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Bemcentinib modulation of inflammatory, fibrotic and tissue repair pathways corresponds with favourable clinical outcomes in hospitalised COVID-19 patients demonstrating higher severity cues: a biomarker perspective

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BACKGROUND: BEMCENTINIB IN COVID-19

Role of AXL in COVID-19 infection

AXL is a receptor tyrosine kinase which has been shown to facilitate internalisation of enveloped viruses such as SARS-CoV-2 via the endosomal pathway.

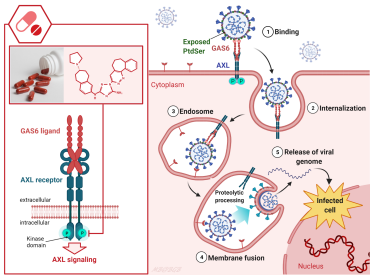
Complexes of AXL and its ligand GAS6, engage in phagocytic engulfment and removal of apoptotic cells. This is a mechanism leveraged and hijacked by the viruses to establish contact and seek entry into the host cell- a process termed as 'apoptotic mimicry'.[1-6]

AXL signalling dampens innate immune responses by inhibiting the expression of type 1 interferons and by polarizing macrophages towards the immune suppressed M2 phenotype further facilitating viral infection.[7] AXL is abundantly expressed in the lung epithelial cells[8] as well as macrophages and has recently been shown to prevent epithelial repair during lung injury.[9]

Bemcentinib, a small molecule inhibitor of AXL has shown to reduce viral entry and viral load in several human cell lines.

Bemcentinib – Oral small molecule TKI highly selective for AXL

Bemcentinib blocks AXL dependent entry through the endosomal pathway

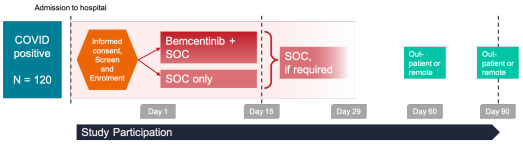


Cartoon showing role of AXL in viral internalization (right) and chemical formula and mode of action of bemcentinib; a tyrosine kinase (TKI) inhibitor for AXL (left)

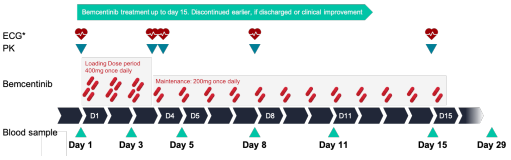
BEMCENTINIB COVID-19 CLINICAL TRIAL

BGBC020 (NCT04890509) – A phase 2a open label study comparing bemcentinib with SoC to SoC alone in treatment of moderate to severe COVID-19 patients, immediately after hospital admission

BGBC020 (NCT04890509): Study Design



BGBC020: Bemcentinib dosing and schedule of assessments



Top: Schema showing **BGBC020 study design**

Bottom: **Schedule of bemcentinib dosing and assessments in the BGBC020 study:** Dosing of bemcentinib (as an add on to SoC) commenced on Day 1 until Day 15 or discharge. The last day of assessments while hospitalized was on Day 29. PK samples were collected as shown. ECGs were carried out on Day 1(pre-loading dose) then pre-maintenance dose and 6 hours postdose (Day 4). Subsequently pre-dose on Days 8 and 15. Blood samples for biomarker analysis were collected on Days 1, 3, 5, 8, 11,15 and 29.

BGBC020: CLINICAL DATA & PATIENT POPULATION

Bemcentinib treatment (up to 14 days) confers early and sustained protection, limiting clinical deterioration.

Safety and efficacy of bemcentinib was first tested in moderate to severe hospitalized COVID-19 patients in a BerGenBio sponsored Clinical Trial BGBC020. This trial compared the SoC control arm with bemcentinib given in combination with SoC.

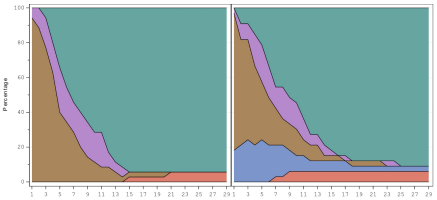
Encouraging data from the BGBC020 study showed that bemcentinib was efficacious in providing early and sustained protection and limiting clinical deterioration in COVID-19.

The **efficaciousness of bemcentinib** was **enhanced** in more severe COVID 19 patients stratified by **plasma CRP levels of greater than equal to 30mg/dl.**

The stacked area chart here, shows that patients in bemcentinib arm had:

- **earlier discharge from hospital,**
- **required less supplementary oxygen**
- **demonstrated a dramatic reduction in disease worsening necessitating intubations and ventilations.**

Bemcentinib with SoC (N=35) **SoC alone (N=33)**



Stacked area charts from a subset of patients with higher baseline inflammatory status as determined by [CRP] plasma ≥30 mg/dL. Stacked area charts show disease state over time after baseline in the bemcentinib and SoC arms. Study included patients in hospital, receiving oxygen or non-invasive ventilatory support; no patients were intubated at baseline . SoC= standard of care therapy; >80% patients were treated with glucocorticoid therapy, 50% treated with remdesivir.

