AXL as a therapeutic target in STK11 mutant NSCLC

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INTRODUCTION

Serine-threonine kinase 11 (STK11/LKB1) is a tumor suppressor, and loss of STK11 protein contributes to tumorigenesis. Mutations in the STK11 gene (STK11m) are present in ~20% of NSCLC, and STK11 is one of the most frequently mutated genes in NSCLC. Inactivation of STK11 is associated with a poorer prognosis, irrespective of treatment modality and represents a sub-group of patients with high unmet need. AXL, a member of the TAM family of receptor tyrosine kinases, is activated in response to inflammatory, hypoxic, cellular stress or tumorigenesis. AXL is a receptor that is activated by a variety of ligands, including growth factors, cell-cell and cell-matrix interactions, triggering molecular mechanisms to ensure survival or escape from the toxic environment (Figure 1). AXL is expressed in both tumor cells, where it enhances survival and drug resistance, and in immune cells, such as dendritic cells (DC) and macrophages, where AXL drives immune suppression (Figure 1). The phenotypic characteristic (both energetic and metabolic stress) of a tumor with inactivated STK11 is likely to promote AXL activation in both tumor cells and/or immune cells of the tumor microenvironment (TME) (Figure 1). The selective AXL inhibitor, bemcentinib, targets key survival and resistance mechanisms in the tumor and restores the antitumor phenotype of immune cells. Specifically, inhibition of AXL in STK11m tumors has been shown to restore T cell activation and induce antitumor responses in preclinical models of STK11m NSCLC (Figure 2).

Inactivation of STK11 is found in approximately 30% of lung adenocarcinomas as a result of either mutations in the STK11 gene (STK11m) or other non-mutation mechanisms. The Kaufman STK11 loss signature (Kaufman et al., 2014) is a 10 gene classifier for identifying tumors lacking STK11 activity in the current work, we have applied the Kaufman STK11 loss signature to publicly available data sets (TCGA/CGA/BCC-5) as well as the BerGenBio trial in 2L NSCLC (BGBC008) to better understand the characteristics and mutational status of these tumors. This signature identifies STK11 mutations as strongly associated with STK11 loss. Differential gene expression analysis confirms that there is a transcriptional consequence of STK11 loss in tumors. AXL expression was confirmed in NSCLC tumors in correlation to STK11m and STK11 loss. Transcriptional changes following AXL inhibition by bemcentinib in a STK11m/KEAP1m NSCLC cell line were measured to further strengthen the rationale for targeting NSCLC patients characterized by STK11 loss with the AXL inhibitor bemcentinib.

ITGAV expression in tumor and immune cells in NSCLC patients with or without STK11 loss

Mutations in STK11 and KEAP1 promote similar transcriptional consequences in NSCLC patients

RESULTS

Mutations in STK11 and KEAP1 and low PD-L1 expression are associated with a STK11 loss signature

Bemcentinib in combination with pembrolizumab in 2L+ NSCLC has similar activity when STK11 is present and absent

A549 with STK11 and KEAP1 mutations

Bemcentinib modulates pathways involved in tumoricnic features of STK11m NSCLC

CONCLUSIONS

Mutations in STK11 and KEAP1 promote similar transcriptional consequences in NSCLC patients

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Bemcentinib modulates pathways involved in tumoricnic features of STK11m NSCLC

Clinical outcomes from the Phase I. 2L+ metastatic NSCLC study (BGBC008) investigating the combination of bemcentinib and pembrolizumab are in agreement with those of the Phase I study (BGBC008) with no similar clinical outcomes seen in two STK11m patients.

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REFERENCES


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