SUMMARY

[0002] Disclosed are methods and compositions related to novel combination therapies comprising oncodriver pulsed dendritic cells and immunoregulator molecules inhibitors. In one aspect, the present disclosure provides an anti-cancer combination therapy comprising at least one dendritic cell pulsed with an oncodriver and at least one immunoregulatory molecule inhibitor; wherein the immunoregulatory molecule comprises Semaphorin 4D or VEGF. In another aspect, the present disclosure provides a use of at least one dendritic cell pulsed with an oncodriver and at least one immunoregulatory molecule inhibitor in the manufacture of a medicament for combination therapy to treat cancer in a subject; wherein the immunoregulatory molecule comprises Semaphorin 4D or VEGF. In yet another aspect, the present disclosure provides a use of at least one dendritic cell pulsed with an oncodriver in the manufacture of a first medicament and use of at least one immunoregulatory molecule inhibitor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer in a subject; and wherein the immunoregulatory molecule comprises Semaphorin 4D or VEGF. In a further aspect, the present disclosure provides a use of at least one dendritic cell pulsed with an oncodriver in the manufacture of a medicament for use in combinatorial therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with of at least one immunoregulatory molecule inhibitor; and wherein the immunoregulatory molecule comprises Semaphorin 4D or VEGF.

[0003] In one example, disclosed herein are anti-cancer combination therapies comprising at least one dendritic cell pulsed with an oncodriver (such as, for example, human epidermal growth factor receptor (HER) 2(HER2)) and at least one inhibitor of an immunoregulatory molecule (such as, for example, Semaphorin (SEMA) 4D (SEMA4D), or VEGF); wherein the immunoregulatory molecule being inhibited effects the vasculature of a tumor.

[0004] In one example, disclosed herein are methods of treating, preventing, reducing, and/or inhibiting a cancer (such as, for example, breast cancer (including triple negative breast cancer, metastatic breast cancer (MBC), ductal carcinoma in situ (DCIS), and invasive breast cancer (IBC)), melanoma, colorectal cancer, pancreatic cancer, prostate cancer, bladder cancer, ovarian cancer, and stomach cancer, and including primary and distant tumors) in a subject comprising administering the anti-cancer combination therapy of any preceding example. Thus, in one example, disclosed herein are methods of treating a cancer in a subject comprising

administering to the subject at least one dendritic cell pulsed with an oncodriver (such as, for example, human epidermal growth factor receptor (HER) 2 (HER2)) and at least one inhibitor of an immunoregulatory molecule (such as, for example, Semaphorin (SEMA) 4D (SEMA4D), or VEGF); wherein the immunoregulatory molecule being inhibited effects the vasculature of a tumor.

[0005] Also disclosed are anti-cancer combination therapies methods treating, preventing, reducing, and/or inhibiting a cancer of any preceding example; wherein the at least one immunoregulatory molecule inhibitor is administered systemically and/or the oncodriver pulsed dendritic cell is administered intratumorally.

[0006] In one example, also disclosed herein are anti-cancer combination therapies methods treating, preventing, reducing, and/or inhibiting a cancer of any preceding example; wherein the oncodriver pulsed dendritic cell is activated with IL-12 prior to administration.

[0007] Also disclosed herein are anti-cancer combination therapies methods treating, preventing, reducing, and/or inhibiting a cancer of any preceding example; wherein the at least one immunoregulator molecule inhibitor comprises an antibody or functional fragment thereof which binds to SEMA4D (also referred to herein as CD100) such as, for example, the anti-SEMA4D antibodies Mab 67 or VX15/2503 (Pepinemab). See, e.g., U.S. Patent No. 8,496,938, incorporated herein by reference.

[0008] In one example, also disclosed herein are anti-cancer combination therapies methods treating, preventing, reducing, and/or inhibiting a cancer of any preceding example; wherein the dendritic cells are removed from the subject and pulsed with oncodriver ex vivo.

[0009] Also disclosed herein are anti-cancer combination therapies methods treating, preventing, reducing, and/or inhibiting a cancer of any preceding example; wherein the pulsed dendritic cells are administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 30, 36 hours, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, 30, 31, 45 days, 2, 3, 4, 5, or 6 months prior to administration of the at least one immunoregulatory molecule inhibitor; are administered concurrently with the at least one immunoregulatory molecule inhibitor; or wherein the at least one immunoregulatory molecule inhibitor is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 30, 36 hours, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, 30, 31, 45 days, 2, 3, 4, 5, or 6 months prior to administration of the pulsed dendritic cells.

