

WHAT IS CLAIMED:

1. Use of an anti-CD73 antibody or antigen binding fragment thereof in the manufacture of a medicament for A method of treating a metastatic pancreatic ductal adenocarcinoma (PDAC) in a subject, wherein the method comprising administering to the subject about 750 mg to about 3000 mg of an anti-CD73 antibody or antigen binding fragment thereof and chemotherapy is to be administered to the subject, wherein a tumor sample obtained from the subject expresses CD73.
2. Use of an anti-CD73 antibody or antigen binding fragment thereof in the manufacture of a medicament for A method of inhibiting the growth of a PDAC tumor in a subject, wherein the method comprising administering to the subject about 750 mg to about 3000 mg of an anti-CD73 antibody or antigen binding fragment thereof and chemotherapy is to be administered to the subject, wherein a tumor sample obtained from the subject expresses CD73.
3. ~~The method of claim 1 or claim 2, wherein the anti-CD73 antibody or antigen binding fragment thereof comprises oleclumab or antigen binding fragment thereof.~~
4. ~~The method of any one of claims 1-3, wherein the oleclumab or antigen binding fragment thereof is administered at a dose of 750 mg.~~
5. ~~The method of any one of claims 1-3, wherein the oleclumab or antigen binding fragment thereof is administered at a dose of 1500 mg.~~
6. ~~The method of any one of claims 1-3, wherein the oleclumab or antigen binding fragment thereof is administered at a dose of 2250 mg.~~
7. ~~The method of any one of claims 1-3, wherein the oleclumab or antigen binding fragment thereof is administered at a dose of 3000 mg.~~

8. — The method of any one of claims 1-7, wherein the dose of oleclumab or an antigen-binding fragment thereof is administered every two weeks for four doses and then every four weeks.

9. — The method of any one of claims 1-8, wherein the chemotherapy comprises gemcitabine and nab-paclitaxel.

10. — The method of claim 9, wherein the gemcitabine is administered at a dose of 1000 mg/m² and the nab-paclitaxel is administered at a dose of 125 mg/m².

11. — The method of claim 9 or 10, wherein the chemotherapy is administered on days 1, 8, and 15 of a 28-day treatment cycle and then the cycle is repeated every 4 weeks.

12. — The method of any one of claims 1-8, wherein the chemotherapy comprises mFOLFOX.

13. — The method of claim 12, wherein the mFOLFOX comprises oxaliplatin administered at a dose of about 85 mg/m², leucovorin administered at a dose of about 400 mg/m², and 5-FU administered in a bolus of about 400 mg/m² followed by administration of a second dose of 5-FU at about 2400 mg/m².

14. — The method of claim 12 or 13, wherein the chemotherapy is administered on days 1 and 15 of a 28-day treatment cycle and then the cycle is repeated every 4 weeks.

15. — The method of any one of claims 1-11, wherein the oleclumab or antigen-binding fragment thereof is administered at a dose of 750 mg every 2 weeks for four doses and then every 4 weeks in the treatment cycle, and wherein the chemotherapy comprises 1000 mg/m² gemcitabine and 125 mg/m² nab-paclitaxel and is administered on days 1, 8, and 15 of the 28-day treatment cycle and then the cycle is repeated every 4 weeks.

16. — The method of any one of claims 1-11, wherein the oleclumab or antigen-binding fragment thereof is administered at a dose of 1500 mg every 2 weeks for four doses and then every 4 weeks in the treatment cycle, and wherein the chemotherapy comprises 1000

~~mg/m² gemcitabine and 125 mg/m² nab-paclitaxel and is administered on days 1, 8, and 15 of the 28-day treatment cycle and then the cycle is repeated every 4 weeks.~~

17. — ~~The method of any one of claims 1-11, wherein the oleclumab or antigen binding fragment thereof is administered at a dose of 2250 mg every 2 weeks for four doses and then every 4 weeks in the treatment cycle, and wherein the chemotherapy comprises 1000 mg/m² gemcitabine and 125 mg/m² nab-paclitaxel and is administered on days 1, 8, and 15 of the 28-day treatment cycle and then the cycle is repeated every 4 weeks.~~

