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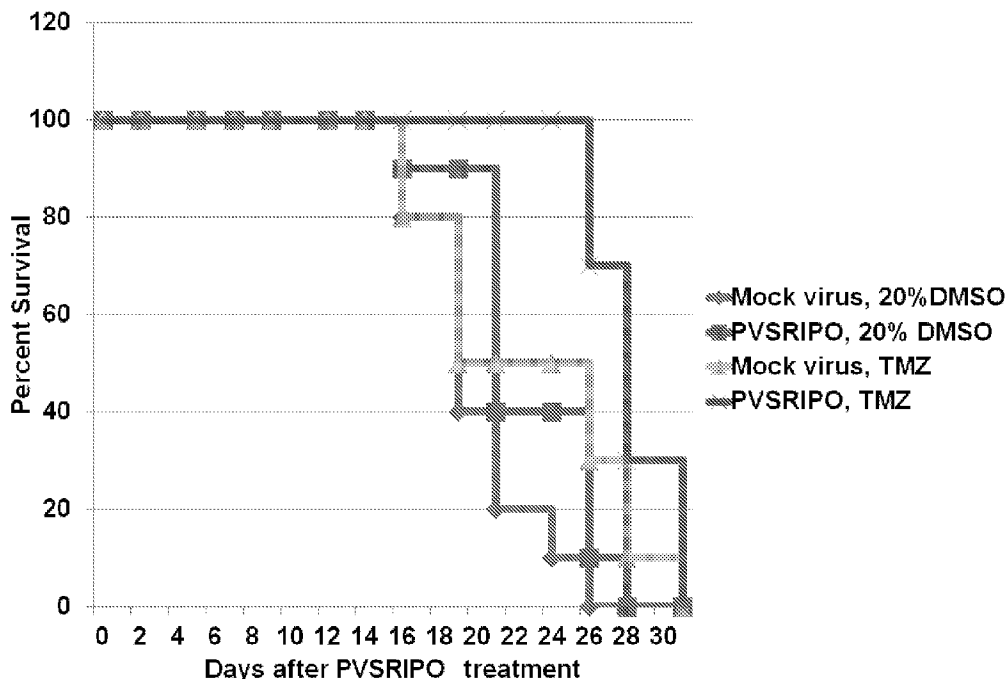
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(57) Abrégé/Abstract:

Human clinical use of a chimeric poliovirus construct has demonstrated excellent anti-tumor effect. Sequential treatment with the virus construct followed by chemotherapy drugs increases the anti-tumor effect. Tumors of different types are susceptible to the combination treatment, including but not limited to melanoma, glioblastoma, renal cell carcinoma, prostate cancer, breast cancer, lung cancer, medulloblastoma, and colorectal cancer.

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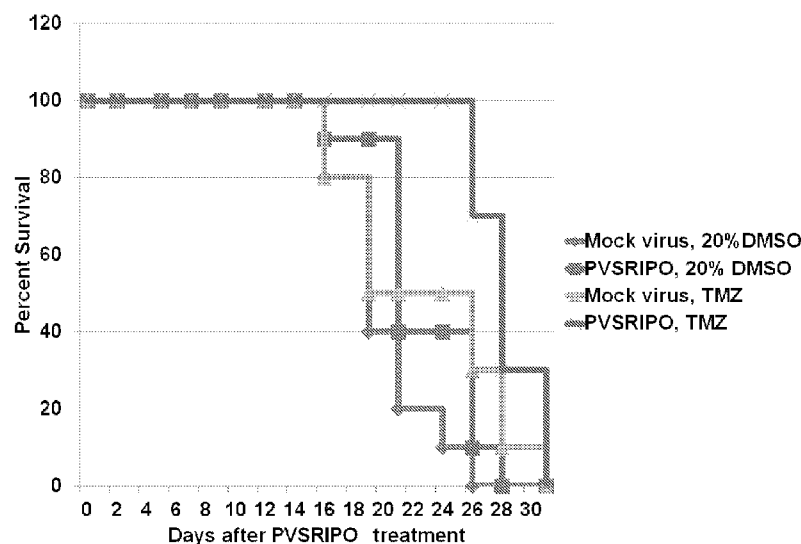


Fig. 7B

(57) Abstract: Human clinical use of a chimeric poliovirus construct has demonstrated excellent anti-tumor effect. Sequential treatment with the virus construct followed by chemotherapy drugs increases the anti-tumor effect. Tumors of different types are susceptible to the combination treatment, including but not limited to melanoma, glioblastoma, renal cell carcinoma, prostate cancer, breast cancer, lung cancer, medulloblastoma, and colorectal cancer.

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SEQUENTIAL ANTI-CANCER TREATMENT

[01] This invention was made using funds provided by the United States government. The U.S. government retains certain rights according to the terms of grants from the National Institutes of Health CA154291, CA197264.

TECHNICAL FIELD OF THE INVENTION

[02] This invention is related to the area of anti-tumor therapy. In particular, it relates to oncolytic virus anti-tumor therapy.

BACKGROUND OF THE INVENTION

[03] PVS-RIPO is an oncolytic poliovirus (PV) recombinant. It consists of the live attenuated type 1 (Sabin) PV vaccine containing a foreign internal ribosomal entry site (IRES) of human rhinovirus type 2 (HRV2). The IRES is a cis-acting genetic element located in the 5' untranslated region of the PV genome, mediating viral, m⁷G-cap-independent translation. The virus has shown exciting signs of efficacy in humans. Nonetheless there is a continuing need in the art to identify and develop anti-cancer treatments that are more effective and that are effective for more humans, particularly for patients with brain tumors.

SUMMARY OF THE INVENTION

[04] According to one aspect of the invention a method of treating a tumor in a patient is provided. A chimeric poliovirus construct is administered to the patient. The construct comprises a Sabin type I strain of poliovirus with a human rhinovirus 2 (HRV2) internal ribosome entry site (IRES) in said poliovirus' 5' untranslated region between said poliovirus' cloverleaf and said poliovirus' open reading frame. A chemotherapy agent is administered to the patient when growth of the tumor progresses after poliovirus administration, or on a schedule, regardless of progression.

- [05] According to another aspect of the invention a kit is provided for treating a tumor with a first agent followed by a second agent after a gap of at least 3 month. The kit comprises as a first agent a chimeric poliovirus construct comprising a Sabin type I strain of poliovirus with a human rhinovirus 2 (HRV2) internal ribosome entry site (IRES) in said poliovirus' 5' untranslated region between said poliovirus' cloverleaf and said poliovirus' open reading frame. The kit comprises as a second agent a chemotherapy agent.
- [06] Also provided as an additional aspect of the invention is a composition for treating a tumor prior to treatment with a chemotherapeutic agent. The composition comprises a chimeric poliovirus construct comprising a Sabin type I strain of poliovirus with a human rhinovirus 2 (HRV2) internal ribosome entry site (IRES) in said poliovirus' 5' untranslated region between said poliovirus' cloverleaf and said poliovirus' open reading frame.
- [07] Additionally provided as an additional aspect of the invention is a composition for treating a tumor subsequent to treatment with a chimeric poliovirus construct comprising a Sabin type I strain of poliovirus with a human rhinovirus 2 (HRV2) internal ribosome entry site (IRES) in said poliovirus' 5' untranslated region between said poliovirus' cloverleaf and said poliovirus' open reading frame. The composition comprises a chemotherapeutic agent.
- [08] These and other aspects which will be apparent to those of skill in the art upon reading the specification provide the art with new therapeutic regimens for treating cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

- [09] Fig. 1—Patient #8 brain scans at times: pre-infusion of PVSRIPO, post drainage of hemorrhage, 7 months after PVSRIPO infusion, at time of first observed progression, at 9 months, after 1 cycle of lomustine (CCNU), at 24 months, and at 28 months.
- [10] Fig. 2—Patient #17 showing response after daily temodar was added to avastin. Brain scans at base line, 3 month, 5 months, 10 months, 12 months, and 14 months. Daily Temodar (temozolomide) was added to avastin regimen at 10 months.

