COMBINATION WITH BCA101 IMPROVES THE EFFICACY OF KRAS-G12C INHIBITOR AND OVERCOMES G12C INHIBITOR-INDUCED RESISTANCE IN LUNG AND COLON CANCER CELL LINES

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Background Kirsten ras oncogene homolog (KRAS)-G12C allele-specific mutations are majorly observed in about 15% of non-small cell lung cancer (NSCLC) and about 3% of colorectal cancers. KRAS mutation-specific inhibitors have had modest benefits in clinical studies. However, the remissions observed are not sustained and most patients relapse after therapy. The mechanisms proposed for G12Ci relapse include upregulation of receptor tyrosine kinase pathways and Epithelial-to-Mesenchymal Transition (EMT) signature triggered by enhanced TGF-β expression within the tumor microenvironment (TME).1-4 In the present study, we evaluated whether BCA101, a bispecific antibody consisting of TGFβRII-extracellular domain fused to a heavy chain of an anti-EGFR antibody, abrogates the KRAS-G12Ci (inhibitor) induced resistance. This is evaluated in lung and colon cancer preclinical models by targeting EGFR and sequestering TGF-β within tumors.

Methods Lung cancer (NCI-H358 and NCI-H1792) and colon cancer (SW837 and SW1463) cell lines were characterized for EGFR expression and TGF-β secretion. These cells were treated with different concentrations of G12Ci and fixed concentrations of BCA101 combination and evaluated for cytotoxicity at 72 hours. Synergistic activity was analyzed by Bliss statistical model. To check whether BCA101 rescues the cells from TGF-β-induced G12Ci resistance or G12Ci-induced acquired resistance, cells were treated with either TGF-β or G12Ci for at least two to four weeks, followed by combination treatment of G12Ci with BCA101. Data were compared with the effect of this combination over appropriate controls in vitro and in vivo.

Results Bliss analysis demonstrated that G12Ci and BCA101 combination showed synergistic cytotoxicity in both lung (figure 1) and colon cancer cell lines. Comparable results were observed with cetuximab, an anti-EGFR antibody in combination with KRAS-G12Ci. Prolonged treatment with TGF-β, induced G12Ci resistance in NCI-H1792 lung cancer cells. When used in combination with G12Ci, BCA101 rescued TGF-β-induced G12Ci resistance while cetuximab did not overcome resistance in this cell line. Additionally, prolonged treatment with KRAS-G12Ci induced TGF-β secretion which correlated with resistance to KRAS-G12Ci. This resistance is rescued by a combination of the G12Ci with BCA101 but not cetuximab. The superior efficacy observed for the combination in vitro, is also supported in xenograft studies in mice.

Conclusions Preclinical results show that BCA101 has the potential to increase the efficacy of G12Ci along with the ability to mitigate G12Ci-induced acquired resistance in lung and colon cancer cell lines. This study provides a rationale to combine BCA101 with G12Ci in G12C mutant lung or colon cancer patients.

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REFERENCES

Ethics Approval Mice were maintained as per the regulations of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India and Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) guidelines. All animal experiments were approved by institutional ethical committee and performed under approved protocols. All animals were maintained at dedicated Syngene vivarium.

Abstract 1426 Figure 1  Evaluating BCA101 and AMGS10(KRAS-G12Ci) mediated cytotoxicity in lung cancer cell lines harboring KRAS-G12Ci mutation. (A) NCI-H358 or (B) NCI-H1792 cell lines were treated with titrating concentrations of AMGS10 and fixed concentration of BCA101 (50μg/mL), and cytotoxicity was evaluated after 72 hours. Synergistic effect of the combination of AMGS10 and BCA101 over single treatment was calculated using bliss statistical model, where Bliss = E A + E B — (E A x E B), where E A and E B is the fractional cytotoxicity obtained by drug A and drug B

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