Phase 1b/2a safety and tolerability study of bemcentinib (BEM) with pembrolizumab/carboplatin/pemetrexed in subjects with untreated advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) without/with a STK11 mutation

Rajwanth Velusamy MD MSCR1, Sheena Bhalla MD2, Ranee Mehra MD3, Marina Garassino MD4, Oleg Gilgich MD5, Cristina Oliva MD6, Claudia Gorcea-Carson MD6, Nigel McCracken6

BACKGROUND

The combination of platinum chemotherapy, pemetrexed and pembrolizumab (CIT) has become a standard of care as first line (1L) treatment in patients with non-squamous (NS) NSCLC. Despite improvements in response rates and survival, the emergence of primary or acquired resistance limits its efficacy.

STK11/LKB1 mutations (STK11m) are common (20%) in NSCLC and are associated with a high unmet medical need.2 The phenotypic characteristics of STK11 mutated tumors (e.g., high cellular stress and immune evasion) drive increased levels of AXL activation (Figure 1).

AXL, a member of the TAM family of receptor tyrosine kinases, is activated in response to inflammation, hypoxia, cellular stress or drug treatment.4,5 Tumor cells use the AXL pathway to sense stress and trigger molecular mechanisms to ensure survival or escape from the toxic environment (Figure 1). AXL is expressed in tumor cells, where it enhances survival, as well as in innate immune cells where it drives immune suppression.

Bemcentinib (BEM), a selective AXL inhibitor, targets key survival and resistance mechanisms within the tumor and the microenvironment of NSCLC tumors (Figure 2). Importantly, AXL inhibition with BEM potentiated the efficacy of combined chemoinmunotherapy in models of NSCLC and BEM has been shown to sensitize STK11m NSCLC to immune checkpoint inhibitors in preclinical studies.2

In summary, based on supportive in vitro and in vivo pharmacology in NSCLC cells and animal models, as well as preliminary clinical data, the addition of BEM to CIT has the potential to improve the 1L treatment outcomes of NSCLC patients, particularly in tumors harboring STK11m.

STUDY DESIGN

BGB126: open-label, multi-centre Ph1b/2a study in 1L NSCLC patients with STK11 mutations

Aims

To assess the safety, tolerability, and preliminary anti-tumor activity of BEM in combination with CIT as 1L treatment in NS-NSCLC patients without actionable mutations.

Main Eligibility Criteria

• Newly-diagnosed patients with advanced (Stage IIib/IIIc) or metastatic (Stage IV) NS-NSCLC
• Absence of actionable mutations
• Any PD-L1 status
• STK11 mutation required only for ph2a

Safety Review

An independent data safety monitoring board (DSMB) will review the safety data at end of the DLT assessment period (first 21 days of cycle 1 for each patient) and will recommend the BEM doses for the phase 2a expansion.

Duration of the Study

Screening: up to 28 days
Treatment: up to 2 years
Follow-up: up to 2 years

The trial is currently enrolling patients in the phase 1b in the US; recruitment for the phase 2a is planned to open in Q2 2023 in Europe and US.

REFERENCES