- [11] Fig. 3—Patient #27 showing response after daily Temodar was added to Avastin. Brain scans at baseline, 2 months, 4 months, 5 months, and 7 months. Avastin was added at 2 months and Temodar was added at 5 months.
- [12] Fig. 4--Patient 21. Response after CCNU (lomustine) was added to Avastin. Brain scans shown at baseline, 1 month, 3 months and 5 months. Avastin was started at 1 month. At 3 months CCNU was added.
- [13] Fig. 5—Patient #23. Response after CCNU was added to Avastin. Brain scans shown at baseline, 3 months, 5 months, 7 months, and 8 months. Avastin was started at 3 months. CCNU was added at 7 months.
- [14] Fig. 6—Patient #28. Response after daily Temodar added to Avastin. Brain scans shown at baseline, 1 month, 3 months, and 5 months. Avastin was started at 1 month. Daily Temodar was added at 3 months.
- [15] Fig. 7A-7C—TRAMP-C2, a syngeneic mouse prostate cancer model (transduced with human poliovirus receptor, CD155) in CD155-transgenic mice was treated as shown in Fig. 7A with PVSRIPO on Day 0 and with temozolomide (TMZ) on days 7-13. This model is commonly used as a negative control for cancer immunotherapy. TRAMP is confirmed to have not a single antigenic epitope that could be recognized by the immune system. Therefore, nothing really works in this model through immunotherapy. We believe that this is the reason that PVSRIPO only has a minimal effect on TRAMP. We deliberately chose this highly resistant model to test synergy of TMZ with PVSRIPO. Fig. 7B shows percentage survival results in a Kaplan-Meier plot. Fig. 7C shows the results of the average tumor size over time.
- [16] Fig. 8—The experimental results of Fig. 7C are shown for individual mice in the cohorts in Fig. 8. The results for number of individual mice with tumors below 1500 mm³ at day 25 are tabulated below.

DETAILED DESCRIPTION OF THE INVENTION

- [17] The inventors have developed a method in which the efficacy of PVSRIPO chimeric poliovirus construct is increased and/or prolonged by subsequent administration of a chemotherapeutic agent. The effects are synergistic. While applicants do not wish to be bound by any particular mechanism of action, the increased/prolonged efficacy may be due to the ability of the chemotherapeutic agents to lymphodeplete. Lymphodepletion may remove competition at the surface of antigen presenting cells, enhance the availability of cytokines which augment T cell activity, deplete regulatory T cells, enhance immune priming and presentation, enhance antigen expression, and/or enhance targets for immune eradication.
- [18] Chemotherapy is preferably administered well after the initial effects of the PVSRIPO chimeric poliovirus construct have been observed. The administration may be at least 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 10 months, 12, months, 18 months, or 24 months after PVSRIPO delivery. The chemotherapy may be administered continuously or in cycles with gaps in the treatment to permit lymphocyte recovery, for example.
- [19] Suitable chemotherapy drugs are those that are lymphodepleting. These include classical alkylating agents such as Nitrogen mustards, including Cyclophosphamide, Mechlorethamine or mustine (HN2) (trade name Mustargen), Uramustine or uracil mustard, Melphalan, Chlorambucil, Ifosfamide, and Bendamustine. These also include the Nitrosoureas, such as Carmustine, Lomustine, and Streptozocin. These also include the Alkyl sulfonates, such as Busulfan. Platinum-based chemotherapeutic drugs (termed platinum analogues) act in a similar manner and may be used similarly. These agents do not have an alkyl group, but nevertheless damage DNA. They permanently coordinate to DNA to interfere with DNA repair, so they are sometimes described as “alkylating-like.” These include Cisplatin, Carboplatin, Nedaplatin, Oxaliplatin, Satraplatin, and Triplatin tetranitrate. Additionally, nonclassical alkylating agents may be used, including but not limited to procarbazine, altretamine, triazenes such as dacarbazine, mitozolomide, and temozolomide.

- [20] Any technique for directly administering the viral preparation to the tumor may be used. Direct administration does not rely on the blood vasculature to access the tumor. The preparation may be painted on the surface of the tumor, injected into the tumor, instilled in or at the tumor site during surgery, infused into the tumor via a catheter, etc. One particular technique which may be used is convection enhanced delivery.
- [21] Metronomic chemotherapy, which refers to the frequent administration of chemotherapeutics at doses significantly below the maximum tolerated dose without prolonged drug-free breaks, may be used. For example, a standard non-metronomic regimen with temozolomide consists of 150 to 200 mg/m² daily for 5 consecutive days repeated every 4 weeks. Metronomic regimen may be, for example, a dose of 50 mg/m²/day daily for 2 or 3 months. Similar low dose regimens with other chemotherapeutic agents may be used. Low dose regimens may also be used with standard timing. Standard dose and timing therapy may also be used.
- [22] Any human tumor can be treated, including both pediatric and adult tumors. The tumor may be in any organ, for example, brain, prostate, breast, lung, colon, and rectum. Various types of tumors may be treated, including, for example, glioblastoma, medulloblastomas, carcinoma, adenocarcinoma, etc. Other examples of tumors include, adrenocortical carcinoma, anal cancer, appendix cancer, grade I (anaplastic) astrocytoma, grade II astrocytoma, grade III astrocytoma, grade IV astrocytoma, atypical teratoid/rhabdoid tumor of the central nervous system, basal cell carcinoma, bladder cancer, breast sarcoma, bronchial cancer, bronchoalveolar carcinoma, cervical cancer, craniopharyngioma, endometrial cancer, endometrial uterine cancer, ependymblastoma, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing's sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, fibrous histiocytoma, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, gestational trophoblastic tumor, gestational trophoblastic tumor, glioma, head and neck cancer, hepatocellular cancer, Hilar cholangiocarcinoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumor, Kaposi sarcoma, Langerhans cell histiocytosis, large-cell undifferentiated lung carcinoma, laryngeal cancer, lip cancer, lung adenocarcinoma,

malignant fibrous histiocytoma, medulloepithelioma, melanoma, Merkel cell carcinoma, mesothelioma, endocrine neoplasia, nasal cavity cancer, nasopharyngeal cancer, neuroblastoma, oral cancer, oropharyngeal cancer, osteosarcoma, ovarian clear cell carcinoma, ovarian epithelial cancer, ovarian germ cell tumor, pancreatic cancer, papillomatosis, paranasal sinus cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumor, pineoblastoma, pituitary tumor, pleuropulmonary blastoma, renal cell cancer, respiratory tract cancer with chromosome 15 changes, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous non-small cell lung cancer, squamous neck cancer, supratentorial primitive neuroectodermal tumor, supratentorial primitive neuroectodermal tumor, testicular cancer, throat cancer, thymic carcinoma, thymoma, thyroid cancer, cancer of the renal pelvis, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, and Wilms tumor.

