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 cell therapeutic composition for use in treatment of cancer, wherein said oncolytic adenoviral vector is

i) 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 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; or

ii) an adenovirus serotype 3 (Ad3) 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 at least one cytokine in the place of the deleted area of E3.

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 cell therapeutic composition, wherein said oncolytic adenoviral vector is

i) 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 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; or

ii) an adenovirus serotype 3 (Ad3) 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 at least one cytokine in the place of the deleted area of E3.

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

i) 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 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; or

ii) an adenovirus serotype 3 (Ad3) 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 at least one cytokine in the place of the deleted area of E3.

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 therapy or T-cell therapy in a tumour of a subject in need thereof, wherein said oncolytic adenoviral vector is

i) 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 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; or

ii) an adenovirus serotype 3 (Ad3) 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 at least one cytokine in the place of the deleted area of E3.

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 cell therapeutic composition and an oncolytic adenoviral vectors coding for at least one cytokine, wherein the adoptive cell therapeutic composition is formulated in a first formulation and the oncolytic adenoviral vectors coding for at least one cytokine are formulated in a second formulation, wherein said oncolytic adenoviral vector is

i) 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 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; or

ii) an adenovirus serotype 3 (Ad3) 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 at least one cytokine in the place of the deleted area of E3.

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 cytokine is selected from a group consisting of interferon alpha, interferon beta, interferon gamma, complement C5a, IL-2, 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, 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, CXCL9, CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, CXCR7 and XCL2.

In one aspect, there is provided 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 ~~a~~ 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 cell therapeutic composition, wherein said oncolytic adenoviral vector is

i) 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 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; or

ii) an adenovirus serotype 3 (Ad3) 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 at least one cytokine in the place of the deleted area of E3.

2. An oncolytic adenoviral vector coding for at least one cytokine together with separate adoptive cell therapeutic composition for use in treatment of cancer, wherein said oncolytic adenoviral vector is

i) 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 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; or

ii) an adenovirus serotype 3 (Ad3) 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 at least one cytokine in the place of the deleted area of E3.

3. The use or the oncolytic adenoviral vector according to any one of claims 1-2, wherein the adoptive cell therapeutic composition comprises a cell type selected from a group consisting of a tumor infiltrating lymphocyte (TIL), T-cell receptor modified lymphocytes and chimeric antigen receptor modified lymphocytes.

4. The use or the oncolytic adenoviral vector according to any one of claims 1-3, wherein the adoptive cell therapeutic composition comprises a cell type selected from a group consisting of T-cells, CD8+ cells, CD4+ cells, NK-cells, delta-gamma T-cells, regulatory T-cells, and peripheral blood mononuclear cells.

5. The use or the oncolytic adenoviral vector according to any one of claims1-4, wherein the adoptive cell therapeutic composition comprises T-cells.

6. The use or the oncolytic adenoviral vector according to any one of claims 1-5, 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.

7. The use or the oncolytic adenoviral vector according to any one of claims 1-6, wherein the subject is a human or an animal.

8. The use or the oncolytic adenoviral vector according to any one of claims 1-7, 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.

9. The use or the oncolytic adenoviral vector according to claim 8, 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.

10. The use or the oncolytic adenoviral vector according to any one of claims 1-9, 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.

11. The use or the oncolytic adenoviral vector according to any one of claims 1-10, wherein the cytokine is selected from a group consisting of interferon alpha, interferon beta, interferon gamma, complement C5a, IL-2, 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, 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, CXCL9, CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, CXCR7 and XCL2.

12. The use or the oncolytic adenoviral vector according to any one of claims 1-11, wherein the oncolytic viral vector codes for two or more cytokines.

13. The use or the oncolytic adenoviral vector according to claim 11, wherein the oncolytic viral vector codes for any two or more cytokines selected from a cytokine group consisting of interferon alpha, interferon beta, interferon gamma, complement C5a, GMCSF, IL-2, 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, 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, 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, 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, CXCL9, CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, CXCR7 and XCL2.

14. The use or the oncolytic adenoviral vector according to claim 12 or 13, wherein the adenoviral vector comprises an internal ribosomal entry site (IRES) or a ribosome shunt site 2A between the two transgenes.

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

16. An oncolytic adenoviral vector for use in increasing the efficacy of separate adoptive cell therapy or T-cell therapy in a tumor of a subject, wherein said oncolytic adenoviral vector is

i) 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 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; or

ii) an adenovirus serotype 3 (Ad3) 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 at least one cytokine in the place of the deleted area of E3.

