Development of a CD137 receptor occupancy assay to support the phase I/II study of BT7480, a Bicycle tumor-targeted immune cell agonist (Bicycle TICA®)

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ABSTRACT

Bicycles are synthetic constrained peptides with antibody-like affinities that target selectively, readily penetrate tumor tissue, have relatively short half-lives, and can be chemically linked to generate multifunctional molecules. BT7480 is a Bicycle TICA® being developed as a first-in-class CD137 therapeutic for the treatment of human cancers associated with Nectin-4 expression and is currently being investigated in an ongoing Phase I/II clinical trial. Monitoring target engagement for a given therapeutic can be a key factor in recommending the Phase II dose. While flow cytometry-based receptor occupancy (RO) assays are commonly used to monitor target engagement in the clinic, a CD137-specific RO assay presents several important challenges that have historically hampered monitoring RO in the clinic, including the dynamic expression of CD137 on unstimulated and stimulated T cells, the low frequency of CD137+ cells in human blood, and limited reagents to confidently detect CD137+ cells in the presence of CD137-targeting drugs. To address these challenges, a fit-for-purpose, 4plex flow cytometry panel was developed that incorporates a fluorescently labeled CD137-specific binding Bicycle®. This Bicycle® was shown to directly compete with a Bicycle TICA® for binding to CD137, but with a fluorescently labeled anti-CD137 antibody, thereby enabling simultaneous detection of various CD137+ immune cell types, as well as receptor occupancy by BT7480 in a single blood sample.

RESULTS

Bicycle CD137 receptor occupancy assay flow cytometry panel development

Panel performance testing across clinically-relevant sample matrices

CONCLUSIONS

This study represents the first report of a clinically-ready CD137 RO assay. Results demonstrate the first clinical flow cytometry assay using fluorescently labelled Bicycle® reagents. Success of this development supports the utility of the Bicycle CD137 RO assay to monitor target engagement in the BT7480 first-in-human clinical trial.

REFERENCES