Bemcentinib (Oral AXL Inhibitor) in combination with Low-dose Cytarabine Is Well Tolerated and Efficacious in Elderly Relapsed AML Patients

Updates from the Ongoing Phase II Trial (NCT02488408) and Preliminary Translational Results indicating Bemcentinib elicits anti-AML immune responses

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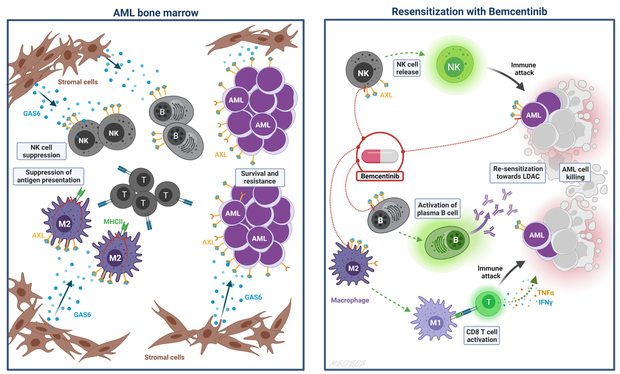
BACKGROUND

- Relapsed (REL) & refractory (REF) AML patients unsuitable for intensive chemotherapy (IC) due to age or co-morbidities, have limited treatment options.
- The lack of a SOC and poor survival, highlight the unmet medical need for new treatments in this patient population.
- AXL is a receptor tyrosine kinase conferring poor prognosis, resistance to chemotherapy and decreased antitumor immune response in several cancers, including AML.
- Bemcentinib (BEM) is a first-in-class highly selective, potent, orally bioavailable AXL-inhibitor
  - inhibits AXL-mediated pro-tumour signalling and reverses AXL-dependent innate immune suppression
  - reduces AML cell survival, enhances efficacy of chemotherapy and overcomes resistance.
- BEM+LDAC combination showed an additive effect in AML.



Bemcentinib MoA

- Single agent anti-tumour efficacy
- Re-sensitizes AML blasts to LDAC
- Re-activates innate and adaptive immunity
  - NK cell activation
  - Innate immune cell antigen presentation
  - T-cell activation
  - Pro-inflammatory cytokine profile

MATERIALS AND METHODS

Clinical study overview

- Patients received combination BEM at 200mg PO/d x3 loading dose, 100 mg maintenance and LDAC SOC schedule.
- Efficacy endpoints were objective response (OR) and clinical benefit rate (CBR=OR+unchanged [UC]+stable disease [SD=unchanged disease for at least 3 BEM cycles]).
- Secondary objectives looked at overall survival (OS) and exploratory biomarker analyses.

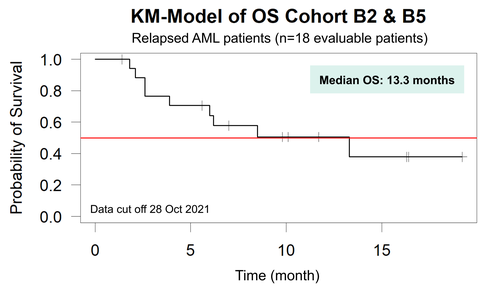
Translational analysis

- Longitudinal BMMNC samples (n=32) from 13 patients were subjected to scRNA-seq and CiteSeq (Chromium 10x genomics; TotalSeq, Biolegend) For scRNA-seq data analyses, Cell Ranger (v3.1.0) and the Seurat (v.4.0.1) in R (v.4.0) were used.
- Patients were stratified by Best Response (CR, CRi, PR for Responders; SD, UC, PD for Non-Responders).
- Cell type annotations were based on the identified clusters and were inferred from the expression of known marker features on both RNA and protein level.

