Claims

1. A recombinant vesicular stomatitis virus encoding in its genome at least one CD80 extracellular domain Fc-fusion protein or a functional variant thereof, wherein the CD80 extracellular domain Fc-fusion protein comprises the extracellular domain of CD80 and further comprises the Fc domain of an IgG, wherein the gene coding for the glycoprotein G of the recombinant vesicular stomatitis virus is replaced by the gene coding for the glycoprotein GP of Lymphocyte choriomeningitis virus (LCMV), and/or the glycoprotein G is replaced by the glycoprotein GP of LCMV.

2. The recombinant vesicular stomatitis virus according to claim 1, wherein the CD80 extracellular domain Fc-fusion protein is selected from the group comprising:
   (i) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1,
   (ii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1,
   (iii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2,
   (iv) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1 and the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2,
   (v) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain consists of amino acids 1-207 of SEQ ID NO:4 or has at least 80% identity to amino acids 1-207 of SEQ ID NO:4 and the Fc domain consists of amino acids 208-433 of SEQ ID NO:4 or has at least 80% identity to amino acids 208-433 of SEQ ID NO:4,
   (vi) a CD80 extracellular domain Fc-fusion protein according to any of (i)-(v) further comprising a signal peptide sequence, and
   (vii) a CD80 extracellular domain Fc-fusion protein, comprising SEQ ID NO:3 or having at least 80% identity to SEQ ID NO:3.

3. The recombinant vesicular stomatitis virus according to claim 2, wherein the genome encodes for a CD80 extracellular domain fused to the Fc domain of an IgG1.

4. The recombinant vesicular stomatitis virus according to claim 3, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1.

5. The recombinant vesicular stomatitis virus according to claim 3, wherein the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2.

6. The recombinant vesicular stomatitis virus according to claim 3, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1 and the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2.

7. The recombinant vesicular stomatitis virus according to any of claims 3 to 6 further comprising a signal peptide sequence.

8. The recombinant vesicular stomatitis virus according to claim 2, wherein the genome encodes for a CD80 extracellular domain Fc-fusion protein comprising SEQ ID NO:3 or having at least 80% identity to SEQ ID NO:3.

9. A recombinant vesicular stomatitis virus, encoding in its genome at least for a vesicular stomatitis virus nucleoprotein (N), large protein (L), phosphoprotein (P), matrix protein (M), glycoprotein (G) and at least one CD80 extracellular domain Fc-fusion protein or a functional variant thereof, wherein the CD80 extracellular domain Fc-fusion protein comprises the extracellular domain of CD80 and further comprises the Fc domain of an IgG, wherein the gene coding for the glycoprotein G of the recombinant vesicular stomatitis virus is replaced by the gene coding for the glycoprotein GP of Lymphocyte choriomeningitis virus (LCMV), and/or the glycoprotein G is replaced by the glycoprotein GP of LCMV.

10. The recombinant vesicular stomatitis virus according to claim 9, wherein the nucleoprotein (N) comprises an amino acid sequence as set forth in SEQ ID NO:7 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:7.

11. The recombinant vesicular stomatitis virus according to any of claims 9 or 10, wherein the phosphoprotein (P) comprises an amino acid sequence as set forth in SEQ ID NO:8 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:8.

12. The recombinant vesicular stomatitis virus according to any of claims 9 to 11, wherein the large protein (L) comprises an amino acid sequence as set forth in SEQ ID NO:9 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:9.

13. The recombinant vesicular stomatitis virus according to any of claims 9 to 12, wherein the matrix protein (M) comprises an amino acid sequence as set forth in SEQ ID NO:10 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:10.

14. The recombinant vesicular stomatitis virus according to any of claims 9 to 13, wherein:
- the nucleoprotein (N) comprises an amino acid sequence as set forth in SEQ ID NO:7 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:7,
- wherein the phosphoprotein (P) comprises an amino acid sequence as set forth in SEQ ID NO:8 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:8,
- wherein the large protein (L) comprises an amino acid sequence as set forth in SEQ ID NO:9 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:9, and
- the matrix protein (M) comprises an amino acid sequence as set forth in SEQ ID NO:10 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:10.

