

ACTIVATABLE ANTI-PDL1 ANTIBODIES, AND METHODS OF USE THEREOF

Related Applications

[0001] This application claims the benefit of U.S. Provisional Application No. 62/513,937, filed June 1, 2017, U.S. Provisional Application No. 62/534,950, filed July 20, 2017, U.S. Provisional Application No. 62/555,598, filed September 7, 2017, and U.S. Provisional Application No. 62/657,567, filed April 13, 2018, the contents of each of which are incorporated herein by reference in its entirety.

Description of the Text File Submitted Electronically

[0002] The contents of the text file submitted electronically herewith are incorporated herein by reference in their entirety: A computer readable format copy of the Sequence Listing (filename: CYTM_052_001US_SeqList_ST25, date recorded: July 24, 2018, file size 80 kilobytes).

Field of the Invention

[0003] This invention generally relates to specific dosing regimens for administering anti-PDL1 activatable antibodies for the treatment of cancer.

Background of the Invention

[0004] Antibody-based therapies have proven effective treatments for several diseases but in some cases, toxicities due to broad target expression have limited their therapeutic effectiveness. In addition, antibody-based therapeutics have exhibited other limitations such as rapid clearance from the circulation following administration.

[0005] In the realm of small molecule therapeutics, strategies have been developed to provide prodrugs of an active chemical entity. Such prodrugs are administered in a relatively inactive (or significantly less active) form. Once administered, the prodrug is metabolized *in vivo* into the active compound. Such prodrug strategies can provide for increased selectivity of the drug for its intended target and for a reduction of adverse effects.

[0006] Accordingly, there is a continued need in the field of antibody-based therapeutics for antibodies that mimic the desirable characteristics of the small molecule prodrug.

Summary of the Disclosure

[0007] In various examples the disclosure provides methods of treating, alleviating a symptom of, or delaying the progression of a cancer in a subject, by administering intravenously at a dose of about between 0.3 mg/kg to 30 mg/kg of an activatable anti-PDL1 antibody to the subject. The activatable antibody has an antibody (AB) that specifically binds to human PDL1. The AB has a heavy chain variable region having a complementarity

determining region 1 (CDRH1) having the amino acid sequence of SEQ ID NO:212, a complementarity determining region 2 (CDRH2) having the amino acid sequence of SEQ ID NO:246, and a complementarity determining region 3 (CDRH3) having the amino acid sequence or SEQ ID NO:235; and a light chain variable region having a light chain complementarity determining region 1 (CDRL1) having the amino acid sequence of SEQ ID NO:209, a light chain complementarity determining region 2, (CDRL2) having the amino acid sequence of SEQ ID NO:215, a light chain complementarity determining region 3 (CDRL3) having the amino acid sequence of SEQ ID NO:228; a cleavable moiety (CM) linked to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and a masking moiety (MM) linked to the CM.

[0007a] In one aspect, the present disclosure refers to use of an activatable anti-PDL1 antibody in the manufacture of a medicament for treating, alleviating a symptom of, or delaying the progression of a cancer in a subject, wherein the activatable anti-PDL1 antibody comprises: a. an antibody (AB) that specifically binds to human PDL1, wherein the AB comprises: i. a heavy chain variable region comprising a complementarity determining region 1 (CDRH1) comprising the amino acid sequence of SEQ ID NO:212, a complementarity determining region 2 (CDRH2) comprising the amino acid sequence of SEQ ID NO:246, and a complementarity determining region 3 (CDRH3) comprising the amino acid sequence or SEQ ID NO:235; and ii. a light chain variable region comprising a light chain complementarity determining region 1 (CDRL1) comprising the amino acid sequence of SEQ ID NO:209, a light chain complementarity determining region 2, (CDRL2) comprising the amino acid sequence of SEQ ID NO:215, a light chain complementarity determining region 3 (CDRL3) comprising the amino acid sequence of SEQ ID NO:228; b. a cleavable moiety (CM) linked to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and c. a masking moiety (MM) linked to the CM, and wherein the activatable antibody is to be administered intravenously at a dose of about between 0.3 mg/kg to 30 mg/kg.

