

Claims

1. An antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof is specifically binding to an integrin alpha10 polypeptide, for use in the treatment and/or prevention of an aggressive cancer form selected from the group consisting of aggressive breast cancer, aggressive lung cancer, aggressive prostate cancer and aggressive pancreatic cancer, or a metastasis of any one of said cancer forms.
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- 10 2. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the aggressive breast cancer is selected from the group consisting of triple negative breast cancer and inflammatory breast cancer.
- 15 3. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the triple negative breast cancer is selected from the group consisting of basal-like 1 breast cancer, basal-like 2 breast cancer, claudin-low breast cancer, metaplastic breast cancer (MBC), interferon-rich breast cancer, immunomodulatory breast cancer, mesenchymal breast cancer, mesenchymal stem-like breast cancer, luminal androgen receptor breast cancer and unstable breast cancer.
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4. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the aggressive lung cancer is selected from the group consisting of squamous cell lung carcinoma, lung adenocarcinoma, large cell lung carcinoma and small-cell lung carcinoma.
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5. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the aggressive prostate cancer is small cell neuroendocrine carcinoma (SCNC).
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6. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the aggressive pancreatic cancer is a neuroendocrine tumor.
- 5 7. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the aggressive pancreatic cancer and/or neuroendocrine tumor is a grade I, grade II or grade III pancreatic cancer.
- 10 8. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the integrin $\alpha 10$ polypeptide is expressed on the surface of a malignant cell and/or a tumor-associated cell.
- 15 9. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the antibody is a monoclonal antibody, polyclonal antibody, a chimeric antibody, a single chain antibody or fragment thereof.
- 20 10. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the antibody is a non-human antibody, a chimeric antibody, a bispecific antibody, a humanized antibody or a human antibody.
- 25 11. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the antibody is a mouse monoclonal antibody.
12. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the antibody is a human monoclonal antibody.
- 30 13. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the antibody has an isotype selected from the group consisting of IgA, IgD, IgG, IgE and IgM.

14. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the antibody is:
- 5 a) a monoclonal antibody, produced by the hybridoma cell line deposited at the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH under the accession number DSM ACC2583; or
- 10 b) an antibody which competes for binding to the same epitope as the epitope bound by the monoclonal antibody produced by the hybridoma deposited at the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH under the accession number DSM ACC2583; or
- 15 c) a fragment of a) or b), wherein said fragment is capable of binding specifically to the extracellular I-domain of the integrin $\alpha 10$ polypeptide chain.
15. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the antibody or antigen binding fragment comprises:
- 20 a heavy chain variable region comprising
- a) a CDR-H1 comprising or consisting of the amino acid sequence of SEQ ID NO: 4;
- 25 b) a CDR-H2 comprising or consisting of the amino acid sequence of SEQ ID NO: 5; and
- c) a CDR-H3 comprising or consisting of the amino acid sequence of SEQ ID NO: 6;
- and/or
- 30 a light chain variable region comprising
- d) a CDR-L1 comprising or consisting of the amino acid sequence of SEQ ID NO: 7;

- e) a CDR-L2 comprising or consisting of the amino acid sequence of SEQ ID NO: 8; and
- f) a CDR-L3 comprising or consisting of the amino acid sequence of SEQ ID NO: 9.

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or a variant of any one of SEQ ID NO:s 4 to 9, wherein any one amino acid has been altered for another amino acid, with the proviso that no more than 3 amino acids have been so altered, for example wherein 2, or 1 amino acids have been so altered.

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16. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region comprising or consisting of the amino acid sequence of SEQ ID NO: 10.

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17. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the antibody or antigen-binding fragment comprises a light chain variable region comprising or consisting of the amino acid sequence of SEQ ID NO: 11.

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18. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is conjugated to an additional moiety.

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19. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the additional moiety comprises a detectable moiety, such as a detectable moiety selected from the group consisting of a fluorophore, an enzyme and a radioactive tracer or radioisotope.

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20. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the additional moiety comprises a cytotoxic moiety.

21. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the cytotoxic moiety is selected from a group consisting of a toxin, a chemotherapeutic agent and a radioactive agent, or combinations thereof.
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22. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the cytotoxic moiety is a toxin.
23. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims wherein said toxin is selected from the group selected from microtubule toxins, DNA toxins and transcription toxins.
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24. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims wherein said microtubule toxins are selected from the group consisting of Auristatin-based toxins, Maytansinoid-based toxins, Tubulysins-based toxins and Eribulin.
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25. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims wherein said transcription toxin is an RNA polymerase II inhibiting agent.
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26. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims wherein said transcription toxin is selected from the group consisting of Doxorubicin, Doxorubicin derivatives and Amanitin.
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27. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the transcription toxin is selected from the group consisting of shiga and shiga-like toxins; type I ribosome inactivating proteins, type II ribosome inactivating proteins and saporin, or combinations thereof.
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28. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the type I ribosome inactivating protein is trichosanthin and/or luffin.

29. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the type II ribosome inactivating protein is ricin, agglutinin and/or abrin.
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30. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the integrin alpha10 polypeptide is a naturally occurring variant of integrin alpha10 polypeptide or an isoform of integrin alpha10 polypeptide.
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31. The antibody or antigen-binding fragment thereof for use according to any of the preceding claims, wherein the antibody and is capable of inducing cell death and/or inhibiting growth and/or inhibiting proliferation and/or inhibiting migration of cells expressing an integrin alpha10 polypeptide.
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32. The antibody or antigen-binding fragment thereof for use according to any of the preceding claims, wherein the cells are malignant cells and/or tumor-associated cells.
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33. The antibody or antigen-binding fragment thereof for use according to any of the preceding claims, wherein the malignant cells or tumor-associated cells are cancer associated fibroblast (CAFs), stromal cells, stem cells and/or stem-like cells.
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34. The antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the integrin alpha10 polypeptide is a part of an integrin alpha10 beta1 heterodimer.
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35. The antibody or antigen-binding fragment thereof for use according to any of the preceding claims, wherein the treatment is prophylactic, ameliorative or curative.

36. The antibody or antigen-binding fragment thereof for use according to any of the preceding claims, wherein the treatment is initiated upon detection of an integrin alpha10 polypeptide in an aggressive cancer cell in a tumor of said subject.
- 5 37. The antibody or antigen-binding fragment thereof for use according to any of the preceding claims, wherein the antibody or antigen-binding fragment is administered to an individual in need thereof in combination with radiation therapy and/or surgical removal of cancer.
- 10 38. The antibody or antigen-binding fragment thereof for use according to any of the preceding claims, wherein the antibody or antigen-binding fragment is administered to an individual in need thereof prior to radiation therapy and/or surgical removal of cancer.
- 15 39. The antibody or antigen-binding fragment thereof for use according to any of the preceding claims, wherein the antibody or antigen-binding fragment is administered to an individual in need thereof after radiation therapy and/or surgical removal of cancer.
- 20 40. An antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof is specifically binding to an integrin alpha10 polypeptide, for use in the diagnosis of an aggressive cancer selected from the group consisting of aggressive breast cancer, aggressive lung cancer, aggressive prostate cancer and aggressive pancreatic cancer, or a metastasis
25 of any one of said aggressive cancer forms.
41. The antibody or antigen-binding fragment thereof according to claim 40, wherein the cancer comprises cells which display equal or higher levels of the integrin alpha10 antigen observed in healthy and/or benign tissue of the same
30 type.
42. The antibody or antigen-binding fragment thereof according to claim 40, wherein the cancer comprises cells which display equal or higher levels of the

integrin alpha10 antigen observed in a less aggressive cancer type of the same tissue type, compared to the diagnosed cancer type.

43. A method of treating an aggressive cancer, wherein said aggressive cancer form is selected from the group consisting of aggressive breast cancer, aggressive lung cancer, aggressive prostate cancer and aggressive pancreatic cancer, or wherein said aggressive cancer form is a metastasis, the method comprising administering a pharmaceutically effective amount of an antibody or antigen-binding fragment thereof specifically binding to an integrin alpha10 polypeptide, to a subject in the need thereof.
44. An method for detecting an aggressive cancer cell in a subject, said method comprising the steps of:
- providing a tissue suspected of comprising cancer cells of the subject;
 - analyzing in the tissue the presence of an antigen comprising an integrin alpha10 polypeptide or a fragment thereof,
 - determining the expression level of the integrin alpha10 antigen, and
 - comparing said expression level determined in c. with a control level, wherein said control level is the average expression level of the antigen observed in healthy and/or benign cells of the same tissue type as the isolated sample,
- wherein an expression level of the antigen higher than the control level is indicative of the presence of an aggressive cancer form in the subject, and wherein said aggressive cancer form is selected from the group consisting of aggressive breast cancer, aggressive lung cancer, aggressive prostate cancer and aggressive pancreatic cancer, or a metastasis of any one of said aggressive cancer forms.
45. A method for detecting an aggressive cancer cell in a subject, said method comprising the steps of:
- providing a tissue suspected of comprising cancer cells of the subject;
 - optionally analyzing in the tissue the presence of one or more cells having a cancer morphology,

