[0005] The disclosures of all publications, patents, patent applications and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

SUMMARY

[0006] The present application provides methods, compositions (including pharmaceutical compositions) and kits for treating bladder cancer in an individual comprising intravesical administration of an oncolytic virus, *e.g.*, CG0070.

[0006a] In one aspect, the present disclosure refers to use of an effective amount of an oncolytic virus in the manufacture of a medicament for treating bladder carcinoma in situ in an individual, wherein the medicament is formulated for intravesical administration to the individual once per week for three or six weeks during a maintenance phase, wherein the oncolytic virus is CG0070.

[0007] In one example, provided herein is a method of treating bladder cancer in an individual, comprising intravesically administering to the individual an effective amount of an oncolytic virus once per week for three weeks during a maintenance phase, wherein the oncolytic virus comprises a viral vector comprising a tumor cell-specific promoter operably linked to a viral gene essential for replication of the oncolytic virus, and a heterologous gene encoding an immune-related molecule. In one aspect, the present disclosure refers to use of an effective amount of an oncolytic virus in the manufacture of a medicament for treating bladder cancer in an individual, wherein the medicament is formulated for intravesical administration to the individual once per week for three or six weeks during a maintenance phase, wherein the oncolytic virus is CG0070.

[0008] In another example, provided herein is a method of bladder preservation in an individual comprising intravesically administering to the individual an effective amount of an oncolytic virus once per week for three weeks during a maintenance phase, wherein the oncolytic virus comprises a viral vector comprising a tumor cell-specific promoter operably linked to a viral gene essential for replication of the oncolytic virus, and a heterologous gene encoding an immune-related molecule. In one aspect, the present disclosure refers to use of an effective amount of an oncolytic virus in the manufacture of a medicament for bladder preservation in an individual having bladder cancer, wherein the medicament is formulated for intravesical administration to the individual once per week for three or six weeks during a maintenance phase, wherein the oncolytic virus is CG0070.

[0009] In some examples, according to any of the methods described above, the oncolytic virus is administered once per week for three weeks every six months during the maintenance phase. In some examples, the method further comprises an induction phase prior to the maintenance phase, wherein the induction phase comprises administering to the induvial an effective amount of oncolytic virus once per week for six weeks. In some examples, the start of the induction phase and the start of the maintenance phase are separated by about 3 months. In some examples, the start of the induction phase and the start of the maintenance phase are separated by about 6 months. In some examples, the induction phase comprises administering to the individual an effective amount of an oncolytic virus once per week for six weeks on month zero and month three of a treatment regimen.

[0010] Also provided herein is a method of treating Ta or T1 bladder cancer in an individual who has not received a transurothelial resection of bladder tumor (TURBT), comprising intravesically administering to the individual an effective amount of an oncolytic virus, wherein the oncolytic virus comprises a viral vector comprising a tumor cell-specific promoter operably

linked to a viral gene essential for replication of the oncolytic virus, and a heterologous gene encoding an immune-related molecule. In one example, the present disclosure refers to use of an effective amount of an oncolytic virus in the manufacture of a medicament for treating Ta or T1 bladder cancer in an individual who has not received a transurothelial resection of bladder tumor (TURBT), wherein the medicament is formulated for intravesical administration to the individual, wherein the oncolytic virus comprises a viral vector comprising a tumor cell-specific promoter operably linked to a viral gene essential for replication of the oncolytic virus, and a heterologous gene encoding an immune-related molecule.

[0011] In one example of the present application, there is provided a method of treating bladder cancer in an individual (such as a human), comprising intravesically administering to the individual an effective amount of an oncolytic virus, wherein the oncolytic virus comprises a viral vector comprising a tumor cell-specific promoter operably linked to a viral gene essential for replication of the oncolytic virus, and a heterologous gene encoding an immune-related molecule. In some examples, the individual only has bladder carcinoma in situ. In some examples, the individual does not have a concurrent papillary carcinoma of Ta or T1 stage. In some examples, the individual has bladder carcinoma in situ and a carcinoma of Ta or Ta stage (CIS + Ta or CIS + T1). In some examples, the individual has Ta or T1 bladder cancer but not carcinoma in situ. In some examples, the individual has Ta or T1 bladder cancer and has not received a transurothelial resection of bladder tumor (TURBT). In some examples, the individual has non-resectable Ta or T1 stage bladder cancer. In some examples, the individual is unresponsive to BCG treatment. In some examples, the individual has disease reoccurrence subsequent to BCG treatment. In some examples, the individual has failed the BCG treatment within about 6 months. In some examples, the individual is refractory to BCG.