[0008] Also included in the disclosure are methods of treating, alleviating a symptom of, or delaying the progression of a cancer in a subject, by administering intravenously at a fixed dose of about between 24 and 2400 mg of an activatable anti-PDL1 antibody to the subject, wherein the activatable antibody has an antibody (AB) that specifically binds to human PDL1, wherein the AB comprises a heavy chain variable region having a complementarity determining region 1 (CDRH1) having the amino acid sequence of SEQ ID NO:212, a complementarity determining region 2 (CDRH2) having the amino acid sequence of SEQ ID NO:246, and a complementarity determining region 3 (CDRH3) having the amino acid sequence or SEQ ID NO:235; and a light chain variable region having a light

chain complementarity determining region 1 (CDRL1) having the amino acid sequence of SEQ ID NO:209, a light chain complementarity determining region 2, (CDRL2) having the amino acid sequence of SEQ ID NO:215, a light chain complementarity determining region 3 (CDRL3) having the amino acid sequence of SEQ ID NO:228; a cleavable moiety (CM) linked to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and a masking moiety (MM) linked to the AB.

[0008a] In one aspect, the present disclosure refers to use of an activatable anti-PDL1 antibody in the manufacture of a medicament for treating, alleviating a symptom of, or delaying the progression of a cancer in a subject, wherein the activatable anti-PDL1 antibody comprises: a. an antibody (AB) that specifically binds to human PDL1, wherein the AB comprises: i. a heavy chain variable region comprising a complementarity determining region 1 (CDRH1) comprising the amino acid sequence of SEQ ID NO:212, a complementarity determining region 2 (CDRH2) comprising the amino acid sequence of SEQ ID NO:246, and a complementarity determining region 3 (CDRH3) comprising the amino acid sequence of SEQ ID NO:235; and ii. a light chain variable region comprising a light chain complementarity determining region 1 (CDRL1) comprising the amino acid sequence of SEQ ID NO:209, a light chain complementarity determining region 2, (CDRL2) comprising the amino acid sequence of SEQ ID NO:215, a light chain complementarity determining region 3 (CDRL3) comprising the amino acid sequence of SEQ ID NO:228; b. a cleavable moiety (CM) linked to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and c. a masking moiety (MM) linked to the CM, and wherein the activatable antibody is to be administered intravenously at a fixed dose of about between 24 and 2400 mg.

[0009] In another example the disclosure provides an activatable anti-PDL1 antibody having an antibody (AB) that specifically binds to human PDL1. The AB has a heavy chain variable region having a complementarity determining region 1 (CDRH1) having the amino acid sequence of SEQ ID NO:212, a complementarity determining region 2 (CDRH2) having the amino acid sequence of SEQ ID NO:246, and a complementarity determining region 3 (CDRH3) having the amino acid sequence of SEQ ID NO:235; and a light chain variable

region having a light chain complementarity determining region 1 (CDRL1) having the amino acid sequence of SEQ ID NO:209, a light chain complementarity determining region 2, (CDRL2) having the amino acid sequence of SEQ ID NO:215, a light chain complementarity determining region 3 (CDRL3) having the amino acid sequence of SEQ ID NO:228; a cleavable moiety (CM) linked to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and a masking moiety (MM) linked to the CM, for use in treating, alleviating a symptom of, or delaying the progression of a cancer in a subject, and wherein the activatable antibody is administered intravenously at a dose of about between 0.3 mg/kg to 30 mg/kg.

[0009a] In one aspect, the present disclosure refers to an activatable anti-PDL1 antibody comprising: a. an antibody (AB) that specifically binds to human PDL1, wherein the AB comprises: i. a heavy chain variable region comprising a complementarity determining region 1 (CDRH1) comprising the amino acid sequence of SEQ ID NO:212, a complementarity determining region 2 (CDRH2) comprising the amino acid sequence of SEQ ID NO:246, and a complementarity determining region 3 (CDRH3) comprising the amino acid sequence or SEQ ID NO:235; and ii. a light chain variable region comprising a light chain complementarity determining region 1 (CDRL1) comprising the amino acid sequence of SEQ ID NO:209, a light chain complementarity determining region 2, (CDRL2) comprising the amino acid sequence of SEQ ID NO:215, a light chain complementarity determining region 3 (CDRL3) comprising the amino acid sequence of SEQ ID NO:228; b. a cleavable moiety (CM) linked to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and c. a masking moiety (MM) linked to the CM, for use in treating, alleviating a symptom of, or delaying the progression of a cancer in a subject, and wherein the activatable antibody is administered intravenously at a dose of about between 0.3 mg/kg to 30 mg/kg.

[0010] In a further example the disclosure provides an activatable anti-PDL1 antibody having an antibody (AB) that specifically binds to human PDL1. The AB has a heavy chain variable region having a complementarity determining region 1 (CDRH1) having the amino acid sequence of SEQ ID NO:212, a complementarity determining region 2 (CDRH2) having the amino acid sequence of SEQ ID NO:246, and a complementarity determining region 3 (CDRH3) having the amino acid sequence or SEQ ID NO:235; and a light chain variable region having a light chain complementarity determining region 1 (CDRL1) having the amino acid sequence of SEQ ID NO:209, a light chain complementarity determining region 2, (CDRL2) having the amino acid sequence of SEQ ID NO:215, a light chain complementarity determining region 3 (CDRL3) having the amino acid sequence of SEQ ID NO:228, a cleavable moiety (CM) linked to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and a masking moiety (MM) linked to the CM, for use in treating, alleviating a symptom of, or delaying the progression of a cancer in a subject, and

wherein the activatable antibody is administered intravenously at a fixed dose of about between 24 and 2400 mg.

