

and a cleaved IgC-type domain (Vogt L. et al., J Clin Invest. (2006) 116: 2817-2826; Helmy KY. et al., Cell (2006) 124: 915-927). VSIG4 is known to inhibit the alternative complement pathway of complement activity by binding to the subunit C3b of a convertase. Moreover, it is reported that, according to binding to an unknown T cell receptor, VSIG4 can inhibit the proliferation of CD4+ and CD8+ T cells. VSIG4 has been studied in relation with an occurrence of auto-immune and/or inflammatory disorders, as it was shown that a soluble VSIG4-Fc fusion protein seems to protect against the development of experimental autoimmune arthritis, uveoretinitis, and hepatitis (He et al., Mol. Immunol. (2008) Molecular Immunology 45(16): 4041-4047). However, it is also recently reported that the expression of VSIG4 is related to the regulation of anti-tumour immunity such as development of lung cancer and poor prognosis of high-grade glioma or the like (Liao Y. et al., Lab Invest. (2014) 94: 706-715; Xu T. et al., Am J Transl Res. (2015) 7: 1172-1180). Furthermore, according to the studies by Jung et al. (Hepatology (2012) 56 (5):1838-48), there is a difference in the binding site of VSIG4 between anti-inflammation and T cell inhibition.

Antibodies directed against VSIG4 have been previously described (see e.g., WO 2020/069507). However, these antibodies only bind one of the two forms of the protein, thereby mediating only partial inhibition of its activity.

Thus there is still a need to provide new anti-VSIG4 antibodies which can establish optimal anti-tumour immunity.

SUMMARY

In one aspect, provided herein is a monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, said antibody being selected in the group consisting of:

- a) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 3, 4 and 5 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 8;
- b) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 9, 10 and 5 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 8;

- 5 c) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 11, 12 and 13 and the three light-chain CDRs of sequences SEQ ID Nos. 14, 15 and 16;
- d) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 17, 18 and 19 and the three light-chain CDRs of sequences SEQ ID Nos. 20, 21 and 22;
- e) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 23, 24 and 3 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 25;
- 10 f) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 26, 27 and 28 and the three light-chain CDRs of sequences SEQ ID Nos. 29, 30 and 31;
- g) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 32, 33 and 34 and the three light-chain CDRs of sequences SEQ ID Nos. 35, 36 and 16;
- 15 h) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 37, 38 and 39 and the three light-chain CDRs of sequences SEQ ID Nos. 40, 41 and 42;
- i) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 43, 44 and 45 and the three light-chain CDRs of sequences SEQ ID Nos. 46, 47 and 48;
- 20 j) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 49, 50 and 51 and the three light-chain CDRs of sequences SEQ ID Nos. 52, 53 and 54;
- 25 k) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 17, 18 and 55 and the three light-chain CDRs of sequences SEQ ID Nos. 56, 57 and 58.

30 In another aspect, provided herein is an immunoconjugate comprising the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one as described herein, wherein said antibody is conjugated to a cytotoxic agent.

In another aspect, provided herein is a polynucleotide encoding a variable region of a light chain (VL) for the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one as described herein.

In another aspect, provided herein is a polynucleotide encoding a variable region of a heavy chain (VH) for the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one as described herein.

5 In another aspect, provided herein is a polynucleotide encoding a VL for the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one as described herein and a VH for the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one as described herein.

In another aspect, provided herein is an expression vector comprising:

- 10
- a polynucleotide as described herein;
 - a polynucleotide as described herein;
 - a polynucleotide as described herein and a polynucleotide as described herein;
 - or
 - a polynucleotide according to as described herein.

15 In another aspect, provided herein is a host cell transformed with the expression vector as described herein.

In another aspect, provided herein is a method of producing the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one as described herein comprising:

- 20
- a) culturing the host cell as described herein under suitable conditions and
 - b) recovering the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, from the culture medium or from the cultured cells.

25 In another aspect, provided herein is a pharmaceutical composition comprising the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one as described herein, or the immunoconjugate as described herein, and a pharmaceutical acceptable carrier and/or an excipient.

In another aspect, provided herein is the pharmaceutical composition of any one as described herein, for simultaneous, separate or sequential use.

30 In another aspect, provided herein is use of the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one as described herein, or the immunoconjugate as described herein, or the pharmaceutical composition of any one

as described herein, in the manufacture of a medicament for the treatment of a cancer in a patient.