RESULTS

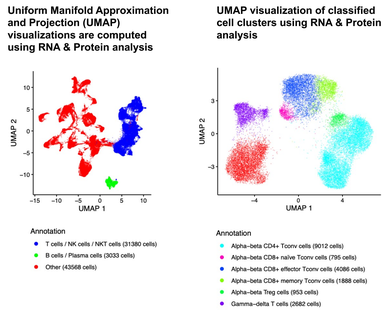
- As of 30 Sept 2021, the B+L cohorts comprised 28 r/r (21 REL, 7 REF) AML patients.
- Overview of the 21 REL patients: median age at enrolment was 76 years (range 66-86) with a male predominance (62%), ECOG 0-2 and median prior lines of therapy 2 (range 1-8).
- 18/21 REL patients were evaluable for efficacy: 4/18 (22%) achieved CR/CRi; CBR 72%.
- CR/CRi was reported between wk13(C5)–wk19(C7). Median ToT 43.9 wks; mDOR 32.71 wks (10-58wks). Late onset responses may reflect AXL-related immunological MoA and contribution to a longer ToT.
- Survival data continues to mature.
- Overall, the BEM+LDAC combination was well tolerated and safe. TRAEs of ≥G3 observed in ≥10% of patients were anaemia (19% BEM) and ECG QT prolonged (11% BEM). No G5 TRAEs reported.

Survival data

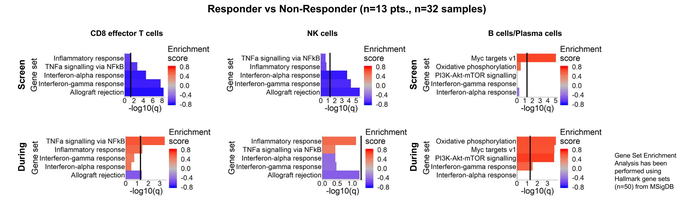


Translational data

- Multiomics of longitudinal samples show differences in the immune compartment pointing to immune-mediated MoA associated with response to BEM.
- CD8+ effector T-cells of responding patients exhibit enhanced pro-inflammatory signatures involving TNF-alpha and IFN-gamma response in comparison to non-responders.
- Furthermore, increased activation of B cells/Plasma cells correlated with response to BEM suggesting that BEM mediates an anti-AML immune response through activation of the two major adaptive immune cell populations.

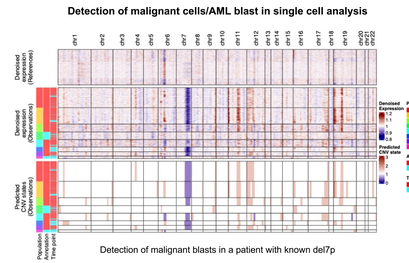


- Gene Set Enrichment Analysis (GSEA) indicates lower baseline activation status of CD8 effector T cells in responders at screening. During treatment, Inflammatory response and TNFα signaling becomes enriched in CD8⁺ T cells of responders vs. non-responders. Differences in GSEA analysis show an enrichment of pro-inflammatory and pro-proliferative gene sets in responders during treatment also in B cells/Plasma cells. This data indicates a BEM-LDAC mediated stimulatory effect on adaptive anti-AML immune responses.



Method

- Cells were subjected to a patient-wise analysis of copy number variations (CNVs) using infercnv (v1.6.0) in “subclusters” mode with corresponding cells from CR/CRi samples as references.
- CNV predictions from three runs were aggregated into a consensus profile containing only reproducibly detected CNVs.
- Subclusters with CNVs that (i) were supported by both the denoised expression values and the consensus CNV predictions and (ii) did not fall into regions of notable variability among the reference cells were called ’likely malignant’.



Conclusion

AML blasts can be identified using CNV analysis and allows investigation in a single cell level.

AIMS

- The ongoing BGBC003 PhII trial aimed to explore safety and efficacy and to pursue translational biomarker analysis in REL/REF older AML patients unfit for IC, treated with BEM+LDAC combination.
- Here, we present preliminary clinical and multiomics (in bone marrow mononuclear cells [BMMNC]) data.

CONCLUSIONS

- BEM+LDAC is well tolerated and efficacious in older unfit REL AML patients.
- Survival benefit was observed, indicating BEM+LDAC warrants evaluation in a randomized clinical study in this population.
- Translational research including scRNA and multiomics, identified specific activation of CD8+ T cells and B cells/Plasma cells associated with response to treatment, indicating that BEM elicits activation of the two major adaptive immune cell populations responsible for anti-AML immune responses.
- Ongoing investigations of longitudinal changes of gene set enrichment in AML blasts will provide further insights into the BEM-LDAC mediated-effects.

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