[00010a] In one aspect, the present disclosure refers to an activatable anti-PDL1 antibody comprising: a. an antibody (AB) that specifically binds to human PDL1, wherein the AB comprises: i. a heavy chain variable region comprising a complementarity determining region 1 (CDRH1) comprising the amino acid sequence of SEQ ID NO:212, a complementarity determining region 2 (CDRH2) comprising the amino acid sequence of SEQ ID NO:246, and a complementarity determining region 3 (CDRH3) comprising the amino acid sequence or SEQ ID NO:235; and ii. a light chain variable region comprising a light chain complementarity determining region 1 (CDRL1) comprising the amino acid sequence of SEQ ID NO:209, a light chain complementarity determining region 2, (CDRL2) comprising the amino acid sequence of SEQ ID NO:215, a light chain complementarity determining region 3 (CDRL3) comprising the amino acid sequence of SEQ ID NO:228; b. a cleavable moiety (CM) linked to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and c. a masking moiety (MM) linked to the CM, for use in treating, alleviating a symptom of, or delaying the progression of a cancer in a subject, and wherein the activatable antibody is administered intravenously at a fixed dose of about between 24 and 2400 mg.

[0011] The MM inhibits the binding of the AB to human PDL1 when the activatable antibody is in an uncleaved state. In some examples the MM had the amino acid sequence of SEQ ID NO: 63.

[0012] In some examples the CM has the amino acid sequence of SEQ ID NO: 377.

[0013] The AB has a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 46 and a light chain variable (VL) having the amino acid sequence of SEQ ID NO: 58 or SEQ ID NO: 137.

[0014] In further examples the activatable antibody has a light chain having the amino acid sequence of SEQ ID NO: 1008 and a heavy chain having the amino acid sequence of SEQ ID NO: 432.

[0015] Alternatively, the activatable antibody having a light chain having the amino acid sequence of SEQ ID NO: 428 and a heavy chain having the amino acid sequence of SEQ ID NO: 432.

[0016] The dose is about between 3 mg/kg to 10 mg/kg. The dose is about between 3 mg/kg to 15 mg/kg. The dose is 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, 15 mg/kg, or 30 mg/kg.

[0017] The fixed dose is 240 mg, 480 mg, 800 mg, 1200 mg, 2400 mg.

[0018] The activatable antibody is administered on a schedule of one dose every 7-28 days. For example activatable antibody is administered on a schedule of one dose every 14 days or 21 days.

[0019] The activatable antibody is administrated as a monotherapy. Alternatively, activatable antibody is administrated as a component of a combination therapy. The combination therapy includes administering a dose of an anti-CTLA-4 antibody or a B-Raf inhibitor

[0020] The anti-CTLA-4 antibody is for example, ipilimumab. The anti-CTLA-4 antibody is administered intravenously. The anti-CTLA-4 antibody is administered at a dose of 3 mg/kg, 6 mg/kg or 10 mg/kg. Alternatively, the anti-CTLA-4 antibody is administered at a fixed dose 240 mg, 480 mg or 800 mg.

[0021] The B-Raf inhibitor is vemurafenib. The B-Raf inhibitor is administered orally. The B-Raf inhibitor is administered at a dose of 960 mg or at a dose of 875 mg. The activatable antibody and the B-Raf inhibitor are administered over a same period of time.

[0022] In some examples the dose of the B-Raf inhibitor is administered twice daily. In other examples at least 4 doses each of the activatable antibody and the B-Raf inhibitor are administered.

[0023] In some examples multiple doses of the activatable antibody and the anti-CTLA-4 antibody are administered over a first period of time, followed by administration of multiple doses of the activatable antibody as a monotherapy over a second period of time.

[0024] In further examples, the activatable antibody and a dose of the anti-CTLA-4 antibody are administered concomitantly as a combination therapy every 21 days for 4 doses, followed by administration of a dose of the activatable antibody as a monotherapy every 14 days.

[0025] In yet another example multiple doses of the activatable antibody as a monotherapy are administered over a first period of time, followed by concomitant administration of multiple doses of the activatable antibody and the anti-CTLA-4 antibody as a combination therapy are administered over a second period of time.