- [23] Optionally, patients may be stratified on the basis of NECL5 expression. This can be assayed at the RNA or protein level, using probes, primers, or antibodies, for example. The NECL5 expression may guide the decision to treat or not treat with the chimeric poliovirus of the present invention. The NECL5 expression may also be used to guide the aggressiveness of the treatment, including the dose, frequency, and duration of treatments.
- [24] Treatment regimens may include, in addition to delivery of the chimeric poliovirus construct, surgical removal of the tumor, surgical reduction of the tumor, chemotherapy biological therapy, and radiotherapy. These modalities are standard of care in many disease states, and the patient need not be denied the standard of care. The chimeric poliovirus may be administered before, during, or after the standard of care. The chimeric poliovirus may be administered after failure of the standard of care.
- [25] Kits may comprise, in a single divided or undivided container, either or both the chimeric poliovirus construct PVSRIPO as well as a chemotherapeutic agent. If both are provided in the kit, the two may be in separate vessels or in a single vessel in

admixture. Instructions for administration may be included. Optionally, an antibody for testing NECL5 expression in the patient is a component of the kit.

[26] While applicants do not wish to be bound by any particular mechanism of action, it is believed that multiple mechanisms may contribute to the efficacy of PVSRIPO. These include lysis of cancer cells, recruitment of immune cells, and specificity for cancer cells. Moreover, the virus is neuro-attenuated. The mechanism of enhancement/prolongation by a chemotherapy agent may also be multifactorial.

[27] The above disclosure generally describes the present invention.

A more complete understanding can be obtained by reference to the following specific examples, which are provided herein for purposes of illustration only, and are not intended to limit the scope of the invention.

EXAMPLE

[28] As of 2/23/2016, of the 20 patients treated on 5×10^7 TCID₅₀ of PVSRIPO, five patients had imaging concerning for disease progression, as well as clinical decline, following PVSRIPO infusion despite being on bevacizumab to help control the cerebral inflammation. Three patients were continued on bevacizumab and initiated on metronomic daily temozolomide at 50 mg/m²/day, with a goal of treating the tumor and helping in controlling the cerebral inflammation. Two patients had significant improvement on imaging at the first MRI follow-up and clinically significant improvement in their functional status. The third patient had a slight improvement on imaging, but failed to improve clinically and thus, the patient elected to proceed with comfort care and is now deceased. For two of the five patients, lomustine was added to bevacizumab. Both patients showed significant imaging and clinical improvement after the first six weeks of therapy (one cycle of lomustine), which is unusual for lomustine. However, one patient decided months later to discontinue lomustine and is now deceased. Three of the five patients remain alive, two on metronomic daily

temozolomide and bevacizumab and one on lomustine and bevacizumab, continue on therapy and are doing well.

- [29] One patient treated with 1.0×10^{10} TCID₅₀ of PVSRIPO experienced a dose limiting toxicity due to intracerebral hemorrhage at the time of catheter removal. The hemorrhage was drained, as well as possibly a significant amount of PVSRIPO. The patient demonstrated disease progression on imaging, confirmed to be recurrent glioblastoma (WHO grade IV) by biopsy, 7 months post PVSRIPO infusion. The patient was then initiated on lomustine and demonstrated significant clinical and imaging response after one cycle of lomustine. The patient completed nine cycles of lomustine 10 months ago and remains disease free (complete tumor disappearance) more 32 months post PVSRIPO infusion. It is to note that it is believed that the patient received less than the planned dose of PVSRIPO (1.0×10^{10} TCID₅₀) given the need to drain the hemorrhage, also the patient never received bevacizumab with the lomustine, given the concern for repeat cerebral hemorrhage.

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CLAIMS

1. Use of a lymphodepleting chemotherapeutic agent in the manufacture of a medicament for treatment of a tumor which has progressed in a patient, wherein the lymphodepleting chemotherapeutic agent is for administration following: (i) a first treatment with a lymphodepleting chemotherapeutic agent, and (ii) a second treatment with a chimeric poliovirus construct comprising a Sabin type I strain of poliovirus with a human rhinovirus 2 (HRV2) internal ribosome entry site (IRES) in said poliovirus' 5' untranslated region between said poliovirus' cloverleaf and said poliovirus' open reading frame, and wherein growth of the tumor has progressed following the first treatment and following the second treatment.
2. Use of a lymphodepleting chemotherapeutic agent for treatment of a tumor which has progressed in a patient, wherein the lymphodepleting chemotherapeutic agent is for administration following: (i) a first treatment with a lymphodepleting chemotherapeutic agent, and (ii) a second treatment with a chimeric poliovirus construct comprising a Sabin type I strain of poliovirus with a human rhinovirus 2 (HRV2) internal ribosome entry site (IRES) in said poliovirus' 5' untranslated region between said poliovirus' cloverleaf and said poliovirus' open reading frame, and wherein growth of the tumor has progressed following the first treatment and following the second treatment.
3. The use of claim 1 or 2 wherein the lymphodepleting chemotherapeutic agent causes transient lymphopenia.
4. The use of claim 1 or 2 wherein the lymphodepleting chemotherapeutic agent is an alkylating agent.
5. The use of claim 1 or 2 wherein the lymphodepleting chemotherapeutic agent is lomustine.

6. The use of claim 1 or 2 wherein the lymphodepleting chemotherapeutic agent is temozolomide.
7. The use of claim 1 or 2 wherein the lymphodepleting chemotherapeutic agent is for administration according to a metronomic schedule.
8. The use of claim 7 wherein the lymphodepleting chemotherapeutic agent is temozolomide.
9. The use of claim 1 or 2 wherein the lymphodepleting chemotherapeutic agent is for administration at least 3 months after administration of the chimeric poliovirus construct.
10. The use of claim 1 or 2 wherein the lymphodepleting chemotherapeutic agent is for administration at least 5 months after administration of the chimeric poliovirus construct.
11. The use of claim 1 or 2 wherein the lymphodepleting chemotherapeutic agent is for administration at least 7 months after administration of the chimeric poliovirus construct.
12. The use of claim 1 or 2 wherein progression of the tumor is assessed by imaging.
13. The use of claim 1 or 2 wherein progression of the tumor is assessed by clinical indices.
14. The use of claim 1 or 2 wherein the tumor is a brain tumor.
15. The use of claim 14 wherein the tumor is a glioblastoma.
16. The use of claim 14 wherein the tumor is astrocytoma or oligodendroglioma.
17. The use of claim 14 wherein the tumor is astro-oligodendroglioma.