15. The recombinant vesicular stomatitis virus according to any of claims 9 to 14, which is replication-competent.

16. The recombinant vesicular stomatitis virus according to any of claims 9 to 15, wherein the CD80 extracellular domain Fc-fusion protein is selected from the group comprising
    (i) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1,
    (ii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1,

(iii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2,

(iv) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1 and the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2,

(v) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain consists of amino acids 1-207 of SEQ ID NO:4 or has at least 80% identity to amino acids 1-207 of SEQ ID NO:4 and the Fc domain consists of amino acids 208-433 of SEQ ID NO:4 or has at least 80% identity to amino acids 208-433 of SEQ ID NO:4,

(vi) a CD80 extracellular domain Fc-fusion protein according to any of (i)-(v) further comprising a signal peptide sequence, and

(vii) a CD80 extracellular domain Fc-fusion protein, comprising SEQ ID NO:3 or having at least 80% identity to SEQ ID NO:3.

17. A recombinant vesicular stomatitis virus encoding in its genome a vesicular stomatitis virus nucleoprotein (N), large protein (L), phosphoprotein (P), matrix protein (M), glycoprotein (G) and at least one CD80 extracellular domain Fc-fusion protein or a functional variant thereof, wherein the CD80 extracellular domain Fc-fusion protein comprises the extracellular domain of CD80 and further comprises the Fc domain of an IgG and is selected from the group comprising:

(i) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1,

(ii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1,

(iii) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2,

(iv) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the CD80 extracellular domain comprises or consists of SEQ ID NO:1 or has at least 80% identity to SEQ ID NO:1 and the Fc domain comprises or consists of SEQ ID NO:2 or has at least 80% identity to SEQ ID NO:2,

(v) a CD80 extracellular domain Fc-fusion protein, comprising a CD80 extracellular domain fused to the Fc domain of an IgG1, wherein the

CD80 extracellular domain consists of amino acids 1-207 of SEQ ID NO:4 or has at least 80% identity to amino acids 1-207 of SEQ ID NO:4 and the Fc domain consists of amino acids 208-433 of SEQ ID NO:4 or has at least 80% identity to amino acids 208-433 of SEQ ID NO:4,

(vi) a CD80 extracellular domain Fc-fusion protein according to any of (i)-(v) further comprising a signal peptide sequence, and

(vii) a CD80 extracellular domain Fc-fusion protein, comprising SEQ ID NO:3 or having at least 80% identity to SEQ ID NO:3,

wherein, the gene coding for the glycoprotein G of the vesicular stomatitis virus is replaced by the gene coding for the glycoprotein GP of lymphocyte choriomeningitis virus (LCMV), and/or the glycoprotein G is replaced by the glycoprotein GP of LCMV, and wherein

- the nucleoprotein (N) comprises an amino acid as set forth in SEQ ID NO:7 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:7,
- the phosphoprotein (P) comprises an amino acid as set forth in SEQ ID NO:8 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:8,
- the large protein (L) comprises an amino acid as set forth in SEQ ID NO:9 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:9, and
- the matrix protein (M) comprises an amino acid as set forth in SEQ ID NO:10 or a functional variant at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:10.

18. A pharmaceutical composition, characterized in that the composition comprises a recombinant vesicular stomatitis virus according to any of claims 9 to 17.

19. A recombinant vesicular stomatitis virus according to any of claims 9 to 17 or a pharmaceutical composition according to claim 18 for use as a medicament.

20. A recombinant vesicular stomatitis virus according to any of claims 9 to 17 or a pharmaceutical composition according to claim 18 for use in the treatment of cancer, preferably solid cancers.

