

TREATMENT OF HAEMATOLOGICAL CANCER

The present disclosure relates to a method of treating haematological cancers (including resistant forms thereof). Also provided are methods of treating aberrantly activated (or reactive) stroma, for example cancer stroma associated with haematological cancers, to change the status thereof, for example to render it/them less permissive to cancer cells and/or to reduce stroma generated resistance to treatment.

BACKGROUND

Cancers are associated with stroma “tissue” made up of infiltrating immune cells and stromal cells. At the early stages, a large number of immune effector cells typically infiltrate the tumour site in an attempt to detect and eliminate the tumour cells in a process known as immune surveillance.

However, as the cancer progresses not only does the tumour manage to evade the immune system, it also insidiously reprograms the function of the immune cells, effectively recruiting them to assist in creating a **tumour microenvironment** (TME) which is more favourable for tumour growth. For example, sustained activation of the NF- κ B pathway in tumour infiltrating leukocytes leads to increased and continued secretion of pro-inflammatory cytokines, which tumour cells make use of for their growth (i.e. pro-tumour cytokines).

As discussed in more detail below normal stroma cells become activated into **tumour associated stroma cells** (TASC). The latter help to create a tumour microenvironment (TME) by creating a “cocoon” of stroma supporting the cancer cells. Immune cells in the tumour microenvironment such as **cancer associated fibroblasts** (CAFs) have a fundamental role in creating this desmoplasia that drives tumour-promoting properties. TGF- β drives upregulation of tenascin-C, a wound healing protein, which is found in the extracellular matrix of the stroma and which has been correlated with a poor prognosis in a number of cancers.

Conceptually it is assumed that stroma is a phenomenon associated with solid tumours. However, surprisingly the present inventors have established support from stroma cells is also vital in haematological cancers.

Some groups have tried to target domains of tenascin C (such as the fibronectin type III repeats) with antibody drug conjugates, simply as a way of directing a toxin/radiolabel to a location near solid cancer cells, see The Journal of Nuclear Medicine Vol 46 No. 6 June 2005 page 1042 to 1051. However, simply delivering a toxin to the vicinity of the stroma provides little added therapeutic value to traditional chemotherapy because:

- traditional cancer therapies have low impact on stroma cells;

- the approach does not address the ability of stroma cells to support cancer cells; and

- the approach does not fundamentally change the tumour microenvironment.

What is more, chemotherapy, surgery and radiotherapy upregulate the expression of tenascin-C, which in turn may promote cancer recurrence. To date these tenascin C antibody drug conjugates have not been progressed to registration.

Tenascin-C has multiple biological functions and is expressed in low levels in normal tissue. Increased levels are found within aberrant stroma and as mentioned above is associated with poor patient prognosis and metastasis. Interestingly, tenascin-C may be upregulated in

tissue before obvious signs of metastasis occur, for example preparing the tissue to receive metastases.

At more advanced stages of cancer the stroma is a heterogenous matrix, which promotes tumour growth by providing energy, nutrients, physical protection, protection from immune cells, immune suppression, down regulation of MHC II, a low oxygen environment (hypoxia), resistance to radiation and resistance to cancer therapies, such as chemotherapeutics, signals for primary cancer cells to proliferate, anti-adhesion signals facilitating metastasis, increased angiogenesis, leaky vasculature and tracks in the stroma to allow escape of tumour cells and aid metastatic spread of disease. Many of the pro-cancer characteristics of the TME/stroma can be linked back to tenascin-C activity.

It has been suggested that tenascin C has a role to play in immune responses in the tumour, for example by promoting the M2 status (a tolerogenic state) of tumour associated macrophages and infiltration of the same into the tumour. Therapeutic monoclonal antibodies that blocked tenascin-C activation of Toll-like receptor 4 reversed this phenotypic switch *in vitro* and reduced tumour growth and lung metastasis *in vivo*, providing enhanced benefit in combination with anti-PD-L1 over either treatment alone.

A lot of work in the field of cancer has been based on stimulating the immune system to fight the cancer cells by activating immune cells within the microenvironment or to recruit active immune cells into the microenvironment. This is referred to as cancer immunotherapy. A number of checkpoint inhibitors (which block a signal that deactivates certain immune cells) have received marketing approval but it is becoming apparent that these therapies are only successful in a subcategory of patients and that other factors are at work.

In addition, cell-based therapies such as CAR-T therapies have been useful in treatment blood cancers (liquid cancers) but may be further improved when used in combination with the therapy according to the present disclosure.

The present inventors believe that the role of the stroma tissue and in particular stromal cells has been underestimated in the importance that they play in cancer. Traditionally it was considered an inert matrix but it is now becoming clear that stromal cells/stroma is/are a vital part of cancer in their own right. What is more there are a number of mechanisms at work in the stroma NOT just one. The stroma cells seem to be able to provide "protection" to the cancer cells. Like a fortified city the castle becomes more vulnerable once the protection provided by the city wall is breached. Like breaching a city wall the present disclosure is about turning one or more defensive mechanisms provided by the stroma and/or reprogramming the tumour microenvironment to be less permissive/supportive to cancer cells. Surprising this concept seems to also apply to haematological cancers.

Tumours have been described as a wound that simply does not heal. During normal wound healing processes, the local stromal cells change into reactive stroma after altering their phenotype. However, under certain conditions, tumour cells can convert these reactive (activated) stromal cells further and transition them into tumour-associated stromal cells (TASCs). The cross-talk between the host stroma and tumour cells is essential for tumour growth and progression.

Research is starting to emerge showing that cancer cells signal to stroma cells and *vice versa*. Whilst not wishing to be bound by theory, as the cancer cells are mutated they may not have all the support systems of a normal cell and may not produce all the “nutrients/components” they need to survive. Therefore the cancers cells may be more dependent on the stroma cells for viability than we realise. The stroma (including stromal cells) may pass nutrients, energy, enzymes, etc to the cancer cells. This process is extremely complicated and is not fully understood. Removal of this support and protection may render cancer cells less viable *per se* and/or sensitive to cancer therapy. Thus stroma cells have a vital function in the formation and the function of the tumour microenvironment. Furthermore, stroma (such as stromal cells) may send signals to the tumor cells to proliferate.

What is more, other cells for example immune cells, such as cancer activated fibroblasts (CAFs) and/or tumour associated macrophages (TAMs), also seem to communicate with the stroma cells and/or cancer cells making a communication loop.

Tenascin C is a soluble protein found in the stroma tissue and is secreted from one or more of the following cells, cancer cells, stroma cells and/or cancer supporting immune cells.

The data generated by the present inventors suggests that tenascin C has an important function in the cross-talk between at cancer cells and stroma cells and may also have an important role in the cross-talk between stroma cells and cancer immune cells and/or cancer cells and cancer immune cells.

The present inventors have established that stroma cells are NOT rendered less viable when treated with a functional antibody which is an inhibitor of the FBG domain of tenascin C and are also NOT necessarily affected by treatment with a cancer therapy, such as ventoclax.

Instead, when treated with the inhibitor of the FBG region, surprisingly these stroma cells have a change of status that renders them less supportive (such as unsupportive) to associated cancer cells and/or other diseased tissue. Interestingly, when the antibody is used as a monotherapy in co-cultures of stromal cells & cancer cells the cancer cells seem to be somewhat less viable after said treatment. Moreover, when a cancer treatment is introduced as a further treatment to said co-culture the cancer cells are significantly sensitized to the cancer treatment by the presence of the antibody BUT only when stroma present i.e. the effect is minimal when cancer cells are cultured in the absence of stroma cells.

Thus the antibody of the present disclosure seems to “block/inhibit” the essential cross-talk between the stroma cells and the cancer cells, for example thereby removing the cancer cells’ “life-line”, for example in the form of one or more of the following: communication, energy, nutrients, physical protection and the like (including properties described above).

Thus the antibody employed in the present disclosure seems to be a cross-talk inhibitor, blocking talk from the cancer cell to the stroma cells and/or from the stroma cell to the cancer.

What is more the antibody according to the present disclosure may also block cross-talk between the cancer cells and immune cells (and/or *vice versa*) and/or stroma cells and immune cells (and/or *vice versa*)

Whilst not wishing to be bound by theory this does not appear to be an immunotherapeutic effect in that it is not simply a specific signal to activate set of immune cells (or the inhibition of a blocking signal to immune cells) and seems a completely different method

of treating stroma cells to change their activation state to a less activated state, which is less supportive of cancer cells (and/or other diseased cells/tissue).

Alternatively or additionally the signaling of cancer cells to the stroma cells may be blocked. The stroma may provide a signal to cancer cells to proliferate. Inhibiting this signal may slow or inhibit cancer growth.

This function of the antibody can be used in the treatment of haematological cancer as a monotherapy and also as combination therapy, for example in that it allows active moieties (including from natural sources within the body)/cancer treatments into the cancer microenvironment and/or facilitates immune cells destroying the cancer.

The inventors believe treatment with the antibody according to the present disclosure **reduces** one or more of the following (for example in the in cancer microenvironment): remodeling/fibrosis, interstitial pressure, active transport of drugs out of the cancer microenvironment, autophagy, signaling between the stromal cells and cancer cells (and/or other cells as described above), transfer of nutrients to cancer cells, secretion of chemokines and/or cytokines that support the cancer metabolism and/or growth etc.

Inhibiting this cross-talk may also result in reduced signaling for primary haematological cancer cells to proliferate.

Thus the present invention may provide a means to reprogram the tumour microenvironment to be less pro-tumour, for example normalize it.

The present inventors believe that this inter-relationship between the haematological cancer cells and stroma cells is a basic mechanism of most cancers, for example based on the cancer perverting natural wound healing mechanisms Cancer Immunol Res. 2015 January; 3(1): 1-11. Thus, this method of treatment is a fundamentally new way of treating cancer for example by deactivating or neutralizing the stroma. It is likely to have broad applications in many cancers, in particular cancers that are hard-to-treat or resistant to existing cancer therapies.

Thus the present invention has broad application to the treatment of haematological cancers for example solid tumours and has particular application in hard to treat cancers, in particular those described herein.

Some groups of researchers have hypothesized that that bone stromal stem cells are mobilized and migrate to cancer microenvironments. Whilst not wishing to be bound by theory it may be that the cancer cells in the local tumour environment are in communication with stromal cells from bone marrow, for example stromal cells in the bone marrow may be activated or programmed to communicate/support the cancer even before leaving the bone marrow and/or in lymph nodes. The present therapy may be able to change this status. Thus this treatment may have a very profound impact on the treatment of cancer.

What is more there may be a negative feedback loop, which means that inhibition of tenascin C by the antibody may result in down regulation of expression of the tenascin-C in the disease tissue, for example leading to disease modification.

In additional treatment according to the present disclosure may reduce or minimize recurrence of cancer after treatment, and/or prolong remission.

SUMMARY OF THE DISCLOSURE

There is provided:

An antibody or antigen binding fragment inhibitor of the FBG region of tenascin C wherein the antibody or antigen binding fragment thereof binds the same epitope as the antibody with a VH of SEQ ID NO: 17 and a VL selected from SEQ ID NO: 8, 11, 28 or 29 (in particular 29) for use in treatment of is a haematological cancer, for example selected from myeloma, lymphoma, Leukaemia, chronic myeloproliferative disease, monoclonal gammopathy of uncertain significance, myelodysplastic syndrome, amyloidosis and plasmacytoma, e.g. CLL.

An antibody or antigen binding fragment for use according to claims 1, wherein the haematological cancer is lymphoma, for example selected from Hodgkin's lymphoma, and non-Hodgkin's lymphoma, in particular non-Hodgkin's lymphoma.

