

CLAIMS

1. Use of a target protein degrader in the manufacture of a medicament for enhancing effects of a therapeutic agent in a subject having a cancer that is resistant or refractory to the therapeutic agent, wherein:

the subject is to be administered (i) the therapeutic agent; and (ii) the target protein degrader, such that the effects of the therapeutic agent are enhanced as compared to that of administration of the therapeutic agent alone;

wherein the target protein degrader comprises a bispecific binding molecule comprising:

 - (a) a target protein binding domain that specifically binds to a target protein on the subject's cancer cells; and
 - (b) a neuropilin-1 (NRP1) binding domain that binds to NRP1 comprising an antibody or NRP-1-binding fragment thereof.
2. The use of claim 1, wherein the target protein is a receptor tyrosine kinase (RTK).
3. The use of claim 2, wherein the receptor tyrosine kinase is selected from epidermal growth factor receptors (EGFRs), platelet-derived growth factor receptors (PDGFRs), fibroblast growth factor receptors (FGFRs), Met receptors tyrosine kinase (METs), and vascular endothelial growth factors (VEGFRs).
4. The use of claim 2, wherein the receptor tyrosine kinase is EGFR.
5. The use of claim 2, wherein the receptor tyrosine kinase is cMET.
6. The use of claim 2, wherein the receptor tyrosine kinase is HER2.
7. The use of claim 2, wherein the receptor tyrosine kinase is IGF1R.
8. The use of claim 1, wherein the target cell is a cancer cell.
9. The use of claim 8, wherein the cancer cell is selected from the group consisting of lung cancer, breast cancer, colon and rectum cancer, head and neck cancer, esophagogastric cancer, liver cancer, glioblastoma, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, kidney cancer, and

pancreatic cancer.

10. The use of claim 8, wherein the cancer cell is a non-small cell lung cancer (NSCLC) cell.
11. The use of claim 1, wherein the target protein binding domain and the NRP1 binding domain are each independently selected from the group consisting of IgG, half antibodies, single-domain antibodies, nanobodies, Fabs, monospecific Fab2, Fc, scFv, minibodies, IgNAR, V-NAR, hcIgG, VHH domain, camelid antibodies, and peptibodies.
12. The use of claim 1, wherein the NRP1 binding domain comprises:
 - (i) an antibody heavy chain variable (VH) domain comprising CDR1, CDR2 and CDR3 regions (HCDR1, HCDR2 and HCDR3, respectively), wherein HCDR1 consists of the sequence shown in SEQ ID NO: 79, HCDR2 consists of the sequence shown in SEQ ID NO: 80, and HCDR3 consists of the sequence shown in any one of SEQ ID NOs: 81-84; and
 - (ii) an antibody light chain variable (VL) domain comprising CDR1, CDR2 and CDR3 regions (LCDR1, LCDR2 and LCDR3, respectively), wherein LCDR1 consists of the sequence shown in any one of SEQ ID NOs: 85-87, LCDR2 consists of the sequence shown in SEQ ID NO: 88, and LCDR3 consists of the sequence shown in SEQ ID NO: 89.
13. The use of claim 12, wherein:
 - (i) HCDR1 consists of the sequence shown in SEQ ID NO: 79, HCDR2 consists of the sequence shown in SEQ ID NO: 80, and HCDR3 consists of the sequence shown in any one of SEQ ID NO: 84; and
 - (ii) LCDR1 consists of the sequence shown in SEQ ID NO: 85, LCDR2 consists of the sequence shown in SEQ ID NO: 88, and LCDR3 consists of the sequence shown in SEQ ID NO: 89.
14. The use of claim 1, wherein the enhanced effects comprise increased tumor growth inhibition.
15. The use of claim 1, wherein the enhanced effects comprise increased median survival time.
16. The use of claim 1, wherein the therapeutic agent targets the EGFR pathway.
17. The use of claim 16, wherein the therapeutic agent is selected from the group consisting of

Lazertinib, Osimertinib (AZD9291), WZ4002, Cyasterone, Erlotinib (OSI-774) HC1, efitinib (ZD1839), Lapatinib (GW-572016) Ditosylate, Afatinib (BIBW2992), Saracatinib (AZD0530), Vandetanib (ZD6474), Neratinib (HKI-272), Canertinib (CI-1033), Lapatinib (GW-572016), AG-490 (Tyrphostin B42), CP-724714, Dacomitinib (PF-00299804), Sapitinib (AZD8931), CUDC-101, AG-1478 (Tyrphostin AG-1478), PD153035 HC1, Pelitinib (EKB-569), AC480 (BMS-599626), AEE788 (NVP-AEE788), AP26113-analog (ALK-IN-1), OSI-420, WZ3146, HER2-Inhibitor-1, WZ8040, Allitinib tosylate, Rociletinib (CO-1686), Genistein (NPI 031L), Varlitinib, TQB33804 (EGFR-IN-7), Icotinib (BPI-2009H), TAK-285, Daphnetin, Tyrphostin 9, AG-18, AG 555, AZ5104, CL-387785 (EKI-785), Tyrphostin AG-258, AG-556, Tucatinib, Erlotinib (OSI-774), Gefitinib-based PROTAC 3, Zorifertinib (AZD 3759), ErbB2, AV-412 free base, AST-1306, JND3229, BI-4020, Theliatinib (HMPL-309), BDTX-189, Lifirafenib (BGB-283), Pyrotinib (SHR-1258), O-Demethyl-Gefitinib, Epertinib hydrochloride, SU5214, Avitinib (AC0010), AG 494, and Poziotinib (HM781-36B).