21. The recombinant vesicular stomatitis virus or the pharmaceutical composition for use according to claim 20, wherein the solid cancer is selected from the list comprising: brain cancer, endometrial cancer, vaginal cancer, anal cancer, oropharyngeal squamous cell carcinoma, gastric cancer, gastroesophageal junction adenocarcinoma, esophageal carcinoma, hepatocellular carcinoma,

pancreatic adenocarcinoma, cholangiocarcinoma, bladder urothelial carcinoma, metastatic melanoma, prostate carcinoma, breast carcinoma, ovarian cancer, a head and neck squamous-cell carcinoma (HNSCC), glioblastoma, non-small cell lung cancer, brain tumor or small cell lung cancer, reproductive tumor, an ovarian tumor, a testicular tumor, an endocrine tumor, a gastrointestinal tumor, a pancreatic tumor, a liver tumor, a kidney tumor, a colon tumor, a colorectal tumor, a bladder tumor, a prostate tumor, a skin tumor, melanoma, a respiratory tumor, a lung tumor, a breast tumor, a head & neck tumor, a head and neck squamous-cell carcinoma (HNSCC) and a bone tumor.

22. The recombinant vesicular stomatitis virus or the pharmaceutical composition for use according to any of claims 19 to 21, wherein recombinant vesicular stomatitis virus, or the pharmaceutical composition is to be administered intratumorally or intravenously.

23. The recombinant vesicular stomatitis virus or the pharmaceutical composition for use according to any of claims 20 to 22, wherein the recombinant vesicular stomatitis virus or the pharmaceutical composition is to be administered at least once intratumorally and subsequently intravenously.

24. The recombinant vesicular stomatitis virus or the pharmaceutical composition for use according to claim 23, wherein the subsequent intravenous administration is given 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days or 31 days after the initial intratumoral administration.

25. Use of a recombinant vesicular stomatitis virus according to any of claims 9 to 17 or a pharmaceutical composition according to claim 18 in the manufacture of a medicament for the treatment of cancer, preferably solid cancers.

26. The use according to claim 25, wherein the solid cancer is selected from the list comprising: brain cancer, endometrial cancer, vaginal cancer, anal cancer, oropharyngeal squamous cell carcinoma, gastric cancer, gastroesophageal junction adenocarcinoma, esophageal carcinoma, hepatocellular carcinoma, pancreatic adenocarcinoma, cholangiocarcinoma, bladder urothelial carcinoma, metastatic melanoma, prostate carcinoma, breast carcinoma, ovarian cancer, a head and neck squamous-cell carcinoma (HNSCC), glioblastoma, non-small cell lung cancer, brain tumor or small cell lung cancer, reproductive tumor, an ovarian tumor, a testicular tumor, an endocrine tumor, a gastrointestinal tumor, a pancreatic tumor, a liver tumor, a kidney tumor, a colon tumor, a colorectal tumor, a bladder tumor, a prostate tumor, a skin tumor, melanoma, a respiratory

tumor, a lung tumor, a breast tumor, a head & neck tumor, a head and neck squamous-cell carcinoma (HNSCC) and a bone tumor.

27. The use according to claim 25 or 26, wherein recombinant vesicular stomatitis virus, or the pharmaceutical composition is to be administered intratumorally or intravenously.

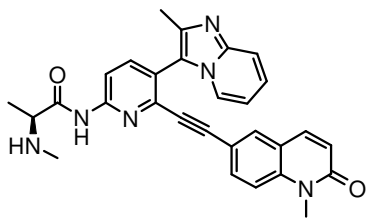
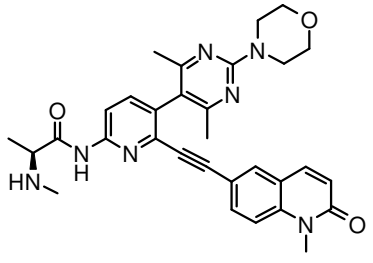
28. The use according to any of claims 25 to 27, wherein the recombinant vesicular stomatitis virus or the pharmaceutical composition is to be administered at least once intratumorally and subsequently intravenously.