18. The use of claim 14 wherein the tumor is medulloblastoma.
19. The use of claim 1 or 2 wherein the tumor is selected from the group consisting of renal cell carcinoma, prostate tumor, bladder tumor, esophagus tumor, stomach tumor, pancreas tumor, colorectal tumor, liver or gall bladder tumor, breast tumor, lung tumor, head and neck tumor, melanoma, and sarcoma.
20. The use of claim 1 or 2 wherein the tumor expresses NECL5 (nectin- like protein 5).
21. The use of claim 1 or 2 wherein the chimeric poliovirus construct is formulated for intracerebral infusion with convection enhanced delivery.
22. The use of claim 1 or 2 wherein the tumor has been tested to ascertain that it expresses NECL5 (nectin- like protein 5).
23. The use of claim 1 or 2 wherein the chimeric poliovirus construct is formulated for administration directly to the tumor.
24. A composition for treating a tumor which has progressed in a patient, wherein the composition is for administration after a first treatment with a lymphodepleting chemotherapeutic agent and before a second treatment with a lymphodepleting chemotherapeutic agent, comprising: a chimeric poliovirus construct comprising a Sabin type I strain of poliovirus with a human rhinovirus 2 (HRV2) internal ribosome entry site (IRES) in said poliovirus' 5' untranslated region between said poliovirus' cloverleaf and said poliovirus' open reading frame, wherein the tumor has progressed following the first treatment and before the second treatment.
25. A composition for use in treating a tumor which has progressed in a patient, wherein the composition comprises: a lymphodepleting chemotherapeutic agent; and wherein the composition is for administration following: (i) a first treatment with a lymphodepleting

- chemotherapeutic agent, and (ii) a second treatment with a chimeric poliovirus construct comprising a Sabin type I strain of poliovirus with a human rhinovirus 2 (HRV2) internal ribosome entry site (IRES) in said poliovirus' 5' untranslated region between said poliovirus' cloverleaf and said poliovirus' open reading frame, and wherein growth of the tumor has progressed following the first treatment and following the second treatment.
26. A kit for treating a tumor which has progressed in a patient, wherein the kit comprises: (i) a first agent which is a chimeric poliovirus construct comprising a Sabin type I strain of poliovirus with a human rhinovirus 2 (HRV2) internal ribosome entry site (IRES) in said poliovirus' 5' untranslated region between said poliovirus' cloverleaf and said poliovirus' open reading frame; and (ii) a second agent which is a lymphodepleting chemotherapeutic agent; wherein the first agent is for administration after a first treatment with a first lymphodepleting chemotherapeutic agent, and wherein the second agent is for administration after the first agent, and wherein the tumor has progressed following treatment with the first lymphodepleting chemotherapeutic agent.
27. The composition of any one of claims 24-25 which is in a kit with an antibody specific for NECL5 (nectin-like protein 5).
28. The kit of claim 26 further comprising an antibody specific for NECL5 (nectin-like protein 5).
29. The composition of any one of claims 24-25 or the kit of claim 26 wherein the lymphodepleting chemotherapeutic agent causes transient lymphopenia.
30. The composition of any one of claims 24-25 or the kit of claim 26 wherein the lymphodepleting chemotherapeutic agent is an alkylating agent.
31. The composition of any one of claims 24-25 or the kit of claim 26 wherein the lymphodepleting chemotherapeutic agent is lomustine.

32. The composition of any one of claims 24-25 or the kit of claim 26 wherein the lymphodepleting chemotherapeutic agent is temozolomide.
33. The composition of any one of claims 24-25 or the kit of claim 26 wherein the lymphodepleting chemotherapeutic agent is for administration according to a metronomic schedule.
34. The composition of claim 33 or the kit of claim 33, wherein the lymphodepleting chemotherapeutic agent is temozolomide.
35. The composition of any one of claims 24-25 or the kit of claim 26 wherein the lymphodepleting chemotherapeutic agent is for administration at least 3 months after administration of the chimeric poliovirus construct.
36. The composition of any one of claims 24-25 or the kit of claim 26 wherein the lymphodepleting chemotherapeutic agent is for administration at least 5 months after administration of the chimeric poliovirus construct.
37. The composition of any one of claims 24-25 or the kit of claim 26 wherein the lymphodepleting chemotherapeutic agent is for administration at least 7 months after administration of the chimeric poliovirus construct.
38. The composition of any one of claims 24-25 or the kit of claim 26 wherein progression of the tumor is assessed by imaging.
39. The composition of any one of claims 24-25 or the kit of claim 26 wherein progression of the tumor is assessed by clinical indices.

40. The composition of any one of claims 24-25 or the kit of claim 26 wherein the tumor is a brain tumor.
41. The composition of any one of claims 24-25 or the kit of claim 26 wherein the tumor is a glioblastoma.
42. The composition of any one of claims 24-25 or the kit of claim 26 wherein the tumor is astrocytoma or oligodendroglioma.
43. The composition of any one of claims 24-25 or the kit of claim 26 wherein the tumor is astro-oligodendroglioma.
44. The composition of any one of claims 24-25 or the kit of claim 26 wherein the tumor is medulloblastoma.
45. The composition of any one of claims 24-25 or the kit of claim 26 wherein the tumor is selected from the group consisting of renal cell carcinoma, prostate tumor, bladder tumor, esophagus tumor, stomach tumor, pancreas tumor, colorectal tumor, liver or gall bladder tumor, breast tumor, lung tumor, head and neck tumor, melanoma, and sarcoma.
46. The composition of any one of claims 24-25 or the kit of claim 26 wherein the tumor expresses NECL5 (nectin- like protein 5).
47. The composition of any one of claims 24-25 or the kit of claim 26 wherein the chimeric poliovirus construct is formulated for intracerebral infusion with convection enhanced delivery.
48. The composition of any one of claims 24-25 or the kit of claim 26 wherein the tumor has been tested to ascertain that it expresses NECL5 (nectin- like protein 5).

49. The composition of any one of claims 24-25 or the kit of claim 26 wherein the chimeric poliovirus construct is formulated for administration directly to the tumor.
50. The use of any one of claims 1-23, wherein the chimeric poliovirus construct is PVS-RIPO.
51. The composition of any one of claims 24-25 or the kit of claim 26, wherein the chimeric poliovirus construct is PVS-RIPO.

