Bemcentinib + Pembrolizumab show promising efficacy in metastatic NSCLC patients harboring mutations associated with poor prognosis: exploratory sub-analysis from the BCG008 trial

Introduction

• Non-small cell lung cancer (NSCLC) is a heterogenous disease with genetic mutations impacting treatment outcomes. Mutations in KEAP1/STK11, KEAP1, SMARCA4, and KRAS are associated with unfavorable responses to therapy4,5,6,7,8. These mutations influence tumor stress, growth status, and the tumor microenvironment9,10,11,12,13. Loss of KEAP1 activity (STK11-4) can be caused by direct mutation or by other mechanisms and can be detected using a gene signature14. This gene signature is strongly associated with KEAP1 mutations15.

• KEAP1, a receptor tyrosine kinase, serves as a biomarker for poor prognosis in NSCLC16. Activated in response to cellular stress, KEAP1 promotes drug resistance, metastasis, and an immune-suppressive response17,18,19,20. Targeting KEAP1 with an oral small molecule inhibitor barbatimin has shown promise when combined with immune-checkpoint inhibition (ICI) in pre-clinical NSCLC models harboring mutations in STK11, KEAP1, SMARCA4 and KRAS11,22,23.

• BCG008 phase 2 study investigated Bemcentinib (pembrolizumab) (PEM) as a second-line therapy for NSCLC patients after platinum-based chemotherapy and/or for ICI, reporting favorable tolerability and efficacy24.

• Top-line mOS/MPS (19/15) months, independent of PD-L1 status.

Here we present exploratory, mutational sub-analyses, focusing on patients with mutations and gene signatures (STK11-4) associated with poor prognosis.

Methods

Patients provided their informed consent.

IB/IEC approval obtained for each study center.

• Tumor material obtained from FFPB biopsy samples taken pre-treatment.

• PD-L1 expression assessed using immunohistochemistry (IHC, 22C3 assay).

• PD-L1 negativity defined as IHC tumor proportion score (TPS)<1.

• AKI expression assessed by IHC (Roche/Ventana assay).

Tumor scoring using H score: 1% with low expression; ≤3% with moderate expression; >3% with high expression.

Immune cells scored as percent AKI+ immune cells/human tumor area.

AKI positive defined as Hiscore ≥5 and/or immune score ≥1.

• Mutations analyzed through whole exome sequencing (WES) of tumors.

• STK11-4 identified via RNA sequencing of biopsies.

• Kaplan-Meier analysis and Cox Proportional Hazard models were calculated in R using the Survival package.

• Comparator Study for expected effects of STK11/KEAP1/MACs.

• MIND Dataset available from dlbCancer20.

• Anti-angiogenic therapies alone or in combination with anti-PD-L1.

• Subset to PD-L1 ≥1% (≥1% with ≥2 time on treatment ≥1d).

• Exempt from the use of ICI in ≥3.5 months after ICI exposure.

Results

Expected result based on published data

Effect of STK11/KEAP1 mutations on 2L treatment outcomes

KEAP1 and KRAS mutations are associated with reduced survival irrespective of treatment regimen or line of therapy12,22.

In 2L, BEM-PEM appears to reduce/eliminate the liability of STK11 and/or KEAP1 mutations, demonstrating approximately equal survival benefit across mutational classes.

Results from BCG008

Effect of KRAS mutations on 2L treatment outcomes

Although SMARCA4 patients have worse survival associated with KRAS mutation, they do not appear to associate with PD-L1.

Effect of M2RCA4 mutations on 2L treatment outcomes

SMARCA4 patients do not appear to negatively impact survival in 2L treatment with BEM + PEM.

2L treatment outcomes in PD-L1 negative patients

Lack of PD-L1 expression was associated with reduced survival in 2L+.

Even with treatment equally effective in PD-L1 negative population.

Conclusions

Mutations in STK11 and KEAP1 have previously been associated with reduced survival irrespective of treatment regimen or line of therapy12.

In 2L, BEM-PEM appears to reduce/eliminate the liability of STK11 and/or KEAP1 mutations, demonstrating approximately equal survival benefit across mutational classes.

Lack of PD-L1 expression has previously been associated with poor survival in 2L, BEM-PEM appears to reduce/eliminate the liability of lack of PD-L1 expression, demonstrating approximately equal survival benefit in PD-L1- (TPS <5%) vs PD-L1+ (TPS ≥5%).

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References