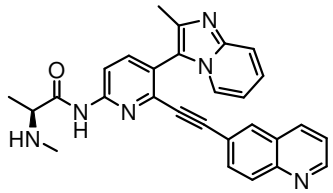
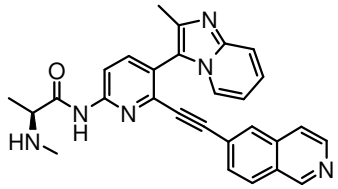
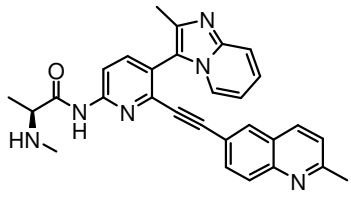
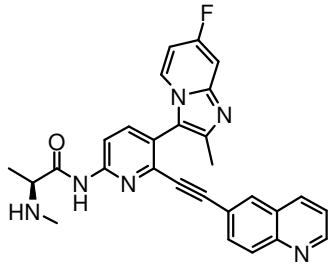
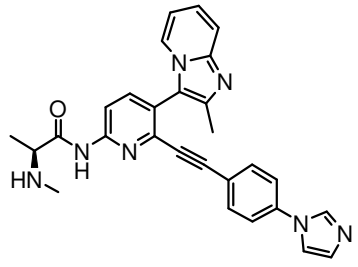
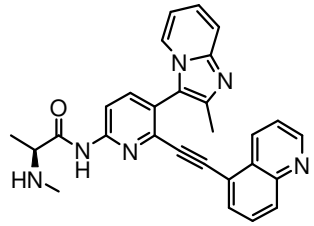
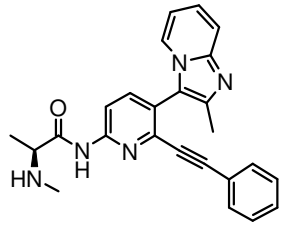
29. The use according to claim 28, wherein the subsequent intravenous administration is given 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days or 31 days after the initial intratumoral administration.

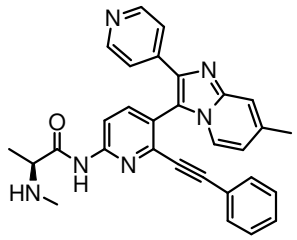
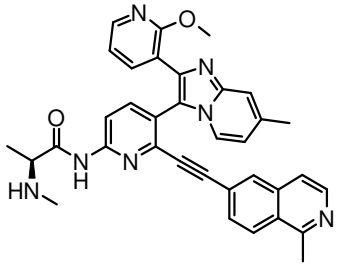
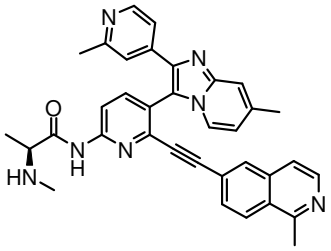
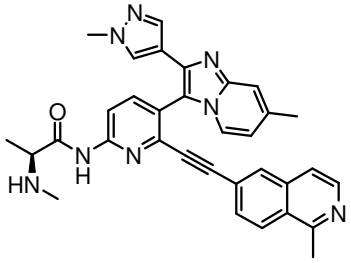
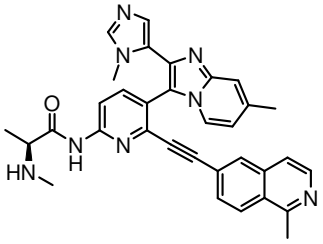
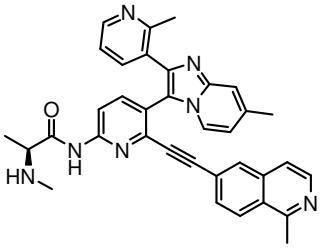
30. A composition comprising a recombinant vesicular stomatitis virus according to any of claims 1 to 17 and further a PD-1 pathway inhibitor or a SMAC mimetic.

