T CELL REPERTOIRE DYNAMICS AND ONCOLYTIC VIRAL THERAPY

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Application No. 62/809,190, filed February 22, 2019, which is incorporated by reference herein in its entirety.

BACKGROUND

Cancer is one of the leading causes of death. Although it has long been the focus of medical research, main cancer therapies remain surgery, radiation therapy and chemotherapy. Each one of these therapies is subject to limitations including, for example, the differing effects of the same therapy to subjects with similar types of cancer.

BRIEF SUMMARY

Provided herein are methods of treating cancer in a subject, and, more particularly, a method of treating cancer in a subject selected for likely treatment success by determining whether the subject demonstrates a T-cell population exhibiting high peripheral clonality after a first round of treatment. The methods include administering to a subject with cancer one or more doses of an oncolytic virus, such as a reovirus; selecting a subject with a T-cell population exhibiting high peripheral clonality (e.g., greater than 0.06) after treatment with one or more doses of the oncolytic virus; and administering to the subject with a T-cell population exhibiting high peripheral clonality one or more subsequent doses of the oncolytic virus. Optionally, the oncolytic virus is administered in combination with one or more additional agents.

The details of one or more ~~embodiments~~ examples are set forth in the accompanying description below. Other features, objects, and advantages will be apparent from the description and from the claims.

In one aspect, provided herein is a use of one or more doses of an oncolytic virus in the manufacture of a medicament for treating cancer in a subject, the use comprising: (i) that the one or more doses of an oncolytic virus are to be administered to the subject; (ii) selecting a subject with a T-cell population exhibiting high peripheral clonality of greater than 0.06 after treatment with the one or more doses of the oncolytic virus; and (iii) that one

or more subsequent doses of the oncolytic virus are to be administered to the subject with a T-cell population exhibiting high peripheral clonality.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing a trend towards decreased peripheral clonality over treatment using the paired Wilcox rank sum test.

Figure 2 is a graph showing a trend towards increased peripheral diversity over treatment using the paired wilcox rank sum test.

WHAT IS CLAIMED IS:

1. Use of one or more doses of an oncolytic virus in the manufacture of a medicament for treating cancer in a subject, the use comprising:

(i) that the one or more doses of an oncolytic virus are to be administered to the subject;

(ii) selecting a subject with a T-cell population exhibiting high peripheral clonality of greater than 0.06 after treatment with the one or more doses of the oncolytic virus; and

(iii) that one or more subsequent doses of the oncolytic virus are to be administered to the subject with a T-cell population exhibiting high peripheral clonality.

~~2. The use of claim 1, wherein the peripheral clonality is greater than 0.06.~~

~~3~~2. The use of claim 1 ~~or 2~~, wherein the subject also has a T cell population with low diversity of less than 1800 rearrangements.

~~4. The use of claim 3, wherein the T cell population diversity is less than 1800 rearrangements.~~

~~5~~3. The use of any one of claims 1-~~4~~2, wherein the cancer is an adenocarcinoma.

~~6~~4. The use of any one of claims 1-~~4~~2, wherein the cancer is breast cancer or pancreatic adenocarcinoma.

~~7~~5. The use of any one of claims 1-~~6~~4, wherein approximately 10^3 to 10^{12} plaque forming units (PFU) of the oncolytic virus is to be administered to the subject.

~~8~~6. The use of any one of claims 1-~~6~~4, wherein approximately 10^8 to 10^{12} PFU of the oncolytic virus is to be administered to the subject.

~~9~~7. The use of any one of claims 1-~~6~~4, wherein approximately 10^8 to 10^{12} TCID50 of the oncolytic virus is to be administered to the subject.

~~10~~8. The use of any one of claims 1-~~9~~7, wherein the oncolytic virus is to be administered as an intravenous infusion.

~~11~~9. The use of any one of claims 1-~~10~~8, further comprising that one or more additional therapeutic agents are to be administered to the subject.

~~12~~ 10. The use of claim ~~11~~9, wherein the additional therapeutic agent is a chemotherapeutic agent.

~~13~~11. The use of claim ~~11~~9, wherein the additional therapeutic agent is an immune checkpoint inhibitor or an aromatase inhibitor.

~~14~~12. The use of claim ~~13~~11, wherein the immune checkpoint inhibitor is a PD-1 or PD-L1 inhibitor.

~~15~~13. The use of claim ~~13~~11, wherein the immune checkpoint inhibitor is selected from the group consisting of nivolumab, lambrolizumab, pembrolizumab, atezolizumab, avelumab, durvalumab, and cemiplimab.

