pared to the effects of only viral vectors comprising cytokine transgene or only adoptive cell transfers.

It is a further object of the present disclosure to provide a combination of tumor infiltrating lymphocytes (TIL) and transgenic (produced from a virally delivered transgene) interleukin-2 (IL-2) for the treatment of malignancy in humans. The above and various other objects and advantages of the present disclosure are achieved by a method of treating malignancy in humans, comprising administering an effective amount of TIL and IL-2, with or without preconditioning chemotherapy and/or radiotherapy, to a patient afflicted with cancer to cause regression or stabilization of the cancer.

The present disclosure relates to a method of treating cancer in a subject, wherein the method comprises separate administration of adoptive cell therapeutic composition and oncolytic (=replication competent in tumor but not normal cells) adenoviral vectors coding for at least one cytokine to a subject.

In one aspect, there is provided an oncolytic adenoviral vector coding for at least one cytokine together with separate adoptive T-cell therapeutic composition for use in treatment of cancer, wherein said oncolytic adenoviral vector is

an adenovirus serotype 5 (Ad5) vector comprising

- a 5/3 chimeric fiber knob,
- E2F1 promoter for tumor specific expression of E1A,
- a 24 bp deletion (D24) in the Rb binding constant region 2 of adenoviral E1,
- a nucleic acid sequence deletion of viral gp19k and 6.7k reading frames, and
- a nucleic acid sequence encoding at least TNFalpha or IL-2 transgene in the place of the deleted gp19k/6.7K in the E3 region resulting in replication-associated control of transgene expression under the viral E3 promoter.

In one aspect, there is provided a use of an oncolytic adenoviral vector coding for at least one cytokine in the manufacture of a medicament for treating cancer in a subject, wherein the medicament is to be administered with separate adoptive T-cell therapeutic composition, wherein said oncolytic adenoviral vector is

an adenovirus serotype 5 (Ad5) vector comprising

- a 5/3 chimeric fiber knob,
- E2F1 promoter for tumor specific expression of E1A,
- a 24 bp deletion (D24) in the Rb binding constant region 2 of adenoviral E1,
- a nucleic acid sequence deletion of viral gp19k and 6.7k reading frames, and
- a nucleic acid sequence encoding at least TNFalpha or IL-2 transgene in the place of the deleted gp19k/6.7K in the E3 region resulting in replication-associated control of transgene expression under the viral E3 promoter.

In one aspect, there is provided an oncolytic adenoviral vector for use in increasing the efficacy of separate adoptive T-cell therapy in a tumor of a subject, wherein said oncolytic adenoviral vector is

an adenovirus serotype 5 (Ad5) vector comprising

- a 5/3 chimeric fiber knob,
- E2F1 promoter for tumor specific expression of E1A,
- a 24 bp deletion (D24) in the Rb binding constant region 2 of adenoviral E1,
- a nucleic acid sequence deletion of viral gp19k and 6.7k reading frames, and
- a nucleic acid sequence encoding at least TNFalpha or IL-2 transgene in the place of the deleted gp19k/6.7K in the E3 region resulting in replication-associated control of transgene expression under the viral E3 promoter.

In one aspect, there is provided a use of an oncolytic adenoviral vector in the manufacture of a medicament for increasing the efficacy of adoptive T-cell therapy in a tumour of a subject in need thereof, wherein said oncolytic adenoviral vector is

an adenovirus serotype 5 (Ad5) vector comprising

- a 5/3 chimeric fiber knob,
- E2F1 promoter for tumor specific expression of E1A,
- a 24 bp deletion (D24) in the Rb binding constant region 2 of adenoviral E1,
- a nucleic acid sequence deletion of viral gp19k and 6.7k reading frames, and
- a nucleic acid sequence encoding at least TNFalpha or IL-2 transgene in the place of the deleted gp19k/6.7K in the E3 region resulting in replication-associated control of transgene expression under the viral E3 promoter.

Also, the present disclosure relates to a method of increasing the efficacy of adoptive cell therapy or T-cell therapy in a subject by administering an oncolytic adenoviral vector to a subject in need thereof.

In one aspect, there is provided a pharmaceutical kit comprising an adoptive T-cell therapeutic composition and an oncolytic adenoviral vector coding for at least one cytokine, wherein the adoptive cell therapeutic composition is formulated in a first formulation and the oncolytic adenoviral vector coding for at least one cytokine is formulated in a second formulation, wherein said oncolytic adenoviral vector is an adenovirus serotype 5 (Ad5) vector comprising

- a 5/3 chimeric fiber knob,
- E2F1 promoter for tumor specific expression of E1A,
- a 24 bp deletion (D24) in the Rb binding constant region 2 of adenoviral E1,
- a nucleic acid sequence deletion of viral gp19k and 6.7k reading frames, and
- a nucleic acid sequence encoding at least TNFalpha or IL-2 transgene in the place of the deleted gp19k/6.7K in the E3 region resulting in replication-associated control of transgene expression under the viral E3 promoter.

