[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, 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.

[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 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.

[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, wherein the medicament is formulated for intravesical administration to the individual 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.

[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 aspect, 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.

[0015] In some examples according to any one of the methods described above, the oncolytic virus is selected from the group consisting of adenovirus, herpes simplex virus, vaccinia virus, mumps virus, Newcastle disease virus, polio virus, measles virus, Seneca valley virus, coxsackie virus, reo virus, vesicular stomatitis virus, maraba and rhabdovirus, and parvovirus. In some examples, the oncolytic virus is an oncolytic adenovirus. In some examples, the viral gene essential for replication of the oncolytic virus is selected from the group consisting of E1A, E1B, and E4. In some examples, the heterologous gene is operably linked to an E1 promoter or an E3 promoter. In some examples, the oncolytic virus is an adenovirus serotype 5, wherein the endogenous E1a promoter of a native adenovirus is replaced by the human E2F-1 promoter, and the endogenous E3 19kD coding region of the native adenovirus is replaced by a nucleic acid encoding human GM-CSF. In some examples, the oncolytic virus is CG0070.

[0016] In some examples according to any one of the methods described above, the oncolytic virus is administered at a dose of about 1 x 10^8 to about 1x 10^{14} viral particles.

[0017] In some examples according to any one of the methods described above, the oncolytic virus is administered weekly. In some examples, the oncolytic virus is administered for about 1 week to about 6 weeks.

[0018] In some examples according to any one of the methods described above, the method further comprises intravesically administering to the individual a transduction enhancing agent prior to the administration of the oncolytic virus. In some examples, the transduction enhancing agent is N-Dodecyl-β-D-maltoside (DDM).

[0019] In some examples according to any one of the methods described above, the method is repeated for at least once.

[0020] In some examples according to any one of the methods described above, the oncolytic virus is not administered in conjunction with an immune checkpoint modulator.

[0021] In some examples according to any one of the methods described above, the oncolytic virus is administered as a single therapeutic agent.

[0022] Also provided in one example is a pharmaceutical composition for treating bladder cancer in an individual (such as a human), wherein the pharmaceutical composition is intravesically administered to the individual, and wherein the pharmaceutical composition comprises 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.

[0023] Further provided in one example is use of an oncolytic virus in the preparation of a medicament for treating bladder cancer in an individual (such as a human), wherein the medicament is administered to the individual intravesically, and 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.

[0024] These and other aspects and advantages of the present disclosure will become apparent from the subsequent detailed description and the appended claims. It is to be understood that one, some, or all of the properties of the various examples described herein may be combined to form other examples of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] FIG. 1 is a schematic diagram of CG0070 and wild type (wt) adenovirus type 5. CG0070 is based on adenovirus serotype 5, but the endogenous E1a promoter and E3 19kD coding region have been replaced by the human E2F-1 promoter and a cDNA coding region of human GM-CSF, respectively.

[0026] FIG. 2 shows percentage of complete response (CR) in patients having high-grade non-muscle-invasive bladder cancer of various stages at 6 months after receiving intravesical CG0070 therapy.

DETAILED DESCRIPTION OF THE INVENTION

[0027] The present invention provides methods and compositions for treating bladder cancer in an individual by intravesically administering to the individual an effective amount of an oncolytic virus, such as CG0070. *In vitro* studies have suggested that using a conditionally replicating oncolytic virus such as CG0070 could be an effective strategy for treating bladder cancer. Ramesh N, Ge Y, Ennist DL, Zhu M, Mina M, Ganesh S, Reddy PS, Yu DC. CG0070, a conditionally replicating granulocyte macrophage colony-stimulating factor-armed oncolytic adenovirus for the treatment of bladder cancer. Clin Cancer Res. 2006; 12:305-13. However, the unexpected efficacy of CG0070 in certain patient populations and the effect of certain dosing regimens as described herein were previously unknown. The methods are bladder-preserving, highly efficacious and well-tolerated in bladder cancer, including those that have previously failed standard-of-care therapies. In a Phase II clinical trial, inventors surprisingly found that 72.2% of patients with pure CIS, who had previously failed BCG therapy, had complete response (CR) after 6 months of intravesical CG0070 therapy. The therapeutic effects of the

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, 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.