5 In another aspect, provided herein is use of the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one as described herein, or the immunoconjugate as described herein, or the pharmaceutical composition of any one as described herein, in the manufacture of a medicament for inducing an immune response in a cancer patient.

In another aspect, provided herein is an in vitro method for detecting a VSIG4-expressing cancer in a subject, said method comprising the steps of:

10 a) contacting a biological sample of said subject with a monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one as described herein; and

b) detecting the binding of said reagent with said biological sample, wherein the binding of VSIG4 indicates the presence of a VSIG4-expressing cancer.

15 In another aspect, provided herein is the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of as described herein, or the immunoconjugate as described herein, or the pharmaceutical composition of any one as described herein for use in therapy.

DESCRIPTION OF THE INVENTION

20 OBJECTIVE

The object of the present disclosure is to provide a novel antibody for VSIG4, or an antigen-binding fragment thereof.

25 An additional, object of the present disclosure is thus to provide a composition for cancer treatment comprising with aforementioned antibodies or antigen-binding fragments.

TECHNICAL METHODS TO ACHIEVE THE ABOVE OBJECT

To achieve the above object, the present invention provides a monoclonal antibody specifically binding to VSIG4, or an antigen-binding fragment thereof. The antibody disclosed herein binds both the long and the short forms of VSIG4, leading to

efficient suppression of VSIG4-mediated anti-inflammatory signals. The anti-VSIG4 antibody disclosed herein thus activates an immune response in a patient in need thereof, thereby conferring protective anti-tumour immunity to the patient.

5 The present disclosure provides in particular an anti-VSIG4 monoclonal antibody, or an antigen-~~biding~~binding fragment thereof, having three heavy-chain CDRs and three light-chain CDRs, wherein the sequences of the CDRs are selected in the group of sequences set forth in SEQ ID NOs. 3-58. More specifically, the antibody disclosed herein comprises three heavy-chain CDRs and three light-chain CDRs as set forth in Table 2.

10 The present disclosure further provides an anti-VSIG4 monoclonal antibody, or an antigen-~~biding~~binding fragment thereof, comprising any one heavy chain variable region selected from the group consisting of the amino acid sequences of SEQ ID NOs: 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, and 149; and any one light chain variable region selected from the group consisting of the amino acid sequences of SEQ
15 ID NOs: 130,132, 134, 136, 138, 140, 142, 144, 146, 148, and 150, and an antigen-binding fragment of the monoclonal antibody.

In addition, the present invention further provides a polynucleotide encoding the heavy chain variable region and light chain variable region of the monoclonal antibody or an antigen-binding fragment thereof.

20 In addition, the present invention further provides an expression vector comprising the polynucleotide.

In addition, the present invention further provides a transformant transformed with the expression vector.

25 In addition, the present invention further provides a method for producing a monoclonal antibody specifically binding to VSIG4 or an antigen-binding fragment thereof by culturing the transformant.

In addition, the present invention further provides a composition for stimulating an immune response comprising as an effective ingredient a monoclonal antibody specifically binding to VSIG4, or an antigen-binding fragment thereof.

BE0001-2 clone OKT3) in the presence of recombinant proteins (hVSIG4(L)-Fc, hVSIG4(S)-Fc, PDL1-Fc (R&D Systems 156-B7) or an isotype control hIgG1 (c9G4)). CD4⁺ T cells proliferation (A) and IFN γ release (B) were determined by flow cytometry.

Fig. 3 is a diagram illustrating the method disclosed herein for screening the monoclonal antibody specifically binding to VSIG4.

Fig. 4 is a diagram illustrating the expression vector for VSIG4 antigen protein.

Fig. 5 shows the result of SDS-PAGE of purified VSIG4 antigen protein.

Fig. 6 shows the result of carrying out polyphage ELISA for testing the specificity of positive poly scFv-phage antibody pool, which has been obtained through the panning process of each round (i.e., first, second, and third round), for an antigen.

Fig. 7 shows the result of carrying out ELISA for selecting positive phages with excellent binding property for antigen VSIG4.

Fig. 8 shows the result of SDS-PAGE analysis of 11 recombinant VSIG4 single human antibodies.