An antibody or antigen binding fragment for use according to claim 1 or 2, wherein the lymphoma is independently selected from anaplastic large cell lymphoma, angioimmunoblastic lymphoma, Burkitt lymphoma, Burkitt-like lymphoma, blastic NK-cell lymphoma, cutaneous T-cell lymphoma, diffuse large B-cell lymphoma, diffuse large B-cell lymphoma, lymphoblastic lymphoma, MALT lymphoma, mantle cell lymphoma, mediastinal large B-cell lymphoma, nodal marginal zone B-cell lymphoma, small lymphocytic lymphoma, thyroid lymphoma, follicular lymphoma, Waldenstrom's macroglobulinaemia and combinations thereof.

An antibody or antigen binding fragment for use according to any preceding claims, wherein the haematological cancer is a chronic myeloproliferative disease, for example selected from essential thrombocythaemia, chronic idiopathic myelofibrosis, and polycythaemia rubra vera.

An antibody or antigen binding fragment for use according to any preceding claims, wherein the haematological cancer is leukaemia, for example selected from AML (acute myeloid leukaemia), ALL (acute lymphoblastic leukaemia), CML (chronic myeloid leukaemia) and CLL (chronic lymphocytic leukaemia), small lymphocytic lymphoma (SLL) and combinations thereof.

An antibody or antigen binding fragment for use according to any preceding claim, wherein the leukaemia is selected from hairy cell leukaemia, acute lymphoblastic leukaemia, and chronic lymphoblastic leukaemia.

An antibody or antigen binding fragment for use according to any preceding claim wherein there is:

- a. neutralization of cancer associated stroma cells such that they have a reduced ability to support the viability of cancers associated therewith, and/or
- b. a reduction in activation state of cancer stroma cells (for example in tumour microenvironment) to render them less permissive to the cancer cell, such as cross-talk between the stroma cells and/or cancer cells and/or *vice versa* is inhibited;

A combination therapy comprising: an antibody or antigen binding fragment thereof which inhibits the FBG region of tenascin C and binds the same epitope as the antibody with a VH of SEQ ID NO: 17 and a VL selected from SEQ ID NO: 8, 11, 28 or 29; and a haematological cancer therapy, for example selected from a therapy disclosed herein such as immune cell therapy (such as CAR-T therapy).for example wherein cancer tissue penetration improved and/or resistance is minimised.

1. An antibody or antigen binding fragment thereof that binds an epitope in the Tenascin C FBG domain wherein the antibody comprises: a) a VH domain comprising SEQ ID NO: 1 for CDRH1, SEQ ID NO: 2 for CDRH2 and CDRH3 selected from SEQ ID NO: 3, 9, 12, 14, 16, 18, 20, 22 and 24 for; and b) a VL domain comprising SEQ ID NO: 5 for CDRL1, SEQ IN NO: 6 for CDRH2, and SEQ ID NO: 7 for use in treatment of cancer characterised in that the stroma cells are neutralized such that they have a reduced ability to support the viability of cancers associated therewith.
- 1A An antibody or antigen binding fragment thereof that binds an epitope in the Tenascin C FBG domain wherein the antibody comprises: a) a VH domain comprising SEQ ID NO: 1 for CDRH1, SEQ ID NO: 2 for CDRH2 and CDRH3 selected from SEQ ID NO: 3, 9, 12, 14, 16, 18, 20, 22 and 24 for; and b) a VL domain comprising SEQ ID NO: 5 for CDRL1, SEQ IN NO: 6 for CDRH2, and SEQ ID NO: 7 for use in treatment of cancer characterised in that the activation state of stroma cells in the tumour microenvironment is altered, to render them less permissive to the haematological cancer cell, for example cross-talk between the stroma cells and cancer cells and vice versa is inhibited.
- 1B An antibody or antigen binding fragment thereof that binds an epitope in the Tenascin C FBG domain wherein the antibody comprises: a) a VH domain comprising SEQ ID NO: 1 for CDRH1, SEQ ID NO: 2 for CDRH2 and CDRH3 selected from SEQ ID NO: 3, 9, 12, 14, 16, 18, 20, 22 and 24 for; and b) a VL domain comprising SEQ ID NO: 5 for CDRL1, SEQ IN NO: 6 for CDRH2, and SEQ ID NO: 7 for use in treatment of haematological cancer activated stroma cells, for example tumour associated stroma cells, in particular to change the status of the same.
- 1C An antibody or antigen binding fragment thereof that binds an epitope in the Tenascin C FBG domain wherein the antibody comprises: a) A VH domain comprising SEQ ID NO: 1 for CDRH1, SEQ ID NO: 2 for CDRH2 and CDRH3 selected from SEQ ID NO: 3, 9, 12, 14, 16, 18, 20, 22 and 24 for; and b) a VL domain comprising SEQ ID NO: 5 for CDRL1, SEQ IN NO: 6 for CDRH2, and SEQ ID NO: 7 for use in treatment to reverse haematological cancer resistance, for example resistance to a cancer treatment such as chemotherapy and/or radiotherapy.
- 1D A combination therapy comprising an antibody or antigen binding fragment thereof that binds an epitope in the Tenascin C FBG domain wherein the antibody comprises: a) a VH domain comprising SEQ ID NO: 1 for CDRH1, SEQ ID NO: 2 for CDRH2 and CDRH3 selected from SEQ ID NO: 3, 9, 12, 14, 16, 18, 20, 22 and 24 for; and b) a VL domain comprising SEQ ID NO: 5 for CDRL1, SEQ IN NO: 6 for CDRH2, and SEQ ID NO: 7; and a further haematological cancer medicament for use in treatment of cancer.
2. An antibody or antigen binding fragment for use according to any preceding paragraph wherein the antibody or fragment comprises 6 CDRs in a combination disclosed herein, such as in the sequence listing, which is set out in families. To the extent that information is lost in the sequence listing it is incorporated herein by reference to the priority documents, which set out the sequence in full.
3. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the VH is selected from SEQ ID NO: 4, 10, 13, 15, 17, 19, 21 and 23.

4. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein VH is/comprises SEQ ID NO: 4.
5. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein VH is/comprises SEQ ID NO: 10.
6. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein VH is/comprises SEQ ID NO: 13.
7. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein, VH is/comprises SEQ ID NO: 15.
8. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein VH is/comprises SEQ ID NO: 17.
9. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein VH is/comprises SEQ ID NO: 19.
10. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein VH is/comprises SEQ ID NO: 21.
11. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein VH is/comprises SEQ ID NO: 23.
12. An antibody or antigen binding fragment for use according to an preceding paragraph, wherein the VL is selected from 8, 11, 28 and 29.
13. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein VL is/comprises SEQ ID NO: 8.
14. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein VL is/comprises SEQ ID NO: 11.
15. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein VL is/comprise SEQ ID NO: 28.
16. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein VL is/comprise SEQ ID NO: 29.
17. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein stroma cell activated status is down regulated.
18. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the cancer cells (eg associated cancer cells) are less viable as a result of modulating the activity of the stroma cells, eg cancer cell are sensitized to cancer treatments.
19. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the haematological cancer cells (such as associated cancer cells) have a lower metabolic rate as a result of modulating the activity of the stroma cells, for example have one or more the following: reduce rate or replication, and/or have a reduced ability to repair damage (such damage to DNA for example caused by radiation and/or chemotherapy).
20. An antibody or antigen binding fragment for use according to any preceding paragraph wherein the stroma cell is a mesenchymal stromal cell.
21. An antibody or antigen binding fragment for use according to any preceding paragraph wherein the stromal cell selected from fibroblasts and pericytes.

22. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the stromal cell is a bone marrow stromal cell.
23. An antibody or antigen binding fragment for use according to any preceding paragraph wherein the stroma cell is located in adipose tissue, endometrium and/or synovial fluid.
24. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the stroma cell is a lymph node stroma, cell, for example selected from fibroblastic reticular cells, follicular dendritic cells, marginal reticular cells, lymphatic endothelial cells, high endothelial cells, alpha-7 integrin pericyte.
25. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the stromal cell is selected from a fibroblast, for example a cancer activated fibroblast, such as a carcinoma associated fibroblast (CAFs).
26. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the stromal cell cancer activity is down regulated, such as inhibited by treatment.
27. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein aberrant stromal cells activity (such as cancer activity) is selected from secretion of nitric oxide, factor-1 alpha, IL-6, IL-8, tenascin-C, matrix metalloproteinases, factor(s) that recruit pro-tumorigenic cells, and combinations thereof.
28. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the aberrant stromal cell activity (such as cancer activity) is secretion of a factor(s) that recruit pro-tumorigenic cells.
29. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the aberrant stromal cell activity (e.g cancer activity) is secretion of factor-1a.
30. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the aberrant stromal cell activity (such as cancer activity) is secretion of IL-6.
31. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the aberrant stromal cell activity (such as cancer activity) is secretion of IL-8.
32. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein aberrant stromal cell activity (such as cancer activity) is secretion of tenascin C (i.e. tenascin C levels are reduced by treatment).
33. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein, aberrant stromal cell activity (such as cancer activity) is secretion of matrix metalloproteinases.
34. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein aberrant stromal cell activity (such as cancer activity) is secretion of nitric oxide.
35. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein new blood vessel formation is reduced.
36. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein fibroblast infiltration is reduced.
37. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein immune cell infiltration is reduced.

38. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the stroma cells mesenchymal properties are down regulated (normalised) by the treatment.
39. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the haematological cancer microenvironment is modulated, for example selected from permeability increased, fibrosis reduced, remodelling reduced, metabolism levels reduced, hypoxia reduced, reduced interstitial pressure, reduced secretion of cytokines and/or chemokines that promote cancer survival/proliferation, reduced energy transfer to cancer cells, reduced "crosstalk", reduced nutrition transfer to cancer cells, reduced autophagy, reduced resistance and combinations of two or more of the same.
40. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39), wherein permeability of the haematological tumour is increase.
41. An antibody or antigen binding fragment for use according to any preceding paragraph (such as a paragraph 39 or 40), wherein fibrosis deposition (i.e. the process of fibrosis) is reduced or halted.
42. An antibody or antigen binding fragment for use according to any preceding paragraphs (such as 39 to 41), wherein the amount of deposited fibrosis is reduced (i.e. the ongoing process of fibrosis is reduced and/or absolute amounts of fibrosis).
43. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 42), wherein the process of cancer remodelling of tissue is reduced or eliminated.
44. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 43), wherein the rate of cancer metabolism is reduced, for example consumption of energy and/or nutrients, and/or the ability to repair DNA damage.
45. An antibody or antigen binding fragment for use according to any preceding paragraphs (such as 39 to 44), wherein the level of hypoxia is stabilised or reduced (for example normalised).
46. An antibody or antigen binding fragment for use according to any preceding paragraphs (such as 39 to 45), wherein interstitial pressure is stabilised or reduced (for example normalised).
47. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 46), wherein secretion of cytokines which support cancer cell viability (such as growth and/or persistence) are reduced.
48. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 47), wherein secretion of cytokines which generate a pro-cancer inflammatory state are reduced.
49. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 48), wherein secretion of cytokines which support ant-cancer activity are increased.
50. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 49), wherein secretion of one or more chemokines which support cancer cell viability (such as growth and/or persistence) is/are reduced.

51. An antibody or antigen binding fragment for use according to any preceding paragraphs (such as 39 to 50), wherein secretion of one or more chemokines which generate an anti-cancer inflammatory state is/are increased.
52. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 51), wherein there is reduced energy transfer to haematological cancer cells.
53. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 52), wherein there is reduced "crosstalk" to cancer cells and/or other cancer associated immune cells (such as cancer associated fibroblasts and/or cancer associated macrophage).
54. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 53), wherein there is reduced nutrition transfer to haematological cancer cells.
55. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 54), wherein there is reduced autophagy by the haematological tumour.
56. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 55), wherein there is reduced resistance to cancer treatment, for example chemotherapy and/or radiotherapy.
57. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 56), wherein there is reduced resistance to chemotherapy.
58. An antibody or antigen binding fragment for use according to any preceding paragraph (such as 39 to 58), wherein there is reduced resistance to radiotherapy.
59. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein neutralisation of immune cells by the tumour microenvironment is reduced, for example neutralisation T cells, is minimised (including native T cells and engineered T cells, such as CAR – T cells).
60. An antibody or antigen binding fragment thereof for use according to any preceding paragraph, wherein upregulation of one or more of VEGFA, FGF2, FGFR2, and PDGFRA on stromal cells is minimised.
61. An antibody or antigen binding fragment thereof for use according to any preceding paragraph, wherein the aberrant expression of PD-L1 by stromal cells is minimised.
62. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein cancer adherence, for example to stromal cells, is modulated for example reduced or increased, in particular increased.
63. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein GDNF upregulation is minimised (such as by stromal cells), for example in response to chemotherapy.
64. An antibody or antigen binding fragment, for use according to any preceding paragraph, wherein aberrant CYP3A4 activity is down regulated.
65. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein upregulation of $\beta 1$ integrin is minimised, for example in response to radiotherapy.

66. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein upregulation $\beta 1$ integrin is minimised in pancreatic stellate cells, for example in response to radiotherapy.
67. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein androgen receptor (AR) is not downregulated on stromal cells.
68. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the oestrogen receptor down regulation is minimised.
69. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the haematological cancer is hard-to-treat.
70. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the cancer is a liquid tumour.
71. An antibody or antigen binding fragment for use according to any preceding paragraph wherein the cancer is NOT a sarcoma.
72. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the cancer is resistant to existing haematological cancer therapy (including resistant to chemotherapy, radiation therapy).
73. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the cancer is metastatic.
74. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein metastasis or risk of metastasis is reduced.
75. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the number of viable cancer cells is reduced with treatment (for example actual number and/or relative number).
76. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the tumour mass or burden is reduced with treatment (for example the tumour shrinks).
77. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein survival of the treated patients increases, for example where the cancer is in remission i.e. cancer free survival.
78. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the patient is a human.
79. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the treatment is adjuvant therapy.
80. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the treatment is pre adjuvant therapy.
81. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein cancer cells are sensitized to treatment, for example treatment with a cancer therapy, such radiotherapy or chemotherapy.
82. An antibody or antigen binding fragment for use according to any preceding paragraph, wherein the antibody or fragment is linked to a payload, for example conjugated or linked as a fusion protein.

83. An antibody or antigen binding fragment for use according to paragraph 82, wherein the payload is therapeutic.
84. An antibody or antigen binding fragment for use according to paragraph 82 or 83, wherein the payload is a detectable label (such as a diagnostic), for example as disclosed herein.
85. An antibody or antigen binding fragment for use according to any one of paragraphs 82 to 84, wherein the payload is a chemotherapeutic agent, for example selected from temozolomide, epothilones, melphalan, carmustine, busulfan, lomustine, cyclophosphamide, dacarbazine, polifeprosan, ifosfamide, chlorambucil, mechlorethamine, busulfan, cyclophosphamide, carboplatin, cisplatin, oxaplatin, thiotepa, capecitabine, streptozocin, bicalutamide, flutamide, nilutamide, leuprolide acetate, doxorubicin (for example hydrochloride or liposomal doxorubicin hydrochloride, bleomycin sulfate, daunorubicin hydrochloride, dactinomycin, liposomal daunorubicin citrate, , epirubicin hydrochloride, idarubicin hydrochloride, mitomycin, valrubicin, anastrozole, toremifene citrate, cytarabine, fluorouracil, fludarabine, floxuridine, interferon α -2b, plicamycin, mercaptopurine, methotrexate, interferon α -2a, medroxyprogesterone acetate, estramustine phosphate sodium, estradiol, leuprolide acetate, megestrol acetate, octreotide acetate, deethylstilbestrol diphosphate, testolactone, goserelin acetate, etoposide phosphate, vincristine sulfate, etoposide, vinblastine, etoposide, vincristine sulfate, teniposide, trastuzumab, gemtuzumab, ozogamicin, rituximab, exemestane, irinotecan hydrochloride, asparaginase, gemcitabine hydrochloride, altretamine, topotecan hydrochloride, hydroxyurea, cladribine, mitotane, procarbazine hydrochloride, vinorelbine tartrate, pentostatin sodium, mitoxantrone, pegaspargase, denileukin diftitix, altretinoin, porfimer, bexarotene, paclitaxel, docetaxel, arsenic trioxide, tretinoin, and combinations of two or more of the same, such as FOLFOX, Xelox, FOLFIRI, FOLFIRINOX.
86. An antibody or antigen binding fragment for use according to any one of paragraphs 82 to 85, wherein the payload is selected from a therapeutic protein, including a receptor, a ligand, a binding domain, such as an antibody or binding fragment thereof; a drug (such as a small chemical entity), an radionuclide, a detectable label, for example a fluorescent label such as Alexa 350, DAPI, rhodamine green or Red; a radiolabel such as carbon-14 or tritium, an enzyme such as alkaline phosphatase or hydrogen peroxidase, or a ligand such as biotin or avidin.
87. An antibody or antigen binding fragment for use according to any one of paragraph 82 to 86, wherein the payload increases targeting/selectivity to the cancer/stroma.
88. An antibody or antigen binding fragment for use according to any preceding paragraph, which is fully human.
89. An antibody or antigen binding fragment for use according to any one of paragraphs 1 to 87, which is chimeric.
90. An antibody or antigen binding fragment for use according to any one of paragraphs 1 to 81, 88 or 89, wherein the antibody or fragment is not linked to a payload.
91. A polynucleotide encoding an antibody or antigen binding fragment as defined in any preceding paragraph, for use in the treatment of a haematological cancer:

- i. characterised in that the antibody or binding fragment neutralizes stroma cells (including TASCs) such that they have a reduced ability to support the viability of cancers associated therewith, and/or
 - ii. wherein the cancer is derived from stromal cells, such as sarcoma
92. A vector comprising a polynucleotide according to paragraph 91, for use according to any one of paragraphs 1 to 90.
 93. A cell, (for example a host cell or an immune cell, such as an engineered immune cell) comprising polynucleotide according to paragraph 91, or a vector according to paragraph 92, in particular for use in treatment according to the present disclosure.
 94. An oncolytic virus encoding an antibody or antigen binding fragment according to any one of paragraphs 1 to 103, for example for use in treatment according to the present disclosure.
 95. A combination therapy comprising an antibody or antigen binding fragment according to any one of paragraphs 1 to 90, a polynucleotide according to paragraph 91 a vector according to paragraph 92, a cell according to paragraph 93 or an oncolytic virus according to paragraph 94, and at least one further anti-cancer therapy.
 96. A combination therapy according to paragraph 95, wherein the therapy is a chemotherapy, for example selected from a chemotherapy selected from temozolomide, epothilones, melphalan, carmustine, busulfan, lomustine, cyclophosphamide, dacarbazine, polifeprosan, ifosfamide, chlorambucil, mechlorethamine, busulfan, cyclophosphamide, carboplatin, cisplatin, oxaplatin, thiotepa, capecitabine, streptozocin, bicalutamide, flutamide, nilutamide, leuprolide acetate, doxorubicin (for example hydrochloride or liposomal doxorubicin hydrochloride), bleomycin sulfate, daunorubicin hydrochloride, dactinomycin, liposomal daunorubicin citrate, , epirubicin hydrochloride, idarubicin hydrochloride, mitomycin, , valrubicin, anastrozole, toremifene citrate, cytarabine, fluorouracil, fludarabine, floxuridine, interferon α -2b, plicamycin, mercaptopurine, methotrexate, interferon α -2a, medroxyprogesterone acetate, estramustine phosphate sodium, estradiol, leuprolide acetate, megestrol acetate, octreotide acetate, deethylstilbestrol diphosphate, testolactone, goserelin acetate, etoposide phosphate, vincristine sulfate, etoposide, vinblastine, etoposide, vincristine sulfate, teniposide, trastuzumab, gemtuzumab ozogamicin, rituximab, exemestane, irinotecan hydrochloride, asparaginase, gemcitabine hydrochloride, altretamine, topotecan hydrochloride, hydroxyurea, cladribine, mitotane, procarbazine hydrochloride, vinorelbine tartrate, pemetrexate sodium, mitoxantrone, pegaspargase, denileukin diftitix, altretnoin, porfimer, bexarotene, paclitaxel, docetaxel, arsenic trioxide, tretinoin, and combinations of two or more of the same, such as FOLFOX, Xelox, FOLFIRI, FOLFIRINOX.
 97. A combination therapy according to paragraph 95 or 96, wherein the further cancer therapy is a biological medicine, for example selected from bevacizumab, trastuzumab, PD-1 inhibitor, PD-L1 inhibitor, bevacizumab, cetuximab, gemtuzumab ozogamicin, ibritumomab tiuxetan, ofatumumab, panitumumab, rituximab, tositumomab.

98. A combination therapy according to paragraph 97, wherein the further cancer therapy is a PD-1 or PD-L1 inhibitor, for example selected from nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, cemiplimab, dostalimab, retifanlimab
99. A combination therapy according to any one of paragraphs 95 to 98, wherein the further cancer therapy is selected from an anti-VEGF therapy, such as axitinib, bevacizumab, cabozantinib, lapatinib, Lenvatinib, pazopanib, ponatinib, ramucirumab, ranibizumab, regrafenib, sorafenib, sunitinib, vandetanib.
100. A combination therapy according to any one of paragraphs 95 to 99, wherein the further cancer therapy is belustine or temozolomide.
101. A combination therapy according to any one of paragraphs 95 to 100, wherein the further cancer therapy is tamoxifen.
102. A combination therapy according to any one of paragraphs 95 to 101, wherein the further cancer therapy is selected from venetoclax, navitoclax and obatoclax, in particular venetoclax.
103. A combination therapy according to any one of paragraphs 95 to 102, wherein the further cancer therapy is an inhibitor of periostin.
104. A combination therapy according to any one of paragraphs 95 to 103, wherein the further cancer therapy is engineered immune cells, such as a CAR-T therapy, for example selected from tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, idecabtagene vicleucel and ciltabtagene autoceucel.
105. A combination therapy according to paragraph 95, 96 and 99 to 104 wherein the further cancer therapy is NOT a PD-1 inhibitor nor a PD-L1 inhibitor (in particular not a PD-1 inhibitor for treatment of breast cancer).
106. A combination therapy according to any one of paragraphs 95 to 105 wherein the further cancer therapy is a PARP inhibitor, for example selected from talazoparib, veliparib, pamiparib, olaparib, rucaparib, veliparib, CEP 9722, E7016, iniparib, 3-aminobenzamide.
107. A combination therapy according to any one of paragraphs 95 to 106, wherein the further cancer therapy is selected from a DHOH inhibitor, a kinase inhibitor, an IDO inhibitor and/or an AhR inhibitor.
108. A combination therapy according to any one of paragraphs 95 to 107, wherein the therapy is selected from surgery, ablation and photo-dynamic therapy.
109. A combination therapy according to any one of paragraphs 95 to 108, wherein the further cancer therapy is a radiotherapy.
110. A combination therapy according to any one of paragraphs 99 to 109, wherein the further cancer therapy is an oncolytic virus, for example an oncolytic adenovirus.

References to "any preceding paragraph" includes unnumbered paragraphs.

In one embodiment the cancer is acute promyelocytic leukaemia.

In one embodiment the cancer is Blastic Plasmacytoid Dendritic Cell Neoplasm.

In one embodiment the cancer is NOT a solid cancer.

- 5 In one embodiment the therapy according to the present disclosure is employed in combination with a cancer immunotherapy.

In one embodiment inhibiting tenascin-C according to the present disclosure indirectly inhibits a receptor on a cancer cells, which as an integrin.

In one embodiment the patient has a pathology, for example cancer wherein one or more cell types express tenascin C.

- 5 In one embodiment the patient is identified as having a pathology expressing tenascin C before administration of a treatment according to the present disclosure, for a blood sample test showing tenascin-C in the serum, or tenascin C and tenascin-W.

In one embodiment the antibody or antigen binding fragment thereof is employed in combination with an approved therapy, and/or standard of care.