[0010] In one example, disclosed herein are anti-cancer combination therapies methods treating, preventing, reducing, and/or inhibiting a cancer of any preceding example; wherein the at least one pulsed dendritic cell is administered at least 1, 2, 3, 4, 5,6 ,7, 8, 9, 10, 11, 12, 13, 14, 15,

16, 17, 18, 19, 20, 21, 22, 23, or 24 times per day or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 times per week for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 days, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks.

[0011] Also disclosed herein are anti-cancer combination therapies methods treating, preventing, reducing, and/or inhibiting a cancer of any preceding example; wherein the at least one immunoregulatory molecule inhibitor is administered at least 1, 2, 3, 4, 5,6 ,7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 times per day or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 times per week for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 days, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks.

Brief Description of the Drawings

[0012] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments and together with the description illustrate the disclosed compositions and methods.

[0013] Figures 1A, 1B, 1C, and 1D show progressive loss of anti-oncodriver Th1 responses with advancing oncodriver-expressing breast disease, and association of anti-oncodriver immunity

Claims

What is claimed is:

1. An anti-cancer combination therapy comprising at least one dendritic cell pulsed with an oncodriver and at least one immunoregulatory molecule inhibitor; wherein the immunoregulatory molecule comprises Semaphorin 4D or VEGF.

2. The anti-cancer combination therapy of claim 1, wherein the oncodriver is human epidermal growth factor receptor (HER) HER2.

3. The anti-cancer combination therapy of claim 1 or claim 2, wherein the oncodriver pulsed dendritic cell is activated with IL-12 prior to administration.

4. The anti-cancer combination therapy of any one of claims 1 to 3, wherein the immunoregulatory molecule inhibitor comprises an antagonist antibody that specifically binds to SEMA4D or VEGF.

5. The anti-cancer combination therapy of claim 4, wherein the antagonist antibody that specifically binds to SEMA4D comprises pepinemab.

6. The anti-cancer combination therapy of any one of claims 1-5, wherein the at least one immunoregulatory inhibitor is formulated for systemic administration.

7. The anti-cancer combination therapy of any one of claims 1-6, wherein the at least one oncodriver pulsed dendritic cell is formulated for intratumoral administration.

8. The anti-cancer combination therapy of any one of claims 1-7, wherein the at least one dendritic cell pulsed with an oncodriver is obtained by removing dendritic cells from a subject to be treated with the anti-cancer combination therapy, and pulsed with the oncodriver *ex vivo*.

9. The anti-cancer combination therapy of any one of claims 1-8, wherein the cancer is breast cancer, melanoma, colorectal cancer, pancreatic cancer, prostate cancer, bladder cancer, ovarian cancer, stomach cancer, any combination thereof, or any metastasis thereof.

10. Use of at least one dendritic cell pulsed with an oncodriver and at least one immunoregulatory molecule inhibitor in the manufacture of a medicament for combination

therapy to treat cancer in a subject; wherein the immunoregulatory molecule comprises Semaphorin 4D or VEGF.

11. Use of at least one dendritic cell pulsed with an oncodriver in the manufacture of a first medicament and use of at least one immunoregulatory molecule inhibitor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer in a subject; and wherein the immunoregulatory molecule comprises Semaphorin 4D or VEGF.

12. Use of at least one dendritic cell pulsed with an oncodriver in the manufacture of a medicament for use in combinatorial therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with of at least one immunoregulatory molecule inhibitor; and wherein the immunoregulatory molecule comprises Semaphorin 4D or VEGF.

13. The use of any one of claims 10-12, wherein the oncodriver is human epidermal growth factor receptor (HER) HER2.

14. The at use of any one of claims 10-13, wherein the oncodriver pulsed dendritic cell is activated with IL-12 prior to administration.

15. The use of any one of claims 10 – 14, wherein the immunoregulatory molecule inhibitor comprises an antagonist antibody that specifically binds to SEMA4D or VEGF.

16. The use of claim 15, wherein the antagonist antibody that specifically binds to SEMA4D comprises pepinemab.

17. The use of any one of claims 10-16, wherein the at least one immunoregulatory inhibitor is formulated for systemic administration.

18. The use of any one of claims 10-17, wherein the at least one oncodriver pulsed dendritic cell is formulated for intratumoral administration.

19. The use of any one of claims 10-18 wherein the at least one dendritic cell pulsed with an oncodriver is obtained by removing dendritic cells from a subject to be treated with the anti-cancer combination therapy, and pulsed with the oncodriver *ex vivo*.

20. The use of any one of claims 10-19 wherein the cancer is breast cancer, melanoma, colorectal cancer, pancreatic cancer, prostate cancer, bladder cancer, ovarian cancer, stomach cancer, any combination thereof, or any metastasis thereof.