Fig. 9 shows the result of FACS analysis of transformed cells overexpressing human VSIG4 by using anti-human VSIG4 antibody linked with an APC fluorescent material.

Fig. 10 shows the result of FACS analysis of the binding specificity of cells overexpressing human VSIG4 for 11 human VSIG4 antibodies. (A) HEK293E: Non specific binding test. (B) hVSIG4/HEK293E: Specific binding to cell surfaced VSIG4.

Fig. 11 illustrates the binding of the 11 human monoclonal anti-VSIG4 antibodies to hVSIG4(S) and hVSIG4(L). (A) Binding to hVSIG4(S) and hVSIG4(L) was assayed by ELISA with the original scFv versions of the 11 human anti-VSIG4 antibodies. (B) Binding to hVSIG4(S) and hVSIG4(L) was assayed by western blotting with the 11 full-length human anti-VSIG4 antibodies. NRH: Non-reduced, heated; RH: Reduced, heated.

Fig. 12 shows that murine m6H8 and its humanised version hz6H8-A2 bind to hVSIG4(L) but not hVSIG4(S). (A) Western blot: rechVSIG4: recombinant hVSIG4 (long and short); 264, 265 and 266: donors from whom PBMS were isolated. AF4646: polyclonal anti-VSIG4 antibody (R&D Systems, Minneapolis, MN, USA). (B) ELISA with

dose or at a different dose. The administration can be repeated once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times, or more. A therapeutically effective amount of anti-VSIG4 antibody or a conjugate thereof (optionally in combination with immune checkpoint inhibitors) can
 5 be administered as a single dose or over the course of a therapeutic regimen, *e.g.*, over the course of a week, two weeks, three weeks, one month, three months, six months, one year, or longer.

Methods of treatment

The ability of the present anti-VSIG4 antibodies to induce an immune response,
 10 *e.g.*, by promoting M2 macrophage differentiation and by inhibiting VSIG4-mediated immunosuppression, makes them useful for treating a variety of conditions mediated by VSIG4, including cancer. Therapeutic intervention on the VSIG4 inhibitory pathway thus represents a promising approach to modulate inflammation and T cell-mediated immunity for the treatment of a wide variety of cancers.

15 The anti-VSIG4 antibody, an antigen-binding fragment thereof, or conjugate, described herein may thus be used in methods for treating cancer, induce the release of pro-inflammatory cytokines by macrophages, induce CD4⁺ T cell proliferation, induce CD8⁺ T cell proliferation, induce CD4⁺ T cell cytokine production, and induce CD8⁺ T cell cytokine production, wherein said methods comprise administering an
 20 effective amount of an anti-VSIG4 antibody, an antigen-binding fragment thereof, or a conjugate to a subject in need thereof. The therapeutic methods described herein may comprise administration of the antibodies ~~bidingbinding~~ specifically VSIG4 described herein, or antigen-binding fragments thereof, or conjugates comprising these antibodies as disclosed herein, to a patient in need thereof. The VSIG4
 25 antibodies, antigen-binding fragments, and conjugates thereof, disclosed herein, are thus useful in regulating immunity, especially T cell immunity, for the treatment of cancer.

Accordingly, an aspect of the present disclosure relates to an anti-VSIG4
 30 antibody or antigen-~~bidingbinding~~ fragment thereof or conjugate thereof for use in the treatment of a cancer in a patient. Also provided herein is a method of treating cancer in a subject in need thereof, said method comprising the administration of an anti-VSIG4 antibody, an antigen-binding fragment thereof, or a conjugate disclosed herein to the patient. The present disclosure also relates to the use of an anti-VSIG4 antibody

or antigen-binding fragment thereof or conjugate thereof for making a medicament for treating a cancer.

In an embodiment, the disclosure relates to a composition comprising an anti-VSIG4 antibody disclosed herein, or an antigen-binding fragment or a conjugate thereof, for use in the treatment of a cancer in a patient. Also provided herein is a method of treating cancer in a subject in need thereof, said method comprising the administration of a composition comprising an anti-VSIG4 antibody disclosed herein, or an antigen-binding fragment or a conjugate thereof, to the patient. The present disclosure also relates to the use of a composition comprising an anti-VSIG4 antibody disclosed herein, or an antigen-binding fragment or a conjugate thereof, for making a medicament for treating a cancer.