17. Use of an oncolytic adenoviral vector in the manufacture of a medicament for increasing the efficacy of adoptive therapy or T-cell therapy in a tumour of a subject in need thereof, wherein said oncolytic adenoviral vector is

i) 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 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; or

ii) an adenovirus serotype 3 (Ad3) 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 at least one cytokine in the place of the deleted area of E3.

18. A pharmaceutical kit comprising an adoptive 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 are formulated in a second formulation, wherein said oncolytic adenoviral vector is

i) 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 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; or

ii) an adenovirus serotype 3 (Ad3) 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 at least one cytokine in the place of the deleted area of E3.

19. The pharmaceutical kit according to claim 18, wherein the first and the second formulations are for simultaneous or sequential, in any order, administration to a subject.

20. 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 cytokine is selected from a group consisting of interferon alpha, interferon beta, interferon gamma, complement C5a, IL-2, 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, 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, CXCL9, CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, CXCR7 and XCL2.

21. 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.

22. The oncolytic adenoviral vector according to claim 21, wherein the transgene is a cytokine selected from the cytokine group of claim 11.

23. The oncolytic adenoviral vector according to claim 22, wherein the transgene is CD40L.

24. The oncolytic adenoviral vector according to any one of claims 20-23, wherein it codes for two or more cytokines.

25. The oncolytic adenoviral vector according to claim 24, wherein it codes for any two or more cytokines selected from the first cytokine group of claim 13 or the

oncolytic adenoviral vector codes for IL-2 and a cytokine or cytokines selected from the second cytokine group of claim 13.

26. The oncolytic adenoviral vector according to claim 24 or 25, wherein it comprises an internal ribosomal entry site (IRES) or optionally a ribosome shunt site 2A between the two transgenes.

27. The oncolytic adenoviral vector according to any one of claims 21-26, wherein the promoter for expression of a transgene in the E3 region is the CMV or E2F promoter.

28. The oncolytic adenoviral vector according to any one of claims 21-27, wherein the vector comprises hTERT promoter for expression of E1A and CMV promoter for expression of CD40L in the E3 region.

29. A pharmaceutical composition comprising an oncolytic vector according to any one of claims 20-28.

30. Use of an oncolytic adenoviral vector according to any one of claims 20-28 in the manufacture of a medicament for treating cancer in a subject in need thereof.

31. An oncolytic adenoviral vector according to any one of claims 20-28 for use in treatment of cancer.

32. The use or the oncolytic adenoviral vector according to any one of claims 1-15, 17, 30-31, wherein the use or the oncolytic adenoviral vector further comprises administration of concurrent or sequential radiotherapy, monoclonal antibodies, chemotherapy or other anti-cancer drugs or interventions to a subject.

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 cell therapeutic composition.

2. An oncolytic adenoviral vector coding for at least one cytokine together with separate adoptive cell therapeutic composition for use in treatment of cancer.

3. The use or the oncolytic adenoviral vector according to any one of claims 1-2, wherein the adoptive cell therapeutic composition comprises a cell type selected from a group consisting of a tumor infiltrating lymphocyte (TIL), T-cell receptor modified lymphocytes and chimeric antigen receptor modified lymphocytes.

4. The use or the oncolytic adenoviral vector according to any one of claims 1-3, wherein the adoptive cell therapeutic composition comprises a cell type selected from a group consisting of T-cells, CD8+ cells, CD4+ cells, NK-cells, delta-gamma T-cells, regulatory T-cells, and peripheral blood mononuclear cells.

5. The use or the oncolytic adenoviral vector according to any one of claims1-4, wherein the adoptive cell therapeutic composition comprises T-cells.

6. The use or the oncolytic adenoviral vector according to any one of claims 1-5, 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 can-

cer, 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.

7. The use or the oncolytic adenoviral vector according to any one of claims 1-6, wherein the subject is a human or an animal.

8. The use or the oncolytic adenoviral vector according to any one of claims 1-7, 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.

9. The use or the oncolytic adenoviral vector according to claim 8, 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.

10. The use or the oncolytic adenoviral vector according to any one of claims 1-9, 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.

11. The use or the oncolytic adenoviral vector according to any one of claims 1-10, wherein the adenoviral vector is selected from Ad5, Ad3 or Ad5/3.

