EGFR x MET TsAb: differentiated MET biparatopic design with optimal MET inhibitory activity to pursue best-in-class opportunity

BeiGene

 # 3015

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Abstract

Acquired resistant mutation after small molecule inhibitor treatment in non-small cell lung cancer (NSCLC) develops invariably through mutations in EGFR or through activation of compensatory pathways such as MET. BG-T187 is a tri-specific antibody (TsAb) targeting EGFR and MET with a differentiated MET biparatopic designation designed to treat tumors driven by activated EGFR and/or MET signaling. Stronger antiproliferative effects and MET signaling inhibition by BG-T187 compared to traditional EGFR/MET bi-specific antibody (BsAb) were observed *in vitro*. Additionally, potent *in vivo* anti-tumor activity and desirable PK profile was observed upon BG-T187 treatment of human tumor xenograft models driven by EGFR activation mutation and/or MET amplification. Interestingly, stronger anti-tumor activity of BG-T187 than that of traditional EGFR/MET bi-specific antibody was observed in xenograft models with MET amplification. Through a comprehensive assessment of EGFR on-target toxicity risk, we demonstrated that BG-T187 show better HEKn selectivity than EGFR/MET bi-specific antibody, indicating potential lower on-target toxicity risk of BG-T187. Collectively, our findings represent a novel EGFR/MET tri-specific antibody with differentiated MET biparatopic and pursue best-in-class potential.

Molecule Design

BG-T187 TsAb comprised of three arms: two Fab arms targeting to two different human MET epitopes and a scFv arm targeting to human EGFR antigen (**Table 1**). The two Fab arms are generated from common light chain engineered mice (RenLite®, Biocytogen). The anti-EGFR scFv arm was fused to N terminal of one cMET arm via GS linker, and Knob-into-hole technology was employed for Fc heterodimerization (**Figure 1**). BG-T187 showed good PK profile in human FcRn-transgenic (hFcRn) mice.

Figure 1. TsAb design

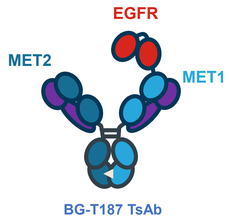
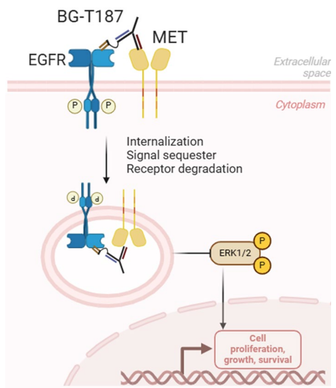


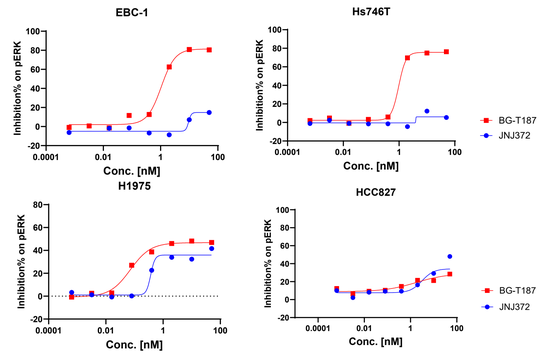
Table 1. SPR binding affinity of BG-T187 and the cMET arms to human and cynomolgus cMET and EGFR antigens

Test Ab	Test Antigen	ka (1/Ms)	kd (1/s)	KD (M)
BG-T187	Human cMet	1.67E+05	2.49E-04	1.49E-09
cMET Arm1	Human cMet	3.51E+05	4.25E-02	1.21E-07
cMET Arm2	Human cMet	1.94E+05	9.87E-04	5.08E-09
BG-T187	Human EGFR	1.50E+05	1.06E-03	7.08E-09
BG-T187	Cyno cMet	1.71E+05	5.00E-04	2.92E-09
cMET Arm1	Cyno cMet	3.51E+05	5.61E-02	1.60E-07
cMET Arm2	Cyno cMet	1.69E+05	2.50E-03	1.48E-08
BG-T187	Cyno EGFR	1.69E+05	1.84E-02	1.09E-07

Stronger MET signaling inhibition by BG-T187 than traditional BsAb

Figure 2. EGFR mut or MET amp cancer cells were incubated with BG-T187 or JNJ-372. The pERK level were measured after 24h incubation.

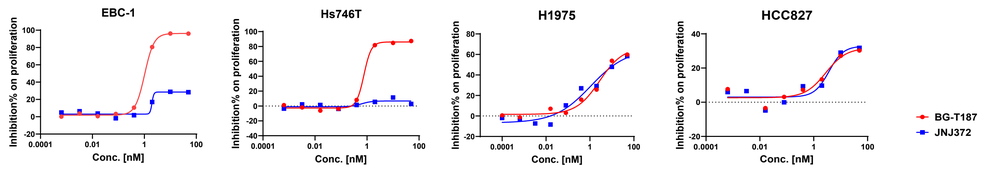




EBC-1 and Hs746T contains MET amplification
H1975 and HCC827 contains EGFR activation mutation and MET Wildtype.