In some embodiments, the cancer is selected from a bladder cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, oesophageal cancer, fallopian tube cancer, gall bladder cancer, gastrointestinal cancer, head-and-neck cancer, haematological cancer (e.g., leukaemia, lymphomas, or myelomas), laryngeal cancer, liver cancer, lung cancer, lymphoma, melanoma, mesothelioma, ovarian cancer, primary peritoneal cancer, salivary gland cancer, sarcoma, stomach cancer, thyroid cancer, pancreatic cancer, renal cell carcinoma, glioblastoma, and prostate cancer.

An embodiment provides an anti-VSIG4 antibody or antigen-binding fragment thereof or conjugate thereof for use in inducing an immune response in a cancer patient. Also provided herein is a method of inducing an immune response in a cancer patient in need thereof, said method comprising the administration of an anti-VSIG4 antibody, an antigen-binding fragment thereof, or a conjugate disclosed herein to the patient. The present disclosure also relates to the use of an anti-VSIG4 antibody or antigen-binding fragment thereof or conjugate thereof for making a medicament for inducing an immune response in a cancer patient.

In an embodiment, the disclosure relates to a composition comprising an anti-VSIG4 antibody disclosed herein, or an antigen-binding fragment or a conjugate thereof, for use in inducing an immune response in a cancer patient. Also provided herein is a method of an immune response in a cancer patient in need thereof, said method comprising the administration of a composition comprising an anti-VSIG4 antibody disclosed herein, or an antigen-binding fragment or a conjugate thereof, to the patient.

The present disclosure also relates to the use of a composition comprising an anti-VSIG4 antibody disclosed herein, or an antigen-binding fragment or a conjugate thereof, for making a medicament for inducing an immune response in a cancer patient.

5 The immune response thus generated by the antibody disclosed herein includes, without limitation, induction of pro-inflammatory cytokines release by macrophages, induction of CD4⁺ T cell proliferation, induction of CD8⁺ T cell proliferation, induction of CD4⁺ T cell cytokine production, and induction of CD8⁺ T cell cytokine production.

10 The anti-VSIG4 antibody, or antigen-binding fragment or conjugate thereof, may be admixed with additional chemotherapeutic agents, cytotoxic agent, antibodies, lymphokine, or hematopoietic growth factor. Notably, the therapeutic methods described herein may comprise the administration of an immune checkpoint inhibitor along with the anti-VSIG4 antibody, or antigen-binding fragment or conjugate thereof. The immune checkpoint inhibitor and the anti-VSIG4 antibody, or antigen-binding fragment or conjugate thereof may be administered simultaneously, separately, or sequentially.

15 As used herein, a “checkpoint inhibitor” refers to a molecule, such as e.g., a small molecule, a soluble receptor, or an antibody, which targets an immune checkpoint and blocks the function of said immune checkpoint. More specifically, a “checkpoint inhibitor” as used herein is a molecule, such as e.g., a small molecule, a soluble receptor, or an antibody, that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells.

20 In a first embodiment, the immune checkpoint inhibitor is an inhibitor of any one of CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4 (belongs to the CD2 family of molecules and is expressed on all NK, $\gamma\delta$, and memory CD8⁺ ($\alpha\beta$) T cells), CD160 (also referred to as BY55), CGEN-15049, CHK 1 and CHK2 kinases, 25 IDO1, A2aR and any of the various B-7 family ligands.

30 Exemplary immune checkpoint inhibitors include anti-CTLA-4 antibody (e.g., ipilimumab), anti-LAG-3 antibody (e.g., BMS-986016), anti-B7-H3 antibody, anti-B7-H4 antibody, anti-Tim3 antibody (e.g., TSR-022, MBG453), anti-BTLA antibody, anti-KIR antibody, anti-A2aR antibody, anti CD200 antibody, anti-PD-1 antibody (e.g., pembrolizumab, nivolumab, cemiplimab, pidilizumab), anti-PD-L1 antibody (e.g., atezolizumab, avelumab, durvalumab, BMS 936559), anti-VISTA antibody (e.g., JNJ