18. — ~~The method of any one of claims 1-11, wherein the oleclumab or antigen binding fragment thereof is administered at a dose of 3000 mg every 2 weeks for four doses and then every 4 weeks in the treatment cycle, and wherein the chemotherapy comprises 1000 mg/m² gemcitabine and 125 mg/m² nab-paclitaxel and is administered on days 1, 8, and 15 of the 28-day treatment cycle and then the cycle is repeated every 4 weeks.~~

19. — ~~The method of any one of claims 1-8 and 12-14, wherein the oleclumab or antigen binding fragment thereof is administered at a dose of 750 mg every 2 weeks for four doses and then every 4 weeks in the treatment cycle, and wherein the chemotherapy comprises mFOLFOX and is administered on days 1 and 15 of the 28-day treatment cycle and then the cycle is repeated every 4 weeks.~~

20. — ~~The method of any one of claims 1-11, wherein the oleclumab or antigen binding fragment thereof is administered at a dose of 1500 mg every 2 weeks for four doses and then every 4 weeks in the treatment cycle, and wherein the chemotherapy comprises mFOLFOX and is administered on days 1 and 15 of the 28-day treatment cycle and then the cycle is repeated every 4 weeks.~~

21. — ~~The method of any one of claims 1-11, wherein the oleclumab or antigen binding fragment thereof is administered at a dose of 2250 mg every 2 weeks for four doses and then every 4 weeks in the treatment cycle, and wherein the chemotherapy comprises mFOLFOX and is administered on days 1 and 15 of the 28-day treatment cycle and then the cycle is repeated every 4 weeks.~~

22. — ~~The method of any one of claims 1-11, wherein the oleclumab or antigen binding fragment thereof is administered at a dose of 3000 mg every 2 weeks for four doses and then every 4 weeks in the treatment cycle, and wherein the chemotherapy comprises mFOLFOX and is administered on days 1 and 15 of the 28 day treatment cycle and then the cycle is repeated every 4 weeks.~~

23. — ~~The method of any one of claims 1-22, wherein the oleclumab or antigen binding fragment and the chemotherapy are administered simultaneously or sequentially.~~

24. — ~~The method of any one of claims 1-23, further comprising administering to the subject about 1500 mg of an anti-PD-L1 antibody or antigen binding fragment thereof.~~

25. — ~~The method of claim 24, wherein the anti-PD-L1 antibody or antigen binding fragment thereof comprises durvalumab or antigen binding fragment thereof.~~

26. — ~~The method of claim 24 or 25, wherein the durvalumab or antigen binding fragment thereof is administered at a dose of 1500 mg.~~

27. — ~~The method of any one of claims 23-26, wherein the dose of durvalumab or antigen binding fragment thereof is administered every four weeks.~~

28. — ~~The method of any one of claims 23-27, wherein the oleclumab or antigen binding fragment thereof, the durvalumab or antigen binding fragment thereof, and the chemotherapy are administered simultaneously or sequentially~~

29. — ~~The method of any one of claims 1-28, wherein the administration is parenteral.~~

30. — ~~The method of claim 29, wherein the administration is intravenous.~~

31. — ~~The method of claim 29 or 30, wherein the administration is via intravenous infusion.~~

32. — ~~The method of any one of claims 1-31, wherein the subject is human.~~

~~33. The method of any one of claims 1-32, wherein the human subject is an adult ≥ 18 years of age with histologically or cytologically confirmed pancreatic adenocarcinoma.~~

~~34. The method of any one of claims 1-33, wherein the subject has previously untreated first-line metastatic PDAC (1L metastatic PDAC).~~

~~35. The method of any one of claims 1-33, wherein the subject has previously untreated second-line metastatic PDAC (2L metastatic PDAC).~~

~~363.~~ The use method of any one of claims 1-~~352~~, wherein the CD73 expression of a tumor sample obtained from the subject is evaluated by an immunohistochemistry (IHC) method.

~~374.~~ The use method of claim 36, wherein the IHC method is an automated IHC method.

~~385.~~ The use method of any one of claims 1-~~437~~, wherein a tumor sample obtained from the subject expresses high levels of CD73.