[0026] In a yet a further example multiple doses of the activatable antibody are administered as a monotherapy over a first period of time, multiple doses of the activatable antibody and the anti-CTLA-4 antibody are subsequently administered as a combination therapy over a second period of time, and multiple doses of the activatable antibody as a monotherapy are administered over a third period of time.

[0027] In other examples, the activatable antibody is administered as a monotherapy every 14 days for 4 doses, followed by administration of a dose of activatable antibody and a dose of anti-CTLA-4 antibody as a combination therapy every 21 days, for 4 doses, followed by administration of a dose of the activatable antibody as a monotherapy every 14 days.

[0028] The cancer is an advanced, unresectable solid tumor or lymphoma. For example, the advanced unresectable tumor is a PDL1-responsive tumor type.

[0029] The cancer is a carcinoma such as carcinoma squamous cell carcinoma.

[0030] The cancer is for example, an anal squamous cell carcinoma, basal cell carcinoma, bladder cancer, bone cancer, bowel carcinoma, breast cancer, carcinoid, castration-resistant prostate cancer (CRPC), cervical carcinoma, colorectal cancer (CRC), colon cancer cutaneous squamous cell carcinoma, endometrial cancer, esophageal cancer, gastric carcinoma, gastroesophageal junction cancer, glioblastoma/ mixed glioma, glioma, head and neck cancer, hepatocellular carcinoma, hematologic malignancy, liver cancer, lung cancer, melanoma, Merkel cell carcinoma, multiple myeloma, nasopharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, peritoneal carcinoma, undifferentiated pleomorphic sarcoma, prostate cancer, rectal carcinoma, renal cancer, sarcoma, salivary gland carcinoma, squamous cell carcinoma, stomach cancer, testicular cancer, thymic carcinoma, thymic epithelial tumor,

thymoma, thyroid cancer, urogenital cancer, urothelial cancer, uterine carcinoma, or uterine sarcoma.

[0031] The cancer is a High Tumor Mutational Burden (hTMB) cancer.

[0032] The breast cancer is triple negative breast cancer or estrogen receptor positive breast cancer.

[0033] The hematologic malignancy is a lymphoma or a leukemia. The lymphoma is for example, a B-cell lymphoma, a T-cell lymphoma, Hodgkin's lymphoma, or an EBV lymphoma, primary mediastinal B-cell lymphoma.

[0034] The cancer is melanoma.

[0035] The bowel carcinoma is for example small bowel carcinoma or small bowel adenocarcinoma. The colon cancer is colon adenocarcinoma,

[0036] The lung cancer is for example non-small cell lung cancer (NSCLC) or small cell lung cancer. The NSCLC is non-squamous NSCLC or squamous NSCLC.

[0037] The prostate cancer is small cell neuroendocrine prostate cancer.

[0038] The renal cancer is renal cell carcinoma or renal sarcoma.

[0039] Preferably, the cancer is undifferentiated pleomorphic sarcoma, small bowel adenocarcinoma, Merkel cell carcinoma, thymic carcinoma, anal squamous cell carcinoma, cutaneous squamous cell carcinoma or triple negative breast cancer.

[0040] The subject exhibits one or more of the following characteristics: PD-1/PDL1 inhibitor-naïve, CTLA-4 inhibitor-naïve, *BRAF*^{V600E} mutation positive, BRAF inhibitor-naïve, PDL1 positive, PDL1 unknown, been previously treated with a PD1/PDL1 inhibitor has no further standard of care available, the PD1/PDL1 inhibitor therapy is not approved for the subject's cancer, been previously treated with a PD-1/PDL1 inhibitor, wherein treatment with the PD-1/PDL1 inhibitor was discontinued for reasons other than toxicity, and wherein the subject is CTLA-4 inhibitor-naïve, is immunotherapy naïve.

[0041] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. In the case of conflict, the present specification,

including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting.

[0042] Other features and advantages of the disclosure will be apparent from the following detailed description and claims.

Brief Description of the Drawings

[0043] FIG. 1A is a schematic representation of the study design for a study in Example 2, where “AA” represents the anti-PDL1 activatable antibody referred to herein as PL07-2001-C5H9v2, which comprises the heavy chain sequence of SEQ ID NO: 432 and the light chain sequence of SEQ ID NO: 428.

[0044] FIG. 1B is a schematic representation of a study design for the study in Example 2, where “AA” represents the anti-PDL1 activatable antibody referred to herein as PL07-2001-C5H9v2, which comprises the heavy chain sequence of SEQ ID NO: 432 and the light chain sequence of SEQ ID NO: 428. As compared to FIG. 1A, this schematic representation includes a further optional Part A2 in the study design.

