

WHAT IS CLAIMED IS:

Claim 1. Use of a CD123 x CD3 bispecific molecule in the manufacture of a medicament for treating a chemo-refractory hematologic malignancy in a patient in need thereof, wherein:

(A) said CD123 x CD3 bispecific molecule is to be administered prior to and/or subsequent to an evaluation, via an *ex vivo* method, of:

(i) the expression of said one or more target gene(s), wherein said one or more target gene(s) comprise: CXCL9, CXCL10, CXCL11, and STAT1; and

(ii) the expression of one or more reference gene(s) which expression is not characteristically associated with said hematologic malignancy, wherein said one or more reference gene(s) comprise: ABCF1, G6PD, NRDE2, OAZ1, and POLR2; and

(B) said CD123 x CD3 bispecific molecule is to be administered at a dosage effective to stimulate the killing of cells of said hematologic malignancy in said patient;

wherein said CD123 x CD3 bispecific molecule is JNJ-63709178, XmAb14045 or APVO436, or is a covalently bonded bispecific diabody comprising:

(a) a first polypeptide chain having the amino acid sequence of **SEQ ID NO:21**; and

(b) a second polypeptide chain having the amino acid sequence of **SEQ ID NO:23**; and

wherein said first and second polypeptide chains are covalently bonded to one another by a disulfide bond.

Claim 2. The use of claim 1, wherein said evaluation comprises evaluating:

(i) the expression of said one or more target gene(s); and

(ii) the expression of one or more reference gene(s) which expression is not characteristically associated with said hematologic malignancy.

- Claim 3. The use of any one of claims 1-2, wherein said method comprises evaluating the expression of said one or more target genes relative to a baseline expression of said one or more reference genes of said patient.
- Claim 4. The use of any one of claims 1-3, wherein said method comprises evaluating the expression of said one or more target genes of said patient relative to the expression of said one or more target genes in a cellular sample(s) obtained from an individual who is suffering from said hematologic malignancy, or from a population of such individuals.
- Claim 5. The use of any one of claims 1-4, wherein a relative expression level of said one or more target genes in said population of individuals is established by averaging the gene expression levels in cellular samples obtained from said population of individuals.
- Claim 6. The use of any one of claims 1-5, wherein said cellular sample is a bone marrow sample.
- Claim 7. The use of any one of claims 1-6, wherein said evaluation of expression or said determination of whether said patient would be a suitable responder to the use of a CD123 x CD3 bispecific molecule to treat a hematologic malignancy comprises the steps of:
- (a) determining the expression level(s) for each of said one or more target gene(s) in one or more cellular sample(s) using a gene expression platform; and
 - (b) comparing said expression level(s) of each of said one or more target gene(s) to an expression level(s) of said one or more reference gene(s).
- Claim 8. The use of any one of claims 1-7, wherein said evaluation of expression or said determination of whether said patient would be a suitable responder to the use of a CD123 x CD3 bispecific molecule to treat a hematologic malignancy comprises the steps of:
- (a) measuring raw RNA levels for each of said one or more target gene(s) in one or more cellular sample(s) using a gene expression platform comprising a reference gene set of housekeeping genes; and

- (b) assigning a relative expression value for each of the measured raw RNA levels for each of said one or more target gene(s) using the measured RNA levels of internal reference genes.

Claim 9. The use of any one of claims 1-8, wherein said one or more target gene(s) additionally comprise:

- (a) one or more of: CCL5, CD27, CD274, CD276, CD8A, CMKLR1, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PDCD1LG2, PSMB10, STAT1, and TIGIT; and/or
- (b) one or more of: AREG, CSF3, CXCL1, CXCL2, CXCL3, CCL20, FOSL1, IER3 (NM_003897.4), IL6 and PTGS2; and/or
- (c) one or more of: CCL2, CCL3/L1, CCL4, CCL7 and CCL8; and/or
- (d) one or more of: MAGEA3/A6, MAGEA1, MAGEA12, MAGEA4, MAGEB2, MAGEC1 and MAGEC2; and/or
- (e) one or more of: APOL6, DTX3L, GBP1, IFI16, IFI27, IFI35, IFI6, IFIH1, IFIT1, IFIT2, IFIT3, IFITM1, IFITM2, IRF1, IRF9, ISG15, MX1, OAS1, OAS2, PARP9, PSMB9, STAT2, TMEM140 and TRIM21; and/or
- (f) one or more of: PSMB8, PSMB9 and PSMB10; and/or
- (g) IL-10; and/or
- (h) CD274; and/or
- (i) PDCD1LG2.

