BI 905711, a novel CDH17-targeting TRAILR2 agonist, effectively triggers tumor cell apoptosis and tumor regressions selectively in CDH17-positive colorectal cancer models.

INTRODUCTION

The tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) has the capability to induce apoptosis in a wide variety of tumor cells and has emerged as an important therapeutic concept for cancer treatment. To date however, TRAILR2 agonistic antibodies, designed to trigger tumor cell apoptosis, have only had limited clinical success due to lack of efficacy or liver toxicity. BI 905711, a tetravalent bispecific antibody targeting both TRAILR2 and CDH17, was designed to overcome the disadvantages of current TRAILR2 antibodies. CDH17-dependent clustering of TRAILR2 permits BI 905711 to selectively induce apoptosis in CDH17-expressing tumor cells. CDH17 was selected as the anchor target due to its restricted sensitivity to TRAILR2 agonists. Here, we report the preclinical activity of BI 905711 using colorectal cancer (CRC) derived cell lines and patient-derived xenograft (PDX) models. We demonstrated that BI 905711 effectively triggered apoptosis in a broad range of CDH17-positive CRC tumor cells in vitro. Furthermore, BI 905711 potently initiated the apoptotic cascade as evidenced by a strong post-treatment increase of both caspase-8 and caspase-3/7. Importantly, induction of extrinsic apoptosis signaling by BI 905711 was strictly CDH17-dependent, as further demonstrated using a pair of CDH17-positive and -negative clones of the cell line GP2d. When comparing the CDH17-negative clone with the parental cell line, the absence of CDH17 translated into a more than 1000-fold drop in BI 905711-dependent efficacy. Moreover, BI 905711 demonstrated single-agent tumor regressions in vivo in different CRC PDX models, showing effective tumor growth inhibition in a q14d dosing schedule. In summary, we demonstrated that BI 905711 potently triggers the extrinsic apoptosis pathway specifically in CDH17-positive tumor cells, which translates into significant tumor growth inhibition in CRC patient-derived xenograft tumors. BI 905711 is a first-in-class molecule that shows superiority to existing TRAILR2 agonists, represents a targeted strategy for the treatment of CRC and additional CDH17-positive cancer types. Together with its potential for a favorable safety profile, these data support our plan for a phase 1 trial of BI 905711 in these patient populations.

METHODS

Cell viability was determined using a CellTiter-Glo assay (Promega) according to the manufacturer’s instructions. Cell viability and apoptosis were measured using Jo-1 FITC (QIAGEN) and caspase 3 and 7 activity was measured using the Caspase-Glo 3/7 (G8091) or Caspase-Glo 8 (G8152) assay (Promega). Cell supernatants or EDTA-plasma samples were evaluated using the Caspase-Glo 3/7 or Caspase-Glo 8 assay. Anti-apoptosis markers were determined using an IHC assay (ABC) according to standard protocols with goat anti-CDH17 (CST 9661) and rabbit anti-TRAILR2 (CST 9496) as primary antibodies. Different CDH17-negative clones of the CRC cell line GP2d were generated using the CRISPR/Cas9 system. Membrane expression of both CDH17/TRAILR2 was analyzed by FACS.

RESULTS

The preclinical activity of BI 905711 was further investigated in vivo in a q14d dosing schedule. BI 905711 demonstrated single-agent tumor regressions after single dose. Importantly, induction of extrinsic apoptosis signaling by BI 905711 was strictly CDH17-dependent, as further demonstrated using a pair of CDH17-positive and -negative clones of the cell line GP2d. When comparing the CDH17-negative clone with the parental cell line, the absence of CDH17 translated into a more than 1000-fold drop in BI 905711-dependent efficacy. Moreover, BI 905711 demonstrated single-agent tumor regressions in vivo in different CRC PDX models, showing effective tumor growth inhibition in a q14d dosing schedule. In summary, we demonstrated that BI 905711 potently triggers the extrinsic apoptosis pathway specifically in CDH17-positive tumor cells, which translates into significant tumor growth inhibition in CRC patient-derived xenograft tumors. BI 905711 is a first-in-class molecule that shows superiority to existing TRAILR2 agonists, represents a targeted strategy for the treatment of CRC and additional CDH17-positive cancer types. Together with its potential for a favorable safety profile, these data support our plan for a phase 1 trial of BI 905711 in these patient populations.

SUMMARY

In a CDH17-dependent manner, BI 905711 triggered apoptosis in CDH17 positive CRC tumor cells in vitro. BI 905711 demonstrated in vivo efficacy after single administration in colorectal cancer xenograft models with sustained tumor regressions up to ~30 days. Decrease in tumor size was accompanied by modulation of apoptosis markers with good correlation between tumor and plasma biomarker modulation. In CRC patient-derived xenograft tumors, BI 905711 also demonstrated a significant tumor growth inhibition.

CONCLUSIONS

BI 905711 is a first-in-class molecule that shows superiority to existing TRAILR2 agonists and, together with its potential for a favorable safety profile, it represents a targeted strategy for the treatment of CRC and additional CDH17-positive cancer diseases.

BI 905711 is scheduled to start phase I clinical trials in Q2/19.