In one aspect, there is provided an oncolytic adenoviral vector comprising

1) an adenovirus serotype 5 (Ad5) nucleic acid backbone comprising a 5/3 chimeric fiber knob:

2) E2F1 promoter for tumor specific expression of E1A;

3) a 24 bp deletion (D24) in the Rb binding constant region 2 of adenoviral E1;

4) a nucleic acid sequence deletion of viral *gp19k* and *6.7k* reading frames; and

5) a nucleic acid sequence encoding at least one cytokine transgene in the place of the deleted *gp19k/6.7K* in the E3 region resulting in replication-associated control of transgene expression under the viral E3 promoter, wherein the at least one cytokine is TNFalpha or IL-2.

Disclosed is a serotype 3 (Ad3) oncolytic adenoviral vector comprising: a promoter for tumor specific expression, a deletion in the E3 area affecting E3 9 kDa, E3 10.2 kDa, E3 15.2 kDa and E3 15.3 kDa and an exogenous or tumor specific promoter for expression of a transgene in the place of the deleted area of E3.

In one aspect, there is provided a pharmaceutical composition comprising an oncolytic vector as defined herein.

Also, the present disclosure relates to a method of treating cancer in a subject, wherein the method comprises administration of the oncolytic adenoviral vector of the present disclosure to a subject in need thereof.In one aspect, there is provided an oncolytic adenoviral vector as defined herein for use in treatment of cancer.

In one aspect, there is provided a use of an oncolytic adenoviral vector as defined herein in the manufacture of a medicament for treating

CLAIMS

1. Use of an oncolytic adenoviral vector coding for at least one cytokine in the manufacture of a medicament for treating cancer in a subject, wherein the medicament is to be administered with separate adoptive T-cell therapeutic composition, wherein said oncolytic adenoviral vector is an adenovirus serotype 5 (Ad5) vector comprising

- a 5/3 chimeric fiber knob,
- E2F1 promoter for tumor specific expression of E1A,
- a 24 bp deletion (D24) in the Rb binding constant region 2 of adenoviral E1,
- a nucleic acid sequence deletion of viral gp19k and 6.7k reading frames, and
- a nucleic acid sequence encoding at least TNFalpha or IL-2 transgene in the place of the deleted gp19k/6.7K in the E3 region resulting in replication-associated control of transgene expression under the viral E3 promoter.

2. An oncolytic adenoviral vector coding for at least one cytokine together with separate adoptive T-cell therapeutic composition for use in treatment of cancer, wherein said oncolytic adenoviral vector is an adenovirus serotype 5 (Ad5) vector comprising

- a 5/3 chimeric fiber knob,
- E2F1 promoter for tumor specific expression of E1A,
- a 24 bp deletion (D24) in the Rb binding constant region 2 of adenoviral E1,
- a nucleic acid sequence deletion of viral gp19k and 6.7k reading frames, and
- a nucleic acid sequence encoding at least TNFalpha or IL-2 transgene in the place of the deleted gp19k/6.7K in the E3 region resulting in replication-associated control of transgene expression under the viral E3 promoter.

