Furthermore, the present disclosure relates to 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.

Furthermore, the present disclosure relates to a 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.

In one aspect, the present disclosure refers to 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 3 (Ad3) vector comprising

- a hTERT promoter for tumor specific expression of E1A,
- 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 CMV or E2F ~~an exogenous or tumor specific~~ promoter for expression of ~~at least one~~a CD40L cytokine transgene in the place of the deleted area of E3.

In another aspect, the present disclosure refers to 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 3 (Ad3) vector comprising

- a hTERT promoter for tumor specific expression of E1A,
- 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 CMV or E2F ~~an exogenous or tumor specific~~ promoter for expression of ~~at least one~~a CD40L cytokine transgene in the place of the deleted area of E3.

In yet another aspect, the present disclosure refers to 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 3 (Ad3) oncolytic adenoviral vector comprising: a hTERT promoter for tumor specific expression of E1A, 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~~a CMV or E2F promoter for expression of a CD40L cytokine transgene in the place of the deleted area of E3~~, wherein the transgene is a cytokine 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, 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~~.

In a further aspect, the present disclosure refers to use of an oncolytic adenoviral vector in the manufacture of a medicament for increasing the

efficacy of adoptive T-cell therapy in a tumor of a subject in need thereof, wherein said oncolytic adenoviral vector is an adenovirus serotype 3 (Ad3) oncolytic adenoviral vector comprising: a hTERT promoter for tumor specific expression of E1A, 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 a tumor specific~~ a CMV or E2F promoter for expression of a CD40L cytokine transgene in the place of the deleted area of E3~~, wherein the transgene is a cytokine 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, 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~~.

In one aspect, the present disclosure refers to 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 3 (Ad3) oncolytic adenoviral vector comprising: a hTERT promoter for tumor specific expression of E1A, 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 a tumor specific~~a CMV or E2F promoter for expression of a CD40L cytokine transgene in the place of the deleted area of E3~~, wherein the transgene is a cytokine 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, 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~~.

In one aspect, the present disclosure refers to a serotype 3 (Ad3) oncolytic adenoviral vector comprising: a hTERT promoter for tumor specific expression of E1A, 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~~a CMV or E2F promoter for expression of a CD40L cytokine transgene in the place of the deleted area of E3~~, wherein the transgene is a cytokine 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, 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~~. In another aspect, the present disclosure refers to a pharmaceutical composition comprising the disclosed oncolytic vector. In yet another aspect, the present disclosure refers to use of the disclosed oncolytic adenoviral vector in the manufacture of a medicament for treating cancer in a subject in need thereof. In a further aspect, the present disclosure refers to the disclosed oncolytic adenoviral vector for use in treatment of cancer.

Still, the present disclosure relates to a pharmaceutical composition comprising an oncolytic vector of the disclosure.

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.Also, the present disclosure relates to an oncolytic adenoviral vector of the present disclosure for use in treatment of cancer.

Also, the present disclosure relates to a use of an oncolytic adenoviral vector of the present disclosure 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 3 (Ad3) vector comprising

- a hTERT promoter for tumor specific expression of E1A,
- 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~~ a CMV or E2F promoter for expression of ~~at least one~~ a CD40L cytokine transgene in the place of the deleted area of E3.

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 3 (Ad3) vector comprising

- a hTERT promoter for tumor specific expression of E1A,
- 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~~ a CMV or E2F promoter for expression of ~~at least one~~ a CD40L cytokine transgene in the place of the deleted area of E3.

3. The use according to claim 1 or the oncolytic adenoviral vector ~~coding for at least one cytokine~~ together with separate adoptive T-cell therapeutic composition for use according to claim 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 according to claim 1 or 3 or the oncolytic adenoviral vector ~~coding for at least one cytokine~~ together with separate adoptive T-cell therapeutic composition for use according to claim 2 or 3, wherein the subject is a human or an animal.

5. The use according to any one of claims 1, 3 and 4 or the oncolytic adenoviral vector ~~coding for at least one cytokine~~ together with separate adoptive T-cell therapeutic composition for use according to any one of claims 2-4, wherein the adoptive cell therapeutic composition and the oncolytic viral vector~~s coding for at least one cytokine~~ are to be administered to a subject simultaneously or consecutively, in any order.

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

7. The use according to any one of claims 1 and 3-6 or the oncolytic adenoviral vector ~~coding for at least one cytokine~~ together with separate adoptive T-cell therapeutic composition for use according to any one of claims 2-6, wherein the adoptive cell therapeutic composition and/or the oncolytic viral vector~~s coding for at least one cytokine~~ are/is to be administered through an

intratumoral, intra-arterial, intravenous, intrapleural, intravesicular, intracavitary or peritoneal injection, or an oral administration.