Claim 10. The use of any one of claims 1-9, wherein said one or more reference gene(s) additionally comprise one or more of: SDHA, STK11IP, TBC1D10B, TBP, and UBB.

Claim 11. The use of any one of claims 1-10, wherein a gene signature score is determined for said one or more target gene(s).

Claim 12. The use of claim 11, wherein said gene signature score is determined by a process comprising:

- (a) measuring raw RNA levels for each of said one or more target gene(s) in one or more cellular sample(s) using a gene expression platform comprising a reference gene set of housekeeping genes,

- (b) normalizing each of the measured raw RNA levels to a geometric mean of said housekeeping genes, and optionally further normalizing each RNA value to a standard,
- (c) log transforming each normalized RNA value,
- (d) multiplying each log transformed RNA value by a corresponding weight factor to generate a weighted RNA value, and
- (e) adding the weighted RNA values, and optionally adding an adjustment factor constant, to generate said gene signature score.

Claim 13. The use of any one of claims 11-12, wherein said gene signature score is determined using the target gene(s) provided in Table 6.

Claim 14. The use of any one of claims 11-13, wherein said gene signature score is determined for one or more of:

- (a) the IFN Gamma Signaling Signature;
- (b) the Tumor Inflammation Signature;
- (c) the Myeloid Inflammation Signature;
- (d) the Inflammatory Chemokine Signature;
- (e) the MAGEs Signature;
- (f) the IFN Downstream Signaling Signature;
- (g) the Immunoproteasome Signature;
- (h) the IL-10 Signature;
- (i) the PD-L1 Signature; and/or
- (j) the PD-L2 Signature.

Claim 15. The use of any one of claims 14, wherein said gene signature is the IFN Gamma Signaling Signature, the Tumor Inflammation Signature, or the IFN Downstream Signaling Signature.

Claim 16. The use of any one of claims 13-15, wherein a patient that exhibits a gene expression signature that is characteristic of an immune-enriched and IFN gamma-dominant tumor microenvironment is indicative of a favorable patient response to treatment with said CD123 x CD3 bispecific molecule.

Claim 17. The use of any one of claims 1-16, wherein said CD123 x CD3 bispecific molecule is said JNJ-63709178, XmAb14045 or APVO436.

- Claim 18. The use of any one of claims 1-16, wherein said CD123 x CD3 bispecific molecule is said covalently bonded bispecific diabody comprising:
- (a) a first polypeptide chain having the amino acid sequence of SEQ ID NO:21; and
 - (b) a second polypeptide chain having the amino acid sequence of SEQ ID NO:23; and
- wherein said first and second polypeptide chains are covalently bonded to one another by a disulfide bond.
- Claim 19. The use of any one of claims 1-18, wherein said hematologic malignancy of said patient is selected from the group consisting of: acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), blastic crisis of CML, Abelson oncogene-associated with CML (Bcr-ABL translocation), myelodysplastic syndrome (MDS), acute B lymphoblastic leukemia (B-ALL), acute T lymphoblastic leukemia (T-ALL), chronic lymphocytic leukemia (CLL), Richter's syndrome, Richter's transformation of CLL, hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), small lymphocytic lymphoma (SLL), Hodgkin's lymphoma, systemic mastocytosis, and Burkitt's lymphoma.
- Claim 20. The use of claim 19, wherein said hematologic malignancy of said patient is AML.
- Claim 21. The use of any one of claims 1-20, wherein said hematologic malignancy of said patient is refractory to chemotherapy.
- Claim 22. The use of any one of claims 1-21, wherein said CD123 x CD3 bispecific molecule is to be administered at a dosage of 30 ng/kg patient weight/day, 100 ng/kg patient weight/day, 300 ng/kg patient weight/day, or 500 ng/kg patient weight/day.
- Claim 23. The use of any one of claims 1-22, wherein said CD123 x CD3 bispecific molecule is to be administered by continuous infusion.
- Claim 24. The use of any one of claims 1-23, wherein said patient is a human patient.