- 10 In one embodiment the present disclosure provides a method of treatment comprising administering a therapeutically effective amount of an antibody or antigen binding fragment according to the present disclosure.

In one embodiment the present disclosure provides an antibody or antigen binding fragment for use in the manufacture of a medicament disclosed herein.

15 DETAILED DISCLOSURE

Unless the context indicates otherwise tumour microenvironment as employed herein relates to the tumour microenvironment of haematological cancer but may also include solid tumours if there is metastasis.

- 20 Same epitope as employed herein refers to an antibody body that binds or overlaps with the binding the same amino acid residues as the referenced antibody, in particular such that there is an overlap in the function (in this instance inhibition) with the referenced antibody.

The epitope bound by the reference antibody is described in WO2018/060462, incorporated herein by reference.

- 25 Tumour associated stroma cell (TASCs) secrete increased levels of proteins and matrix metalloproteinases (MMPs), in comparison to non-reactive (non-activated) stroma cells.

In one embodiment the modulation in status of stromal cells reduces secretion/expression of pro-inflammatory cytokines.

In one embodiment the modulation in status of stromal cells reduce secretion/expression of pro- cancer cytokines.

- 30 TASCs may secrete one or more of: fibroblast activating protein, alpha smooth muscle actin, vascular endothelial growth factor (VEGF), stromal-derived factor-1 alpha, IL-6, IL-8, tenascin-C.

- In one embodiment when the TASCs is modulated expression/secretion of one or more these is reduced, for example two or more are reduced, such as fibroblast activating protein & alpha smooth muscle actin; fibroblast activating protein & VEGF; fibroblast activating protein & stromal-derived factor-1 alpha; fibroblast activating protein & IL-6; fibroblast activating protein & IL-8; fibroblast activating protein & tenascin C; alpha smooth muscle actin & VEGF; alpha smooth muscle actin & stromal-derived factor-1 alpha; alpha smooth muscle actin & IL-6; alpha smooth muscle actin & IL-8; alpha smooth muscle actin & tenascin C; VEGF & stromal-derived factor-1 alpha; VEGF & IL-6; VEGF & IL-8; VEGF & tenascin C; stromal-derived factor-1 alpha & IL-6; stromal-derived factor-1 alpha & IL-8; stromal-derived factor-1 alpha & tenascin C; IL-6 & IL-8; IL-6 & tenascin C; IL-8 & tenascin C; VEGF, IL-6 & IL-8; VEGF, IL-6 & tenascin C; VEGF,
- 35
40

IL-8 & tenascin C, IL-6, IL-8 & tenascin C; VEGF, IL-6, IL-8 & tenascin C, such as all are reduced/normalized.

In one embodiment treatment downregulates expression of tenascin C.

In one embodiment the modulation in status of stromal cells reduce
5 secretion/expression of CCL21 and/or CXCL12.

In one embodiment the present therapy is employed as a monotherapy.

In one embodiment the present therapy is employed as a combination therapy with a further cancer therapy, for example selected from a therapy described herein.

In one embodiment the present therapy is employed a pre-adjuvant therapy.

10 In one embodiment the present therapy is employed as adjuvant therapy.

In one aspect there is provided a method/use of treating activated stroma cells associated with a cancer, in particular TASCs, using an antibody or antigen binding fragment thereof.

In one aspect there is provided an antibody or antigen binding fragment thereof in the manufacture of a medicament for the treatment of activated stromal cells associated with cancer
15 cells, in particular TASCs.

In one embodiment treatment with the antibody according to the present disclosure blocks/inhibits cross-talk between stroma cells and immune cells in the TME, such as cancer associated fibroblasts and/or cancer associated macrophages.

20 In one embodiment treatment with the antibody according to the present disclosure block/inhibit cross-talk between cancer cells and immune cells in the TME, such as cancer associated fibroblasts and/or cancer associated macrophages.

In one embodiment treatment with the antibody according to the present also block/inhibits/reduces metastasis.

25 In one embodiment the method/use is useful in treatment of a cancer resistant to therapy, for example a cancer resistance to chemotherapy and/or radiation therapy.

In one embodiment the treatment according to the present disclosure is useful in a combination therapy, for example with a further anticancer agent.

30 In one embodiment the stroma cells are cancer stroma cells, for example co-located with cancer cells, in particular under the control of/activated by cancer cells. This may be evident by one or more of the following: a pro-inflammatory profile, secretion of high levels of cytokines (such as growth factors), MMPs, fibroblast activating protein and alpha-smooth muscle actin.

In one embodiment the cancer reduced viability in the context of the present disclosure is not due to the activation of immune cells i.e. is not an immunotherapeutic effect *per se*, although the immune system and cells may be better able to access and clear cancer cells once
35 the status of the stroma (such as TASC) is changed.

In one embodiment after treatment the cancer cells have an increased susceptibility to apoptosis.

In one embodiment after treatment the stromal cells viability remains unchanged.

40 In one embodiment of the present disclosure aberrant integrin signalling is down regulated, in particular in stromal cells.

In one embodiment the desmoplasia of stromal cells is downregulated by treatment.

In one embodiment fibrosis is downregulated by treatment, in particular in and/or around the TME.

In one embodiment stromal cells does not refer to cells, such as immune cells that have infiltrated the stroma.

5 In one embodiment treatment reduces cancer cell division.

In one embodiment the treatment reduces the rate of cancer metabolism.

In one embodiment the cytokines secreted from the stromal cells are reduced

In one embodiment the activation of stromal cells is not an effect on the status of tumour associated macrophages.

10 In one embodiment the stromal cell is a cancer activated fibroblast, for example signalling between a mesenchymal stroma cell and a cancer activated fibroblast is blocked/inhibited.

In one embodiment the stromal cell is a cancer activated myofibroblast.

In one embodiment the stromal cell is a activated fibroblast.

15 In one embodiment the stromal cell is a activated myofibroblast.

In one embodiment the carcinoma-associated fibroblasts phenotype is downregulated by treatment.

In one embodiment the stromal cell is not a cancer activated fibroblast and/or an activated fibroblast.

20 In one embodiment the stromal cell is not a cancer activated myofibroblast and/or an activated myofibroblast.

In one embodiment stromal cell refers to any cell in the cancer stroma, including immune cells that have infiltrated the same, in particular those cells that support the cancer.

25 In one embodiment stromal cell does not include immune cells and other cells that have infiltrated the stroma, for example refers to only mesenchymal stromal cells and cells with an stroma component (such as red blood cells), in particular only mesenchymal stromal cells.

In one embodiment the stroma is associated with a haematological cancer cell, such as a red blood cell.

In one embodiment the epithelial cancer is a carcinoma.

30 In one embodiment the cancer is an ovarian stromal tumour, for example disclosed herein.

In one embodiment the cancer therapy of the present disclosure is used in combination with a PARP inhibitor.

35 In one embodiment the therapy according to the present disclosure is used in combination with a further inhibitor of cancer stroma, for example wherein the target is stromal antigen selected from CD163, CD206, CD68, CD11c, CD11b, CD14, CSF1 receptor, CD15, CD33 and CD66b, fibroblast activation protein (FAP), TREM1, IGFBP7, FSP-1, platelet-derived growth factor- α receptor (PDGFR- α), platelet-derived growth factor- β receptor (PDGFR- β) and vimentin.

40 There appears to be at least nine aspects to the activity of Tenascin-C in cancer:

1. It is found at the invasive margin of the primary tumour
2. It has anti-adhesive properties and is involved in metastasis

3. It promotes angiogenesis
4. It is an immunomodulator
5. It helps to create immune suppression in the TME, including hypoxia from leaky vascular system, stiffness, pressure, secretion on pro-cancer cytokines
- 5 6. It participates in maintaining the TME
7. **It mediates cross-talking between cells to render them pro-tumourigenic**
8. It is involved in creating resistance to cancer therapies.
9. It may promote cancer cell proliferation

10 The treatment according to the present disclosure may improve one or more of the same, such as all of the above.

The C-terminal fibrinogen-like globe (FBG) domain of Tenascin C (TNC) is able to activate TLR4 on either macrophages or fibroblasts. TLR4 is a key component of the innate immune system and when activated stimulates the secretion of pro-inflammatory cytokines such as IL6, IL8, or TNF α .

15 Tenascin C activation of latent TGF β shows the potential involvement of tenascins in tumour immunomodulation.

Tenascin C is important for conferring cancer cell resistance to doxorubicin- and docetaxel-based neoadjuvant chemotherapy integrin β 1/ by activating the mTOR pathway. Moreover, a correlation of high tenascin C expression with tamoxifen resistance was identified

20 in a clinical study analyzing 1286 primary breast tumours by qPCR.

Unless the context indicates otherwise stroma and cancer stroma are used interchangeably herein to refer to network of connective tissue that builds up around cancer cells, in particular the tissue that encapsulates the cancer cell and/or tumour microenvironment (TME).

25 Thus, as employed herein stromal cell refers to a mesenchymal stromal cell and also cells that have a stromal component, such as red blood cells.

A mesenchymal stromal cell (MSC), is a type of non-haematopoietic adult stem cell that is found in various tissues throughout the body, including bone marrow and umbilical cord tissue. Stromal cells are multipotent and can differentiate into a variety of cell types, including

30 osteoblasts, chondrocytes, adipocytes, and myocytes, among others.

The International Society for Cellular Therapy has defined MSCs as cells that meet the following criteria: 1) The cells must adhere to plastic surfaces under standard tissue culture conditions; 2) The cells must express specific surface markers, including CD105, CD73, and CD90, while lacking expression of haematopoietic markers such as CD45, CD34, CD14, or

35 CD11b, CD79 α or CD19, and HLA-DR; and The cells must have the ability to differentiate into osteoblasts, adipocytes, and chondrocytes *in vitro*.

These criteria have been widely adopted in the field and are used to identify and characterize stromal cells in research and clinical applications.

40 Normally stromal cells are generated and are stored in the bone marrow until maturation and differentiation. They are located in the stroma and aid haematopoietic cells in forming the elements of the blood. While a majority are found in the bone marrow, stromal cells

can be found in a variety of different tissues as well. These can include adipose tissue, endometrium, synovial fluid, dental tissue.

MSCs are generally hypoinmunogenic and have trilineage differentiation capacity where they are able to adapt into osteoblast, chondrocytes, and adipocytes.

5 An activated cancer cell as employed herein refers to a cancer cell which exhibits one or more functions that promote tumorigenesis, for example by inducing the recruitment of regulatory CD4+ T cells (Tregs) which help to counteract other anti-tumour immune cells.

10 Activated stroma cell (also referred to herein as cancer activated stroma cells) as employed herein refers to a stromal cell which exhibits one or more functions that promote tumorigenesis, for example forming a scaffold to support the expansion of a tumour. In one embodiment the stroma cells is associated with a cancer cell (also referred to herein as a tumour associated stromal cell (TASC)).

15 In comparison to non-reactive stromal cells, TASCs secrete increased levels of proteins and matrix metalloproteinases (MMPs). These proteins include fibroblast activating protein and alpha-smooth muscle actin. Furthermore, TASCs secrete many pro-tumorigenic factors such as vascular endothelial growth factor (VEGF), stromal-derived factor-1 alpha, IL-6, IL-8, tenascin-C, and others.

20 Activation state of the stromal cells as employed herein refers to whether the stromal cell is activated (cancer activated) or in has a "normal" healthy status (also referred to herein as non-reactive).

Associated cancer cell as employed herein refers to a cancer cell in communication with one or more activated stromal cells, for example such that said cancer obtains a benefit from same, in particular improved viability.

25 Factors secreted by activated stromal cells, such as TASCs, recruit additional tumour and pro-tumorigenic cells. The cross-talk between the host stroma and tumour cells is essential for tumour growth and progression. Tumour stromal production exhibits similar qualities as normal wound repair such as new blood vessel formation, immune cell and fibroblast infiltration, and considerable remodelling of the extracellular matrix.