[0045] FIG. 2 shows a series of graphs depicting detection of cleaved and intact anti-PD-L1 activatable antibodies in tumor and plasma samples determined using the WES system (ProteinSimple, San Jose, CA) under conditions similar to those described in the WES instrumentation manual.

[0046] FIGS. 3A and 3B are a series of graphs depicting screening of PL07-2001-C5H9v2 anti-idiotypic (anti-id) clones against 37% one-armed activated activatable antibody at 0.11, 0.33 and 1 ug/ml in human plasma at 1:100. FIG. 3A is an electropherogram showing 17G1 detection of decreasing concentration of one arm activated PL07-2001-C5H9v2 (1, 0.33, and 0.11 ug/ml, referred to in the FIG. as AA MIX). FIG. 3B demonstrates relative activation percent for the top 6 clones of one arm activated activatable antibody. The relative activation rate is preserved at different concentrations. 21H10 and 27C1 clones have lower affinity resulting in no data for the 0.11 ug/ml concentration.

[0047] FIGS. 4A, 4B, 4C, and 4D are a series of graphs depicting that the antibody referred to herein as 17G1 has high specificity to the activatable antibody (AA) PL07-2001-C5H9v2. 17G1 was assessed on the Wes for specificity by spiking 160 ng/ml of one arm activated PL07-2001-C5H9v2 (activated AA) into either human plasma (FIG. 4C) or lung tumor lysates (FIG. 4D).

Claims

What is claimed:

1. An activatable anti-PDL1 antibody comprising:
 - a. an antibody (AB) that specifically binds to human PDL1, wherein the AB comprises:
 - i. a heavy chain variable region comprising a complementarity determining region 1 (CDRH1) comprising the amino acid sequence of SEQ ID NO:212, a complementarity determining region 2 (CDRH2) comprising the amino acid sequence of SEQ ID NO:246, and a complementarity determining region 3 (CDRH3) comprising the amino acid sequence of SEQ ID NO:235; and
 - ii. a light chain variable region comprising a light chain complementarity determining region 1 (CDRL1) comprising the amino acid sequence of SEQ ID NO:209, a light chain complementarity determining region 2, (CDRL2) comprising the amino acid sequence of SEQ ID NO:215, a light chain complementarity determining region 3 (CDRL3) comprising the amino acid sequence of SEQ ID NO:228;
 - b. a cleavable moiety (CM) linked to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and
 - c. a masking moiety (MM) linked to the CM,for use in treating, alleviating a symptom of, or delaying the progression of a cancer in a subject, and wherein the activatable antibody is administered intravenously at a dose of about between 0.3 mg/kg to 30 mg/kg.
2. An activatable anti-PDL1 antibody comprising:
 - a. an antibody (AB) that specifically binds to human PDL1, wherein the AB comprises:
 - i. a heavy chain variable region comprising a complementarity determining region 1 (CDRH1) comprising the amino acid sequence of SEQ ID NO:212, a complementarity determining region 2 (CDRH2) comprising the amino acid sequence of SEQ ID NO:246, and a complementarity

- determining region 3 (CDRH3) comprising the amino acid sequence or SEQ ID NO:235; and
 - ii. a light chain variable region comprising a light chain complementarity determining region 1 (CDRL1) comprising the amino acid sequence of SEQ ID NO:209, a light chain complementarity determining region 2, (CDRL2) comprising the amino acid sequence of SEQ ID NO:215, a light chain complementarity determining region 3 (CDRL3) comprising the amino acid sequence of SEQ ID NO:228;
 - b. a cleavable moiety (CM) linked to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and
 - c. a masking moiety (MM) linked to the CM,
- for use in treating, alleviating a symptom of, or delaying the progression of a cancer in a subject, and wherein the activatable antibody is administered intravenously at a fixed dose of about between 24 and 2400 mg.
3. Use of of an activatable anti-PDL1 antibody in the manufacture of a medicament for treating, alleviating a symptom of, or delaying the progression of a cancer in a subject, wherein the activatable anti-PDL1 antibody comprises:
- a. an antibody (AB) that specifically binds to human PDL1, wherein the AB comprises:
 - i. a heavy chain variable region comprising a complementarity determining region 1 (CDRH1) comprising the amino acid sequence of SEQ ID NO:212, a complementarity determining region 2 (CDRH2) comprising the amino acid sequence of SEQ ID NO:246, and a complementarity determining region 3 (CDRH3) comprising the amino acid sequence or SEQ ID NO:235; and
 - ii. a light chain variable region comprising a light chain complementarity determining region 1 (CDRL1) comprising the amino acid sequence of SEQ ID NO:209, a light chain complementarity determining region 2, (CDRL2) comprising the amino acid sequence of SEQ ID NO:215, a light chain complementarity determining region 3 (CDRL3) comprising the amino acid sequence of SEQ ID NO:228;