12. The use or the oncolytic adenoviral vector according to claim 11, wherein the adenoviral vector is Ad5/3 comprising an Ad5 nucleic acid backbone and Ad3 fiber knob or Ad5/3 chimeric fiber knob.

13. The use or the oncolytic adenoviral vector according to any one of claims 1-12, wherein the cytokine is selected from a group consisting of interferon alpha, interferon beta, interferon gamma, complement C5a, IL-2, 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, 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, CXCL9, CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, CXCR7 and XCL2.

14. The use or the oncolytic adenoviral vector according to any one of claims 1-13, wherein the oncolytic viral vector codes for two or more cytokines.

15. The use or the oncolytic adenoviral vector according to claim 13, wherein the oncolytic viral vector codes for any two or more cytokines selected from a cytokine group consisting of interferon alpha, interferon beta, interferon gamma, complement C5a, GMCSF, IL-2, 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, 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, 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, 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, CXCL9, CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, CXCR7 and XCL2.

16. The use or the oncolytic adenoviral vector according to claim 14 or 15, wherein the adenoviral vector comprises an internal ribosomal entry site (IRES) or optionally a ribosome shunt site 2A between the two transgenes.

17. The use or the oncolytic adenoviral vector according to any one of claims 1-16, wherein oncolytic adenoviral vectors coding for at least one cytokine are administered in an amount of $1x10^{10}$- $1x10^{14}$ virus particles.

18. The use or the oncolytic adenoviral vector according to any one of claims 1-17, wherein

the adoptive cell therapeutic composition and oncolytic adenoviral vectors are to be administered simultaneously or sequentially, in any order, to a subject.

19. An oncolytic adenoviral vector for use in increasing the efficacy of separate adoptive cell therapy or T-cell therapy in a tumor of a subject.

20. Use of an oncolytic adenoviral vector in the manufacture of a medicament for increasing the efficacy of adoptive therapy or T-cell therapy in a tumour of a subject in need thereof.

21. A pharmaceutical kit comprising an adoptive cell therapeutic composition and oncolytic adenoviral vectors coding for at least one cytokine, wherein the adoptive cell therapeutic composition is formulated in a first formulation and the oncolytic adenoviral vectors coding for at least one cytokine are formulated in a second formulation.

22. The pharmaceutical kit according to claim 21, wherein the first and the second formulations are for simultaneous or sequential, in any order, administration to a subject.

23. 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 cytokine is selected from a group consisting of interferon alpha, interferon beta, interferon gamma, complement C5a, IL-2, 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, 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, CXCL9, CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, CXCR7 and XCL2.

24. Serotype 3 (Ad3) oncolytic adenoviral vector comprising: a deletion in the E3 area and a tumor specific promoter for expression of a transgene in the place of the deleted area of E3.

25. The oncolytic adenoviral vector according to claim 24, wherein the transgene is a cytokine selected from the cytokine group of claim 13.

26. The oncolytic adenoviral vector according to claim 25, wherein the transgene is CD40L.

27. The oncolytic adenoviral vector according to any one of claims 23-26, wherein it codes for two or more cytokines.

28. The oncolytic adenoviral vector according to claim 27, wherein it codes for any two or more cytokines selected from the first cytokine group of claim 15 or the oncolytic adenoviral vector codes for IL-2 and a cytokine or cytokines selected from the second cytokine group of claim 15.

29. The oncolytic adenoviral vector according to claim 27 or 28, wherein it comprises an internal ribosomal entry site (IRES) or optionally a ribosome shunt site 2A between the two transgenes.

30. The oncolytic adenoviral vector according to any one of claims 24-29, wherein the promoter for expression of a transgene in the E3 region is the CMV or E2F promoter.

31. The oncolytic adenoviral vector according to any one of claims 24-30, wherein the vector comprises hTERT promoter for expression of E1A and CMV promoter for expression of CD40L in the E3 region.

32. A pharmaceutical composition comprising an oncolytic vector according to any one of claims 23-31.

33. Use of an oncolytic adenoviral vector according to any one of claims 23-31 in the manufacture of a medicament for treating cancer in a subject in need thereof.

34. An oncolytic adenoviral vector according to any one of claims 23-31 for use in treatment of cancer.

35. The use or the oncolytic adenoviral vector according to any one of claims 1-17, 20 or 33-34, wherein the use or the oncolytic adenovial vector further comprises administration of concurrent or sequential radiotherapy, monoclonal antibodies, chemotherapy or other anti-cancer drugs or interventions to a subject.