~~396.~~ The use method of any one of claims 1-~~538~~, wherein the IHC method comprises IHC scoring.

~~407.~~ The use method of claim ~~639~~, wherein the IHC scoring is defined by scoring the staining intensity of cells expressing CD73 within the tumor sample with the value 0, 1, 2, or 3.

~~418.~~ The use method of claim ~~639~~, wherein the IHC scoring is defined by scoring the staining intensity of cells expressing CD73 within the tumor sample with the value 1, 2, or 3.

~~429.~~ The use method of any one of claims ~~336-841~~, wherein the percentage of cells expressing CD73 at each value in the tumor sample is calculated.

~~4310~~. The use method of claim ~~942~~, wherein the tumor sample comprises cells having staining intensities of 1, 2, and 3.

~~4411~~. The use method of claim ~~7-1040-43~~, wherein the tumor sample comprises at least about 50% to about 90% of cells having staining intensities of 1, 2, and 3.

~~4512~~. The use method of claim ~~1144~~, wherein the tumor sample comprises at least about 50%, about 60%, about 70%, about 80%, or about 90% cells having staining intensities of 1, 2, and 3.

~~4613~~. The use method of any one of claims ~~7-1040-43~~, wherein the tumor sample comprises cells having staining intensities of 2 and 3.

~~4714~~. The use method of claim ~~1346~~, wherein the tumor sample comprises at least about 30% to about 70% of cells having staining intensities of 2 and 3.

~~4815~~. The use method of claim ~~1447~~, wherein the tumor sample comprises at least about 30%, about 40%, about 50%, about 60%, or about 70% of cells having staining intensities of 2 and 3.

~~4916~~. The use method of any one of claims ~~1-1548~~, wherein at least about 70% of the cells in a tumor sample obtained from the subject have a staining intensity score of at least 1.

~~5017~~. The use method of any one of claims ~~1-1649~~, wherein at least about 50% of the cells in a tumor sample obtained from the subject have a staining intensity score of at least 2.

~~5118~~. The use method of any one of claims ~~1-1750~~, wherein the anti-CD73 antibody or antigen binding fragment thereof comprises oleclumab which comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 3-5, and wherein

the light chain variable domain comprises CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 6-8.

~~5219.~~ The ~~use method~~ of claim ~~1851~~, wherein the oleclumab comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 2.

~~5320.~~ The ~~use method~~ of any one of claims ~~1-1924-52~~, wherein about 1500 mg of an anti-PD-L1 antibody or antigen binding fragment thereof is to be administered to the subject, the anti-PD-L1 antibody or antigen binding fragment thereof comprises durvalumab which comprises a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 11-13, and wherein the light chain variable domain comprises CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 14-16.

~~5421.~~ The ~~use method~~ of claim ~~2053~~, wherein the durvalumab comprises a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 10.

~~5522.~~ The ~~use method~~ of any one of claims 1-~~1952~~, wherein the anti-CD73 antibody or antigen binding fragment thereof is to be administered every 2 weeks for four doses and then every 4 weeks in a treatment cycle, and wherein the chemotherapy is to be administered on days 1, 8, and 15 of the 28-day cycle treatment cycle and then the cycle is repeated every 4 weeks.

~~5623.~~ The ~~use method~~ of any one of claims 1-~~1952~~, wherein the anti-CD73 antibody or antigen binding fragment thereof is to be administered every 2 weeks for four doses and then every 4 weeks in a treatment cycle, and wherein the chemotherapy is to be administered on days 1 and 15 of the 28-day cycle treatment cycle and then the cycle is repeated every 4 weeks.

~~5724.~~ The ~~use method~~ of any one of claims ~~2024-2154~~, wherein anti-CD73 antibody or antigen binding fragment thereof is to be administered every 2 weeks for four doses and

then every 4 weeks in a treatment cycle, and wherein the anti-PD-L1 antibody or antigen binding fragment thereof is to be administered every four weeks in the treatment cycle, wherein the chemotherapy is to be administered on days 1, 8, and 15 of the 28-day treatment cycle, and then the cycle is repeated every 4 weeks.

5825. The use method of any one of claims ~~336-2356~~, wherein about 30% to about 70% of cells in a tumor sample obtained from the human subject have a staining intensity of at least 2.