30 Additionally, the recruitment of local normal host stromal cells, such as bone marrow mesenchymal stromal cells, endothelial cells, and adipocytes, help create a conspicuously heterogeneous composition. Furthermore, these cells secrete an abundance of factors that help regulate tumour development. Potential targets for tumour-associated stromal cell recruitment have been identified in the following host tissue: bone marrow, connective tissue, adipose tissue, and blood vessels. Moreover, evidence suggests that tumour-associated stroma is a prerequisite for metastasis and tumour cell invasion. These are known to arise from at least six different origins: immune cells, macrophages, adipocytes, fibroblasts, pericytes, and bone marrow mesenchymal stromal cells. Furthermore, the tumour stroma is primarily composed of the basement membrane, fibroblasts, extracellular matrix, immune cells, and blood vessels. Typically, most host cells in the stroma are characterized by tumour-suppressive abilities. However, during malignancy, the stroma will undergo alterations to consequently incite growth, invasion, and metastasis. These changes include the formation of cancer-associated fibroblasts

(CAFs) which comprises a major portion of the reactive tissue stroma and plays a critical role in regulating tumour progression.

Certain types of skin cancers (basal cell carcinomas) cannot spread throughout the body because the cancer cells require nearby stromal cells to continue their division. The loss of these stromal growth factors when the cancer moves throughout the body prevents the cancer from invading other organs.

Cancer stroma (depending on the context may be referred to as simply stroma) is made up of the non-malignant cells, but can provide an extracellular matrix on which tumour cells can grow. Stromal cells may also limit T-cell proliferation via nitric oxide production, hindering immune capability.

There are several types of lymph node stromal cells, including fibroblastic reticular cells (FRCs), lymphatic endothelial cells (LECs), and blood endothelial cells (BECs). FRCs are the most abundant stromal cell type in lymph nodes and are involved in the organisation of the lymphoid tissue. They form a network of reticular fibres that provide a physical scaffold for the immune cells to interact with each other and with antigen-presenting cells.

In addition to their structural roles, lymph node stromal cells also play an important role in regulating the immune response. They express a variety of cytokines and chemokines that help to recruit immune cells to the lymph node and regulate their function. Lymph node stromal cells are also involved in the development of lymphoid tissue and the maintenance of immune cell populations.

Lymph node stromal cells are a group of non-haematopoietic cells that make up the structural framework of lymph nodes. They are an important component of the lymphoid tissue and play a critical role in regulating the immune response.

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Thus the functions of lymph node stromal cells include: creating an internal tissue scaffold for the support of haematopoietic cells; the release of small molecule chemical messengers that facilitate interactions between haematopoietic cells; the facilitation of the migration of haematopoietic cells; the presentation of antigens to immune cells at the initiation of the adaptive immune system; and the homeostasis of lymphocyte numbers.

Interactions between stromal and haematopoietic cells are important for the development of lymph nodes. Crosstalk LEC, lymphoid tissue inducer cells and mesenchymal stromal organizer cells initiate the formation of lymph nodes.

The stroma on red blood cells may be activated to serve/support cancer cells. Minimising and/or blocking activation of stroma on red blood cells may help to limit the ability to the cancer to signal and communicate beyond the local area.

5 The stroma of the haematopoietic tissues includes a number of diverse cell types, i.e., bone-lining cells and related capsular and trabecular structures, epithelial-reticular cells and other epithelial cells, reticular cells, macrophages, and antigen-presenting cells. These stromal cells possess a variety of mechanical and metabolic functions. They support and confine the haematopoietic tissues and their vasculature. They regulate the migrations of blood and haematopoietic cells. Stromal cells contribute to the microenvironment that induces the
10 differentiation of stem cells into the several blood-cell lines. The nature of the interactions of stromal and haematopoietic cells depends upon long- and short-range humoral factors, and upon such cell-surface compounds as immunoglobulins and major histocompatibility antigens. Blood cells themselves, as neutrophils and lymphocytes, play regulatory roles in haematopoiesis along with stromal cells. Moreover, certain stromal cells, such as macrophages, originate as
15 blood cells and have migratory phases. Distinctions between blood cells, their derivatives, and stromal cells may therefore be difficult to draw. Given the above the present inventors believe that the stroma of the haematopoietic tissues is intimately involved in the development of haematological cancers (Am J Anat 1984 Jul;170(3):447-63).

20 Whilst not wishing to be bound by theory by changing the activation state of stromal cells using the antibody or binding fragment thereof according to the present disclosure, it may also be possible to treat, minimise and/or block invasion of lymph nodes by cancer cells, for example lymph nodes local to the cancer. What is more lymph nodes may also be strategic in recruiting bone marrow stromal cells to support cancer.

25 In one embodiment there is provided the method/use of the present disclosure which minimises and/or blocks invasion of lymph nodes by cancer cells and/or early stages thereof.

In one embodiment there is provided the method/use of the present disclosure which, minimises and/or blocks bone stromal cells from supporting cancer.

Lymph node stromal cells can be grouped into six sub-populations, known by their expression of surface markers. The sub-populations include: fibroblastic reticular cells (FRCs);
30 follicular dendritic cells (FDCs); lymphatic endothelial cells (LECs); blood endothelial cells (BECs); alpha-7 integrin pericytes (AIPs); and double negative cells (DNCs).

The surface markers include: glycoprotein CD31 and glycoprotein podoplanin GP38. The different sub-populations are also known by their production of small molecules; where they are located; and their function. Most also express common markers such as desmin,
35 laminin, various subunits of integrins, vascular cell adhesion molecule 1 (VCAM-1) and mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1).

Fibroblastic reticular cells (FRCs) are located in the T cell zone of the cortex. FRCs produce collagen alpha-1(III) rich reticular fibres that form a dense network within the lymphoid tissue. These are connected by collagen XIV, small leucine-rich proteoglycans and
40 lysyl oxidase. The network of fibres supports and guides the movement of dendritic cells (DCs), T lymphocytes and B lymphocytes.[1] It also creates a porous molecular sieve in the lymph node.

The lymph carries chemokines (molecular chemical messengers) and antigens to the lymph node. At the lymph node, the lymph passes quickly through the reticular network to the T cell zone and the high endothelial venules. FRCs express chemokines such as CCL21 and CCL19 which assist the movement of T cells and dendritic cells with CCR7 receptors.

5 FRCs also produce components of extracellular matrix, such as ER-TR7, fibrillin, laminin, fibronectin and intracellular components such as desmin and α -actin smooth muscle that may influence the formation of the reticular fibre network. For example, the chemokine CCL21 attaches to the surface of the FRCs through collagen and glycosaminoglycan molecules.

FRCs express cytokine IL-7, a regulator of the survival of resting T lymphocytes.

10 **Follicular dendritic cells** (FDCs) are found in the centre of B lymphocyte follicles. They form a dense network of cellular filaments. They also express the Fc receptors, CD16, CD23 and CD32; the complement receptors CD21 and CD35 and complement components. The network of cellular filaments and receptors help the FDCs capture antigens as immune complexes and present them to other immune cells.

15 FDCs assist the development of the germinal centre via an interaction with B lymphocytes and helper T-lymphocytes. B lymphocytes proliferate and differentiate into plasma cells and memory cells. FDCs produce chemokine CXCL13 which promotes migration of B lymphocytes to the primary B cell follicle. B lymphocytes need a factor B cell activating factor (BAFF) for their survival, also produced by FDCs.

20 **Marginal reticular cells** (MRCs) form a layer of cells beneath the subcapsular sinuses. Via the reticular network, the MRCs bring antigens from the sub-capsular sinuses to the B cell follicles. MRCs express the molecule TRANCE (also known as RANKL), a type of tumour necrosis factor. They are one of organizer cells involved in the formation of the structure of lymph node during organogenesis. They express CXCL13 at the edges of B cell follicles.

25 **Lymphatic endothelial cells** (LECs) line lymphatic vessels. They express adhesion molecules, chemokine CCL21, and lymphatic vessel endothelial hyaluronan receptor-1 (LYVE1), a homologue of CD44. These molecules allow the entry of haematopoietic cells into the lymphatic vessels. During an inflammatory state, the numbers of adhesion molecules on the surfaces of LECs increase.

30 **High endothelial cells** (HECs) are specialized vascular endothelial cells. In the thymus, they line the high endothelial venules (HEVs) where lymphocytes originate. The HEVs of the lymph node express adhesion molecules like peripheral node addressin (PNAd) that are essential for the migration of naive T cells from the peripheral blood to the lymph node. In mouse lymph nodes the HECs also express the chemokine CCL21 which will bind its receptor CCR7 on the naive T-cell and enhance the migration.

35 **Alpha-7 integrin pericytes** (AIPs) express several types of integrin chains which generate heterodimers. Integrin chains allow integrin pericytes to interact with haematopoietic cells and promote their migration.

Fibroblast as employed herein includes a myofibroblast.

40 **A cancer-associated fibroblast** (CAF) (also known as tumour-associated fibroblast; carcinogenic- associated fibroblast; activated fibroblast) is a type of stromal cell within the tumour microenvironment. They are activated fibroblasts that have been reprogrammed by

cancer cells to promote tumour growth and progression, for example that promotes tumourigenic features by initiating the remodelling of the extracellular matrix or by secreting cytokines.

5 CAFs are heterogeneous and can be derived from different sources, including tissue fibroblasts, bone marrow-derived mesenchymal stem cells, and epithelial cells undergoing mesenchymal transition. CAFs are characterised by their expression of specific markers such as alpha-smooth muscle actin (α -SMA), fibroblast activation protein (FAP), and platelet-derived growth factor receptor beta (PDGFR β).

10 CAFs play a critical role in tumour progression by secreting extracellular matrix components, growth factors, and cytokines that promote tumour cell survival, proliferation, and invasion. CAFs also contribute to the immunosuppressive environment of the tumour by inhibiting immune cell function and promoting the recruitment of regulatory T cells.

The functions of these CAFs have been known to stimulate angiogenesis, supporting the formation of tumours and thus proliferation of cancer cell and metastasis.

15 These CAFs then go on to support tumour growth by secreting growth factors such as Vascular Endothelial Growth Factor (VEGF), Platelet Derived Growth Factor (PDGF) and Fibroblast Growth Factor (FGF) and other chemokines to stimulate angiogenesis and thus the growth of a tumour.

20 In addition to their role in tumour progression, CAFs have been implicated in resistance to cancer therapy. CAFs can interact with cancer cells and other stromal cells to promote drug resistance through various mechanisms.

CAFs are a complex and abundant cell type contribute to resistance to apoptosis.

25 In contrast normal fibroblasts aid in the production of components of the extracellular matrix such as collagens, fibres, glycosaminoglycans and glycoproteins and are therefore vital in tissue repair in wound healing.

CAFs however, are derived from either normal fibroblasts, pericytes, smooth muscle cells, fibrocytes or mesenchymal stem cells

30 Unless the context indicates otherwise, stromal antigen as employed herein is an "antigen" only found in stromal tissue or on stromal cells i.e. it does not include an "antigen" also present on cancer cells. Thus, antigens expressed on cancer cells and stromal cells are considered to be cancer antigens in the context of the present specification. Thus, stromal antigens may be presented on the surface of stromal cells (a cell located in the stroma) and/or on soluble molecules located in the stromal matrix.

