RESULTS: GENE EXPRESSION ANALYSIS

BT7455 shows α of the second protein, EphA2 (2).

INTRODUCTION

Gene expression profiling of BT7455-treated tumors revealed modulation of the tumor immune microenvironment, • BT7455 engages EphA2 and CD137 with high affinity resulting in potent EphA2-dependent production of interleukin-2 (IL-2).

ABSTRACT

Compelling preclinical data characterization of BT7480 [2] led us to develop a second ABSTRACT (BCY14796) BT7455 across CD4+ and CD8+ T cells from 2 donors was 0.72

RESULTS: RECEPTOR OCCUPANCY ASSAYS

Figure 3. Cell based receptor occupancy assays for CD137 and EphA2 show competitive binding by BT7455 but not non-binding controls. Receptor occupancy was calculated from flow cytometry data using the formula: \%RO=([1-1nM] [E/Max]-([BM]/[E/Max]))×100. A) EphA2 ROI assay in A549 cells with BT7455 (black) and control non-EphA2 binding analogue of BT7455 (BCY14797; blue). Unoccupied receptors were detected in the assay when PBMCs are co-culture assay.

RESULTS: CO-CULTURE ASSAYS

Figure 5. BT7455 elicits potent EphA2-binding dependent CD137 agonism in vitro. A&B) BT7455 shows response in a PBMC/tumor cell co-culture assay with MC38 cells (black) but not MC38 cells with EphA2.

RESULTS: IN VIVO RESPONSE

Figure 6. Intermittent BT7455 exposure led to complete responses in the MC38 syngeneic mouse model. Tumor bearing mice (n=10) with vehicle alone (white) or 0.5 mg/kg i.v. on days 0, 7, 14 and 20 were challenged with vehicle (black) or BT7455 (BCY12491, yellow) after treatment with vehicle (veh). BT7455 (8 mg/kg, 0 and 24 h, p=0.1; RPMI-1401 mg/kg, p=0.07), or CD137 (Unimmunized animals; 2 ng/ml). Transcriptional analysis was performed using Nanostring. A) BT7455 induced a burst of cytokine and chemokine expression, whereas the effect of -CD137 and -PD-1 was more modest. Significant changes were observed in NF-κB signaling (B), cytokine and chemokine signaling (E), and cytotoxicity (D) gene sets after BT7455 treatment but not after anti-PD-1 or anti-CD137 treatment.

CONCLUSIONS

BT7455 is a highly potent EphA2 expression dependent CD137 agonist.

BT7455 has optimal target binding, pharmacologic, and pharmacokinetic properties that enable intermittent dosing for curative effect through modulation of the tumor immune microenvironment in syngeneic mouse models.

BT7455 is currently being evaluated in IND-enabling studies.

REFERENCES


