

Claims

1. An antibody-drug conjugate (ADC) comprising a humanized anti-PVR antibody, or antigen binding portion thereof, conjugated to a toxin, the antibody or antigen binding portion thereof comprises a heavy chain and a light chain, wherein the heavy chain
5 comprises a variable region having an amino acid sequence at least about 90% identical to SEQ ID NO: 1, and wherein the light chain comprises a variable region having an amino acid sequence at least about 90% identical to SEQ ID NO: 2
2. The antibody-drug conjugate of claim 1, wherein the heavy-chain variable region comprises the CDR sequences set forth in SEQ ID NO: 3 (NYWIE), SEQ ID NO: 4
10 (EIFPGSGRINFNEKFKG) and SEQ ID NO: 5 (TKIYGNSFDY), and the light-chain variable region comprises the CDR sequences set forth in SEQ ID NO: 6 (KASQDVGTAHV), SEQ ID NO: 7 (WASSRHE) and SEQ ID NO: 8 (QQYSRYPLT).
3. The antibody-drug conjugate of any one of claims 1 or 2, wherein the humanized
15 antibody comprising a heavy chain comprising a variable region having an amino acid sequence at least about 95% identical to SEQ ID NO: 1.
4. The antibody-drug conjugate of any one of the preceding claims, wherein the humanized antibody comprising a light chain comprising a variable region having an amino acid sequence at least about 95% identical to SEQ ID NO: 2.
- 20 5. The antibody-drug conjugate of any one of the preceding claims, wherein the humanized antibody comprises a heavy chain comprising a variable region having an amino acid sequence set forth in SEQ ID NO: 1 and a light chain comprising a variable region having an amino acid sequence set forth in SEQ ID NO: 2.
- 25 6. The antibody-drug conjugate of any one of the preceding claims, wherein the humanized the humanized antibody or antigen binding portion thereof is a monoclonal antibody, Fab, F(ab)₂, a single-domain antibody, or a single chain variable fragment (scFv).
7. The antibody-drug conjugate of any one of the preceding claims, wherein the toxin is
30 selected from the group consisting of microtubule inhibitor, DNA synthesis inhibitor, topoisomerase inhibitor and RNA polymerase inhibitor.
8. The antibody-drug conjugate of any one of the preceding claims, wherein the toxin is auristatin or a derivative thereof.
9. The antibody-drug conjugate of claim 8, wherein the auristatin derivative is monomethyl auristatin E (MMAE) or monomethyl auristatin F (MMAF).

10. The antibody-drug conjugate of any one of claims 1 to 7, wherein the toxin is a maytansine derivative.
11. The antibody-drug conjugate of claim 10, wherein the maytansine derivative is DM4 or DM1.
- 5 12. The antibody-drug conjugate of any one of claims 1 to 7, wherein the toxin is quinoline alkaloid.
13. The antibody-drug conjugate of claim 12, wherein the quinoline alkaloid is SN-38.
14. The antibody-drug conjugate of any one of claims 1 to 7, wherein the toxin is selected from the group consisting of DM4, MMAE and SN-38.
- 10 15. The antibody-drug conjugate of any one of the preceding claims, wherein the antibody and the toxin are linked through a linker.
16. The antibody-drug conjugate of claim 15, wherein the linker is cleavable.
17. The antibody-drug conjugate of claim 16, wherein the cleavable linker is selected from the group consisting of an enzymatic cleavable linker, a pH-sensitive linker and a reducible linker.
- 15 18. The antibody-drug conjugate of claim 16, wherein the linker is selected from the group consisting of Maleimidocaproyl (MC), Maleimidocaproyl-Valine-Citrulline- p-amino-benzyloxycarbonyl (MC-VC-PAB), Maleimidomethyl cyclohexane-1-carboxylate (SMCC), N-succinimidyl-4-(2-pyridyldithio)butanoate (SPDB), Valine-Alanine (VA) and Lys-PAB-CO (Lysine- p-aminobenzyl -C=O).
- 20 19. The antibody-drug conjugate of any one of claims 1 to 7, wherein the conjugate comprises the toxin MMAE and the linker MC-VC-PAB (denoted herein NTX1088-MMAE).
20. The antibody-drug conjugate of any one of claims 1 to 7, wherein the conjugate comprises the toxin MMAF and the linker MC (denoted herein NTX1088-MMAF).
- 25 21. The antibody-drug conjugate of any one of claims 1 to 7, wherein the conjugate comprises the toxin DM1 and the linker SMCC (denoted herein NTX1088-DM1).
22. The antibody-drug conjugate of any one of claims 1 to 7, wherein the conjugate comprises the toxin DM4 and the linker SPDB (denoted herein NTX1088-DM4).
- 30 23. The antibody-drug conjugate of any one of claims 1 to 7, wherein the conjugate comprises the toxin SN38 and the linker Lys-PAB-CO (denoted herein NTX1088-SN38).
24. The antibody-drug conjugate of any one of claims 1 to 7, wherein the conjugate comprises the toxin Exatecan.