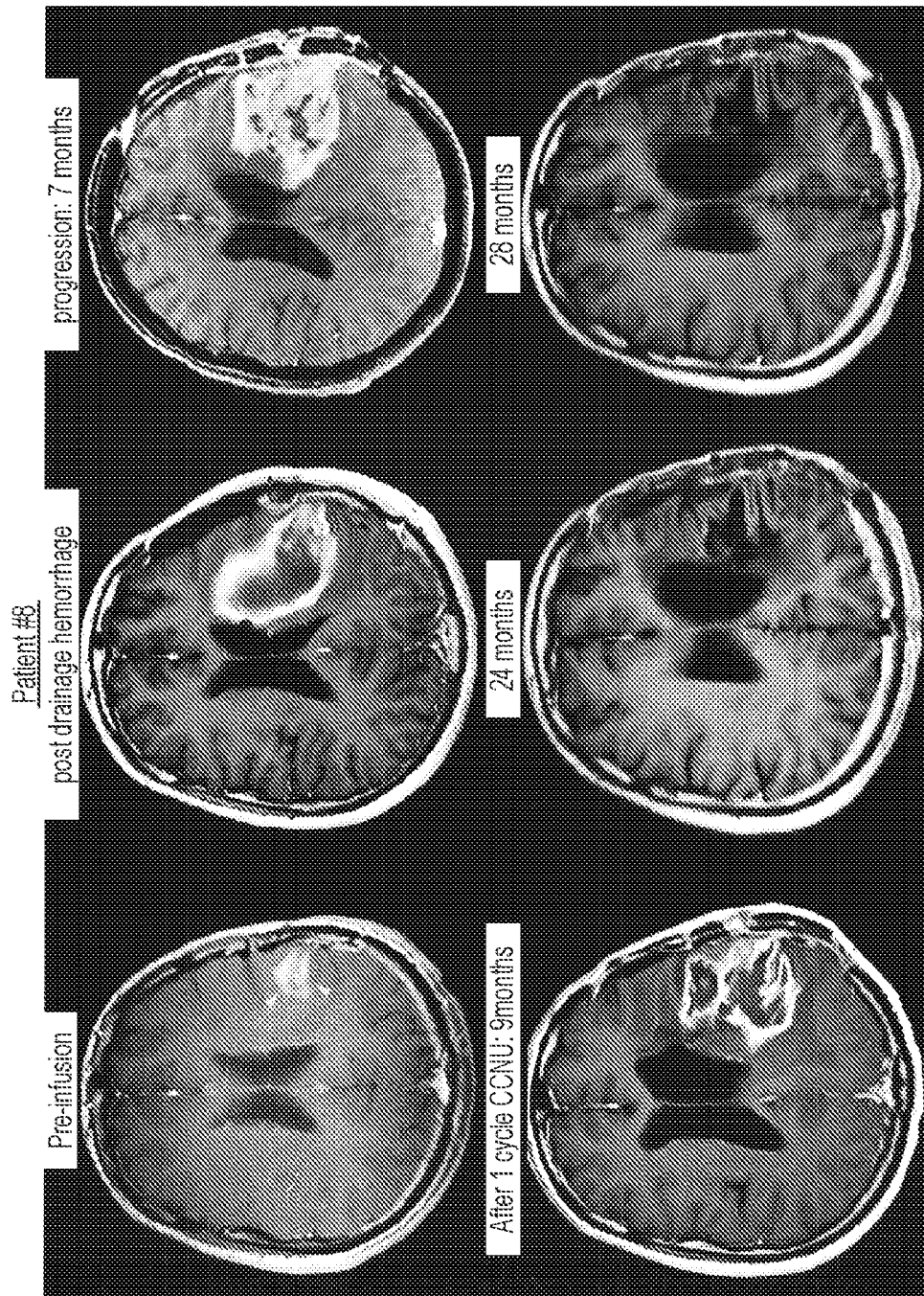


Fig. 1

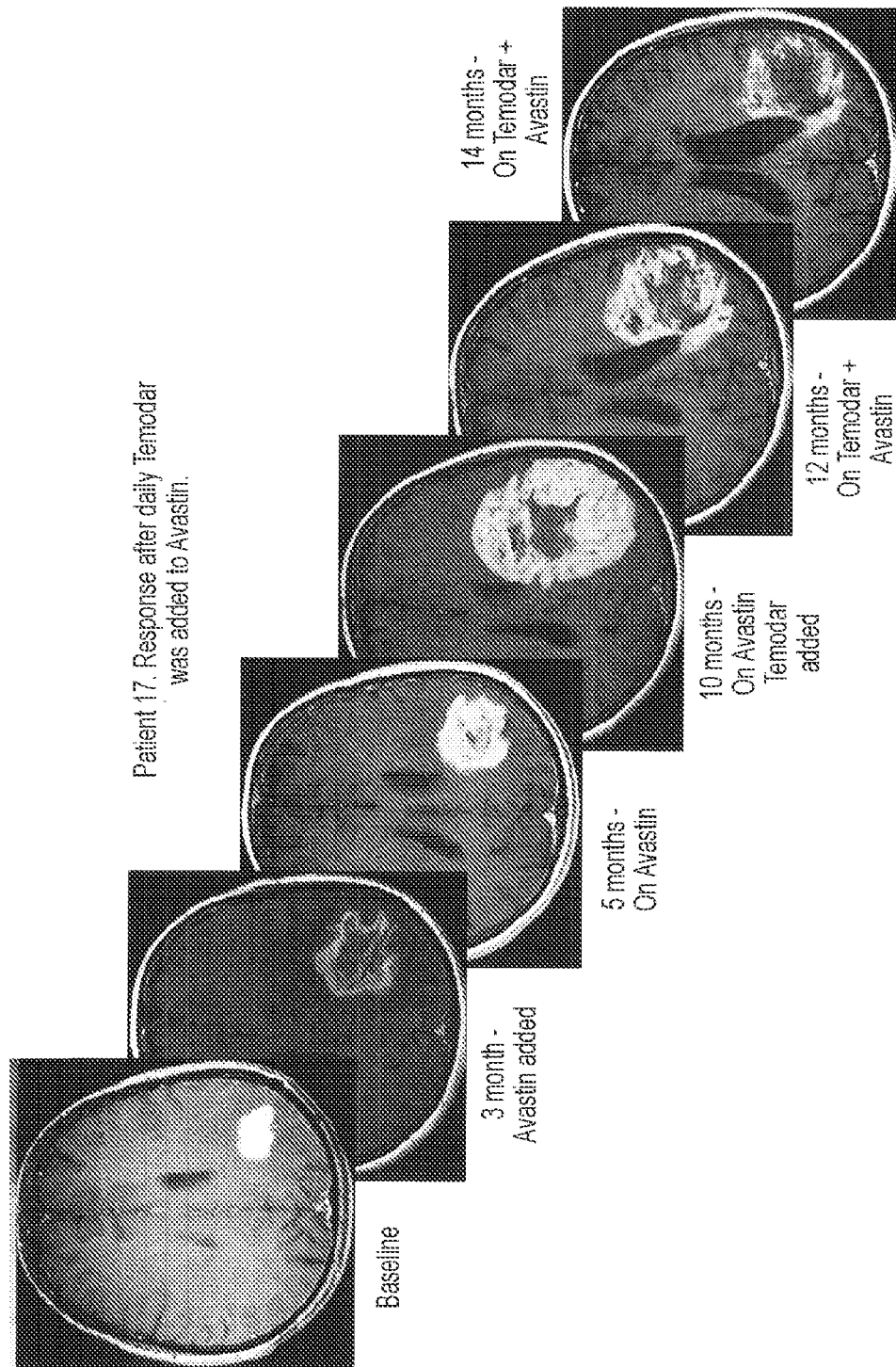


Fig. 2