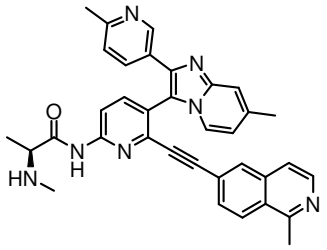
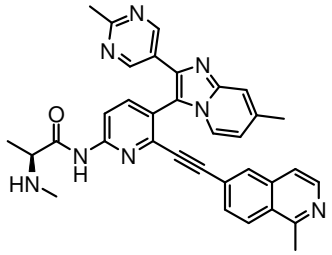
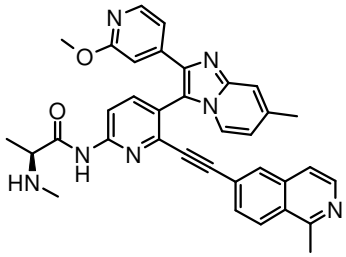
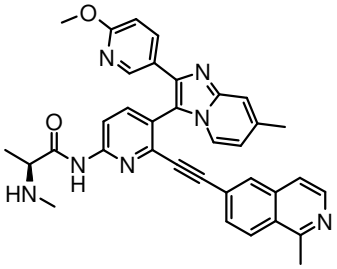
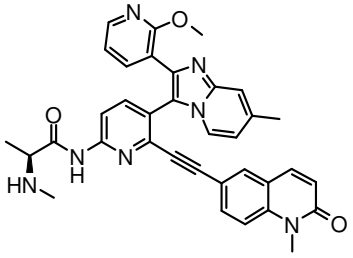
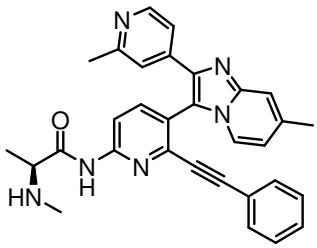
31. The composition according to claim 30, wherein the PD-1 pathway inhibitor is an antagonistic antibody, which is directed against PD-1 or PD-L1.

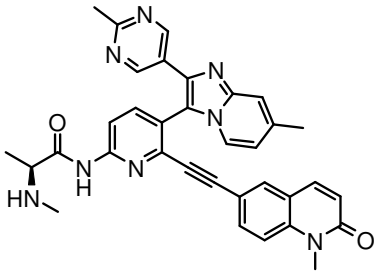
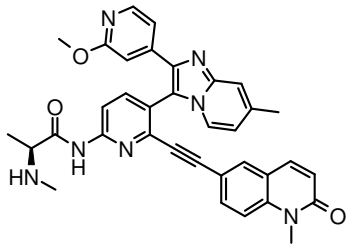
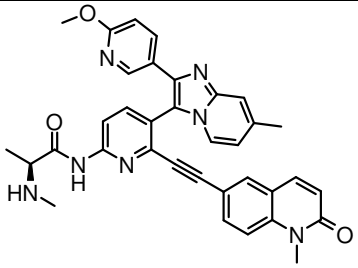
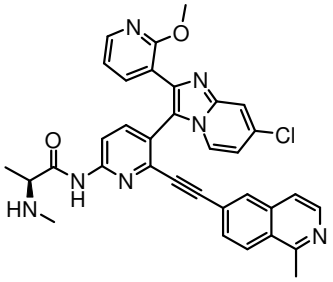
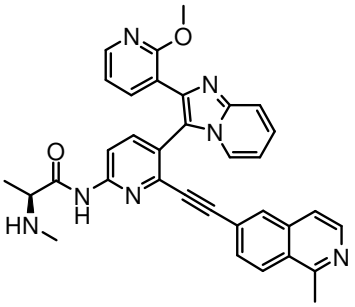
32. The composition according to claim 30, wherein the SMAC mimetic is selected from the group consisting of any one of compounds 1 to 26:

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or a pharmaceutically acceptable salt of one of these compounds.

33. The composition according to claim 30, wherein the PD-1 pathway inhibitor is an antagonist selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, atezolizumab, avelumab, durvalumab, PDR-001, PD1-1, PD1-2, PD1-3, PD1-4 and PD1-5.