- b. a cleavable moiety (CM) linked to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and
 - c. a masking moiety (MM) linked to the CM,

and wherein the activatable antibody is to be administered intravenously at a dose of about between 0.3 mg/kg to 30 mg/kg.
- 4. Use of an activatable anti-PDL1 antibody in the manufacture of a medicament for treating, alleviating a symptom of, or delaying the progression of a cancer in a subject, wherein the activatable anti-PDL1 antibody comprises:
 - a. an antibody (AB) that specifically binds to human PDL1, wherein the AB comprises:
 - i. a heavy chain variable region comprising a complementarity determining region 1 (CDRH1) comprising the amino acid sequence of SEQ ID NO:212, a complementarity determining region 2 (CDRH2) comprising the amino acid sequence of SEQ ID NO:246, and a complementarity determining region 3 (CDRH3) comprising the amino acid sequence or SEQ ID NO:235; and
 - ii. a light chain variable region comprising a light chain complementarity determining region 1 (CDRL1) comprising the amino acid sequence of SEQ ID NO:209, a light chain complementarity determining region 2, (CDRL2) comprising the amino acid sequence of SEQ ID NO:215, a light chain complementarity determining region 3 (CDRL3) comprising the amino acid sequence of SEQ ID NO:228;
 - b. a cleavable moiety (CM) linked to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and
 - c. a masking moiety (MM) linked to the CM,

and wherein the activatable antibody is to be administered intravenously at a fixed dose of about between 24 and 2400 mg.
- 5. The activatable anti-PDL1 antibody of claim 1 or 2 or the use of claim 3 or 4, wherein the MM inhibits the binding of the AB to human PDL1 when the activatable antibody is in an uncleaved state.
- 6. The activatable anti-PDL1 antibody or the use of any one of claims 1-5, wherein the MM comprises the amino acid sequence of SEQ ID NO: 63.

7. The activatable anti-PDL1 antibody or the use of any of claims 1-6, wherein the CM comprises the amino acid sequence of SEQ ID NO: 377.
8. The activatable anti-PDL1 antibody or the use of any one claims 1-7, wherein the AB comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 46 and a light chain variable (VL) comprising the amino acid sequence of SEQ ID NO: 58 or SEQ ID NO: 137.
9. The activatable anti-PDL1 antibody of claim 1 or 2 or the use of claim 3 or 4, wherein the activatable antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 1008 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 432.
10. The activatable anti-PDL1 antibody of claim 1 or 2 or the use of claim 3 or 4, wherein the activatable antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 428 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 432.
11. The activatable anti-PDL1 antibody or the use of any of claims 1, 3 and 5-10, wherein the dose is about between 3 mg/kg to 10 mg/kg.
12. The activatable anti-PDL1 antibody or the use of any of claims 1, 3 and 5-10, wherein the dose is about between 3 mg/kg to 15 mg/kg.
13. The activatable anti-PDL1 antibody or the use of any of claims 1, 3 and 5-10, wherein dose is 0.3 mg/kg.
14. The activatable anti-PDL1 antibody or the use of any of claims 1, 3 and 5-10, wherein dose is 1 mg/kg.
15. The activatable anti-PDL1 antibody or the use of any of claims 1, 3 and 5-10, wherein dose is 3 mg/kg.
16. The activatable anti-PDL1 antibody or the use of any of claims 1, 3 and 5-10, wherein dose is 6 mg/kg.
17. The activatable anti-PDL1 antibody or the use of any of claims 1, 3 and 5-10, wherein dose is 10 mg/kg.
18. The activatable anti-PDL1 antibody or the use of any of claims 1, 3 and 5-10, wherein dose is 15 mg/kg.
19. The activatable anti-PDL1 antibody or the use of any of claims 1, 3 and 5-10, wherein dose is 30 mg/kg.

