Bemcentinib modulation of inflammatory, fibrinous 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 invasion of SARS-CoV-2 via the endothelial 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 ‘apoptotic mimicry’.1-2

AXL signaling dampens innate immune responses by inhibiting the expression of type I interferon and by polarizing macrophages towards the immune-suppressed 2C phenotype further facilitating viral infection.3 AXL is clearly expressed in the lung epithelial cells as well as macrophages and has recently been shown to prevent epithelial repair during lung injury.4

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

BEMCENTINIB COVID-19 CLINICAL TRIAL

BGCBO20 (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

BGCBO20 (NCT04890509): Study Design

BGCBO20: 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 hospitalised COVID-19 patients in a BGCBO20 study. This compared the SoC control arm with bemcentinib given in combination with SoC.

Encouraging data from the BGCBO20 study showed that bemcentinib was efficacious in providing early and sustained protection and limiting clinical deterioration in COVID-19.5

This efficaciousness of bemcentinib was enhanced in more severe COVID-19 patients stratified by plasmatic CRP levels of greater than or equal to 30mg/L.

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

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

Table summarizes the BGCBO20 study population: 105 patients were recruited in the study.

BGCBO20: Clinical data & patient population

BGCBO20: Biomarker data

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

Key Observations:
1. Reduction in acute inflammation with Bemcentinib treatment. (Blue arrow indicate reduction in cytokines and other serum factors associated with disease severity)
2. Reduction in CXCL2, a marker of GDF5+ymnocytosis associated with increased NE Tiss and critical-severity COVID-19 illness (orange dot)
3. Reduction in pro-Rhodocytosis cytokines and increase in protective factors (green)
4. Changes in biomarkers in patients with more serious disease (high CRP, high NLR ratio or increased G usage).

BGCBO20: Action on variants of concern (pre-clinical data)

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

Bemcentinib inhibition 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 demonstrated 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 design of bemcentinib as a viral entry blocker independent of the spike protein, thereby apoptotic memory, and is thus independent of the viral genome.

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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