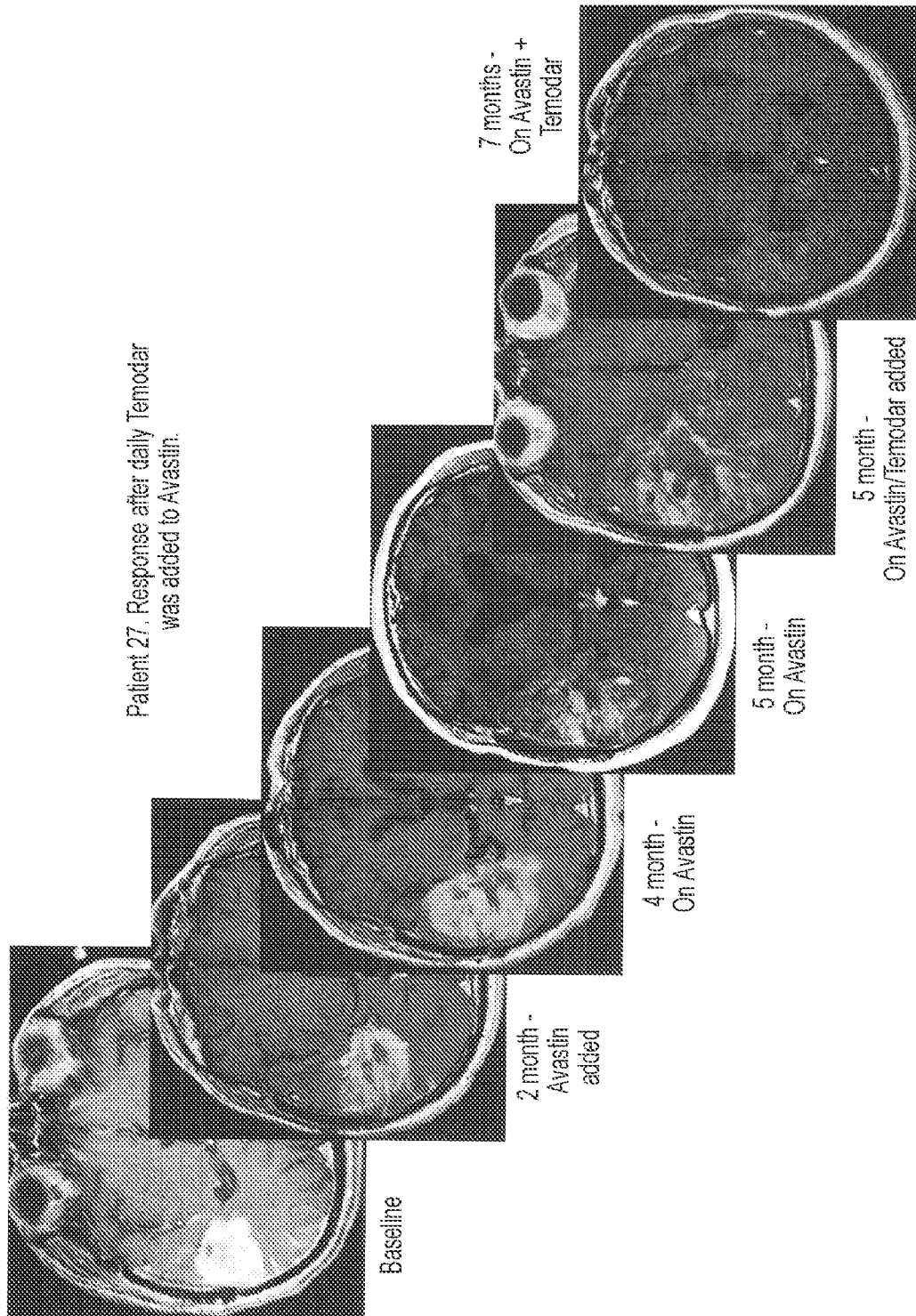


Fig. 3

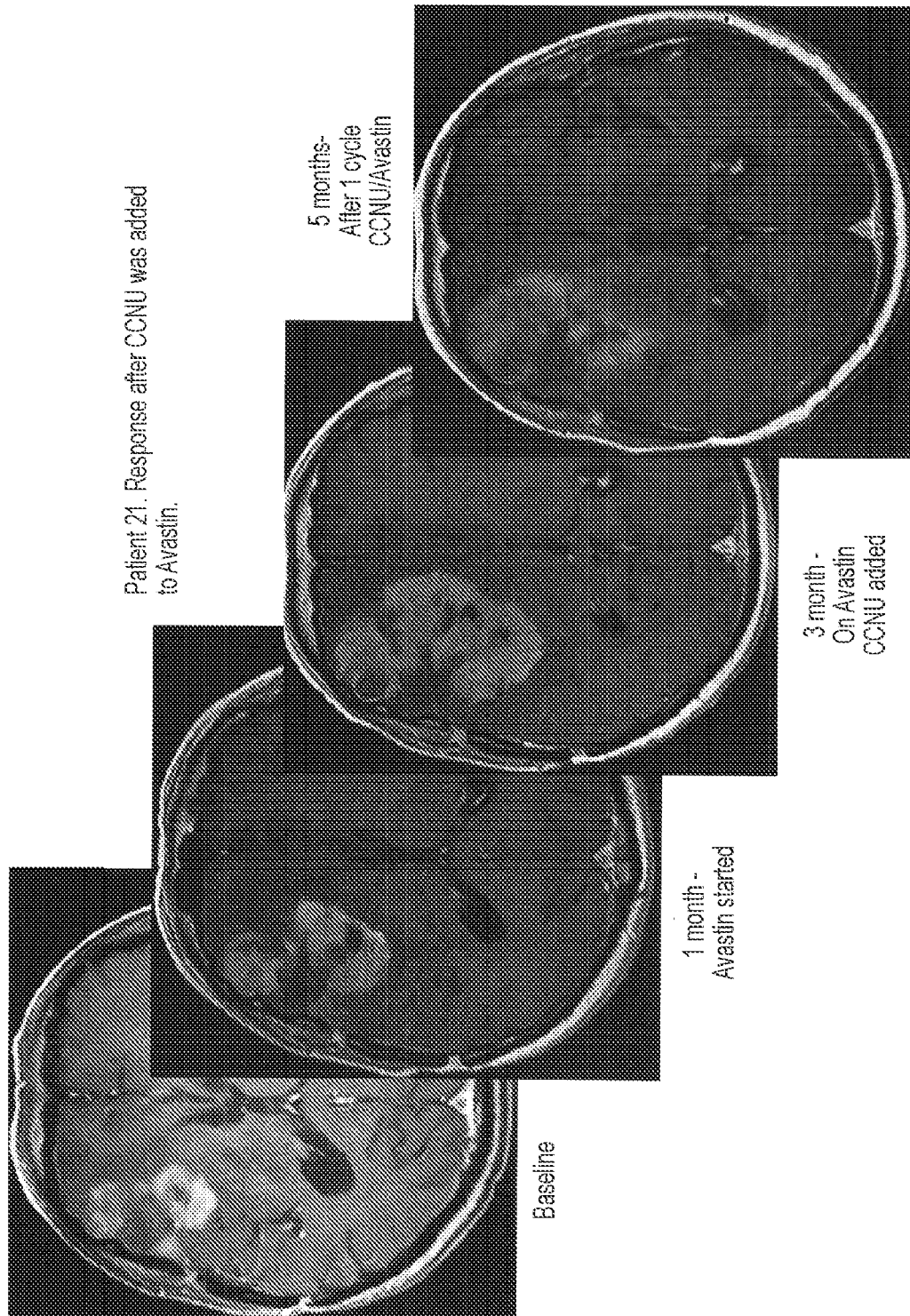


Fig. 4

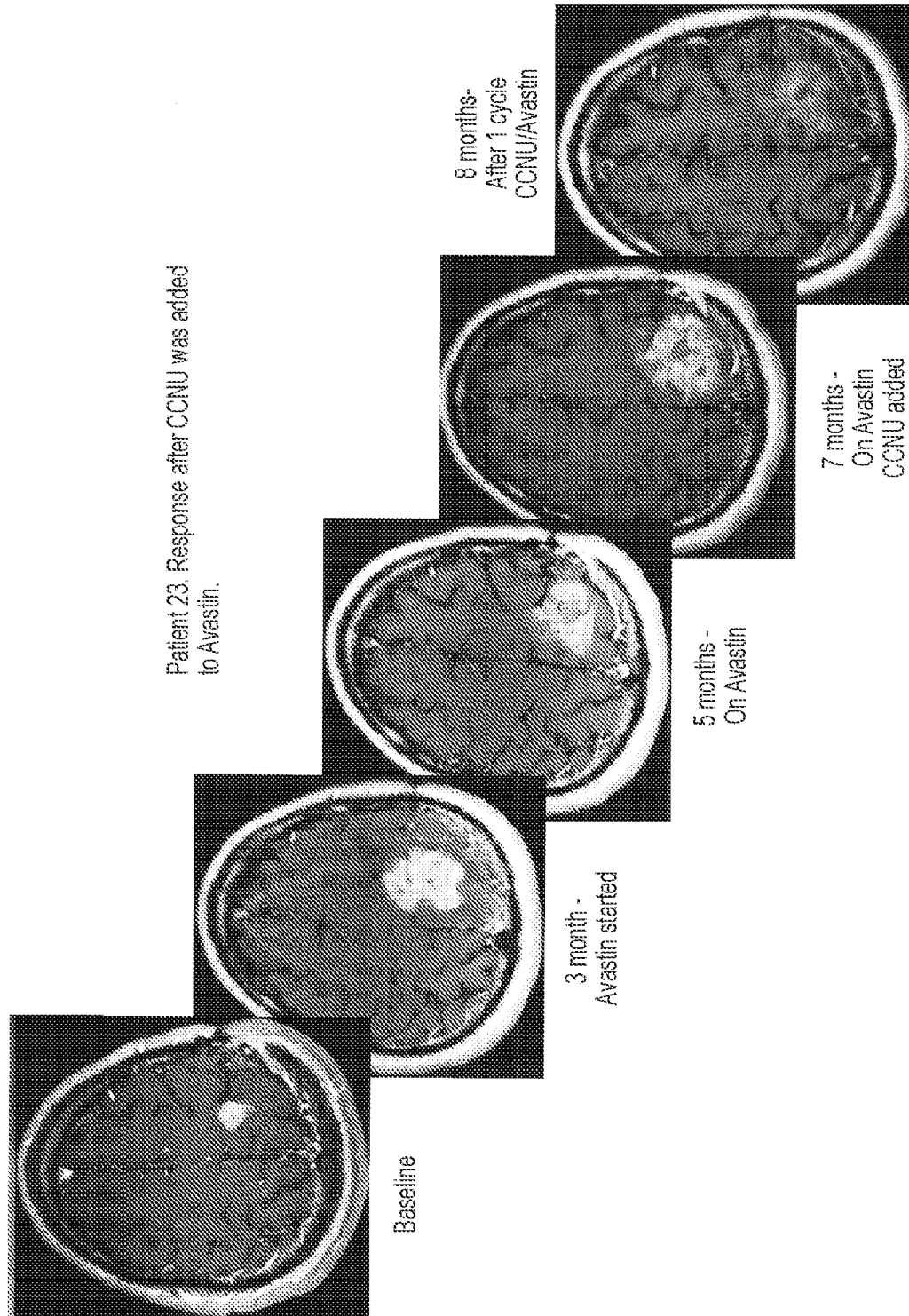