CLAIMS

- 1) A monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, said antibody being selected in the group consisting of:
- a) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 3, 4 and 5 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 8;
 - b) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 9, 10 and 5 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 8;
 - c) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 11, 12 and 13 and the three light-chain CDRs of sequences SEQ ID Nos. 14, 15 and 16;
 - d) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 17, 18 and 19 and the three light-chain CDRs of sequences SEQ ID Nos. 20, 21 and 22;
 - e) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 23, 24 and 3 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 25;
 - f) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 26, 27 and 28 and the three light-chain CDRs of sequences SEQ ID Nos. 29, 30 and 31;
 - g) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 32, 33 and 34 and the three light-chain CDRs of sequences SEQ ID Nos. 35, 36 and 16;
 - h) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 37, 38 and 39 and the three light-chain CDRs of sequences SEQ ID Nos. 40, 41 and 42;
 - i) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 43, 44 and 45 and the three light-chain CDRs of sequences SEQ ID Nos. 46, 47 and 48;
 - j) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 49, 50 and 51 and the three light-chain CDRs of sequences SEQ ID Nos. 52, 53 and 54;

k) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 17, 18 and 55 and the three light-chain CDRs of sequences SEQ ID Nos. 56, 57 and 58.

- 5 2) The monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, of **claim 1**, wherein the antibody is selected among single chain antibodies, camelised antibodies, chimeric antibodies, humanised antibodies, and human antibodies.
- 3) The monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, of any one of **claims 1 or 2**, wherein the antibody is a human antibody.
- 10 4) The monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, of any one of **claims 1 to 3**, wherein the antibody is selected among IgA1 antibodies, IgA2 antibodies, IgD antibodies, IgE antibodies, IgG1 antibodies, IgG2 antibodies, IgG3 antibodies, IgG4 antibodies and IgM antibodies.
- 15 5) The monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, of any one of **claims 1 to 3**, wherein the antigen-binding fragment is selected in the group consisting of Fab, Fab', (Fab')₂, Fv, scFv (sc for single chain), Bis-scFv, scFv-Fc fragments, Fab2, Fab3, minibodies, diabodies, triabodies, tetrabodies, and nanobodies.
- 6) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 5**, wherein said antigen-binding fragment is an scFv.
- 20 7) The monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, of any one of **claims 1 to 6**, wherein the antibody is selected in the group consisting of:
 - 25 a) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 129 or any sequence exhibiting at least 80% identity with SEQ ID No. 129 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 8;
 - b) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 131 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 131 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 8;
 - 30 c) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 133 or any sequence exhibiting at least 80%, 85%, 90%, 95%

- or 98% identity with SEQ ID No. 133 and the three light-chain CDRs of sequences SEQ ID Nos. 14, 15 and 16;
- 5 d) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 135 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 135 and the three light-chain CDRs of sequences SEQ ID Nos. 20, 21 and 22;
- 10 e) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 137 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 137 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 25;
- 15 f) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 139 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 139 and the three light-chain CDRs of sequences SEQ ID Nos. 29, 30 and 31;
- 20 g) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 141 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 141 and the three light-chain CDRs of sequences SEQ ID Nos. 35, 36 and 16;
- h) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 143 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 143 and the three light-chain CDRs of sequences SEQ ID Nos. 40, 41 and 42;
- 25 i) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 145 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 145 and the three light-chain CDRs of sequences SEQ ID Nos. 46, 47 and 48;
- 30 j) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 147 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 147 and the three light-chain CDRs of sequences SEQ ID Nos. 52, 53 and 54;
- k) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 149 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 149 and the three light-chain CDRs of sequences SEQ ID Nos. 56, 57 and 58.

- 8) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 6**, the antibody being selected in the group consisting of:
- a) an antibody comprising a light chain variable domain of sequence SEQ ID No. 130 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 130 and the three heavy-chain CDRs of sequences SEQ ID Nos. 3, 4, and 5;
 - b) an antibody comprising a light chain variable domain of sequence SEQ ID No. 132 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 132 and the three heavy-chain CDRs of sequences SEQ ID Nos. 9, 10, and 5;
 - c) an antibody comprising a light chain variable domain of sequence SEQ ID No. 134 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 134 and the three heavy-chain CDRs of sequences SEQ ID Nos. 11, 12, and 13;
 - d) an antibody comprising a light chain variable domain of sequence SEQ ID No. 136 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 136 and the three heavy-chain CDRs of sequences SEQ ID Nos. 17, 18, and 19;
 - e) an antibody comprising a light chain variable domain of sequence SEQ ID No. 138 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 138 and the three heavy-chain CDRs of sequences SEQ ID Nos. 23, 24 and 3;
 - f) an antibody comprising a light chain variable domain of sequence SEQ ID No. 140 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 140 and the three heavy-chain CDRs of sequences SEQ ID Nos. 26, 27 and 28;
 - g) an antibody comprising a light chain variable domain of sequence SEQ ID No. 142 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 142 and the three heavy-chain CDRs of sequences SEQ ID Nos. 32, 33 and 34;
 - h) an antibody comprising a light chain variable domain of sequence SEQ ID No. 144 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 144 and the three heavy-chain CDRs of sequences SEQ ID Nos. 37, 38 and 39;

