Microinjection of Nectin-4/CD137 tumor-targeted immune cell agonist (TICA™) activates the local tumor microenvironment

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ABSTRACT

• After disappointing first clinical experiences with agonistic anti-CD137 (4-1BB) antibodies, a new generation of both systems and targets CD137 agonists is entering clinical development (1-3). These strategies rely on biological agents with substantial properties for CD137 agonism due to their relatively large sizes and long circulating half-lives. These properties may limit their ability to penetrate and spare sustained agonism resulting in overstimulation and activation-induced cell death of lymphocytes due to continuous exposure.

• Fully synthetic constrained bicyclic peptides (Bicycles) with antibody-like affinities and target selectivity are actively being sought to meet the above demands in clinical targeted CD137 agonist therapies. BCY11864 was shown to activate cytotoxic T cells around the BCY11864 injection area by 24 hours and to activate CD8+ T cells in contrast to vehicle and MMAE. Biosynthesis BCY11864 induces immune activation markers CCL10 and IFN-γ in a dose dependent manner.

• Comparative In Vivo Oncology (CIVO) platform was developed to enable in situ investigation of multiple microdosed drugs simultaneously in human tumors (5) with safety and feasibility of this platform validated via use of tumoral accessibility to trackable drug microdoses.

• Here we report on an evaluation of the feasibility of using the CIVO platform to demonstrate the action of our tumor-targeted CD137 agonist TICA.

RESULTS

• BCY11864 increases the numbers of cytotoxic CD8+ T cells

• Simultaneous microinjection of multiple drugs into the same tumor microenvironment, therefore BCY11864 was included to investigate impacts of the CIVO platform to demonstrate the action of our tumor-targeted CD137 agonist TICA.

• Known HDA to be dosed drugs demonstrated in clinic (7) Analysis platform for immune profiles/PO biomarkers as x-axis

MATERIALS AND METHODS

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INTRODUCTION

Activating CD137 through receptor cross-linking

CONCLUSIONS/SUMMARY

• We have validated pre-clinical the CIVO platform for investigating target engagement and the mechanism of action of tumor-targeted immune cell agonists in accessible tumor tissues.

• Microinjection of BCY11864 into Nectin-4-expressing tumor cells induces immune activation marker in a dose dependent manner

• BCY11864 activates cytotoxic T cells around the BCY11864 injection area by 24 hours

REFERENCES