

Claims

1. An antigen-binding molecule that specifically binds ALPPL2 and ALPP but not ALPL and ALPI, comprising:
 - a) a heavy chain variable region (V_H) comprising VHCDR1, VHCDR2 and VHCDR3 amino acid sequences; and
 - b) a light chain variable region (V_L) comprising VLCDR1, VLCDR2 and VLCDR3 amino acid sequences; wherein the combination of VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3 amino acid sequences are shown below:

	V_H	V_L
CDR1 CDR2 CDR3	FSFSSGYNIC (SEQ ID NO: 115) LIACIYTSSSGSTYY (SEQ ID NO: 116) RGEAYYAYGYVGYAYYHGAFDP (SEQ ID NO: 117)	HSISKYFS (SEQ ID NO: 118) LLIYEASTLAS (SEQ ID NO: 119) QSYYYGTSSSYA (SEQ ID NO: 120)
CDR1 CDR2 CDR3	FTISNNYWIC (SEQ ID NO: 1) WIGCIATGDGSTYY (SEQ ID NO: 2) RGAAGSSWTTYFDF (SEQ ID NO: 3)	QNIDNYLS (SEQ ID NO: 4) LLIYRASTLAS (SEQ ID NO: 5) QNNNGGSTFTGFP (SEQ ID NO: 6)
CDR1 CDR2 CDR3	FSFSSSYWIS (SEQ ID NO: 19) WIACIAIGSSGTYY (SEQ ID NO: 20) RSGDGYTYVEL (SEQ ID NO: 21)	QSISSYLA (SEQ ID NO: 22) LLIYRASTLAS (SEQ ID NO: 23) QNYDIDDSNT (SEQ ID NO: 24)
CDR1 CDR2 CDR3	FSFSSSYMC (SEQ ID NO: 37) WIACIYTTYGGTWY (SEQ ID NO: 38) RSSISDVTFNL (SEQ ID NO: 39)	QSISSNYLA (SEQ ID NO: 40) LLIYRASTLES (SEQ ID NO: 41) QSYDNNNYA (SEQ ID NO: 42)
CDR1 CDR2 CDR3	FSFSSYWTC (SEQ ID NO: 49) WLGCTDGGSSGDTYY (SEQ ID NO: 50) RNLITWDL (SEQ ID NO: 51)	ESVYNNNQLS (SEQ ID NO: 52) LLIYWASKLAS (SEQ ID NO: 53) AGYKSSITDGNA (SEQ ID NO: 54)
CDR1 CDR2 CDR3	FDFSSNGMC (SEQ ID NO: 91) WIACIYVDSSDNTNY (SEQ ID NO: 92) RGYGYVGSAMD (SEQ ID NO: 93)	QSISSNELS (SEQ ID NO: 94) LLIYGASTLES (SEQ ID NO: 95) QSAYYSSSSSYANT (SEQ ID NO: 96)
CDR1 CDR2 CDR3	FSFSSSYMC (SEQ ID NO: 181) WIACIYAGSTFSTYY (SEQ ID NO: 182) RSDSYTYGYAGYAYAIFNL (SEQ ID NO: 183)	ESIYSNLA (SEQ ID NO: 184) LLIYLASTLAS (SEQ ID NO: 185) QSAYYSSSADIA (SEQ ID NO: 186)

2. The antigen-binding molecule of claim 1, wherein the antigen-binding molecule specifically binds to ALPPL2 and ALPP or a cell expressing ALPPL2 or ALPP with an affinity of between about 14 pm to about 10 nM or wherein the antigen-binding molecule specifically binds to rhesus macaque ALPPL2/ALPP ortholog.
3. The antigen-binding molecule of claim 1, wherein the antigen-binding molecule comprises a) a heavy chain variable region (V_H) comprising SEQ ID NO: 115, SEQ ID NO: 116 and SEQ ID NO: 117; and b) a light chain variable region (V_L) comprising SEQ ID NO: 118, SEQ ID NO: 119 and SEQ ID NO: 120.
4. The antigen-binding molecule of claim 1, wherein the antigen-binding molecule comprises:
 - a) a V_H amino acid sequence having at least 90% (including at least 91% to 100% and all integer percentages therebetween) sequence identity to a V_H amino acid sequence as shown below, and
 - b) a V_L amino acid sequence having at least 90% sequence identity (including at least 91% to 100% and all integer percentages therebetween) to a V_L amino acid sequence as shown below:

	V _H	V _L
hC36	EVQLVESGGGLVQPGGSLRLSCAASG FSFSSGYNICWVRQAPGKGLE LIACIYTSSSGSTYYASWAKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCA RGEAYYAYGYVGYAYYHGAFDPWGQ GTLTVSS (SEQ ID NO: 291)	DIQMTQSPSSLSASVGDRVTITCQAS HSISKYFSWYQQKPGKVPK LLIYEASTLASGVPSRFSGSGSG TDFTLTISLQPEDVATYYC QSYYYGTSSSYAFGQGTKVEIK (SEQ ID NO: 292)
hC4	EVQLVESGGGLVQPGGSLRLSCAASG FTISNNYWICWVRQAPGKGLE WIGCIATGDGSTYYASWAKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCA RGAAGSSWTTYFDFWGQGTTLTVSS (SEQ ID NO: 281)	DIQMTQSPSSLSASVGDRVTITCQAG QNIDNYLSWYQQKPGKVPK LLIYRASTLASGVPSRFSGSGSG TDFTLTISLQPEDVATYYC QNNNGGSTFTGFPGQGTKVEIK (SEQ ID NO: 282)
hC12	EVQLVESGGGLVQPGGSLRLSCAASG FSFSSSYWISWVRQAPGKGLE WIACIAGSSGTTYASWAKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCA RSGDGYTYVELWGQGTTLTVSS	DIQMTQSPSSLSASVGDRVTITCQAS QSISSYLAWYQQKPGKVPK LLIYRASTLASGVPSRFSGSGSG TDFTLTISLQPEDVATYYC QNYDIDDSNTFGQGTKVEIK

	(SEQ ID NO: 283)	(SEQ ID NO: 284)
hC15	EVQLVESGGGLVQPGGSLRLSCAASG <u>FSFSSSYMCWVRQAPGKGLE</u> <u>WIACIYTTYGGTWYASWAKGRFTISRDN</u> SKNTLYLQMNSLRAEDTAVYYCA <u>RSSISDVTFNFWGQGTLVTVSS</u> (SEQ ID NO: 285)	DIQMTQSPSSLSASVGDRVTITCQAS <u>QSI SNYLA</u> WYQQKPGKVPK <u>LLIYRASTLES</u> GVPSRFSGSGSG TDFTLTISLQPEDVATYYC <u>QSYDNNNYA</u> FGQGGTKVEIK (SEQ ID NO: 286)
hC18	EVQLVESGGGLVQPGGSLRLSCAASG <u>FSFSSYWT</u> CWVRQAPGKGLE <u>WLGCTDGGSSGDTYYATWAKGRFTISRDN</u> SKNTLYLQMNSLRAEDTAVYYCA <u>RNLITWDL</u> WGQGTLVTVSS (SEQ ID NO: 287)	DIQMTQSPSSLSASVGDRVTITCQAS <u>ESVYNNNQ</u> LSWYQQKPGKVPK <u>LLIYWASKLAS</u> GVPSRFSGSGSG TDFTLTISLQPEDVATYYC <u>AGYKSSITD</u> GNAFGQGGTKVEIK (SEQ ID NO: 288)
hC31	EVQLVESGGGLVQPGGSLRLSCAASG <u>FD</u> FSSNGMCWVRQAPGKGLE <u>WIACIYVDSSDNTNYASWVNGRFTISRDN</u> SKNTLYLQMNSLRAEDTAVYYCA <u>RGYGYVGSAMD</u> LWGQGTLVTVSS (SEQ ID NO: 289)	DIQMTQSPSSLSASVGDRVTITCQAS <u>QSI SNEL</u> SWYQQKPGKVPK <u>LLIYGASTLES</u> GVPSRFSGSGSG TDFTLTISLQPEDVATYYC <u>QSAYYSSSSYANT</u> FGQGGTKVEIK (SEQ ID NO: 290)
hC131	EVQLVESGGGLVQPGGSLRLSCAASG <u>FSFSSSYMCWVRQAPGKGLE</u> <u>WIACIYAGSTFSTYYASWAKGRFTISRDN</u> SKNTLYLQMNSLRAEDTAVYYCA <u>RSDSYTYGYAGYAYAIFNL</u> WGQGTLVTVSS (SEQ ID NO: 293)	DIQMTQSPSSLSASVGDRVTITCQAS <u>ESIYSNL</u> AWYQQKPGKVPK <u>LLIYLASTLAS</u> GVPSRFSGSGSG TDFTLTISLQPEDVATYYC <u>QSAYYSSSADIA</u> FGQGGTKVEIK (SEQ ID NO: 294)