20. The activatable anti-PDL1 antibody or the use of any of claims 2 and 4-10, wherein the fixed dose is 240 mg
21. The activatable anti-PDL1 antibody or the use of any of claims 2 and 4-10, wherein the fixed dose is 480 mg.
22. The activatable anti-PDL1 antibody or the use of any of claims 2 and 4-10, wherein the fixed dose is 800 mg.
23. The activatable anti-PDL1 antibody of any of claims 2 and 4-10, wherein the fixed dose is 1200 mg.
24. The activatable anti-PDL1 antibody of any of claims 2 and 4-10, wherein the fixed dose is 2400 mg.
25. The activatable anti-PDL1 antibody or the use of any one of the preceding claims, wherein the activatable antibody is to be administered on a schedule of one dose every 7-30 days.
26. The activatable anti-PDL1 antibody or the use of claim 25, wherein the activatable antibody is to be administered on a schedule of one dose every 14 days.
27. The activatable anti-PDL1 antibody or the use of claim 25, wherein the activatable antibody is to be administered on a schedule of one dose every 21 days.
28. The activatable anti-PDL1 antibody or the use of any one of the preceding claims, wherein the activatable antibody is to be administered as a monotherapy.
29. The activatable anti-PDL1 antibody or the use of any one of the preceding claims, wherein the activatable antibody is to be administered as a component of a combination therapy.
30. The activatable anti-PDL1 antibody or the use of claim 29, wherein the combination therapy comprises administration of a dose of an anti-CTLA-4 antibody or a B-RAF inhibitor
31. The activatable anti-PDL1 antibody or the use of claim 30 wherein the anti-CTLA-4 antibody is ipilimumab.
32. The activatable anti-PDL1 antibody or the use of claim 29 or 30, wherein the anti-CTLA-4 antibody is to be administered intravenously.
33. The activatable anti-PDL1 antibody or the use of any one of claims 30-32 wherein the anti-CTLA-4 antibody is to be administered at a dose of 3 mg/kg, 6 mg/kg or 10 mg/kg.

34. The activatable anti-PDL1 antibody or the use of any one of claims 30-32 wherein the anti-CTLA-4 antibody is to be administered at a fixed dose 240 mg, 480 mg or 800 mg.
35. The activatable anti-PDL1 antibody or the use of claim 30, wherein the B-RAF inhibitor is vemurafenib.
36. The activatable anti-PDL1 antibody or the use of claim 30 or 35, wherein the B-RAF inhibitor is to be administered orally.
37. The activatable anti-PDL1 antibody or the use of any of claims 30, 35 or 36, wherein B-RAF inhibitor is to be administered at a dose of 960 mg.
38. The activatable anti-PDL1 antibody or the use of any of claims 30, 35 or 36, wherein B-RAF inhibitor is to be administered at a dose of 875 mg.
39. The activatable anti-PDL1 antibody or the use of any of claims 30, 35-38, wherein the activatable antibody and the B-RAF inhibitor are to be administered over a same period of time.
40. The activatable anti-PDL1 antibody or the use of any of claims 30, 35-39, wherein a dose of the B-RAF inhibitor is to be administered twice daily.
41. The activatable anti-PDL1 antibody or the use of any of claims 30, 35-40, wherein at least 4 doses each of the activatable antibody and the B-RAF inhibitor are to be administered.
42. The activatable anti-PDL1 antibody or the use of any of claims 30-34, wherein multiple doses of the activatable antibody and the anti-CTLA-4 antibody are to be administered over a first period of time, followed by administration of multiple doses of the activatable antibody as a monotherapy over a second period of time.
43. The activatable anti-PDL1 antibody or the use of any of claims 30-34, wherein a dose of the activatable antibody and a dose of the anti-CTLA-4 antibody are to be administered concomitantly as a combination therapy every 21 days for 4 doses, followed by administration of a dose of the activatable antibody as a monotherapy every 14 days.
44. The activatable anti-PDL1 antibody or the use of any of claims 30-34, wherein multiple doses of the activatable antibody are to be administered as a monotherapy over a first period of time, followed by concomitant administration of multiple doses of the activatable antibody and the anti-CTLA-4 antibody as a combination therapy over a second period of time.