~~59. — The method of claim 58, wherein at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, or about 70% of cells in a tumor sample obtained from the human subject have a staining intensity of at least 2.~~

~~60. — A method of inhibiting the growth of a tumor in a human subject comprising administering (i) oleclumab or antigen binding fragment thereof, (ii) durvalumab or antigen binding fragment thereof, and (iii) chemotherapy to the subject, wherein at least about 50% to about 90% of cells in a tumor sample obtained from the human subject have a staining intensity of 1, 2, or 3, as determined by IHC;~~

~~—— and wherein the oleclumab or antigen binding fragment is administered to the subject at a dose of 750 mg every 2 weeks for four doses and then every 4 weeks in a treatment cycle; the durvalumab or antigen binding fragment thereof is administered to the subject at a dose of 1500 mg every four weeks in the treatment cycle; and the chemotherapy comprises 1000 mg/m² gemcitabine and 125 mg/m² nab-paclitaxel and is administered on days 1, 8, and 15 of the 28-day treatment cycle and then the cycle is repeated every 4 weeks.~~

~~61. — A method of inhibiting the growth of a tumor in a human subject comprising administering (i) oleclumab or antigen binding fragment thereof, (ii) durvalumab or antigen binding fragment thereof, and (iii) chemotherapy to the subject, wherein at least about 50% to about 90% of cells in a tumor sample obtained from the human subject have a staining intensity of 1, 2, or 3, as determined by IHC;~~

~~—— and wherein the oleclumab or antigen binding fragment is administered to the subject at a dose of 1500 mg every 2 weeks for four doses and then every 4 weeks in a~~

treatment cycle; the durvalumab or antigen binding fragment thereof is administered to the subject at a dose of 1500 mg every four weeks in the treatment cycle; and the chemotherapy comprises 1000 mg/m² gemcitabine and 125 mg/m² nab-paclitaxel and is administered on days 1, 8, and 15 of the 28-day cycle and then the cycle is repeated every 4 weeks.

62. — A method of inhibiting the growth of a tumor in a human subject comprising administering (i) oleclumab or antigen binding fragment thereof, (ii) durvalumab or antigen binding fragment thereof, and (iii) chemotherapy to the subject, wherein at least about 50% to about 90% of cells in a tumor sample obtained from the human subject have a staining intensity of 1, 2, or 3, as determined by IHC;

— and wherein the oleclumab or antigen binding fragment is administered to the subject at a dose of 2250 mg every 2 weeks for four doses and then every 4 weeks in a treatment cycle; the durvalumab or antigen binding fragment thereof is administered to the subject at a dose of 1500 mg every four weeks in the treatment cycle; and the chemotherapy comprises 1000 mg/m² gemcitabine and 125 mg/m² nab-paclitaxel and is administered on days 1, 8, and 15 of the 28-day cycle and then the cycle is repeated every 4 weeks.

6326. Use of an anti-CD73 antibody or antigen binding fragment thereof in the manufacture of a medicament for A method of inhibiting the growth of a tumor in a human subject,

wherein the anti-CD73 antibody is comprising administering (i) oleclumab or antigen binding fragment thereof,

(ii) wherein the oleclumab or antigen binding fragment thereof is to be administered with durvalumab or antigen binding fragment thereof, and ~~(iii)~~ chemotherapy to the subject, wherein at least about 50% to about 90% of cells in a tumor sample obtained from the human subject have a staining intensity of 1, 2, or 3, as determined by IHC;

and wherein the oleclumab or antigen binding fragment is to be administered to the subject at a dose of 3000 mg every 2 weeks for four doses and then every 4 weeks in a treatment cycle; the durvalumab or antigen binding fragment thereof is to be administered to the subject at a dose of 1500 mg every four weeks in the treatment cycle; and the chemotherapy comprises 1000 mg/m² gemcitabine and 125 mg/m² nab-paclitaxel and is to

be administered on days 1, 8, and 15 of the 28-day cycle and then the cycle is repeated every 4 weeks.