2. The use of claim 1, wherein the individual only has bladder carcinoma in situ.

3. The use of claim 2, wherein the individual does not have a concurrent papillary carcinoma of Ta or T1 stage.

4. The use of any one of claims 1-3, wherein:

(i) the oncolytic virus is to be administered weekly;

(ii) the oncolytic virus is to be administered for about 1 week to about 6 weeks; and/or

(iii) the treatment is to be repeated for at least once.

5. 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 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.

6. Use of an effective amount of an oncolytic virus in the manufacture of a medicament for bladder preservation in an individual, wherein the medicament is formulated for intravesical administration to the individual 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.

7. The use of claim 5 or 6, wherein the oncolytic virus is administered once per week for three weeks every six months during the maintenance phase.

8. The use of claim 7, further comprising an induction phase prior to the maintenance phase, wherein the induction phase comprises administering to the individual an effective amount of an oncolytic virus once per week for six weeks, optionally wherein:

(i) the start of the induction phase and the start of the maintenance phase are separated by about 3 months or about 6 months; and/or

(ii) 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.

9. The use of any one of claims 5-8, wherein the individual has carcinoma in situ.

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

11. The use of any one of claims 5-9, wherein the individual has Ta or T1 stage bladder cancer.

12. 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.

13. The use of any one of claims 1-12, wherein:

(i) the individual is unresponsive to BCG treatment;

(ii) the individual has disease reoccurrence subsequent to BCG treatment; and/or

(iii) the individual has failed the BCG treatment within about 6 months.

14. The use of any one of claims 1-13, wherein:

(i) the individual has not received a cystectomy; and/or

(ii) the individual has refused or is ineligible for a cystectomy.

15. The use of any one of claims 1-14, wherein the oncolytic virus preferentially replicates in a cancer cell, optionally wherein:

(i) the cancer cell is defective in the Rb pathway;

(ii) the tumor cell-specific promoter is an E2F-1 promoter; and/or

(iii) the E2F-1 promoter comprises the nucleotide sequence set forth in SEQ ID NO:1.

16. The use of any one of claims 1-15, wherein:

(i) 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, optionally wherein the immune-related molecule is GM-CSF;

(ii) the heterologous gene is operably linked to a viral promoter; and/or

(iii) the oncolytic virus is selected from the group consisting of adenovirus, herpes simplex virus, vaccinia virus, mumps virus, Newcastle disease virus, polio virus, measles virus, Seneca valley virus, coxsackie virus, reo virus, vesicular stomatitis virus, maraba and rhabdovirus, and parvovirus.

17. The use of claim 16, wherein the oncolytic virus is an oncolytic adenovirus, optionally wherein:

(i) the viral gene essential for replication of the oncolytic virus is selected from the group consisting of E1A, E1B, and E4;

(ii) the heterologous gene is operably linked to an E1 promoter or an E3 promoter; and/or

(iii) the oncolytic virus is an adenovirus serotype 5, wherein the endogenous E1a promoter of a native adenovirus is replaced by the human E2F-1 promoter, and the endogenous E3 19kD coding region of the native adenovirus is replaced by a nucleic acid encoding human GM-CSF.

18. The use of claim 17, wherein the oncolytic virus is CG0070.

19. The use of any one of claims 1-18, wherein:

(i) the oncolytic virus is administered at a dose of about 1 x 10^8 to about 1x 10^{14} viral particles;

(ii) the oncolytic virus is administered in a volume of 50 mL; and/or

(iii) 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 administered in conjunction with an immune checkpoint modulator; and/or

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