45. The activatable anti-PDL1 antibody or the use of any of claims 30-34, wherein (i) multiple doses of the activatable antibody are to be administered as a monotherapy over a first period of time, (ii) subsequently multiple doses of the activatable antibody and the anti-CTLA-4 antibody as a combination therapy are to be administered over a second period of time, and (iii) subsequently multiple doses of the activatable antibody as a monotherapy are to be administered over a third period of time.
46. The activatable anti-PDL1 antibody or the use of any of claims 30-34, wherein a dose of activatable antibody is to be administered as a monotherapy every 14 days for 4 doses, followed by administration of a dose of activatable antibody and a dose of anti-CTLA-4 antibody as a combination therapy every 21 days, for 4 doses, followed by administration of a dose an activatable antibody as a monotherapy every 14 days.
47. The activatable anti-PDL1 antibody or the use of any one of the preceding claims, wherein the cancer is an advanced, unresectable solid tumor or lymphoma.
48. The activatable anti-PDL1 antibody or the use of claim 47, wherein the advanced unresectable tumor is a PDL1-responsive tumor type.
49. The activatable anti-PDL1 antibody or the use of any one of the preceding claims, wherein the cancer is a carcinoma.
50. The activatable anti-PDL1 antibody or the use of claim 49, wherein the carcinoma squamous cell carcinoma.
51. The activatable anti-PDL1 antibody or the use of any one of the preceding claims, wherein the cancer is anal squamous cell carcinoma, basal cell carcinoma, bladder cancer, bone cancer, bowel carcinoma, breast cancer, carcinoid, castration-resistant prostate cancer (CRPC), cervical carcinoma, colorectal cancer (CRC), colon cancer cutaneous squamous cell carcinoma, endometrial cancer, esophageal cancer, gastric carcinoma, gastroesophageal junction cancer, glioblastoma/ mixed glioma, glioma, head and neck cancer, hepatocellular carcinoma, hematologic malignancy. liver cancer, lung cancer, melanoma, Merkel cell carcinoma, multiple myeloma, nasopharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, peritoneal carcinoma, undifferentiated pleomorphic sarcoma, prostate cancer, rectal carcinoma, renal cancer, sarcoma, salivary gland carcinoma, squamous cell carcinoma, stomach cancer, testicular cancer, thymic

- carcinoma, thymic epithelial tumor, thymoma, thyroid cancer, urogenital cancer, urothelial cancer, uterine carcinoma , or uterine sarcoma.
52. The activatable anti-PDL1 antibody or the use of any one of the preceding claims, wherein the cancer is a High Tumor Mutational Burden (hTMB) cancer,
 53. The activatable anti-PDL1 antibody or the use of claim 51, wherein the breast cancer is triple negative breast cancer or estrogen receptor positive breast cancer.
 54. The activatable anti-PDL1 antibody or the use of claim 51, wherein the hematologic malignancy is a lymphoma or a leukemia.
 55. The activatable anti-PDL1 antibody or the use of claim 54, wherein the lymphoma is a B-cell lymphoma, a T-cell lymphoma, Hodgkin's lymphoma, or an EBV lymphoma, primary mediastinal B-cell lymphoma.
 56. The activatable anti-PDL1 antibody or the use of claim 51, wherein the cancer is melanoma
 57. The activatable anti-PDL1 antibody or the use of claim 51, wherein the bowel carcinoma is small bowel carcinoma or small bowel adenocarcinoma.
 58. The activatable anti-PDL1 antibody or the use of claim 51, the colon cancer is colon adenocarcinoma,
 59. The activatable anti-PDL1 antibody or the use of claim 51, the lung cancer is non-small cell lung cancer (NSCLC) or small cell lung cancer.
 60. The activatable anti-PDL1 antibody or the use of claim 59, wherein the NSCLC is non-squamous NSCLC or squamous NSCLC.
 61. The activatable anti-PDL1 antibody or the use of claim 51, wherein the prostate cancer is small cell neuroendocrine prostate cancer.
 62. The activatable anti-PDL1 antibody or the use of claim 51, wherein the renal cancer, renal cell carcinoma or renal sarcoma
 63. The activatable anti-PDL1 antibody or the use of claim 51, wherein the cancer is undifferentiated pleomorphic sarcoma, small bowel adenocarcinoma, Merkel cell carcinoma, thymic carcinoma, anal squamous cell carcinoma, cutaneous squamous cell carcinoma or triple negative breast cancer.
 64. The activatable anti-PDL1 antibody or the use of any one of the preceding claims, wherein the subject exhibits one or more of the following characteristics:

- a. PD-1/PDL1 inhibitor-naïve,
 - b. CTLA-4 inhibitor-naïve,
 - c. *BRAF*^{V600E} mutation positive,
 - d. BRAF inhibitor-naïve,
 - e. PDL1 positive,
 - f. PDL1 unknown, and
 - g. been previously treated with a PD1/PDL1 inhibitor.
65. The activatable anti-PDL1 antibody or the use of any one of the preceding claims, wherein the subject has no further standard of care available.
66. The activatable anti-PDL1 antibody or the use of any one of the preceding claims, wherein PD1/PDL1 inhibitor therapy is not approved for the subject's cancer.
67. The activatable anti-PDL1 antibody or the use of any one of the preceding claims, wherein the subject has been previously treated with a PD-1/PDL1 inhibitor, wherein treatment with the PD-1/PDL1 inhibitor was discontinued for reasons other than toxicity, and wherein the subject is CTLA-4 inhibitor-naïve.
68. The activatable anti-PDL1 antibody or the use of any one of the preceding claims, wherein the subject is immunotherapy naïve.