~~16~~14. The use of any one of claims 1-~~15~~13, wherein selection of the subject with a T cell population with high peripheral clonality and low diversity results in longer progression free survival or overall survival of the subject treated with the oncolytic virus as compared subjects without selection or as compared to subjects lacking a T cell population with high peripheral clonality and low diversity after one or more doses of the oncolytic virus.

~~17~~15. The use of any one of claims 1-~~16~~14, wherein the oncolytic virus is selected from the group consisting of a reovirus, a Newcastle disease virus (NDV), a vesicular stomatitis virus (VSV), an adenovirus, a vaccinia virus, a parapox orf virus, a Sindbis virus, and a herpes simplex virus.

~~18~~16. The use of claim ~~17~~15, wherein the reovirus is a mammalian reovirus.

~~19~~17. The use of claim ~~18~~16, wherein the reovirus is a human reovirus.

~~20~~18. The use of claim ~~18~~16, wherein the reovirus is selected from the group consisting of serotype 1 reoviruses, serotype 2 reoviruses, serotype 3 reoviruses.

~~21~~19. The use of claim ~~20~~18, wherein the reovirus is a serotype 3 reovirus.

~~22~~20. The use of claim ~~21~~19, wherein the serotype 3 reovirus is a Dearing strain reovirus .

~~23~~21. The use of claim ~~18~~16, wherein the reovirus is deposited as IDAC Accession No. 190907-01.

~~24~~22. The use of claim ~~18~~16, wherein the reovirus comprises a lambda-3 polypeptide having one or more amino acid modifications, a sigma-3 polypeptide having one or more amino acid modifications, a mu-1 polypeptide having one or more amino acid modifications, a mu-2 polypeptide having one or more amino acid modifications, or any combination thereof.

~~25~~23. The use of claim ~~18~~16, wherein the reovirus comprises one or more of the following polypeptides:

a sigma-3 polypeptide having one or more amino acid modifications, wherein the one or more amino acid modifications are selected from the group consisting of a Leu at residue 14, a Lys at residue 198, or any combination thereof, numbered relative to GenBank Accession No. K02739 (SEQ ID NO:25), wherein when the amino acid sequence comprises a Leu at residue 14, the amino acid sequence further comprises at least one additional modification in the amino acid sequence;

a mu-1 polypeptide having at least one amino acid modification, wherein the at least one amino acid modification comprises an Asp at residue 73 numbered relative to GenBank Accession No. M20161.1 (SEQ ID NO:27);

a lambda-3 polypeptide having one or more amino acid modifications, wherein the one or more amino acid modifications are selected from the group consisting of a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue 963, a Leu at residue 979, an Arg at residue 1045, a Val at residue 1071, or any combination thereof, numbered relative to GenBank Accession No. M24734.1 (SEQ ID NO:23), wherein when the amino acid sequence comprises a Val at

residue 214 or a Val at residue 1071, the amino acid sequence further comprises at least one additional modification in the amino acid sequence; or

a mu-2 polypeptide having at least one amino acid modification, wherein the at least one amino acid modification comprises a Ser at residue 528 numbered relative to GenBank Accession No. AF461684.1 (SEQ ID NO:29).

~~26~~24. The use of claim ~~18~~16, wherein the reovirus comprises one or more of the following genome segments:

a S4 genome segment having one or more nucleic acid modifications, wherein the one or more nucleic acid modifications in the S4 genome segment are selected from the group consisting of an A at position 74 and an A at position 624, numbered relative to GenBank Accession No. K02739 (SEQ ID NO:24);

a M2 genome segment having at least one nucleic acid modification, wherein the at least one nucleic acid modification comprises a C at position 248, numbered relative to GenBank Accession No. M20161.1 (SEQ ID NO:26);

a L1 genome segment comprising one or more nucleic acid modifications, wherein the one or more nucleic acid modifications are selected from the group consisting of a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, a C at position 2953, an A at position 3153, a G at position 3231, numbered relative to GenBank Accession No. M24734.1 (SEQ ID NO:22); or

a M1 genome segment having at least one nucleic acid modification, wherein the at least one nucleic acid modification comprises a T at position 1595, numbered relative to GenBank Accession No. AF461684.1 (SEQ ID NO:28).

~~27~~25. The use of claim ~~18~~16, wherein the reovirus is a recombinant reovirus.

~~28~~26. The use of claim ~~18~~16, wherein the reovirus is a modified reovirus.