5. The antigen-binding molecule of claim 1, wherein the antigen-binding molecule comprises:

- a) a VH amino acid sequence having at least 90% (including at least 91% to 100% and all integer percentages therebetween) sequence identity to SEQ ID NO: 291, and
- b) a VL amino acid sequence having at least 90% sequence identity (including at least 91% to 100% and all integer percentages therebetween) to SEQ ID NO: 292.

6. The antigen binding molecule of claim 1, wherein the antigen-binding molecule is an antibody or antigen-binding fragment thereof or a chimeric antigen receptor (CAR), optionally wherein the antibody or antigen-binding fragment thereof is humanized or chimerized, or wherein the antibody or antigen-binding fragment thereof is a full-length antibody, a substantially intact antibody, a Fab fragment, scFab, Fab', a single chain variable fragment (scFv) or a one-armed antibody, or wherein the antibody is a bispecific or trispecific antibody.
7. The antigen-binding molecule of claim 6, wherein the antibody is a bispecific or trispecific antibody, optionally wherein the bispecific antibody comprises a first antigen-binding site that specifically binds ALPPL2 and a second antigen-binding site that specifically binds CD3.
8. A chimeric molecule comprising an antigen-binding molecule according to any one of claim 1 to 7 and a heterologous moiety.
9. The chimeric molecule of claim 8, wherein the heterologous moiety is a detectable moiety, a half-life extending moiety, or a therapeutic moiety, optionally wherein the therapeutic moiety is monomethyl auristatin F (MMAF) or monomethyl auristatin E (MMAE).
10. An isolated polynucleotide comprising a nucleic acid sequence encoding the antigen-binding molecule according to any one of claims 1 to 7.
11. A construct comprising a nucleic acid sequence encoding the antigen-binding molecule according to any one of claims 1 to 7 in operable connection with one or more control sequences.
12. A host cell that contains the construct of claim 11.
13. A pharmaceutical composition comprising the antigen-binding molecule according to any one of claims 1 to 7, or the chimeric molecule of claim 8 or 9, and a pharmaceutically acceptable carrier.
14. An antigen-binding molecule according to any one of claim 1 to 7 or a chimeric molecule of claim 8 or 9 for use in the treatment of cancer.

15. Use of an antigen-binding molecule according to any one of claims 1 to 7 or a chimeric molecule of claim 8 or 9 in the manufacture of a medicament for the treatment of cancer.
16. A kit for detecting cancer, the kit comprising an antigen-binding molecule according to any one of claims 1 to 7 or a chimeric molecule of claim 8 or 9.
17. A method of determining the likelihood of a cancer in a subject, wherein the method comprises detecting ALPPL2 in a sample obtained from the subject, wherein an increased level of ALPPL2 in the sample as compared to a reference indicates the likelihood of cancer in the subject.
18. The method of claim 17, wherein the method comprises detecting ALPPL2 with an antigen-binding molecule according to any one of claims 1 to 7 or a chimeric molecule of claim 8 or 9.
19. A method of identifying a subject who is likely to be responsive to treatment with an anti-ALPPL2 antibody, the method comprising detecting ALPPL2 in a sample obtained from the subject, wherein an increased level of ALPPL2 indicates that the subject is likely to be responsive to treatment with the ALPPL2 antibody.
20. The method of claim 19, wherein the method comprises detecting ALPPL2 with an antigen-binding molecule according to any one of claims 1 to 7 or a chimeric molecule of claim 8 or 9.