Fig. 5

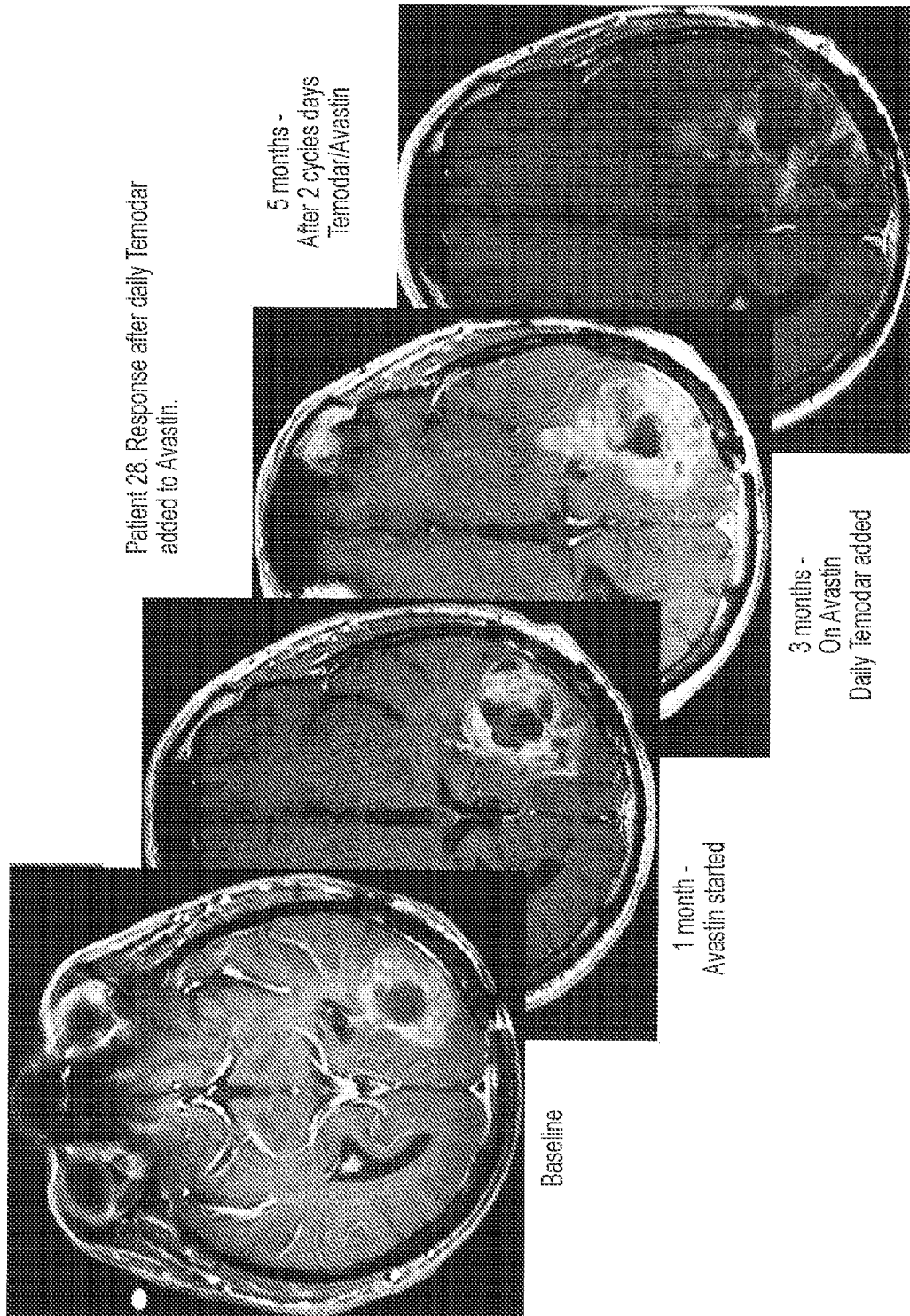
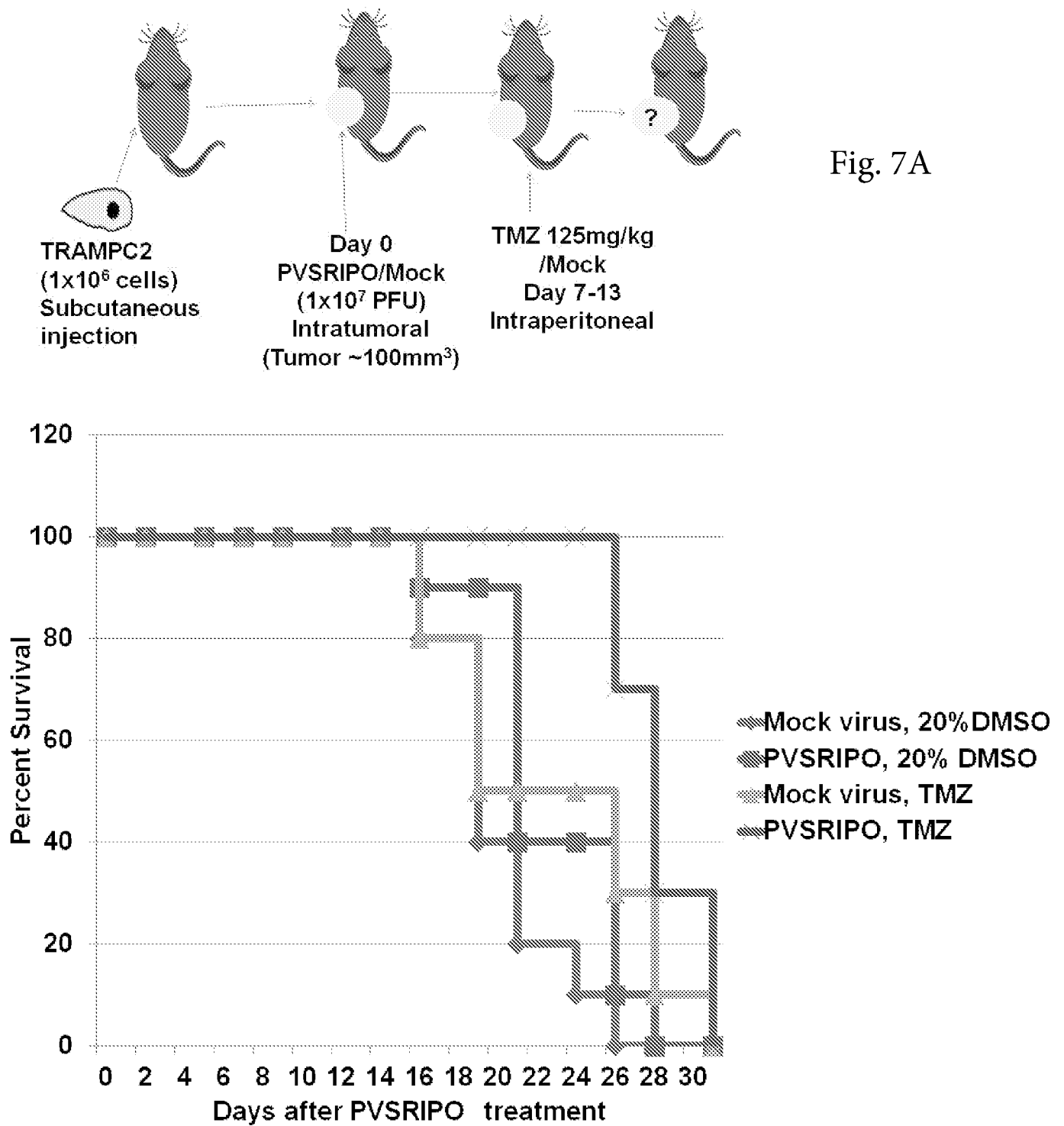