Stronger anti-proliferation by BG-T187 than traditional BsAb in METamp cells

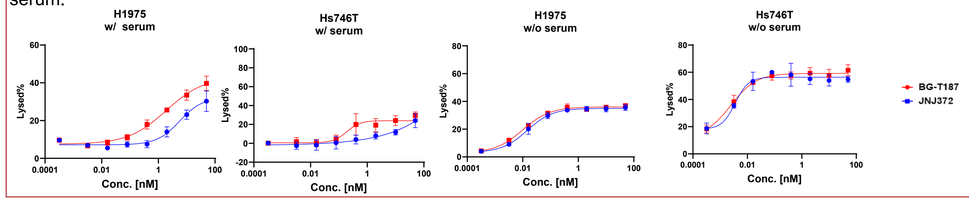
Figure 3. EGFR mut or MET amp cancer cells were incubated with BG-T187 or JNJ-372. The anti-proliferation level were measured after 6 days incubation.



EBC-1 and Hs746T contains MET amplification
H1975 and HCC827 contains EGFR activation mutation and MET Wildtype.

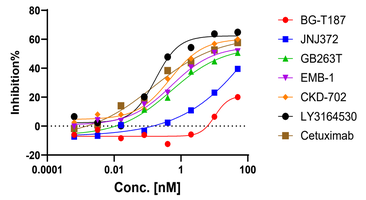
Comparable Fc function to traditional BsAb

Figure 4. BG-T187-mediated human PBMC killing activity on cancer cells in conditions with or without addition of human serum.



Weaker HEKn killing comparing to other anti-EGFR antibody drugs

Figure 5. Human epidermal keratinocytes, neonatal (HEKn) were incubated with BG-T187. The anti-proliferation level were measured after 6 days incubation.



Stronger *in vivo* anti-tumor activity by BG-T187 than traditional BsAb

BG-T187 show stronger anti-tumor activity than EGFR/MET BsAb (JNJ-372) in xenograft model EBC-1 and Hs746T, which contains MET amplification, at same dose level (**Figure 6**). Whereas BG-T187 show comparable anti-tumor activity to JNJ-372 in xenograft model H1975 and HCC827, which contains EGFR activation mutation and MET wildtype, at same dose level (**Figure 7**)

Figure 6. Subcutaneous EBC-1 or Hs-746T xenograft with bi-weekly intravenously administration of BG-T187 (red) and JNJ-372 (blue). Shown is mean tumor volume ± SEM. BG-T187 exhibits better anti-tumor activity than JNJ-372

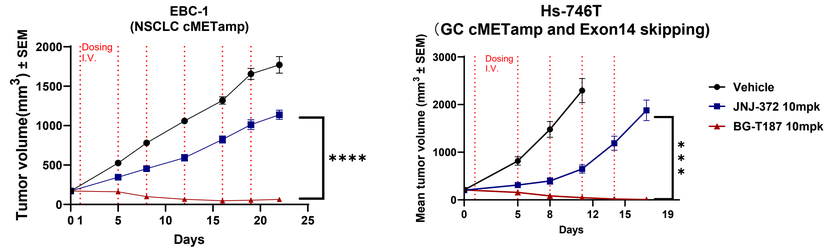
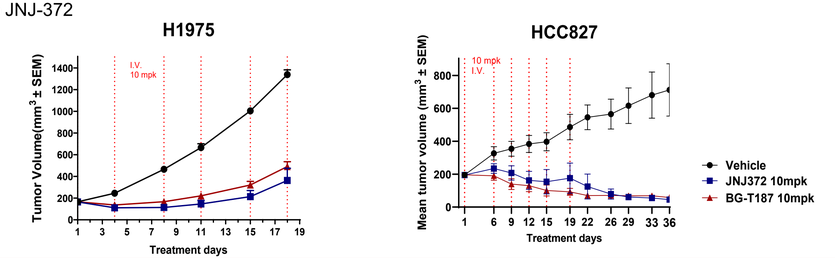


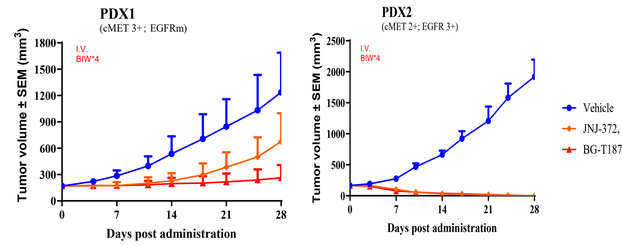
Figure 7. Subcutaneous H1975 or HCC827 xenograft with bi-weekly intravenously administration of BG-T187 (red) and JNJ-372 (blue). Shown is mean tumor volume ± SEM. BG-T187 exhibits comparable anti-tumor activity to JNJ-372



Potent anti-tumor activity by BG-T187 in TKI resistance PDX model

Figure 8. Subcutaneously heterogeneous Osi-resistant patient derived xenograft model (PDX) with bi-weekly intravenously administration of BG-T187 (red) and JNJ-372 (blue). Shown is mean tumor volume ± SEM.

- BG-T187 exhibits potent anti-tumor activity in PDX models
- BG-T187 exhibits stronger anti-tumor activity in PDX with high MET expression
- BG-T187 exhibits comparable anti-tumor activity in PDX with EGFR high expression



Conclusion

BG-T187 is a tri-specific antibody targeting EGFR and MET with a differentiated biparatopic design showing stronger signaling inhibition and stronger anti-tumor activity than traditional EGFR/MET Bi-specific antibody.

- Stronger signaling inhibition *in vitro*.
- Stronger tumor inhibition *in vitro* and *in vivo*.
- Weaker HEKn killing.