64. — A method of inhibiting the growth of a tumor in a human subject comprising administering (i) ~~oleclumab or antigen binding fragment thereof~~, (ii) ~~durvalumab or antigen binding fragment thereof~~, and (iii) ~~chemotherapy to the subject~~, wherein at least about 50% to about 90% of cells in a tumor sample obtained from the human subject have a staining intensity of 1, 2, or 3, as determined by IHC;

~~and wherein the oleclumab or antigen binding fragment is administered to the subject at a dose of 750 mg every 2 weeks for four doses and then every 4 weeks in a treatment cycle; the durvalumab or antigen binding fragment thereof is administered to the subject at a dose of 1500 mg every four weeks in the treatment cycle; and the chemotherapy comprises mFOLFOX and is administered on days 1 and 15 of the 28-day treatment cycle and then the cycle is repeated every 4 weeks.~~

65. — A method of inhibiting the growth of a tumor in a human subject comprising administering (i) ~~oleclumab or antigen binding fragment thereof~~, (ii) ~~durvalumab or antigen binding fragment thereof~~, and (iii) ~~chemotherapy to the subject~~, wherein at least about 50% to about 90% of cells in a tumor sample obtained from the human subject have a staining intensity of 1, 2, or 3, as determined by IHC;

~~and wherein the oleclumab or antigen binding fragment is administered to the subject at a dose of 1500 mg every 2 weeks for four doses and then every 4 weeks in a treatment cycle; the durvalumab or antigen binding fragment thereof is administered to the subject at a dose of 1500 mg every four weeks in the treatment cycle; and the chemotherapy comprises mFOLFOX and is administered on days 1 and 15 of the 28-day treatment cycle and then the cycle is repeated every 4 weeks.~~

66. — A method of inhibiting the growth of a tumor in a human subject comprising administering (i) ~~oleclumab or antigen binding fragment thereof~~, (ii) ~~durvalumab or antigen binding fragment thereof~~, and (iii) ~~chemotherapy to the subject~~, wherein at least about 50% to about 90% of cells in a tumor sample obtained from the human subject have a staining intensity of 1, 2, or 3, as determined by IHC;

~~and wherein the oleclumab or antigen binding fragment is administered to the subject at a dose of 2250 mg every 2 weeks for four doses and then every 4 weeks in a treatment cycle; the durvalumab or antigen binding fragment thereof is administered to the subject at a dose of 1500 mg every four weeks in the treatment cycle; and the chemotherapy comprises mFOLFOX and is administered on days 1 and 15 of the 28-day treatment cycle and then the cycle is repeated every 4 weeks.~~

6727. Use of an anti-CD73 antibody or antigen binding fragment thereof in the manufacture of a medicament for ~~A method of inhibiting the growth of a tumor in a human subject comprising administering (i)~~

wherein the anti-CD73 antibody is oleclumab, or antigen binding fragment thereof,
wherein the oleclumab or antigen binding fragment thereof is to be administered
with (ii) durvalumab or antigen binding fragment thereof, and (iii) chemotherapy to the
 subject, wherein at least about 50% to about 90% of cells in a tumor sample obtained from the human subject have a staining intensity of 1, 2, or 3, as determined by IHC;

and wherein the oleclumab or antigen binding fragment is to be administered to the subject at a dose of 3000 mg every 2 weeks for four doses and then every 4 weeks in a treatment cycle; the durvalumab or antigen binding fragment thereof is to be administered to the subject at a dose of 1500 mg every four weeks in the treatment cycle; and the chemotherapy comprises mFOLFOX and is to be administered on days 1 and 15 of the 28-day treatment cycle and then the cycle is repeated every 4 weeks.

~~68. The method of any one of claims 60-67, wherein at least about 30% to about 70% of cells in a tumor sample obtained from the human subject have a staining intensity of at least 2.~~

~~69. The method of any one of claims 60-68, wherein at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, or about 70% of cells in a tumor sample obtained from the human subject have a staining intensity of at least 2.~~

~~70. The method of any one of claims 60-69, wherein the tumor is a 1st line metastatic pancreatic ductal adenocarcinoma.~~

71. ~~The method of any one of claims 60-69, wherein the tumor is a 2nd line metastatic pancreatic ductal adenocarcinoma.~~