# Comprehensive Analysis of the Dose Escalation, Expansion and Correlates in the Ph I/II Trial BGBC003 with the Selective Oral AXL Inhibitor Bemcentinib (BGB324) in Relapsed/Refractory AML and MDS

Loges S[1], Hauser M[2], Chromik J[3], Vigil E C[4], Pascha P[5], Ben-Batalla I[1], Akyüz N[6], Micklem D[7], Holt R[7], Brown A[7], Lorens J[7], Yule M[7], Kebenko M[1], Janning M[1], Binder M[1], Fiedler W[1], Cortes E J[8], Gjertsen B[9]

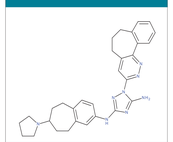
[1]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2] Hannover Medical School, Hannover Germany; [3]Universitätsklinkum Frankfurt am Main Germany; [4]University of Iowa, Iowa City, IA; [5]University Hospital Ulm, Ulm, Germany; [6]UKE Hamburg, Hamburg, Germany; [7] BerGenBio ASA, Bergen, Norway; [8]MD Anderson Cancer Center, Houston, TX; [9]Haukeland University Hospital, Bergen, Norway;

Poster # 2672

## Bemcentinib (BGB324) monotherapy dose escalation and expansion in R/R AML/MDS

### Bemcentinib, first-in-class, highly selective orally bioavailable 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 over expression has been established as an independent negative prognostic factor in AML whereas AXL inhibition via bemcentinib has shown anti-leukemic 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 and melanoma across a broad range of phase II clinical trials.

**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.

**Ongoing Phase II trial in AML /high & int-2 risk MDS**
dose escalation (complete, presented here)

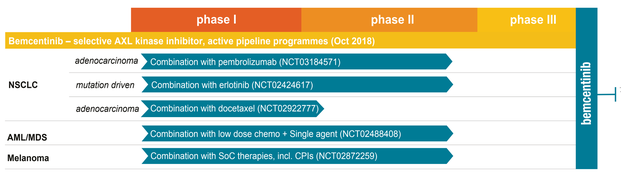
- up to 75 patients
- AML unsuitable for int. chemo
- prev. treated MDS, exc del(5q)
- High/Int-2 risk MDS
- Not a transplant candidate

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

- Safety
- ORR
- PFS
- OS

### Bemcentinib evaluated in a broad phase II clinical programme

**Bemcentinib is developed in combination with checkpoint inhibitors, targeted and chemotherapy in NSCLC, AML/MDS and melanoma.**





### AXL receptor tyrosine kinase is negatively regulated by receptor shedding

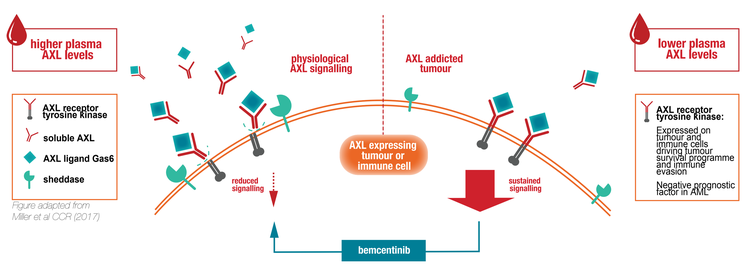



*Figure adapted from Miller et al CCR (2017)*

**AXL receptor tyrosine kinase is negatively regulated by shedding of its extracellular domain: plasma sAXL correlates inversely with AXL signalling**
Receptor shedding by proteolytic cleavage of the extracellular domain is a mechanism to downregulate receptor tyrosine kinase signalling and is particularly prominent in the case of AXL. Blockade of AXL signalling has been shown to lead to increased shedding of the plasma soluble extracellular domain of AXL (sAXL) - sAXL is thus inversely correlated with AXL signalling. Conversely, reduced shedding of AXL (reduced sAXL) has been implicated with AXL mediated therapy resistance and worse outcomes in melanoma (Miller *et al*, CCR 2017).

## Phase I/II dose escalation and expansion of bemcentinib monotherapy in R/R AML & MDS

### Bemcentinib exhibits target inhibition & manageable safety

#### Baseline demographics and patient disposition

| | |
|---|---|
| **Median age (range)** | 74.5 (51-85) |
| **Prior therapies (range)** | 2 (1-6) |
| **Male, n (%)** | 22 (61) |
| **Ethnicity, n (%)** | |
| Not Hispanic or Latino | 36 (100) |
| Hispanic or Latino | 0 (0) |
| **ECOG at screening, n (%)** | |
| 0 (%) | 7 (19) |
| 1 (%) | 19 (53) |
| 2 (%) | 10 (28) |

| | |
|---|---|
| **Myeloblast % at screening (n=30), n (%)** | |
| ≥20% | 21 (70) |
| <20% | 9 (30) |
| **Risk assessment (n=17), n (%)** | |
| Favourable | 1 (6) |
| Intermediate | 3 (18) |
| Poor (incl 5 pts with FLT3 mutation) | 13 (76) |
| **Refractory or relapsed (n=35), n (%)** | |
| Refractory | 18 (51) |
| Relapsed | 17 (49) |