18. The use of claim 16, wherein the therapeutic agent is Osimertinib.

19. The use of claim 1, wherein the therapeutic agent targets the cMET pathway.

20. The use of claim 19, wherein the therapeutic agent is selected from the group consisting of Crizotinib, Cabozantinib, Foretinib, PHA-665752, SU11274, SGX-523, BMS-777607, Tivantinib, JNJ-38877605, PF-04217903, Amuvatinib (MP-470), MGCD-265 analog, Capmatinib, BMS-754807, BMS-794833, AMG-208, MK-2461, Golvatinib, AMG-458, NVP-BVU972, AMG 337, Merestinib, JNJ-38877618, Crizotinib hydrochloride, Ningetinib, AMG-1, UNC2025, Pamufetinib, Altiratinib, NPS-1304, Savolitinib.

21. The use of claim 19, wherein the therapeutic agent is Crizotinib.

22. The use of claim 1, wherein the therapeutic agent targets a KRAS protein.

23. The use of claim 22, wherein the therapeutic agent is selected from the group consisting of MRTX1133, Sotorasib (AMG510), Adagrasib (MRTX849), LC-2, Deltarasin, BAY-293, ARS-1620, BI-2852, ARS-853 (ARS853), BI-3406, ASP2453, Sotorasib (AMG510) racemate, Pan-RAS-IN-1, MRTX-1257, Zoledronic acid (ZOL 446), Lonafernib (SCH66336), K-Ras(G12C) inhibitor 9, Salirasib, Alamandine, (Rac)-Antineoplaston A10, K-Ras-IN-1, MCP110, 6H05, K-Ras(G12C) inhibitor 12, Kobe0065, K-Ras(G12C) inhibitor 6, BQU57, Kobe2602, NAV-2729, Antineoplaston A10, Fendiline

hydrochloride, KRpep-2d, Pei'illy' alcohol, RBC8, KY1220, CID-1067700, and Zoledronic acid monohydrate.

24. The use of claim 23, wherein the therapeutic agent is sotorasib.

25. The use of claim 1, wherein the therapeutic agent targets a protein selected from the group consisting of HER2, IGF1R, ALK, Braf, VEGF, and PDGF.

26. The use of claim 1, wherein the subject is to be administered a second therapeutic agent, wherein the effects of the second therapeutic agent are enhanced by the protein target degrader as compared to that of administration of the second therapeutic agent alone.

27. The use of claim 26, wherein the therapeutic agent targets EGFR and the second therapeutic agent targets cMET.

28. The use of claim 27, wherein the therapeutic agent is Osimertinib and the second therapeutic agent is sotorasib.

29. Use of a target protein degrader in the manufacture of a medicament for enhancing effects of a receptor tyrosine kinase (RTK) inhibitor in a subject having a cancer that is resistant or refractory to the RTK inhibitor, wherein:

the subject is to be administered (i) the RTK inhibitor; and (ii) the target protein degrader, such that the effects of the RTK inhibitor are enhanced as compared to that of administration of the RTK inhibitor alone;

wherein the target protein degrader comprises a bispecific binding molecule comprising:

(a) a target protein binding domain that specifically binds to an RTK on the subject's cancer cells; and

(b) a neuropilin-1 (NRP1) binding domain that binds to NRP1 comprising an antibody or NRP-1-binding fragment thereof.

30. Use of a target protein degrader in the manufacture of a medicament for enhancing effects of an epidermal growth factor receptor (EGFR) inhibitor in a subject having a cancer that is resistant or refractory to the EGFR inhibitor, wherein:

the subject is to be administered (i) the EGFR inhibitor; and (ii) the target protein degrader, such that the effects of the EGFR inhibitor are enhanced as compared to that of administration of the EGFR inhibitor alone;

wherein the target protein degrader comprises a bispecific binding molecule comprising:

- (a) a target protein binding domain that specifically binds to EGFR on the subject's cancer cells; and
- (b) a neuropilin-1 (NRP1) binding domain that binds to NRP1 comprising an antibody or NRP-1-binding fragment thereof.