[0012] In some examples according to any one of the methods described above, the individual has not received a cystectomy. In some examples, the individual has refused or is ineligible for a cystectomy. In some examples, the cystectomy is radical cystectomy.

[0013] In some examples according to any one of the methods described above, the oncolytic virus preferentially replicates in a cancer cell. In some examples, the cancer cell is defective in the Rb pathway. In some examples, the tumor-specific promoter is an E2F-1 promoter. In some examples, the E2F-1 promoter comprises the nucleotide sequence set forth in SEQ ID NO:1.

[0014] In some examples according to any one of the methods described above, the immune-related molecule is selected from the group consisting of GM-CSF, IL-2, IL-12, interferon, CCL4, CCL19, CCL21, CXCL13, TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, RIG-I, MDA5, LGP2, and LTαβ. In some examples, the immune-related molecule is GM-CSF. In some examples, the heterologous gene is operably linked to a viral promoter.

CLAIMS

What is claimed is:

1. Use of an effective amount of an oncolytic virus in the manufacture of a medicament for treating bladder carcinoma in situ in an individual, wherein the medicament is formulated for intravesical administration to the individual once per week for three or six weeks during a maintenance phase, wherein the oncolytic virus is CG0070.

2. Use of an effective amount of an oncolytic virus in the manufacture of a medicament for treating bladder cancer in an individual, wherein the medicament is formulated for intravesical administration to the individual once per week for three or six weeks during a maintenance phase, wherein the oncolytic virus is CG0070.

3. Use of an effective amount of an oncolytic virus in the manufacture of a medicament for bladder preservation in an individual having bladder cancer, wherein the medicament is formulated for intravesical administration to the individual once per week for three or six weeks during a maintenance phase, wherein the oncolytic virus is CG0070.

4. The use of any one of claims 1-3, wherein the medicament is to be administered once per week for three weeks every six months during the maintenance phase.

5. The use of claim 4, wherein the medicament is to be administered to the individual once per week for six weeks during an induction phase prior to the maintenance phase.

6. The use of claim 5, wherein the start of the induction phase and the start of the maintenance phase are separated by 3 months or 6 months.

7. The use of claim 5 or 6, wherein the medicament is to be administered to the individual once per week for six weeks on month zero and month three of a treatment regimen during the induction phase.

8. The use of any one of claims 1-7, wherein the individual has carcinoma in situ.

9. The use of claim 8, wherein the individual does not have a concurrent papillary carcinoma of Ta or T1 stage.

10. The use of any one of claims 1-8, wherein the individual has Ta or T1 stage bladder cancer.

11. The use of claim 10, wherein the individual does not have carcinoma in situ.

12. The use of any one of claims 1-11, wherein the individual is unresponsive to Bacillus Calmette-Guerin (BCG) treatment.

13. The use of any one of claims 1-12, wherein the individual has disease reoccurrence subsequent to BCG treatment.

14. The use of any one of claims 1-13, wherein the individual has failed the BCG treatment within 6 months.

15. The use of any one of claims 1-14, wherein the individual has not received a cystectomy.

16. The use of any one of claims 1-15, wherein the individual has refused or is ineligible for a cystectomy.

17. The use of any one of claims 1-16, wherein the oncolytic virus is to be administered at a dose of t1 x 10^8 to 1x 10^{14} viral particles.

18. The use of any one of claims 1-17, wherein the oncolytic virus is to be administered in a volume of 50 mL.

19. The use of any one of claims 1-18, wherein the individual is to be further administered a transduction enhancing agent prior to the administration of the oncolytic virus, optionally wherein the transduction enhancing agent is N-Dodecyl-β-D-maltoside (DDM).

20. The use of any one of claims 1-19, wherein:

(i) the oncolytic virus is not to be administered in conjunction with an immune checkpoint modulator; and/or

(ii) the oncolytic virus is to be administered as a single therapeutic agent.