**N = 36 patients enrolled in ph I/II dose escalation/expansion**

- 27 evaluable for efficacy*
- 26 with available SAXL status (25 evaluable)

*8 patients did not complete 1 cycle of treatment, 1 patient was first-line

1 patient remains ongoing

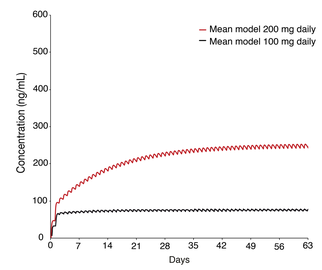
6 responses reported on bemcentinib monotherapy
+
1 addtl response in combination with decitabine

#### TRAEs in > 1 patient (N=36 patients)

| Preferred term, n (%) | Any grade | Grades 3/4 |
|---|---|---|
| **Haematological** | | |
| Thrombocytopenia | 3 (8) | 3 (8) |
| Neutropenia | 2 (6) | 2 (6) |
| **Non-haematological** | | |
| Diarrhoea | 10 (28) | 2 (6) |
| QTc prolongation | 7 (19) | 2 (6) |
| Nausea | 6 (17) | 2 (6) |
| Vomiting | 4 (11) | 1 (3) |
| Fatigue | 2 (6) | 1 (3) |
| Dysgeusia | 2 (6) | 1 (3) |
| Decreased appetite | 2 (6) | |
| Stomatitis | 2 (6) | |

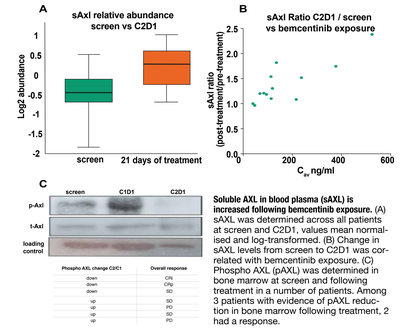
| Incidence of early mortality | | | |
|---|---|---|---|
| Within 30 days of enrolment | Within 60 days of enrolment | Fatal infection within 60 days of enrolment | Incidence of prolonged (>10 days) neutropenia |
| 2.8% | 13.9% | 8.3% | 11.1% |

#### Pharmacokinetics




**The use of a loading dose achieved steady state**

#### Pharmacodynamics




**Soluble AXL in blood plasma (sAXL) is increased following bemcentinib exposure.** (A) sAXL was determined across all patients at screen and C2D1, values mean normalised and log-transformed. (B) Change in sAXL levels from screen to C2D1 was correlated with bemcentinib exposure. (C) Phospho AXL (pAXL) was determined in bone marrow at screen and following treatment in a number of patients. Among 3 patients with evidence of pAXL reduction in bone marrow following treatment, 2 had a response.

### Bemcentinib monotherapy exhibits anti-leukaemic activity & screen plasma levels of soluble AXL (sAXL) are predictive of patient response

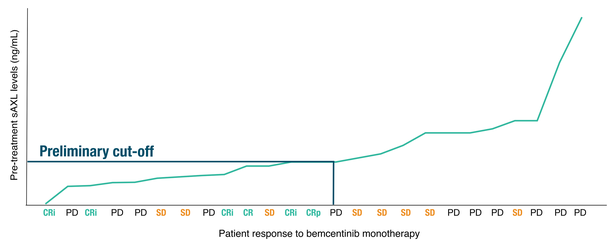
#### Responses in evaluable patients (n = 27)

| | Overall (n=27) | | sAXL low (n=14) | | sAXL high (n=11) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| CR/CRi/CRp | 6 | 22% | 6 | 43% | 0 | 0% |
| SD | 8 | 30% | 3 | 21% | 5 | 45% |
| PD* | 13 | 48% | 5 | 36% | 6 | 55% |
| **ORR** | **6** | **22%** | **6** | **43%** | **0** | **0%** |

+ 2 evaluable patients were not evaluable for sAXL status
+ Monotherapy responses. One additional response was reported in combination with decitabine for a total of 7 responses in phase I/II.
+ 1 CR, 4 CRi, 1 CRp

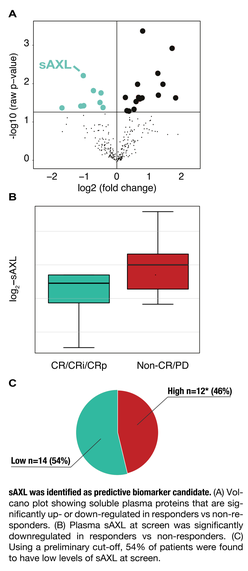
** PD includes patients who progressed or came off study before having completed 3 cycles of treatment.*

#### Identification of a preliminary cut-off for sAXL levels at screen predictive of response



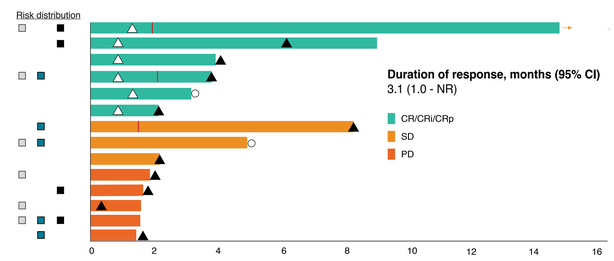

**Preliminary cut-off used to predict response to treatment in post hoc analysis.** Absolute plasma levels of sAXL at screen are plotted against best response on bemcentinib monotherapy treatment. The preliminary cut-off used in this analysis is indicated.