35 In one embodiment the present therapy is used in combination with an antibody used to target cancer.

Antibodies that target cancer include: avelumab, bevacizumab, brentuximab, cemiplimab, cetuximab, daratumumab, dinutuximab, elotuzumab, enfortumab, gemtuzumab, ibritumomab, inotuzumab, ipilimumab, isatuximab, mogamulizumab, moxetumomab, necitumumab, nivolumab, obinutuzumab, ofatumumab, olaratumab, panitumumab, pembrolizumab, pertuzumab, polatuzumab, ramucirumab, rituximab, Sacituzumab, 40 tositumomab, trastuzumab, Fab-G8 & Fab-Hyb3 (which targets EADPTGHSY in MAGE A1); G2D12, & G3G4 (which target KTWGQYWQV in GP100); 1A9, 1C8, 1A11, 1A7 & G1 (which target

IMDQVPFSV in GP100); 2F1, 2B2, 2C5 & 2D1 (which target YLEPGPVT/A in GP100); GPA7 (which targets ITDQVPFSV); 4A9 & 4G9 (which targets ILAFLHWL in hTERT) 3H2 & 3G3 (which targets RLVDDFLLV in hTERT); 3M4E5 (which targets SLIMWITQC in NY-ESO-1); 7D4, 8A11, 2G12 & 9E6 (which target FLWGPRALV in MAGE3); RL4B/3.2G1 & 1B10 (which target GVLPALPQV in hCG β); 3F9 (which target TMTRVLQGV in hCG β); 1B8 (which targets KIFGSLAFL in Her2/Neu); CAG10 & CLA12 (which EAAGIGILTV in Melan-A/MARR-1); Fab-D2 (which targets FLRNFSML in TARP); I3.M3-2A6 (which targets LLGRNSFEV in p53); T1-116C, T1-29D & T1-84C (which targets RMPEAAPPV in p53); T2-108A & T2-2A, T2-116A (which target GLAPPQHLIRV in p53); T2A (which is specific to YMDGTMSQV in tyrosinase); RL6A (which is specific to YLLPAIVHI in p68); RL21A (which is specific to FLSELTQQL in MIF); 8FA (which is specific to VLQELNVTV in Proteinase 3); ESK1 F2, F3 & Clone45 (which are specific to RMFPNAPYL in WT1); #131 (which is specific to VLHDDLLEA in HA-1H) and Pr20 (which is specific to ALYVDSLFFL).

In combination with as employed herein refers to administrations in a combination therapy protocol where each component is administered separately, and also includes administrations of combinations in a mixture.

The methods/uses according to the present disclosure may also limit effects such as cancer cachexia.

CANCER

The presently claimed disclosure is useful in treating cancer including solid and liquid cancers.

In one embodiment the therapy according to the present disclosure is employed in combination with a cancer therapy such as chemotherapy and optionally other cancer therapies.

In one embodiment the therapy according to the present disclosure is employed in combination with at least as kinase inhibitor, for example selected from sorafenib and varlitinib, in particular for the treatment of cancer, such as liver and/or biliary tract cancer, in particular biliary tract cancer.

In one embodiment the therapy according to the present disclosure is employed in combination with at least a tyrosine kinase inhibitor, for example axitinib, dasatinib, erlotinib, imatinib, nilotinib, pazopanib, sunitinib.

In one embodiment the therapy according to the present disclosure is employed in combination with at least PI3K inhibitor.

In one embodiment the therapy according to the present disclosure is employed in combination with at least an AhR inhibitor.

In one embodiment the therapy according to the present disclosure is employed in combination with at least an IDO inhibitor, such as an IDO-1 inhibitor.

In one embodiment the therapy according to the present disclosure is used in combination with a PD-1 or PD-L1 inhibitor, such as atezolizumab and/or bevacizumab, for example in the treatment of a cancer disclosed herein, such as liver cancer, biliary tract cancer and/or pancreatic cancer, in particular liver cancer.

Chemotherapeutic agent and chemotherapy or cytotoxic agent are employed interchangeably herein unless the context indicates otherwise.

Chemotherapy as employed herein is intended to refer to specific antineoplastic chemical agents or drugs that are "selectively" destructive to malignant cells and tissues, for example alkylating agents, antimetabolites including thymidylate synthase inhibitors, anthracyclines, anti-microtubule agents including plant alkaloids, topoisomerase inhibitors, 5 parp inhibitors and other antitumour agents. Selectively in this context is used loosely because of course many of these agents have serious side effects.

The preferred dose may be chosen by the practitioner, based on the nature of the cancer being treated.

10 Examples of alkylating agents, which may be employed in the method of the present disclosure include an alkylating agent nitrogen mustards, nitrosoureas, tetrazines, aziridines, platins and derivatives, and non-classical alkylating agents.

Example a platinum containing chemotherapeutic agent (also referred to as platins), such as cisplatin, carboplatin, oxaliplatin, satraplatin, picoplatin, nedaplatin, triplatin and lipoplatin (a liposomal version of cisplatin), in particular cisplatin, carboplatin and oxaliplatin.

15 The dose for cisplatin ranges from about 20 to about 270 mg/m² depending on the exact cancer. Often the dose is in the range about 70 to about 100mg/m².

Nitrogen mustards include mechlorethamine, cyclophosphamide, melphalan, chlorambucil, ifosfamide and busulfan.

20 Nitrosoureas include N-Nitroso-N-methylurea (MNU), carmustine (BCNU), lomustine (CCNU) and semustine (MeCCNU), fotemustine and streptozotocin. Tetrazines include dacarbazine, mitozolomide and temozolomide.

Aziridines include thiotepa, mytomycin and diaziquone (AZQ).

25 Examples of antimetabolites, which may be employed in the method of the present disclosure, include anti-folates (for example methotrexate and pemetrexed), purine analogues (for example thiopurines, such as azathiopurine, mercaptopurine, thiopurine, fludarabine (including the phosphate form), pentostatin and cladribine), pyrimidine analogues (for example fluoropyrimidines, such as 5-fluorouracil and prodrugs thereof such as capecitabine [Xeloda®]), floxuridine, gemcitabine, cytarabine, decitabine, raltitrexed (tomudex) hydrochloride, cladribine and 6-azauracil.

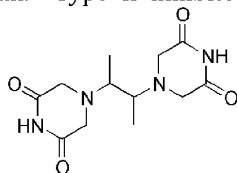
30 Examples of anthracyclines, which may be employed in the method of the present disclosure, include daunorubicin (Daunomycin), daunorubicin (liposomal), doxorubicin (Adriamycin), doxorubicin (liposomal), epirubicin, idarubicin, valrubicin currently used only to treat bladder cancer and mitoxantrone an anthracycline analog, in particular doxorubicin.

35 Examples of anti-microtubule agents, which may be employed in the method of the present disclosure, include vinca alkaloids and taxanes.

Vinca alkaloids include completely natural chemicals for example vincristine and vinblastine and also semi-synthetic vinca alkaloids, for example vinorelbine, vindesine, and vinflunine.

40 Taxanes include paclitaxel, docetaxel, abraxane, carbazitaxel and derivatives of thereof. Derivatives of taxanes as employed herein includes reformulations of taxanes like taxol, for example in a micelluar formulations, derivatives also include chemical derivatives wherein synthetic chemistry is employed to modify a starting material which is a taxane.

Topoisomerase inhibitors, which may be employed in a method of the present disclosure include type I topoisomerase inhibitors, type II topoisomerase inhibitors and type II topoisomerase poisons. Type I inhibitors include topotecan, irinotecan, indotecan and indimitecan. Type II inhibitors include genistein and ICRF 193 which has the following



5 structure:

Type II poisons include amsacrine, etoposide, etoposide phosphate, teniposide and doxorubicin and fluoroquinolones.

In one embodiment the chemotherapeutic is a PARP inhibitor, for example olaparib, niraparib, pamiparib, rucaparib, talazoparib, veliparib, CEP 9722, E7016, iniparib and 3-aminobenzamide (may be particularly useful in the treatment of pancreatic cancer), in particular olaparib, niraparib, rucaparib, talazoparib.

In one embodiment a combination of chemotherapeutic agents employed is, for example a platin and 5-FU or a prodrug thereof, for example cisplatin or oxaplatin and capecitabine or gemcitabine, such as FOLFOX.

15 In one embodiment the chemotherapy comprises a combination of chemotherapy agents, in particular cytotoxic chemotherapeutic agents.

In one embodiment the chemotherapy combination comprises a platin, such as cisplatin and fluorouracil or capecitabine.

20 In one embodiment the chemotherapy combination in capecitabine and oxaliplatin (Xelox).

In one embodiment the chemotherapy is a combination of folinic acid and 5-FU, optionally in combination with oxaliplatin.

In one embodiment the chemotherapy is a combination of folinic acid, 5-FU and irinotecan (FOLFIRI), optionally in combination with oxaliplatin (FOLFIRINOX). The regimen consists of: irinotecan (180 mg/m² IV over 90 minutes) concurrently with folinic acid (400 mg/m² [or 2 x 250 mg/m²] IV over 120 minutes); followed by fluorouracil (400–500 mg/m² IV bolus) then fluorouracil (2400–3000 mg/m² intravenous infusion over 46 hours). This cycle is typically repeated every two weeks. The dosages shown above may vary from cycle to cycle.

30 In one embodiment the chemotherapy combination employs a microtubule inhibitor, for example vincristine sulphate, epothilone A, N-[2-[(4-Hydroxyphenyl)amino]-3-pyridinyl]-4-methoxybenzenesulfonamide (ABT-751), a taxol derived chemotherapeutic agent, for example paclitaxel, abraxane, or docetaxel or a combination thereof.

In one embodiment the chemotherapy combination employs an mTor inhibitor. Examples of mTor inhibitors include: everolimus (RAD001), WYE-354, KU-0063794, papamycin (Sirolimus), Temsirolimus, Deforolimus (MK-8669), AZD8055 and BEZ235 (NVP-BEZ235).

In one embodiment the chemotherapy combination employs a MEK inhibitor. Examples of MEK inhibitors include: AS703026, CI-1040 (PD184352), AZD6244 (Selumetinib), PD318088, PD0325901, AZD8330, PD98059, U0126-EtOH, BIX 02189 or BIX 02188.

In one embodiment the chemotherapy combination employs an AKT inhibitor.
5 Examples of AKT inhibitors include: MK-2206 and AT7867.

In one embodiment the combination employs an aurora kinase inhibitor. Examples of aurora kinase inhibitors include: Aurora A Inhibitor I, VX-680, AZD1152-HQPA (Barasertib), SNS-314 Mesylate, PHA-680632, ZM-447439, CCT129202 and Hesperadin.

In one embodiment the chemotherapy combination employs a p38 inhibitor, for example
10 as disclosed in WO2010/038086, such as *N*-[4-({4-[3-(3-*tert*-Butyl-1-*p*-tolyl-1*H*-pyrazol-5-yl)ureido]naphthalen-1-yloxy)methyl}pyridin-2-yl]-2-methoxyacetamide.

In one embodiment the combination employs a Bcl-2 inhibitor. Examples of Bcl-2 inhibitors include: obatoclax mesylate, ABT-737, ABT-263 (navitoclax) and TW-37.

In one embodiment the chemotherapy combination comprises an antimetabolite such as
15 capecitabine (xeloda), fludarabine phosphate, fludarabine (fludara), decitabine, raltitrexed (tomudex), gemcitabine hydrochloride and cladribine.

In one embodiment the chemotherapy combination comprises ganciclovir, which may assist in controlling immune responses and/or tumour vasculature.

The following therapies are described in the context of the diseases they are currently
20 approved for, but these may be applied to other blood cancers in combination with the antibody or antigen binding fragment according to the present disclosure.

Lymphoma therapy for use in combination with the present invention include: acalabrutinib, axicabtagene ciloleucel, belinostat, bexarotene, bortezomib, brentuximab vedotin, brexucabtagene autoleucel, corpanlisib hydrochloride, crizotinib, denileukin diftitox,
25 duvelisib, epcoritamab-bysp, glofitamab-gxhm, ibritumomab tiuxetan, ibrutinib, loscabragene maraleucel, loncastuximab tesirine-lpyl, mogamulizumab-kpkc, mosumetuzumab-axgb, nivolumab, Obinutuzumab, pembrolizumab, pemigatinib, pirtobrutinib, polatuzumab vedotin-piiq, pralatrexate, rituximab, rituximab and hyaluronidase human, romidepsin, Selinexor, siltuximab, tafasitamab cxix, tazemetostat hydrobromide, tisagenlecleucel, venetoclax,
30 vorinostat, zanubrutinib.