~~8. The use according to any one of claims 1 and 3-7 or the oncolytic adenoviral vector coding for at least one cytokine together with separate adoptive T-cell therapeutic composition for use according to any one of claims 2-7, 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, 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.~~

~~9~~8. The use according to any one of claims 1 and ~~3-8~~3-7 or the oncolytic adenoviral vector ~~coding for at least one cytokine~~ together with separate adoptive T-cell therapeutic composition for use according to any one of claims ~~2-8~~2-7, wherein the oncolytic viral vector codes for two or more cytokines.

~~10~~9. The use according to claim ~~9~~ 8 or the oncolytic adenoviral vector ~~coding for at least one cytokine~~ together with separate adoptive T-cell therapeutic composition for use according to claim ~~9~~8, wherein the oncolytic viral vector codes for ~~any two or more cytokines~~ a further cytokine transgene 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, 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.

~~11~~10. The use according to claim ~~9~~ 8 or ~~10~~ 9 or the oncolytic adenoviral vector ~~coding for at least one cytokine~~ together with separate adoptive T-cell therapeutic composition for use according to claim ~~9~~ 8 or ~~10~~9, wherein the adenoviral

vector comprises an internal ribosomal entry site (IRES) or optionally a ribosome shunt site 2A between the two transgenes.

~~12~~11. The use according to any one of claims 1 and 3-~~11~~ 10 or the oncolytic adenoviral vector ~~coding for at least one cytokine~~ together with separate adoptive T-cell therapeutic composition for use according to any one of claims 2-~~11~~10, wherein the oncolytic adenoviral vector~~s coding for at least one cytokine are~~ is to be administered in an amount of $1x10^{10}$- $1x10^{14}$ virus particles.

~~13~~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 3 (Ad3) oncolytic adenoviral vector comprising: a hTERT promoter for tumor specific expression of E1A, 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 a tumor specific~~a CMV or E2F promoter for expression of a CD40L cytokine transgene in the place of the deleted area of E3~~, wherein the transgene is a cytokine selected from the cytokine group of claim 8~~.

~~14~~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 3 (Ad3) oncolytic adenoviral vector comprising: a hTERT promoter for tumor specific expression of E1A, 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 a tumor specific~~ a CMV or E2F promoter for expression of a CD40L cytokine transgene in the place of the deleted area of E3~~, wherein the transgene is a cytokine selected from the cytokine group of claim 8~~.

~~15~~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 3 (Ad3) oncolytic adenoviral vector comprising: a hTERT promoter for tumor specific expression of E1A, 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 a tumor specific~~ a CMV or E2F promoter for expression of a CD40L cytokine transgene in the place of the deleted area of E3~~, wherein the transgene is a cytokine selected from the cytokine group of claim 8~~.

~~16~~15. The pharmaceutical kit according to claim ~~15~~14, wherein the

first and the second formulations are for simultaneous or sequential, in any order, administration to a subject.

~~17~~16. Serotype 3 (Ad3) oncolytic adenoviral vector comprising: a hTERT promoter for tumor specific expression of E1A, 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~~ a CMV or E2F promoter for expression of a CD40L cytokine transgene in the place of the deleted area of E3~~, wherein the transgene is a cytokine selected from the cytokine group of claim 8~~.

~~18. The oncolytic adenoviral vector according to claim 17, wherein it codes for CD40L.~~

~~19~~17. The oncolytic adenoviral vector according to claim ~~17 or 18~~16, wherein it codes for two or more cytokines.

~~20~~18. The oncolytic adenoviral vector according to claim ~~19~~17, wherein it comprises an internal ribosomal entry site (IRES) or optionally a ribosome shunt site 2A between the two transgenes.

~~21. The oncolytic adenoviral vector according to any one of claims 17-20, wherein the promoter for expression of a transgene in the E3 region is the CMV or E2F promoter.~~

~~22~~19. A pharmaceutical composition comprising an oncolytic vector according to any one of claims ~~17-21~~16-18.

~~23~~20. Use of an oncolytic adenoviral vector according to any one of claims ~~17-21~~16-18 in the manufacture of a medicament for treating cancer in a subject in need thereof.

~~24~~21. An oncolytic adenoviral vector according to any one of claims ~~17-21~~16-18 for use in treatment of cancer.

~~25~~22. The use according to any one of claims 1, 3-12, ~~14~~ 13 and ~~23~~20, the oncolytic adenoviral vector ~~coding for at least one cytokine~~ together with separate adoptive T-cell therapeutic composition for use according to any one of claims ~~2-12~~2-11, or the ~~the~~ oncolytic adenoviral vector for use according to claim ~~24~~21, 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.