Fig. 6

Fig. 7A-7C
TRAMPC2 PVSRIPO TMZ Combination Experiment



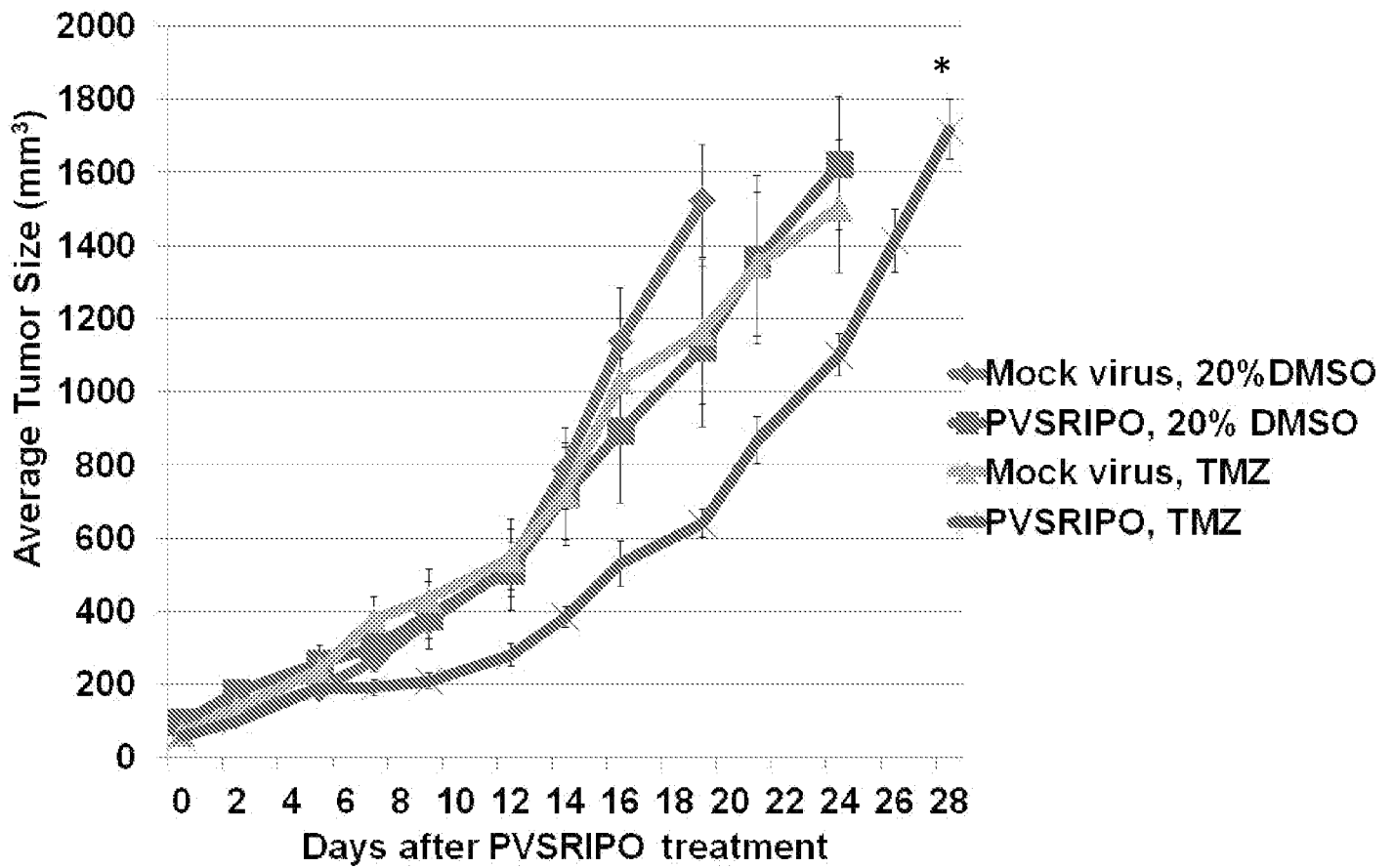


Fig. 7C

Fig. 8. TRAMPC2 PVSRIPO TMZ Combination Experiment