ALL treatments for use in combination with the present invention include: Arranon (Nelarabine), Asparaginase Erwinia Chrysanthemi, Asparaginase Erwinia Chrysanthemi (Recombinant)-rywn, Asparlas (Calaspargase Pegol-mknl), Besponsa (Inotuzumab Ozogamicin), Blinatumomab, Blincyto, Calaspargase Pegol-mknl, Clofarabine, Clolar,
35 Cyclophosphamide, Cytarabine, Dasatinib, Daunorubicin Hydrochloride, Dexamethasone, Doxorubicin Hydrochloride, Erwinaze (Asparaginase Erwinia Chrysanthemi), Gleevec (Imatinib Mesylate), Iclusig (Ponatinib Hydrochloride), Inotuzumab Ozogamicin, Imatinib Mesylate, Kymriah (Tisagenlecleucel), Mercaptopurine, Methotrexate Sodium, Nelarabine, Oncaspar (Pegaspargase), Pemazyre (Pemigatinib), Pemigatinib, Pegaspargase, Ponatinib Hydrochloride,
40 Prednisone, Purinethol (Mercaptopurine), Purixan (Mercaptopurine), Rituxan (Rituximab), Rituximab, Rylaze (Asparaginase Erwinia Chrysanthemi [Recombinant]-rywn), Sprycel

(Dasatinib), Tisagenlecleucel, Trexall (Methotrexate Sodium), Vincristine Sulfate and Hyper-CVAD.

AML treatments for use in combination with the present invention include: Arsenic Trioxide, Azacitidine, Cyclophosphamide, Cytarabine, Daunorubicin Hydrochloride, 5 Daunorubicin Hydrochloride and Cytarabine Liposome, Daurismo (Glasdegib Maleate), Dexamethasone, Doxorubicin Hydrochloride, Enasidenib Mesylate, Gemtuzumab Ozogamicin, Gilteritinib Fumarate, Glasdegib Maleate, Idamycin PFS (Idarubicin Hydrochloride), Idarubicin Hydrochloride, Idhifa (Enasidenib Mesylate), Ivosidenib, Midostaurin, Mitoxantrone Hydrochloride, Mylotarg (Gemtuzumab Ozogamicin), Olutasidenib, Onureg (Azacitidine), 10 Pemazyre (Pemigatinib), Pemigatinib, Prednisone, Quizartinib Dihydrochloride, Rezlidhia (Olutasidenib), Rituxan (Rituximab), Rydapt (Midostaurin), Tabloid (Thioguanine), Thioguanine, Tibsovo (Ivosidenib), Tisagenlecleucel (Kymriah), Trisenox (Arsenic Trioxide), Vanflyta (Quizartinib Dihydrochloride), Venetoclax, Vincristine Sulfate, Vyxeos (Daunorubicin Hydrochloride and Cytarabine Liposome), Xospata (Gilteritinib Fumarate), and ADE.

15 **Blastic Plasmacytoid Dendritic Cell Neoplasm** for use in combination with the present invention include: Elzonris (Tagraxofusp-erzs) and Tagraxofusp-erzs.

Leukemia treatments for use in combination with the present invention include: acalabrutinib, alemtuzumab, asiminib hydrochloride, avapritinib, blinatumomab, bosutinib, brexucbtogene autoleucel, dasatinib, duvelisib, enasidenib mesylate, gemtuzumab ozogamicin, 20 gilteritinib fumerate, glasdegib maleate, ibrutinib, idelalisib, imatinib mesylate, inotuzumab ozogamicin, ivosidenib, midostaurin, moxetumomab pasudotox-tdfk, nilotinib, obinutuzumab, ofatumumab, pemigatinib, ponatinib, quizartinib, rituximab and hyaluronidase human, tagraxofusp-erzs, tisagenlecleucel, tretinoin, venetoclax and zanubrinib.

Hairy Cell Leukemia treatments for use in combination with the present invention 25 include: Cladribine, Intron A (Recombinant Interferon Alfa-2b), Moxetumomab Pasudotox-tdfk, and Recombinant Interferon Alfa-2b.

Mast Cell Leukemia treatments for use in combination with the present invention include: Midostaurin.

30 **Meningeal Leukemia** treatments for use in combination with the present invention include: Cytarabine.

Systemic mastocytosis for use in combination with the present invention include avapritinib, imatinib mesylate, midostaurin.

Multiple myeloma therapy for use in combination with the present invention includes bortezomib, carfilzomib, ciltacabtagene autoleucel, daratumumab, daratumumab and 35 hyaluronidate-fihj, elranatamab, elotuzumab, idecabtagene vicleucel, isatuximab-irfc, ixazomib citrate, talquetamab-tgvs, Selinexor, teclistamab-cqyv.

Myelodysplastic and myeloproliferative disorders for use in combination with the present invention include fedratinib, imatinib, momelotinib, pacritinib citrate, pemigatinib, 40 ruxolitinib.

CLL therapies for use in combination with the present invention include: Rituximab, ofatumumab, obinutuzumab, alemtuzumab (alone and in combination with chemotherapy) acalabrutinib, Zanubrutinib, ibrutinib, idelalisib, BCL2 inhibitors, tyrosine kinase inhibitors,

CAR-T therapies, Acalabrutinib, Alemtuzumab, Arzerra (Ofatumumab), Bendamustine Hydrochloride, Breyanzi (Lisocabtagene Maraleucel), Brukinsa (Zanubrutinib), Calquence (Acalabrutinib), Campath (Alemtuzumab), Chlorambucil, Copiktra (Duvelisib), Cyclophosphamide, Dexamethasone, Duvelisib, Fludarabine Phosphate, Gazyva (Obinutuzumab), Ibrutinib, Imbruvica (Ibrutinib), Jaypirca (Pirtobrutinib), Leukeran (Chlorambucil), Lisocabtagene Maraleucel, Obinutuzumab, Ofatumumab, Pirtobrutinib, Prednisone, Riabni (Rituximab), Rituxan Hycela (Rituximab and Hyaluronidase Human), Treanda (Bendamustine Hydrochloride), Venetoclax, Zanubrutinib, Zydelig (Idelalisib), CHLORAMBUCIL-PREDNISONE, and CVP.

10 LABELS

A label in accordance with the present disclosure is defined as any moiety which may be detected using an assay. Non-limiting examples of reporter molecules include enzymes, radiolabels, haptens, fluorescent labels, phosphorescent molecules, chemiluminescent molecules, chromophores, photoaffinity molecules, colored particles or ligands, such as biotin.

15 Label conjugates are generally preferred for use as diagnostic agents. Diagnostic agents generally fall within two classes, those for use in *in vitro* diagnostics, and those for use *in vivo* diagnostic protocols, generally known as “directed imaging.” Many appropriate imaging agents are known in the art, as are methods for their attachment to peptides and polypeptides (see, for *e.g.*, US 5,021,236, 4,938,948, and 4,472,509). The imaging moieties used can be paramagnetic ions, radioactive isotopes, fluorochromes, NMR-detectable substances, and X-ray imaging agents.

In the case of paramagnetic ions, one might mention by way of example ions such as chromium (III), manganese (II), iron (III), iron (II), cobalt (II), nickel (II), copper (II), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), vanadium (II), terbium (III), dysprosium (III), holmium (III) and/or erbium (III), with gadolinium being particularly preferred. Ions useful in other contexts, such as X-ray imaging, include but are not limited to lanthanum (III), gold (III), lead (II), and especially bismuth (III).

In the case of radioactive isotopes for therapeutic and/or diagnostic application, one might mention astatine²¹¹, ¹⁴carbon, ⁵¹chromium, ³⁶chlorine, ⁵⁷cobalt, ⁵⁸cobalt, copper⁶⁷, ¹⁵²Eu, gallium⁶⁷, ³hydrogen, iodine¹²³, iodine¹²⁵, iodine¹³¹, indium¹¹¹, ⁵⁹iron, ³²phosphorus, rhenium¹⁸⁶, rhenium¹⁸⁸, ⁷⁵selenium, ³⁵sulphur, technetium^{99m} and/or yttrium⁹⁰. ¹²⁵I is often being preferred for use in certain embodiments, and technetium^{99m} and/or indium¹¹¹ are also often preferred due to their low energy and suitability for long range detection. Radioactively labeled peptides and polypeptides may be produced according to well-known methods in the art. For instance polypeptides, such as antibodies, can be iodinated by contact with sodium and/or potassium iodide and a chemical oxidizing agent such as sodium hypochlorite, or an enzymatic oxidizing agent, such as lactoperoxidase. Polypeptides may be labeled with technetium^{99m} by ligand exchange process, for example, by reducing pertechnetate with stannous solution, chelating the reduced technetium onto a Sephadex column and applying the peptide to this column. Alternatively, direct labeling techniques may be used, *e.g.*, by incubating pertechnetate, a reducing agent such as SnCl_2 , a buffer solution such as sodium-potassium phthalate solution, and the peptide. Intermediary functional groups which are often used to bind radioisotopes which exist

as metallic ions to peptide are diethylenetriaminepentaacetic acid (DTPA) or ethylene diaminetetracetic acid (EDTA).

Among the fluorescent labels contemplated for use as conjugates include Alexa 350, Alexa 430, AMCA, BODIPY 630/650, BODIPY 650/665, BODIPY-FL, BODIPY-R6G, BODIPY-TMR, BODIPY-TRX, Cascade Blue, Cy3, Cy5,6-FAM, Fluorescein Isothiocyanate, HEX, 6-JOE, Oregon Green 488, Oregon Green 500, Oregon Green 514, Pacific Blue, REG, Rhodamine Green, Rhodamine Red, Renographin, ROX, TAMRA, TET, Tetramethylrhodamine, and/or Texas Red.

Another type of conjugate contemplated is that intended primarily for use *in vitro*, where the polypeptide is linked to a secondary binding ligand and/or to an enzyme (an enzyme tag) that will generate a colored product upon contact with a chromogenic substrate. Examples of suitable enzymes include urease, alkaline phosphatase, (horseradish) hydrogen peroxidase or glucose oxidase. Preferred secondary binding ligands are biotin and avidin and streptavidin compounds. The use of such labels is well known to those of skill in the art and is described, for example, in US 3,817,837, 3,850,752, 3,939,350, 3,996,345, 4,277,437, 4,275,149 and 4,366,241.

Other methods are known in the art for the attachment or conjugation of a peptide to its conjugate moiety. Some attachment methods involve the use of a metal chelate complex employing, for example, an organic chelating agent such a diethylenetriaminepentaacetic acid anhydride (DTPA); ethylenetriaminetetraacetic acid; N-chloro-p-toluenesulfonamide; and/or tetrachloro-3 α -6 α -diphenylglycouril-3 attached to the antibody (U.S. Patents 4,472,509 and 4,938,948). Peptides or polypeptides may also be reacted with an enzyme in the presence of a coupling agent such as glutaraldehyde or periodate. Conjugates with fluorescein markers are prepared in the presence of these coupling agents or by reaction with an isothiocyanate

"Is" as employed herein means comprising.

In the context of this specification "comprising" is to be interpreted as "including".

Embodiments of the invention comprising certain features/elements are also intended to extend to alternative embodiments "consisting" or "consisting essentially" of the relevant elements/features.

Where technically appropriate, embodiments of the invention may be combined.

Technical references such as patents and applications are incorporated herein by reference.

The technical backgrounds is part of the technical disclosure of the present specification and may be used as basis for amendments because the discussion therein is not limited to discussing the prior art as it also includes a discussion of the technical problems encountered in the field and the application of the present technology.

Any embodiments specifically and explicitly recited herein may form the basis of a disclaimer either alone or in combination with one or more further embodiments.

Specific values in the examples can be extracted from the examples and used in isolation from the other features therein as basis for amendment.

The present application claims from SG10202301006Y filed 11 April 2023, SG10202302846W filed 5 October 2023, and SG10202302916W filed 13 October 2023, each incorporated by reference. The disclosure therein can be used as basis for correction of the present specification. The background section contains technically relevant details may be used as basis for an amendment.