3. The use or the oncolytic adenoviral vector according to claim 1 or 2, wherein the cancer is selected from a group consisting of nasopharyngeal cancer, synovial cancer, hepatocellular cancer, renal cancer, cancer of connective tissues, melanoma, lung cancer, bowel cancer, colon cancer, rectal cancer, colorectal cancer, brain cancer, throat cancer, oral cancer, liver cancer, bone cancer, pancreatic cancer, choriocarcinoma, gastrinoma, pheochromocytoma, prolactinoma, T-cell leukemia/lymphoma, neuroma, von Hippel-Lindau disease, Zollinger-Ellison syndrome, adrenal cancer, anal cancer, bile duct cancer, bladder cancer, ureter cancer, brain cancer, oligodendroglioma, neuroblastoma, meningioma, spinal cord tumor, bone cancer, osteochondroma, chondrosarcoma, Ewing's sarcoma, cancer of unknown primary site, carcinoid, carcinoid of gastrointestinal tract, fibrosarcoma, breast cancer, Paget's disease, cervical cancer, colorectal cancer, rectal cancer, esophagus cancer, gall bladder cancer, head cancer, eye cancer, neck cancer, kidney cancer, Wilms' tumor, liver cancer, Kaposi's sarcoma, prostate cancer, lung cancer, testicular cancer, Hodgkin's disease, non-Hodgkin's lymphoma, oral cancer, skin cancer, mesothelioma, multiple myeloma, ovarian cancer, endocrine pancreatic cancer, glucagonoma, pancreatic cancer, parathyroid cancer, penis cancer, pituitary cancer, soft tissue sarcoma, retinoblastoma, small intestine cancer, stomach cancer, thymus cancer, thyroid cancer, trophoblastic cancer, hydatidiform mole, uterine cancer, endometrial cancer, vagina cancer, vulva cancer, acoustic neuroma, mycosis fungoides, insulinoma, carcinoid syndrome, somatostatinoma, gum cancer, heart cancer, lip cancer, meninges cancer, mouth cancer, nerve cancer, palate cancer, parotid gland cancer, peritoneum cancer, pharynx cancer, pleural cancer, salivary gland cancer, tongue cancer and tonsil cancer.

4. The use or the oncolytic adenoviral vector according to any one of claims 1-3, wherein the subject is a human or an animal.

5. The use or the oncolytic adenoviral vector according to any one of claims 1-4, wherein the adoptive cell therapeutic composition and oncolytic viral vectors coding for at least one cytokine are to be administered to a subject simultaneously or consecutively, in any order.

6. The use or the oncolytic adenoviral vector according to claim 5, wherein there is a time period of one minute to four weeks between the consecutive administration of adoptive cell therapeutic composition and oncolytic viral vectors coding for at least one cytokine and/or there are several administrations of adoptive cell therapeutic composition and oncolytic viral vectors.

7. The use or the oncolytic adenoviral vector according to any one of claims 1-6, wherein the adoptive cell therapeutic composition and/or oncolytic viral vectors coding for at least one cytokine are to be administered through an intratumoral, intra-arterial, intravenous, intrapleural, intravesicular, intracavitary or peritoneal injection, or an oral administration.

8. The use or the oncolytic adenoviral vector according to any one of claims 1-7, wherein the oncolytic viral vector codes for two or more cytokines.

9. The use or the oncolytic adenoviral vector according to claim 8, wherein the second or further cytokines is/are selected from a cytokine group consisting of interferon alpha, interferon beta, interferon gamma, complement C5a, GMCSF, CD40L, IL12, IL-23, IL15, IL17, CCL1, CCL11, CCL12, CCL13, CCL14-1, CCL14-2, CCL14-3, CCL15-1, CCL15-2, CCL16, CCL17, CCL18, CCL19, CCL2, CCL20, CCL21, CCL22, CCL23-1, CCL23-2, CCL24, CCL25-1, CCL25-2, CCL26, CCL27, CCL28, CCL3, CCL3L1, CCL4, CCL4L1, CCL5 (=RANTES), CCL6, CCL7, CCL8, CCL9, CCR10, CCR2, CCR5, CCR6, CCR7, CCR8, CCRL1, CCRL2, CX3CL1, CX3CR, CXCL1, CXCL10, CXCL11, CXCL12,

CXCL13, CXCL14, CXCL15, CXCL16, CXCL2, CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8, CXCL9, CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, CXCR7 and XCL2, or the oncolytic viral vector codes for IL-2 and a cytokine or cytokines selected from a cytokine group consisting of interferon alpha, interferon beta, interferon gamma, complement C5a, GMCSF, TNFalpha, CD40L, IL12, IL-23, IL15, IL17, CCL1, CCL11, CCL12, CCL13, CCL14-1, CCL14-2, CCL14-3, CCL15-1, CCL15-2, CCL16, CCL17, CCL18, CCL19, CCL2, CCL20, CCL21, CCL22, CCL23-1, CCL23-2, CCL24, CCL25-1, CCL25-2, CCL26, CCL27, CCL28, CCL3, CCL3L1, CCL4, CCL4L1, CCL5, CCL6, CCL7, CCL8, CCL9, CCR10, CCR2, CCR5, CCR6, CCR7, CCR8, CCRL1, CCRL2, CX3CL1, CX3CR, CXCL1, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16, CXCL2, CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8, CXCL9, CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, CXCR7 and XCL2.

10. The use or the oncolytic adenoviral vector according to claim 8 or 9, wherein the adenoviral vector comprises an internal ribosomal entry site (IRES) or a ribosome shunt site 2A between the two transgenes.