- c. analyzing in the tissue the presence of an antigen comprising an integrin alpha10 polypeptide or a fragment thereof,
- d. optionally determining the expression level of the integrin alpha10 antigen, wherein presence of one or more cells having a cancer morphology in combination with expression of integrin alpha10 antigen are indicative of the presence of an aggressive cancer form in the subject, and wherein said aggressive cancer form is selected from the group consisting of aggressive breast cancer, aggressive lung cancer, aggressive prostate cancer and aggressive pancreatic cancer, or a metastasis of any one of said aggressive cancer forms.
46. A method for diagnosis of an aggressive cancer form in a subject, the method comprising the steps of:
- a. providing a tissue suspected of comprising cancer cells of the subject;
- b. analyzing in the tissue the presence of an antigen comprising an integrin alpha10 polypeptide or a fragment thereof,
- c. determining the expression level of the integrin alpha10 antigen, and
- d. comparing the expression level determined in c. with a control level, wherein said control level is the average expression level of the antigen; and
- wherein an expression level of the antigen higher than the control level is indicative of the presence of an aggressive cancer form in a sample, wherein said aggressive cancer form is selected from the group consisting of aggressive breast cancer, aggressive lung cancer, aggressive prostate cancer and aggressive pancreatic cancer, or a metastasis of any one of said aggressive cancer forms, or a metastasis of any one of said aggressive cancer forms, thereby diagnosing an aggressive cancer form in a subject.
47. A method for diagnosis of an aggressive cancer form in a subject, the method comprising the steps of:
- a. providing a tissue suspected of comprising cancer cells of the subject;
- b. optionally analyzing in the tissue the presence of one or more cells having a cancer morphology;

- c. analyzing in the sample the presence of an antigen comprising an integrin alpha10 polypeptide or a fragment thereof,
 - d. optionally determining the expression level of the integrin alpha10 antigen, and
- 5 wherein presence of one or more cells having a cancer morphology in combination with expression of integrin alpha10 antigen are indicative of the presence of an aggressive cancer form in a sample, wherein said aggressive cancer form is selected from the group consisting of aggressive breast cancer, aggressive lung cancer, aggressive prostate cancer and aggressive pancreatic
- 10 cancer, or a metastasis of any one of said aggressive cancer forms, thereby diagnosing an aggressive cancer form in a subject.
- 48. A method for classification of a triple negative breast cancer tumor sample of a subject, said method comprising:
 - 15 a. providing a breast tissue suspected of comprising cancer cells of the subject;
 - b. isolating breast cancer cells characterized as being ER negative, PR negative and HER2 negative;
 - c. determining in the isolated cells an expression level of an antigen
 - 20 comprising an integrin alpha10 polypeptide or a fragment thereof, and
 - d. comparing the expression level determined in c. to a control level, wherein said control level is the average expression level of the antigen observed in healthy and/or benign breast tissue;
- 25 wherein an expression level of the antigen in the breast cancer cells higher than a control level, and an expression status of ER negative, PR negative and HER2 negative are indicative of a basal-like triple negative breast cancer or a luminal triple negative breast cancer,
- thereby classifying the triple negative breast cancer tumor sample as belonging to a basal-like triple negative breast cancer tumor or to a luminal triple negative
- 30 breast cancer tumor.
- 49. A method for determining a prognosis for an aggressive cancer form for a subject, the method comprising:
 - a. providing a cancer tumor tissue of the subject;

- 5 b. analyzing in the sample the presence of an antigen comprising an integrin alpha10 polypeptide or a fragment thereof,
- c. determining the expression level of the integrin alpha10 antigen,
- d. comparing the expression level determined in c. to a control level, wherein the control level is the average expression level of the antigen observed in healthy and/or benign tissue of the same tissue type as the sample;
- 10 e. determining an unfavorable prognosis of the aggressive cancer form when the expression level of the integrin alpha10 antigen is higher than the control level,
- wherein the aggressive cancer form selected from the group consisting of aggressive breast cancer, aggressive lung cancer, aggressive prostate cancer and aggressive pancreatic cancer, or a metastasis of any one of said aggressive cancer forms.
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50. A method for determining a prognosis for an aggressive cancer form for a subject, the method comprising:
- a. providing a cancer tumor tissue of the subject;
- 20 b. optionally analyzing in the tissue the presence of one or more cells having a cancer morphology;
- c. analyzing in the sample the presence of an antigen comprising an integrin alpha10 polypeptide or a fragment thereof,
- d. optionally determining the expression level of the integrin alpha10 antigen, and comparing the determined expression level to a control level, wherein the control level is the average expression level of the antigen observed in healthy and/or benign tissue of the same tissue type as the sample;
- 25 e. determining an unfavorable prognosis of the aggressive cancer form when one or more cells having a cancer morphology are present in the tissue in combination with expression of the integrin alpha10 antigen, and/or
- 30 the expression level of the integrin alpha10 antigen is higher than the control level,

wherein the aggressive cancer form selected from the group consisting of aggressive breast cancer, aggressive lung cancer, aggressive prostate cancer and aggressive pancreatic cancer, or a metastasis of any one of said aggressive cancer forms.