- Discharged Alive
- In hospital without need for supplementary Oxygen
- Supplementary Oxygen or non-invasive ventilation/ high flow O2
- Intubated and ventilated
- Death

Table summarises the BGBC020 study population. 115 patients were recruited in the study. **Location,** n(%): 60 (52%) patients were recruited in **India** and 55 (48%) in **South Africa.**
Baseline WHO ordinal score: Grade 3 (in hospital, not receiving oxygen), Grade 4 (supplementary oxygen only), Grade 5 (non-invasive ventilation or high-flow nasal oxygen). Number of patients in each subcategory n (%), Grade 3= 11 (10%); Grade 4 without corticosteroids= 16 (14%); Grade 4 and steroid used= 76 (66%); Grade 5 without corticosteroid= 4 (3%); Grade 5 and steroid used = 7 (6%); <12 days from symptom onset= 109 (95%).

BGBC020: Patient population

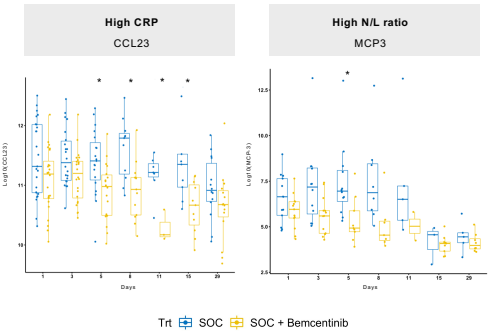
Characteristic	Statistic	Bemcentinib + SoC (N=58)	SoC (N=57)	Total (N=115)
Age (years)	Mean (SD)	54.4 (12.97)	51.5 (15.48)	53.0 (14.28)
Male	n (%)	41 (71)	35 (61)	76 (66)
Female	n (%)	17 (29)	22 (39)	39 (34)
Baseline BMI (kg/m²)	Mean (SD)	27.97 (5.835)	29.30 (6.485)	28.61 (6.163)
Any significant comorbidity	n (%)	32 (55)	30 (53)	62 (54)

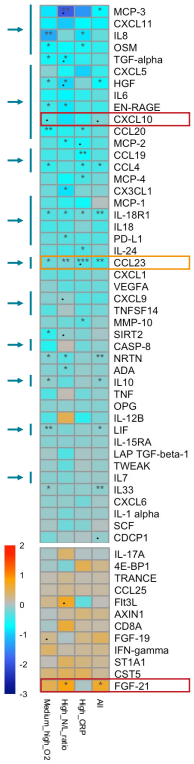
BGBC020: BIOMARKER DATA

Bemcentinib treatment reduces markers of acute inflammation, profibrotic cytokines and increases expression of protective factors.

Key Observations:

1. Reduction in acute inflammation with Bemcentinib treatment. *Blue arrows* indicate reduction in cytokines and other serum factors associated with disease severity[10]
2. Reduction in CCL23, a marker of DEspR^{high} neutrophils associated with increased NETosis and critical-severity COVID-19 illness *(orange box)*
3. Reduction in pro-fibrotic cytokines and increase in protective factors *(red boxes)*
4. Changes more pronounced in patients with more serious disease (high CRP, high N/L ratio or increased O_2 usage).





Longitudinal data from serum on days 1, 3, 5, 8, 11, 15 and 29, were analysed using a biomarker panel from Olink (92 analytes).
Right: **Heat Map shows:** Log2 Fold-change by AUC analysis (day 1-15), Wilcox test, unadjusted p-values. • significant on individual days, Kruskal test, adjusted for multiple comparisons.

Above: **Plots show** comparison between bemcentinib and SoC arms at each timepoint. Non-parametric (rank-based) Kruskall-Wallis or Anova was applied (adjusted p-value < 0.05). Cohorts were analysed by treatment arm, with subgroup analysis by: CRP threshold (30mg/L) and Neutrophil/Lymphocyte ratio (N/L) (tertile thresholds 3.4, 6.5).

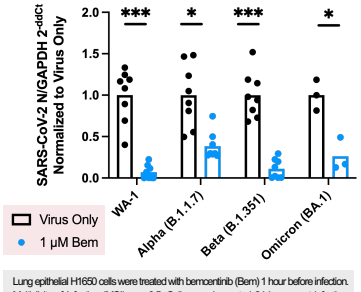
BEMCENTINIB ACTION ON VARIANTS OF CONCERN (PRE-CLINICAL DATA)

Bemcentinib prevents infection of SARS-CoV-2 independently of spike protein interactions and variant evolution.

Bemcentinib inhibits infection of multiple SARS-CoV-2 variants of concern in a lung epithelial cell line.

In vitro, data in lung epithelial cells infected with several variants of concern of SARS-CoV-2 including **Alpha, Beta and Omicron,** indicated that bemcentinib successfully reduced viral load and infection irrespective of the variant.

This data shows that the antiviral activity of bemcentinib isn't affected by the viral spike protein mutations and supports the idea that bemcentinib blocks viral entry independently of the spike protein, by blocking apoptotic mimicry, and is thus independent of the viral genome.[6]



Lung epithelial H1650 cells were treated with bemcentinib (Bem) 1 hour before infection. Multiplicity of infection (MOI) was 0.5. Cells were harvested 24 hours post infection. mRNA was isolated and analysed by RT-PCR for SARS-CoV-2 nucleocapsid (N). N-3-6.Data have been normalized to virus only, on a per-variant basis.

CONCLUSIONS

Bemcentinib treatment:

- Inhibits viral infection independent of spike protein variants
- Reduces clinical deterioration and need for invasive ventilation
- Exerts a broad anti-inflammatory and pro-repair effect on blood biomarkers

Confirmation of therapeutic utility of bemcentinib will be evaluated in the

EUSolidAct platform study; a European placebo-controlled, randomised study in up to 500 hospitalised patients with COVID-19.

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