11. The use or the oncolytic adenoviral vector according to any one of claims 1-10, wherein oncolytic adenoviral vectors coding for at least one cytokine is to be administered in an amount of $1x10^{10}$- $1x10^{14}$ virus particles.

12. An oncolytic adenoviral vector for use in increasing the efficacy of separate adoptive T-cell therapy in a tumor of a subject, wherein said oncolytic adenoviral vector is an adenovirus serotype 5 (Ad5) vector comprising

- a 5/3 chimeric fiber knob,
- E2F1 promoter for tumor specific expression of E1A,
- a 24 bp deletion (D24) in the Rb binding constant region 2 of adenoviral E1,
- a nucleic acid sequence deletion of viral gp19k and 6.7k reading frames, and
- a nucleic acid sequence encoding at least TNFalpha or IL-2 transgene in the place of the deleted gp19k/6.7K in the E3 region resulting in replication-associated control of transgene expression under the viral E3 promoter.

13. Use of an oncolytic adenoviral vector in the manufacture of a medicament for increasing the efficacy of adoptive T-cell therapy in a tumour of a subject in need thereof, wherein said oncolytic adenoviral vector is an adenovirus serotype 5 (Ad5) vector comprising

- a 5/3 chimeric fiber knob,
- E2F1 promoter for tumor specific expression of E1A,
- a 24 bp deletion (D24) in the Rb binding constant region 2 of adenoviral E1,
- a nucleic acid sequence deletion of viral gp19k and 6.7k reading frames, and
- a nucleic acid sequence encoding at least TNFalpha or IL-2 transgene in the place of the deleted gp19k/6.7K in the E3 region resulting in replication-associated control of transgene expression under the viral E3 promoter.

14. A pharmaceutical kit comprising an adoptive T-cell therapeutic composition and an oncolytic adenoviral vector coding for at least one cytokine, wherein the adoptive cell therapeutic composition is formulated in a first formulation and the oncolytic adenoviral vector coding for at least one cytokine is formulated in a second formulation, wherein said oncolytic adenoviral vector is
an adenovirus serotype 5 (Ad5) vector comprising

- a 5/3 chimeric fiber knob,
- E2F1 promoter for tumor specific expression of E1A,
- a 24 bp deletion (D24) in the Rb binding constant region 2 of adenoviral E1,
- a nucleic acid sequence deletion of viral gp19k and 6.7k reading frames, and
- a nucleic acid sequence encoding at least TNFalpha or IL-2 transgene in the place of the deleted gp19k/6.7K in the E3 region resulting in replication-associated control of transgene expression under the viral E3 promoter.

15. The pharmaceutical kit according to claim 14, wherein the first and the second formulations are for simultaneous or sequential, in any order, administration to a subject.

16. An oncolytic adenoviral vector comprising

1) an adenovirus serotype 5 (Ad5) nucleic acid backbone comprising a 5/3 chimeric fiber knob:

2) E2F1 promoter for tumor specific expression of E1A;

3) a 24 bp deletion (D24) in the Rb binding constant region 2 of adenoviral E1;

4) a nucleic acid sequence deletion of viral *gp19k* and *6.7k* reading frames; and

5) a nucleic acid sequence encoding at least one cytokine transgene in the place of the deleted *gp19k/6.7K* in the E3 region resulting in replication-associated control of transgene expression under the viral E3 promoter, wherein the at least one cytokine is TNFalpha or IL-2.

17. The oncolytic adenoviral vector according to claim 16, wherein it codes for two or more cytokines.

18. The oncolytic adenoviral vector according to claim 17, wherein the

oncolytic adenoviral vector codes for IL-2 and a cytokine or cytokines selected from the second cytokine group of claim 9.

19. The oncolytic adenoviral vector according to claim 17 or 18, wherein it comprises an internal ribosomal entry site (IRES) or optionally a ribosome shunt site 2A between the two transgenes.

20. The oncolytic adenoviral vector according to any one of claims 17-19, wherein the promoter for expression of a transgene in the E3 region is the CMV or E2F promoter.

21. A pharmaceutical composition comprising an oncolytic vector according to any one of claims 16-20.

22. Use of an oncolytic adenoviral vector according to any one of claims 16-20 in the manufacture of a medicament for treating cancer in a subject in need thereof.

23. An oncolytic adenoviral vector according to any one of claims 16-20 for use in treatment of cancer.

24. The use or the oncolytic adenoviral vector according to any one of claims 1-11, 13, 22-23, wherein the oncolytic adenoviral vector is to be administered with concurrent or sequential radiotherapy, monoclonal antibodies, chemotherapy or other anti-cancer drugs or interventions to a subject.