BRIEF DESCRIPTION OF FIGURES

- Figure 1** shows graphs comparing the viability of CLL tumour cells in the presence of C3* and optionally in the presence of venetoclax when bone marrow stroma cells were cultured alone or when co-cultured with CLL cells.
- 5 **Figure 2** shows a graph of the viability of CLL tumour cells when co-cultured with bone marrow stroma cells in the presence of C3* as a single agent.
- Figure 3A** shows a graph of the viability of CLL tumour cells when co-cultured with bone marrow stroma cells in the presence of C3* and Venetoclax at different concentrations.
- 10 **Figure 3B** shows a graph of the viability of CLL tumour cells when co-cultured with bone marrow stroma cells in the presence of Venetoclax at 2.5 nM or 5 nM in combination with C3* or control.

EXAMPLES

Example 1 Bone Stroma Cells Cultured alone or Co-cultured with CLL Cells optionally in presence of venetoclax

15 Bone marrow stromal cells (commercially available from Lonza) were plated 24 hours prior to the addition of chronic lymphocytic leukemia (CLL) cells. C3* SEQ ID NO;30 and 31 was added at specified concentrations and incubated for 2 hours prior to the addition of patient primary CLL cells.

20 The CLL cells were seeded in co-culture conditions and incubated for 24 hours with C3* at specified concentrations.

Venetoclax was added to specified conditions 24 hours later and incubated for 48 hours.

Viability was assessed using flow cytometric analysis of Annexin-V and DAPI staining.

The results are shown in Figure 1

25 **Example 2 Single Agent Experiment**

Bone marrow stromal cells were plated 24 hours prior to the addition of CLL cells. C3* was added at specified concentrations and incubated for 2 hours prior to the addition of patient primary CLL cells. The CLL cells were seeded in co-culture conditions and incubated for 72 hours with C3* at specified concentrations. Viability was assessed using flow cytometric analysis of Annexin-V and DAPI staining.

30

Results are shown in Figure 2.

Example 3 Long Term Experiment

Bone marrow stromal cells were plated 24 hours prior to the addition of CLL cells. C3* was added at 10µg/ml and incubated for 2 hours prior to the addition of patient primary CLL cells.

35 The CLL cells were seeded in co-culture conditions and incubated for 24 hours with C3* at specified concentrations. Venetoclax was added to specified conditions 24 hours later and incubated for 120 hours. Viability was assessed using flow cytometric analysis of Annexin-V and DAPI staining.

Results are shown in Figure 3.

40 **SEQUENCES are in the sequence listing which forms part of the specification**

Claims

1. An antibody or antigen binding fragment inhibitor of the FBG region of tenascin C wherein the antibody or antigen binding fragment thereof binds the same epitope as the antibody with a VH of SEQ ID NO: 17 and a VL selected from SEQ ID NO: 8, 11, 28 or 29 (in particular 29) for use in treatment of is a haematological cancer, e.g. selected from myeloma, lymphoma, Leukaemia, chronic myeloproliferative disease, monoclonal gammopathy of uncertain significance, myelodysplastic syndrome, amyloidosis and plasmacytoma.
2. An antibody or antigen binding fragment for use according to claims 1, wherein the haematological cancer is lymphoma, for example selected from Hodgkin's lymphoma, and non-Hodgkin's lymphoma, in particular non-Hodgkin's lymphoma.
3. An antibody or antigen binding fragment for use according to claim 1 or 2, wherein the lymphoma is independently selected from anaplastic large cell lymphoma, angioimmunoblastic lymphoma, Burkitt lymphoma, Burkitt-like lymphoma, blastic NK-cell lymphoma, cutaneous T-cell lymphoma, diffuse large B-cell lymphoma, diffuse large B-cell lymphoma, lymphoblastic lymphoma, MALT lymphoma, mantle cell lymphoma, mediastinal large B-cell lymphoma, nodal marginal zone B-cell lymphoma, small lymphocytic lymphoma, thyroid lymphoma, follicular lymphoma, Waldenstrom's macroglobulinaemia and combinations thereof.
4. An antibody or antigen binding fragment for use according to any preceding claims, wherein the haematological cancer is a chronic myeloproliferative disease, for example selected from essential thrombocythaemia, chronic idiopathic myelofibrosis, and polycythaemia rubra vera.
5. An antibody or antigen binding fragment for use according to any preceding claims, wherein the haematological cancer is leukaemia, for example selected from AML (acute myeloid leukaemia), ALL (acute lymphoblastic leukaemia), CML (chronic myeloid leukaemia) and CLL (chronic lymphocytic leukaemia), small lymphocytic lymphoma (SLL) and combinations thereof.
6. An antibody or antigen binding fragment for use according to any preceding claim, wherein the leukaemia is selected from hairy cell leukaemia, acute lymphoblastic leukaemia, and chronic lymphoblastic leukaemia.
7. An antibody or antigen binding fragment i for use according to any preceding claim wherein there is: a) neutralization of cancer associated stroma cells such that they have a reduced ability to support the viability of cancers associated therewith, and/or b) a reduction in activation state of cancer stroma cells (for example in tumour microenvironment) to render them less permissive to the cancer cell, such as cross-talk between the stroma cells and/or cancer cells and/or *vice versa* is inhibited.
8. An antibody or antigen binding fragment according to any preceding claim for use in treatment of cancer activated stroma cells to reprogram the tumour microenvironment to render it less pro-oncogenic (tumourigenic).
9. An antibody or antigen binding fragment according to any preceding claim for use in treatment of cancer to reverse/prevent cancer resistance, for example resistance to a cancer treatment such as chemotherapy, radiotherapy or a therapy disclosed herein.

10. An antibody or antigen binding fragment for use according to any preceding claim, wherein:
a) treated cancer are less viable, for example as a result of modulating the activity of cancer stroma cells; b) treated cancer cell are sensitized to cancer treatments, and/or c) treated cancer cells have a lower metabolic rate, e.g. a reduced rate of proliferation.
11. An antibody or antigen binding fragment for use according to any preceding claim wherein the stroma cell is a mesenchymal stromal cell, e.g. selected from fibroblasts and pericytes.
12. An antibody or antigen binding fragment for use according to any preceding claim, wherein the stromal cell is selected from: a) a bone marrow stromal cell; b) a lymph node stroma cell, e.g. selected from fibroblastic reticular cells, follicular dendritic cells, marginal reticular cells, lymphatic endothelial cells, high endothelial cells, alpha-7 integrin pericyte.
13. An antibody or antigen binding fragment for use according to any preceding claim wherein the stromal cell is selected from a fibroblast, for example a cancer activated fibroblast, such as a carcinoma associated fibroblast (CAFs).
14. An antibody or antigen binding fragment for use according to any preceding claim, wherein the stromal cell cancer activity is down regulated, such as inhibited by treatment, for example inhibition of secretion of nitric oxide, factor-1 alpha, IL-6, IL-8, tenascin-C, matrix metalloproteinases, factor(s) that recruit pro-tumourigenic cells, matrix metalloproteinases and combinations thereof.
15. An antibody or antigen binding fragment for use according to any preceding claims, wherein the stroma cells mesenchymal properties are down regulated (normalised) by the treatment.
16. An antibody or antigen binding fragment for use according to any preceding claim, wherein the cancer microenvironment is modulated, for example selected from permeability increased, fibrosis reduced, remodelling reduced, metabolism levels reduced, hypoxia reduced, reduced interstitial pressure, reduced secretion of cytokines and/or chemokines that promote cancer survival/proliferation, reduced energy transfer to cancer cells, reduced "crosstalk", reduced nutrition transfer to cancer cells, reduced autophagy, reduced resistance and combinations of two or more of the same.
17. An antibody or antigen binding fragment for use according to any preceding claim, wherein secretion of chemokines which support cancer cell viability (such as growth and/or persistence) are reduced.
18. An antibody or antigen binding fragment for use according to any preceding claim, wherein secretion of chemokines which generate an anti-cancer inflammatory state are increased.
19. An antibody or antigen binding fragment for use according to any preceding, wherein there is reduced autophagy by the tumour.
20. An antibody or antigen binding fragment for use according to any preceding claim, wherein neutralisation of immune cells by the tumour microenvironment is reduced, for example neutralisation T cells, is minimised (including native T cells and engineered T cells, such as CAR – T cells).
21. An antibody or antigen binding fragment for use according to any preceding claim, wherein upregulation of $\beta 1$ integrin is minimised, for example in response to radiotherapy.

22. An antibody or antigen binding fragment for use according to any preceding claim, wherein survival of the treated patients increases, for example where the cancer is in remission i.e. cancer free survival.
23. A combination therapy comprising: an antibody or antigen binding fragment thereof which inhibits the FBG region of tenascin C and binds the same epitope as the antibody with a VH of SEQ ID NO: 17 and a VL selected from SEQ ID NO: 8, 11, 28 or 29; and a haematological cancer therapy, for example selected from a therapy disclosed herein such as immune cell therapy (such as CAR-T therapy).
24. A combination therapy according to preceding claim 23, wherein the therapy is: a) **a chemotherapy**, for example selected from a chemotherapy selected from temozolomide, epothilones, melphalan, carmustine, busulfan, lomustine, cyclophosphamide, dacarbazine, polifeprosan, ifosfamide, chlorambucil, mechlorethamine, busulfan, cyclophosphamide, carboplatin, cisplatin, oxaplatin, thiotepa, capecitabine, streptozocin, bicalutamide, flutamide, nilutamide, leuprolide acetate, doxorubicin (for example hydrochloride or liposomal doxorubicin hydrochloride), bleomycin sulfate, daunorubicin hydrochloride, dactinomycin, liposomal daunorubicin citrate, , epirubicin hydrochloride, idarubicin hydrochloride, mitomycin, , valrubicin, anastrozole, toremifene citrate, cytarabine, fluorouracil, fludarabine, floxuridine, interferon α -2b, plicamycin, mercaptopurine, methotrexate, interferon α -2a, medroxyprogesterone acetate, estramustine phosphate sodium, estradiol, leuprolide acetate, megestrol acetate, octreotide acetate, deithylstilbestrol diphosphate, testolactone, goserelin acetate, etoposide phosphate, vincristine sulfate, etoposide, vinblastine, etoposide, vincristine sulfate, teniposide, trastuzumab, gemtuzumab ozogamicin, rituximab, exemestane, irinotecan hydrochloride, asparaginase, gemcitabine hydrochloride, altretamine, topotecan hydrochloride, hydroxyurea, cladribine, mitotane, procarbazine hydrochloride, vinorelbine tartrate, pentostatin sodium, mitoxantrone, pegaspargase, denileukin difitix, altretinoin, porfimer, bexarotene, paclitaxel, docetaxel, arsenic trioxide, tretinoin, and combinations of two or more of the same, such as FOLFOX, Xelox, FOLFIRI, FOLFIRINOX; b) **anti-VEGF therapy**, such as axitinib, bevacizumab, cabozantinib, lapatinib, Lenvatinib, pazopanib, ponatinib, ramucirumab, ranibizumab, regrafenib, sorafenib, sunitinib, vandetanib; and c) **engineered immune cells**, such as a CAR-T therapy in particular selected from tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, idecabtagene vicleucel and ciltabtagene autoceucel.
25. An antibody or antigen binding fragment for use according to any preceding claim, wherein the antibody or binding fragment comprises: a) a VH domain comprising SEQ ID NO: 1 for CDRH1, SEQ ID NO: 2 for CDRH2 and CDRH3 selected from SEQ ID NO: 3, 9, 12, 14, 16, 18, 20, 22 and 24 for; and a VL domain comprising SEQ ID NO: 5 for CDRL1, SEQ IN NO: 6 for CDRH2, and SEQ ID NO: 7.
26. An antibody or antigen binding fragment for use according to any preceding claim, wherein the VH comprises SEQ ID NO: 17 and the VL comprises a sequence selected from SEQ ID NO: 8, 11, 28 or 29.