#### sAXL is a predictive biomarker

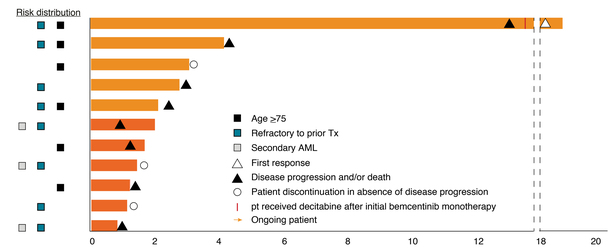



**sAXL was identified as predictive biomarker candidate.** (A) Volcano plot showing soluble plasma proteins that are significantly up- or down-regulated in responders vs non-responders. (B) Plasma sAXL at screen was significantly downregulated in responders vs non-responders. (C) Using a preliminary cut-off, 54% of patients were found to have low levels of sAXL at screen.

#### Duration of treatment: sAXL low patients, months (n=14)




#### Duration of treatment: sAXL high patients, months (n=11)




### Methods

Blood soluble AXL measurements:

The DiscoveryMap panel (Myriad RBM) was used to measure blood plasma protein bio marker levels in patients with matched samples availble for pre-dose and after one cycle of treatment to identify CDx candidates modulated in response to bemcentinib.

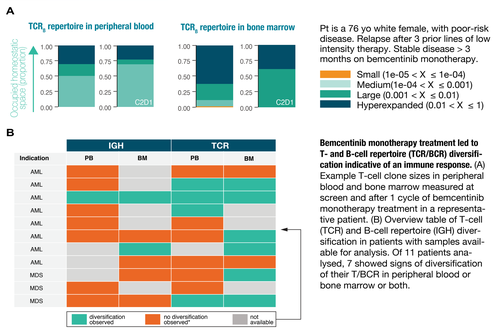
Safety:

Adverse events were assessed by CTCAE v4.03.

Efficacy evaluation:

Responses were assessed according to European Leukaemia Net recommendations (Doehner *et al*, Blood, 2017). Stable disease was defined a non-PD/non-CR/non-PR for ≥ 3 cycles.

### Bemcentinib increases T- & B-cell repertoire diversification




Pt is a 76 yo white female, with poor-risk disease. Relapse after 3 prior lines of low intensity therapy. Stable disease > 3 months on bemcentinib monotherapy.

- Small (1e-05 < X ≤ 1e-04)
- Medium(1e-04 < X ≤ 0.001)
- Large (0.001 < X ≤ 0.01)
- Hyperexpanded (0.01 < X ≤ 1)

**Bemcentinib monotherapy treatment led to T- and B-cell repertoire (TCR/BCR) diversification indicative of an immune response.** (A) Example T-cell clone sizes in peripheral blood and bone marrow measured at screen and after 1 cycle of bemcentinib monotherapy treatment in a representative patient. (B) Overview table of T-cell (TCR) and B-cell repertoire (IGH) diversification in patients with samples available for analysis. Of 11 patients analysed, 7 showed signs of diversification of their T/BCR in peripheral blood or bone marrow or both.

## Conclusions

The study enrolled a predominantly elderly relapsed/refractory patient population, with a median of 2 prior treatment regimens (1 – 6).

CR/CRi/CRp rate was 43% in patients with low serum AXL levels at screen, ORR in all patients was 22%.

Bemcentinib monotherapy had a mild and manageable side effect profile with a low incidence of Grade 3/4 events. The incidence of haematological toxicity was low.

Bemcentinib monotherapy treatment showed evidence of T- & B-cell receptor repertoire diversification in peripheral blood and bone marrow indicative of an immune mode of action.

## Contact

**BerGenBio ASA**
Jonas Lies vei 91
5009 Bergen
Norway

www.bergenbio.com
@BGenBio

**BerGenBio Ltd.**
1 Robert Robinson Ave
OX4 4GA
Oxford, UK

post@bergenbio.com
+47 559 61 159

**Sonja Loges**
University Hamburg-Eppendorf
Martinistr. 52
20246 Hamburg
Germany

s.loges@uke.de
+49 7410 51538

## Acknowledgements

The authors wish to thank patients, their families and caretakers as well as investigators and site staff for participation in this study.

Conflict of Interest disclosure: Prof Loges received travel support and funding for pre-clinical research from BerGenBio ASA.



This poster was presented at the ASH Annual Meeting 2018, San Diego, CA (Dec 1 - 4, 2018)