- i) an antibody comprising a light chain variable domain of sequence SEQ ID No. 146 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 146 and the three heavy-chain CDRs of sequences SEQ ID Nos. 43, 44 and 45;
 - 5 j) an antibody comprising a light chain variable domain of sequence SEQ ID No. 148 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 148 and the three heavy-chain CDRs of sequences SEQ ID Nos. 49, 50 and 51; and
 - 10 k) an antibody comprising a light chain variable domain of sequence SEQ ID No. 150 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 150 and the three heavy-chain CDRs of sequences SEQ ID Nos. 17, 18 and 55.
- 9) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 8**, the antibody being selected in the group consisting of:
- 15 a) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 129 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 129 and a light chain variable domain of sequence SEQ ID No. 130 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 130;
 - 20 b) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 131 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 131 and a light chain variable domain of sequence SEQ ID No. 132 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID NO. 132;
 - 25 c) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 133 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 133 and a light chain variable domain of sequence SEQ ID No. 134 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 134;
 - 30 d) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 135 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 135 and a light chain variable domain of sequence SEQ ID No. 136 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 136;

- e) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 137 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 137 and a light chain variable domain of sequence SEQ ID No. 138 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 138;
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- f) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 139 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 139 and a light chain variable domain of sequence SEQ ID No. 140 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 140;
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- g) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 141 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 141 and a light chain variable domain of sequence SEQ ID No. 142 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID NO. 142;
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- h) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 143 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 143 and a light chain variable domain of sequence SEQ ID No. 144 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 144;
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- i) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 145 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 145 and a light chain variable domain of sequence SEQ ID No. 146 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 146;
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- j) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 147 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 147 and a light chain variable domain of sequence SEQ ID No. 148 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 148; and
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- k) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 149 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 149 and a light chain variable domain of sequence SEQ ID No. 150 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 150.
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- 10) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 9**, the antibody being an internalising antibody.
- 11) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 10**, the antibody being an antibody which binds to at least one amino acid in one or more epitope, the epitope being selected in the group consisting of:
- a) an epitope M1 comprising residues E24, V25, E27, V29, and/or T30 of the sequence set forth in SEQ ID No. 2;
 - b) an epitope M2 comprising residues D36, N38, L39, and/or T42 of the sequence set forth in SEQ ID No. 2;
 - c) an epitope M3 comprising residues Q59, G61, S62, D63, and/or V65 of the sequence set forth in SEQ ID No. 2;
 - d) an epitope M4 comprising residues I77, A80, Y82, and/or Q83 of the sequence set forth in SEQ ID No. 2;
 - e) an epitope M5 comprising residues H87, H90, K91, and/or V92 of the sequence set forth in SEQ ID No. 2;
 - f) an epitope M6 comprising residues S97, Q99, S101, and/or T102 of the sequence set forth in SEQ ID No. 2;
 - g) an epitope M7 comprising residues R108, S109, H110, T112, and/or E114 of the sequence set forth in SEQ ID No. 2;
 - h) an epitope M8 comprising residues T119, P120, D121, N123, Q124, and/or V125 of the sequence set forth in SEQ ID No. 2.
- 12) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of **claim 11**, wherein said antibody binds:
- a) at least one of the amino acids in M1;
 - b) at least one of the amino acids in M4, and optionally at least one of the residues of M3;
 - c) at least one of the amino acids in M7;
 - d) at least one of the amino acids in M8;
 - e) at least one of the amino acids in M7 and at least one of the amino acids in M8; or
 - f) at least one of the amino acids in M3, at least one of the amino acids in M7, and at least one of the amino acids in M8, and optionally at least one of the residues of M2 and/or at least one of the residues of M4.