34. A kit of parts comprising:
    a) a recombinant vesicular stomatitis virus according to any of claims 1 to 17 or a pharmaceutical composition according to any of claims 19 and 30 to 33, and
    b) a PD-1 pathway inhibitor or SMAC mimetic as defined in any of claims 30 to 33.

35. A recombinant vesicular stomatitis virus, or a pharmaceutical composition for use according to any of claims 19 to 21 in combination with a PD-1 pathway inhibitor or a SMAC mimetic.

36. The recombinant vesicular stomatitis virus, or the pharmaceutical composition for use according to claim 35, wherein the recombinant vesicular stomatitis virus, or the pharmaceutical composition is to be administered concomittantly, sequentially or alternately with the PD-1 pathway inhibitor or the SMAC mimetic.

37. The recombinant vesicular stomatitis virus, or the pharmaceutical composition for use according to claims 35 or 36, wherein the SMAC mimetic is selected from the group consisting of any one of compounds 1 to 26 according to claim 32 or a pharmaceutically acceptable salt of one of these compounds.

38. The recombinant vesicular stomatitis virus, or the pharmaceutical composition for use according to claims 35 or 36, wherein the PD-1 pathway inhibitor is selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, atezolizumab, avelumab, durvalumab, PDR-001, PD1-1, PD1-2, PD1-3, PD1-4 and PD1-5.

39. The recombinant vesicular stomatitis virus, or the pharmaceutical composition for use according to any of claims 35 to 37, wherein the recombinant vesicular stomatitis virus, or the pharmaceutical composition is to be administered via a different administration route then the PD-1 pathway inhibitor or the SMAC mimetic.

40. The recombinant vesicular stomatitis virus, or the pharmaceutical composition for use according to any of claims 35 to 37, wherein the recombinant rhabdovirus, the recombinant vesicular stomatitis virus, or the pharmaceutical composition are to be administered at least once intratumorally and the PD-1 pathway inhibitor or the SMAC mimetic is to be administered intravenously.

41. The use according to claim 25 or 26, wherein the medicament is to be administered in combination with a PD-1 pathway inhibitor or a SMAC mimetic.

42. The use according to claim 41, wherein the recombinant vesicular stomatitis virus, or the pharmaceutical composition is to be administered concomittantly, sequentially or alternately with the PD-1 pathway inhibitor or the SMAC mimetic.

43. The use according to claim 41 or 42, wherein the SMAC mimetic is selected from the group consisting of any one of compounds 1 to 26 according to claim 32 or a pharmaceutically acceptable salt of one of these compounds.

44. The use according to claim 41 or 42, wherein the PD-1 pathway inhibitor is selected from the group consisting of pembrolizumab, nivolumab, pidilizumab, atezolizumab, avelumab, durvalumab, PDR-001, PD1-1, PD1-2, PD1-3, PD1-4 and PD1-5.

45. The use according to any of claims 41 to 43, wherein the recombinant vesicular stomatitis virus, or the pharmaceutical composition is to be administered via a different administration route then the PD-1 pathway inhibitor or the SMAC mimetic.

46. The use according to any of claims 41 to 43, wherein the recombinant rhabdovirus, the recombinant vesicular stomatitis virus, or the pharmaceutical composition are to be administered at least once intratumorally and the PD-1 pathway inhibitor or the SMAC mimetic is to be administered intravenously.

47. A virus producing cell, characterized in that the cell produces a recombinant vesicular stomatitis virus according to any of claims 1 to 17.

48. The virus producing cell of claim 47, characterized in that the cell is a Vero cell, a HEK cell, a HEK293 cell, a Chinese hamster ovary cell (CHO), or a baby hamster kidney (BHK) cell.

49. A recombinant vesicular stomatitis virus encoding in its RNA genome at least one CD80 extracellular domain Fc-fusion protein or a functional variant thereof, wherein the CD80 extracellular domain Fc-fusion protein comprises the extracellular domain of CD80 and further comprises the Fc domain of an IgG, wherein the RNA genome of the recombinant rhabdovirus comprises or consists of a coding sequence identical or at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 24.