25. A pharmaceutical composition comprising the antibody-drug conjugate according to any one of the preceding claims and a pharmaceutically acceptable excipient, carrier, or diluent.
- 5 26. The pharmaceutical composition of claim 25, formulated for any one of injection, infusion, intravenous administration and/or intratumoral administration.
27. The pharmaceutical composition of claim 25, for use in therapy.
28. Use of the pharmaceutical composition of claim 25 or the antibody-drug conjugate of any one of claims 1 to 24 in the manufacture of a medicament for treating a cancer in an individual in need of such treatment, wherein the medicament is to be administered to the individual.
- 10 29. The use of claim 28, wherein at least one additional anti-cancer therapy is to be administered or performed.
30. The use of claim 29, wherein the additional anticancer therapy is surgery, chemotherapy, radiotherapy, or immunotherapy.
- 15 31. The use of claim 28, wherein an additional anti-cancer agent selected from the group consisting of immune-modulator, activated lymphocyte cell, kinase inhibitor and chemotherapeutic agent is to be administered.
32. The use of claim 28, wherein the cancer is a resistant or hard-to-treat cancer.
33. The use of any one of claims 28 or 32, wherein the cancer is resistant to chemotherapy or radiation.
- 20 34. The use of claim 28, wherein the cancer is selected from the group consisting of liver cancer, lung cancer, colon cancer, glioblastoma, adrenal cancer, uterine cancer, testis cancer, head and neck cancer, pancreatic cancer, and breast cancer.
35. The use of any one of claims 28 or 32, wherein the individual has become resistant to prior immune-oncology therapy, chemotherapy or radiation treatment.
- 25 36. A conjugate comprising a humanized anti-PVR antibody, or antigen binding portion thereof, conjugated to a detectable moiety, a radioactive moiety, or labeling tag, the antibody or antigen binding portion thereof comprises a heavy chain and a light chain, wherein the heavy chain comprises a variable region having an amino acid sequence at least about 90% identical to SEQ ID NO: 1, and wherein the light chain comprises a variable region having an amino acid sequence at least about 90% identical to SEQ ID NO: 2.
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37. A method of diagnosing or prognosing cancer in a subject, the method comprises determining the expression level of PVR in a biological sample of said subject using at least one conjugate according to claim 37.

5 38. An antibody-drug conjugate (ADC) comprising a humanized anti-PVR antibody conjugated to a toxin, for use in therapy, wherein the antibody comprises a heavy chain comprising a variable region having a sequence set forth in SEQ ID NO: 1, and a light chain comprising a variable region having a sequence set forth in SEQ ID NO: 2.

10 39. Use of an antibody-drug conjugate (ADC) comprising a humanized anti-PVR antibody conjugated to a toxin, in the manufacture of a medicament for treating a resistant or hard-to-treat cancer, wherein the antibody comprises a heavy chain comprising a variable region having a sequence set forth in SEQ ID NO: 1, and a light chain comprising a variable region having a sequence set forth in SEQ ID NO: 2.