- 13) An immunoconjugate comprising the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**, wherein said antibody is conjugated to a cytotoxic agent.
- 14) A polynucleotide encoding a variable region of a light chain (VL) for the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**.
- 15) A polynucleotide encoding a variable region of a heavy chain (VH) for the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**.
- 16) A polynucleotide encoding a VL for the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12** and a VH for the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**.
- 17) An expression vector comprising:
- a polynucleotide according to **claim 14**;
 - a polynucleotide according to **claim 15**;
 - a polynucleotide according to **claim 14** and a polynucleotide according to **claim 15**; or
 - a polynucleotide according to **claim 16**.
- 18) A host cell transformed with the expression vector of **claim 17**.
- 19) A method of producing the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12** comprising:
- a) culturing the host cell of **claim 18** under suitable conditions and
 - b) recovering the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, from the culture medium or from the cultured cells.
- 20) A pharmaceutical composition comprising the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**, or the immunoconjugate of **claim 13**, and a pharmaceutical acceptable carrier and/or an excipient.

- 21) The pharmaceutical composition of **claim 20**, further comprising an immune checkpoint inhibitor.
- 22) The pharmaceutical composition of **claim 21**, wherein said immune checkpoint inhibitor is an inhibitor of any one of CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD 160, CGEN-15049, CHK 1 and CHK2 kinases, IDO1, A2aR and any of the various B-7 family ligands.
- 23) The pharmaceutical composition of any one of **claims 20 or 21**, wherein said immune checkpoint inhibitor is selected in the group consisting of ipilimumab, pembrolizumab, nivolumab, cemiplimab, pidilizumab, atezolizumab, avelumab, durvalumab, BMS 936559, JNJ 61610588, urelumab, 9B12, PF-04518600, BMS-986016, TSR-022, MBG453, MEDI6469, MEDI6383, and epacadostat.
- 24) The pharmaceutical composition of any one of **claims 20 or 21**, for simultaneous, separate or sequential use.
- 25) Use of tThe monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**, or the immunoconjugate of **claim 13**, or the pharmaceutical composition of any one of **claims 20 to 24**, ~~for use~~ in the manufacture of a medicament for the treatment of a cancer in a patient.
- 26) Use of tThe monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**, or the immunoconjugate of **claim 13**, or the pharmaceutical composition of any one of **claims 20 to 24**, ~~for use~~ in the manufacture of a medicament for inducing an immune response in a cancer patient.
- 27) The ~~monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of claims 1 to 12, or the immunoconjugate of claim 13, or the pharmaceutical composition of any one of claims 20 to 24, for the use of claim 25~~, wherein the immune response includes induction of pro-inflammatory cytokines release by macrophages, induction of CD4⁺ T cell proliferation, induction of CD8⁺ T cell proliferation, induction of CD4⁺ T cell cytokine production, and induction of CD8⁺ T cell cytokine production.
- 28) The ~~monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of claims 1 to 12, or the immunoconjugate of claim 13, or the pharmaceutical~~

- ~~composition of any one of claims 20 to 24, for the~~ use of any one of **claims 25 to 27**, wherein the cancer is selected from bladder cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, oesophageal cancer, fallopian tube cancer, gall bladder cancer, gastrointestinal cancer, head-and-neck cancer, haematological cancer (e.g., leukaemia, lymphoma, or myeloma), laryngeal cancer, liver cancer, lung cancer, lymphoma, melanoma, mesothelioma, ovarian cancer, primary peritoneal cancer, salivary gland cancer, sarcoma, stomach cancer, thyroid cancer, pancreatic cancer, renal cell carcinoma, glioblastoma, and prostate cancer.
- 5
- 10 29) An *in vitro* method for detecting a VSIG4-expressing cancer in a subject, said method comprising the steps of:
- a) contacting a biological sample of said subject with a monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**; and
- 15 b) detecting the binding of said reagent with said biological sample,
- wherein the binding of VSIG4 indicates the presence of a VSIG4-expressing cancer.
- 30) The method of claim 29, wherein the monoclonal anti- VSIG4 antibody, or antigen-binding fragment thereof, is labelled with a detectable label.
- 20 31) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**, or the immunoconjugate of **claim 13**, or the pharmaceutical composition of any one of **claims 20 to 24** for use in therapy.