The immunomodulatory activity of bemcentinib (BGB324) – a first-in-class selective, oral AXL inhibitor in patients with relapsed/refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome.

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Ph II Multicenter Open-label Study of Bemcentinib in Patients with AML or MDS (NCT02488408)

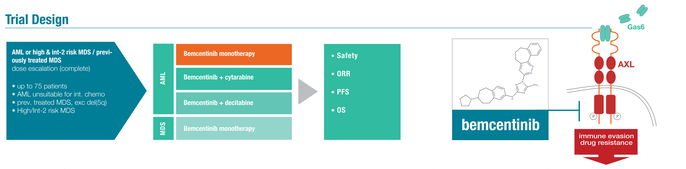
Bemcentinib: selective, oral small molecule inhibtor of AXL

The receptor tyrosine kinase AXL represents a novel therapeutic target in AML promoting proliferation and therapy resistance (Ben-Batalla, 2013). In addition, AXL suppresses immune responses by decreasing antigen presentation and inhibiting NK cells. Bemcentinib (BGB324) is a first-in-class, orally bioavailable, highly selective AXL kinase inhibitor which is being evaluated as a therapy for solid tumours and myeloid malignancies. Selective blockade of AXL by bemcentinib in AML is currently being evaluated in the Phase 1/2 trial BGBC003 (NCT02488408). Additional phase II clinical trials are ongoing with bemcentinib in combination with pembrolizumab in adenocarcinoma of the lung (NCT03184571), TNBC (NCT03184558) and melanoma (NCT02872259) as well as in NSCLC in combination with erlotinib (NCT02424617) or docetaxel (NCT02922777).

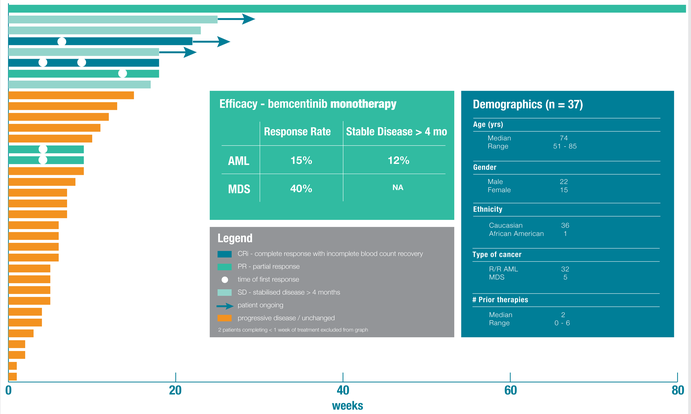
Bemcentinib selectivity profile

Kinase	Kinome Scan (Kd)	
	nM	Fold
Axl	0.4	1
Mer	100	250
Tyro	>1000	>1000

Trial Design



Duration of Treatment & Outcome - bemcentinib **monotherapy** in relapsed & refractory AML and MDS (status Jan 17th 2017)



Efficacy - bemcentinib monotherapy

	Response Rate	Stable Disease > 4 mo
AML	15%	12%
MDS	40%	NA

Legend

- CR - complete response with incomplete blood count recovery
- PR - partial response
- time of first response
- SD - stabilised disease > 4 months
- patient ongoing
- progressive disease / unchanged

2 patients completing < 1 week of treatment excluded from graph

Demographics (n = 37)

Age (yrs)	
Median	74
Range	51 - 85
Gender	
Male	22
Female	15
Ethnicity	
Caucasian	36
African American	1
Type of cancer	
R/R AML	32
MDS	5
# Prior therapies	
Median	2
Range	0 - 6

Safety: Study treatment-related TEAEs experienced by more than one patient (dose escalation cohort)

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

Immune Effects of AXL Inhibition via Bemcentinib

Treatment with bemcentinib can increase the diversity of the TCR_β repertoire in AML patients

Methods: The TCR_β repertoire was quantified by Next Generation Sequencing of DNA isolated from peripheral blood MNCs using an Illumina MiSeq sequencer. TCR_β gene containing the entire V_β, D_β and J_β segments were amplified with BIOMED2-TCR_β-A and –B primer pools.

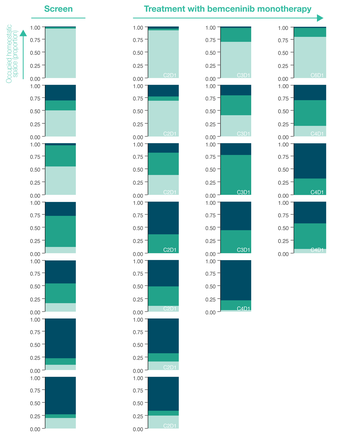
The IGH repertoire was analysed using BIOMED2-FR1/-FR3 primer pools. Using genomic DNA as template, the amplicons were tagged with Illumina adapters and indices in two consecutive PCR reactions. Demultiplexing and FastQ formated data output was generated by the MiSeq reporter.