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51. The method according to any one of claims 49 to 50, wherein the prognosis is overall survival rate or recurrence free survival rate.

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52. The method according to any one of claims 44 to 51, wherein the step of analyzing in the sample the presence of an antigen comprising an integrin alpha10 polypeptide or a fragment thereof, comprises imaging the tissue and/or tissue sample.

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53. The method according to any one of claims 44 to 52, wherein the step of determining the expression level of the integrin alpha10 antigen comprises imaging the tissue and/or tissue sample.

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54. A method of preventing metastasis from a primary aggressive cancer selected from the group consisting of aggressive breast cancer, aggressive lung cancer, aggressive prostate cancer and aggressive pancreatic cancer, the method comprising administering a therapeutically effective amount of an antibody or antigen-binding fragment thereof, wherein the antibody is specific for integrin alpha10 polypeptide, to a patient in the need thereof.

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55. The method according to claim 54 wherein the antibody or antigen-binding fragment is administered upon detection of the primary cancer.

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56. A method of inhibiting integrin alpha10-mediated signaling of at least one cancer cell, the method comprising contacting the at least one cancer cell with an effective amount of an antibody or antigen-binding fragment thereof specific for integrin alpha10 polypeptide, wherein the at least one cancer cell is selected from the group consisting of an aggressive breast cancer cell, an aggressive lung cancer cell, an aggressive prostate cancer cell, an aggressive pancreatic cancer cell, and a metastatic tumor cell.

57. A method of inhibiting cellular functions of at least one cancer cell, the method comprising contacting the at least one cancer cell with an effective amount of an antibody or antigen-binding fragment specific for integrin alpha10 polypeptide, wherein the at least one cancer cell is selected from the group consisting of an aggressive breast cancer cell, an aggressive lung cancer cell, an aggressive prostate cancer cell, an aggressive pancreatic cancer cell, and a metastatic tumor cell.
58. The method according to any one of claims 44 to 57, wherein the antigen comprising an integrin alpha10 polypeptide or a fragment thereof is expressed on the surface of the cells.
59. The method of inhibiting cellular functions of at least one cancer cell according to any one of claims 57 to 58, wherein the at least one cancer cell is in an aggressive and/or metastatic tumor, and wherein inhibiting is selected from the group consisting of:
- a. inhibiting proliferation of the at least one cancer cell;
 - b. inhibiting self-renewal of the at least one cancer cell;
 - c. inhibiting anchorage-independent growth of the at least one cancer cell;
 - d. inhibiting migration of the at least one cancer cell;
 - e. inhibiting invasion of the at least one cancer cell;
 - f. inhibiting viability of the at least one cancer cell;
 - g. inhibiting adhesion of the at least one cancer cell; and/or combinations thereof.
60. The method of inhibiting cellular functions of at least one cancer cell according to any one of claims 57 to 59, wherein the at least one cancer cell is in an aggressive and/or metastatic tumor, and inhibiting cellular functions of at least one cancer cell inhibits at least one of:
- a. growth of the aggressive and/or metastatic tumor;
 - b. proliferation of the aggressive and/or metastatic tumor;
 - c. migration of the aggressive and/or metastatic tumor;
 - d. invasion of the aggressive and/or metastatic tumor;

- e. spreading of new aggressive and/or metastatic tumors;
- f. initiation of new aggressive and/or metastatic tumors;
- g. infiltration of new aggressive and/or metastatic tumors; and/or combinations thereof.

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61. The method according to any one of claims 56 to 60, wherein the at least one cancer cell is characterized by an expression level of an antigen comprising an integrin alpha10 polypeptide or a fragment thereof, higher than a control level, wherein the control level is the average expression level of the antigen observed in healthy and/or benign cells of the same tissue type as the cancer cell.
62. The method or antibody according to any one of claims 40 to 61, wherein the antibody or antigen-binding fragment thereof is according to any one of claims 1 to 39.
63. The method according to any one of claims 43 to 62, wherein the method further comprises administering to said subject an antibody or antigen-binding fragment thereof according to any one of claims 1 to 39.
64. The method according to any one of claims 44 to 63, wherein the method is an *in vitro* method, and wherein the tissue is a tissue sample obtained from the subject.
65. The antibody or antigen-binding fragment thereof according to claim 40, wherein the diagnosis is an *in vitro* diagnosis.
66. Use of an antibody or antigen-binding fragment thereof, wherein the antibody is specific for integrin alpha10 polypeptide, for the manufacture of a medicament for the treatment and/or prevention of an aggressive cancer selected from the group consisting of aggressive breast cancer, aggressive lung cancer, aggressive prostate cancer and aggressive pancreatic cancer, or a metastasis of any one of said cancer forms.

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