL low | 1 | 3 | 2 | 1 | 7 | 43 | 86 |
| MDS | sAXL high | 1 | | | | 1 | 0 | 0 |
| | sAXL low | | 3 | 1 | 2 | 6 | 50 | 100 |

### Blood plasma levels of soluble AXL (sAXL) are decreased at screen in patients experiencing benefit. sAXL levels increase in response to treatment with bemcentinib




### Blood and BM plasma levels of sAXL are correlated & sAXL levels are elevated in BM plasma upon treatment




## Immune activation in response to bemcentinib monotherapy

### Summary table of observed B-cell (IGH) and T-cell receptor (TCR) repertoire diversification in peripheral blood (PB) and bone marrow (BM)

| | IGH | | TCR | |
|---|---|---|---|---|
| Indication | PB | BM | PB | BM |
| AML | | | | |
| AML | | | | |
| AML | | | | |
| AML | | | | |
| AML | | | | |
| AML | | | | |
| AML | | | | |
| AML | | | | |
| MDS | | | | |
| MDS | | | | |
| MDS | | | | |

diversification observed; no diversification observed*; TBD

* in samples analysed to date

## Methods

**Blood soluble AXL measurements:** The DiscoveryMap panel (Myriad RBM) was used to measure blood plasma protein biomarker levels in patients with matched samples available for pre-dose and after one cycle of treatment to identify CDx candidates modulated in response to bemcentinib. Protein measurements were normalised by calculating the ratio between individual protein levels and the mean of each protein across all samples, before log2-transformation. An assessment of potential confounding factors (gender, age, type of cancer, ethnicity, pre-treatment history, mutation status) was carried out. Statistical hypothesis testing utilised normalised data as inputs and linear modelling with subsequent Bayesian analysis to identify proteins that are significantly different between sample groups as well as the magnitude of difference (i.e. up- vs. down-regulation). The Bioconductor package limma was used (Ritchie, 2015).The comparisons tested were: (1) Pts experiencing benefit (CRi, PR, SD) vs. non-responders (PD / unchanged) at pre-dose; (2) paired timepoint comparison, all samples; (3) paired timepoint comparison, pts experiencing benefit; (4) paired timepoint comparison, non-responders.

**BM soluble AXL measurements**: Levels of soluble AXL, a predictive biomarker cadidate for treatment with bemcentinib, were measured in patient peripheral blood (PB) plasma as well as bone marrow (BM) plasma using a custom ELISA assay.Tested time-points inlcuded pre-dose, after four days of treatment and after one cycle of treatment.

## Conclusions

**Blood plasma levels of sAXL were identified as predictive for patient benefit with an - at time of data cutoff - ORR of 46% and CBR of 92%, respectively, in R/R AML and MDS patients with low serum AXL at screen.**

**Monotherapy treatment with the selective AXL inhibitor bemcentinib was well tolerated. Treatment emerging adverse events were mainly low grade and reversible.**

**T-cell and B-cell receptor repertoire diversification was observed in a number of patients.**

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