Analysis of TCR_β and IGH data was performed on a Microsoft Cloud using our in-house analysis pipeline Pippa, which relies on MiXCR analysis tools.

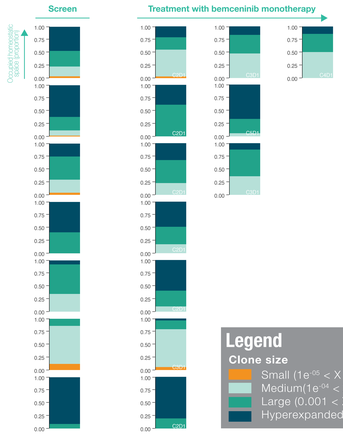
Summary table of observed B-cell and T-cell receptor repertoire diversification in peripheral blood (PB) and bone marrow (BM)

	TCR diversification						
Patient	in Blood Plasma	in Bone Marrow	Dose (mg/d)	Age	Gender	Duration of treatment (wks)	Best response
1	no	no	100	71	F	24	SD
2	yes		100	77	F	18	PR
3	no		200	78	M	9	UC
4	no	yes	200	75	F	Ongoing	SD
5	no	yes	200	80	M	7	UC
6		yes	200	62	M	10	UC
7		no	200	66	F	6	UC
8	yes	yes	300	61	M	5	UC
9	yes	yes	300	76	F	13	UC

TCR_β repertoire in peripheral blood



TCR_β repertoire in bone marrow



Legend

Clone size

- Small ($1e^{-05} < X \leq 1e^{-04}$)
- Medium($1e^{-04} < X \leq 0.001$)
- Large ($0.001 < X \leq 0.01$)
- Hyperexpanded ($0.01 < X \leq 1$)

Identification of Candidate Biomarkers Potentially Indicative of Response to Bemcentinib Monotherapy

Blood plasma markers identified that correlate with clinical benefit (CRi, PR, SD) in patients treated with bemcentinib monotherapy

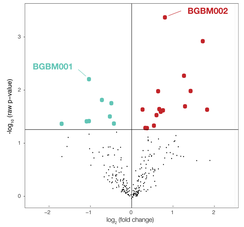
Methods: The DiscoveryMap panel (Myriad RBM) was used to measure blood plasma protein biomarker levels in patients with matched samples available for pre-dose and after one cycle of treatment to identify CDx candidates modulated in response to monotherapy treatment with bemcentinib.

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.

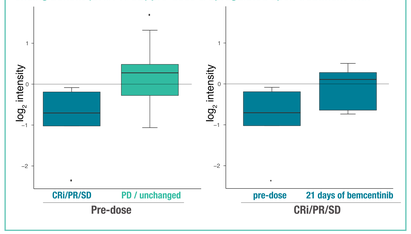
Statistical hypothesis testing utilised normalised data as inputs and linear modelling with subsequent Bayesian analysis to identify proteins that are significantly different between sample groups as well as the magnitude of difference (i.e. up- vs. down-regulation). The Bioconductor package limma was 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.

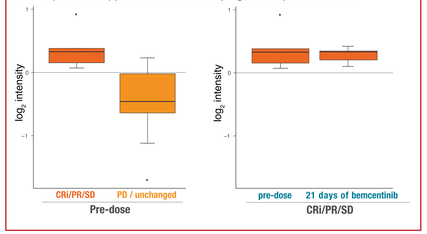
Candidate biomarkers potentially predictive of response to treatment with bemcentinib:



Candidate marker of response BGBM001 is down-regulated in patients experiencing benefit (CRi/PR/SD) pre-dose & upregulated upon treatment with



Candidate marker of response BGBM002 is up-regulated in patients experiencing benefit (CRi/PR/SD) pre-dose & remains upregulated upon treatment



Conclusions

Bemcentinib induces diversification of the T-cell receptor repertoire in AML patients.

Bemcentinib has anti-leukeamic activity in refractory AML and MDS patients.

Bemcentinib is well tolerated in elderly and heavily pre-treated AML and MDS patients.

Several potentially predictive biomarker candidates for response to bemcentinib were identified.

References

Ben-Batalla *et al* **Blood** (2013)

Ritchie *et al* **Nucleic Acids Res** (2015)

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