



US 20050112061A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2005/0112061 A1**

Holash et al.

(43) **Pub. Date: May 26, 2005**

(54) **USE OF A VEGF ANTAGONIST IN
COMBINATION WITH RADIATION
THERAPY**

(76) Inventors: **Jocelyn Holash**, Alameda, CA (US);
George Yancopoulos, Yorktown
Heights, NY (US); **Phyllis R.
Wachsberger**, Berwyn, PA (US); **Adam
P. Dicker**, Cherry Hill, NJ (US); **Randy
Burd**, Wayne, PA (US)

Correspondence Address:
REGENERON PHARMACEUTICALS, INC
777 OLD SAW MILL RIVER ROAD
TARRYTOWN, NY 10591 (US)

(21) Appl. No.: **10/909,011**

(22) Filed: **Jul. 30, 2004**

Related U.S. Application Data

(60) Provisional application No. 60/492,864, filed on Aug.
6, 2003.

Publication Classification

(51) **Int. Cl.⁷** **A61K 51/00**; A61K 39/395;
A61K 38/17

(52) **U.S. Cl.** **424/1.49**; 424/145.1; 514/12

(57) **ABSTRACT**

Methods of treating cancer and/or reducing or inhibiting
tumor growth in a subject in need thereof, comprising
administering pharmaceutical composition comprising a
vascular endothelial cell growth factor (VEGF) trap, in
combination with radiation therapy and/or a therapeutic
radiopharmaceutical.

USE OF A VEGF ANTAGONIST IN COMBINATION WITH RADIATION THERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 USC § 119(e) of U.S. Provisional application 60/492,864 filed 6 Aug. 2003, which application is herein specifically incorporated by reference in its entirety.

BACKGROUND

[0002] 1. Field of the Invention

[0003] The field of the invention is related to methods of treating cancer in a mammal with a vascular endothelial growth factor (VEGF) trap capable of binding and inhibiting the biological activity of VEGF in combination with radiation therapy.

[0004] 2. Description of Related Art

[0005] Vascular endothelial growth factor (VEGF) has been recognized as a primary stimulus of angiogenesis in pathological conditions. Approaches to methods of blocking VEGF include soluble receptor constructs, antisense molecules, RNA aptamers, and antibodies. See, for example, PCT WO/0075319, for a description of VEGF-receptor based trap antagonists.

[0006] Radiation therapy is widely used for the treatment of cancer both alone and in conjunction with surgery and/or anti-neoplastic agents. Combination therapies using radiation and squalamine are known (see U.S. Pat. No. 6,596,712). Recent preclinical studies have suggested that radiation therapy in combination with VEGF targeting agents can enhance the therapeutic ratio of ionizing radiation by targeting both tumor cells and tumor vessels.

BRIEF SUMMARY OF THE INVENTION

[0007] The invention is based in part on the results of experiments described below that show that the combined treatment of a VEGF trap with radiation therapy results in a significant inhibition of tumor growth in a clinically relevant human glioblastoma model.

[0008] Thus, in a first aspect, the invention features a method of treating cancer in a subject in need thereof, comprising administering to the subject a VEGF trap in combination with radiation therapy such that the cancer is treated. In one embodiment of the invention, the VEGF trap is Flt1D2.Flk1D3.FcΔC1(a) (SEQ ID NOs: 1-2), or VEGFR1R2-FcΔC1(a) (SEQ ID NOs:3-4).

[0009] In specific embodiments, the amount of VEGF trap administered is in a low dose, e.g., approximately about or less than 1 mg/kg. In another embodiment, the amount of VEGF trap administered is at a high dose, about or more than 2.5 mg/kg. Administration may be by any method known in the art, including subcutaneous, intramuscular, intradermal, intraperitoneal, intravenous, intranasal, epidural, or oral. Preferably, administration is subcutaneous or intravenous, or a combination thereof. Administration may be concurrently (e.g., simultaneous) with, or sequentially (e.g., prior to or following radiation administration). In one embodiment, a low dose (≤ 1.0 mg/kg) of VEGF trap is administered concurrently with radiation once per week or at

2-4 week intervals. In another embodiment, a high dose (≥ 2.5 mg/kg) is administered with radiation once per month or at 2-4 month intervals. In another embodiment, a high dose (≥ 2.5 mg/kg) of VEGF trap is administered concurrently with radiation once per week or at 2-4 week intervals. In another embodiment, a low dose (≤ 1.0 mg/kg) is administered with radiation once per month or at 2-4 month intervals.

[0010] Radiation therapy, including therapeutic radiopharmaceuticals, can be administered to the mammal according to protocols commonly employed in the art and known to the skilled artisan. Such therapy may include cesium, iridium, iodine, or cobalt radiation. In one embodiment, the radiation therapy is ionizing radiation therapy.

[0011] In a second aspect, the invention features a method of reducing or inhibiting tumor growth in a subject in need thereof, comprising administering to the subject a VEGF trap in combination with radiation therapy such that tumor growth is reduced or inhibited. In one embodiment of the invention, the VEGF trap is Flt1D2.Flk1D3.FcΔC1(a) (SEQ ID NOs: 1-2), or VEGFR1R2-FcΔC1(a) (SEQ ID NOs:3-4).

[0012] In a third aspect, the invention features a method of treating a human patient suffering from cancer, comprising administering an effective amount of a vascular endothelial growth factor (VEGF) trap and radiation to the human patient, the method comprising administering to the patient an initial dose of ≤ 1.0 mg/kg of the VEGF trap with radiation therapy. In specific embodiments, the initial administration of VEGF trap and radiation are followed by a plurality of subsequent doses of the VEGF trap and radiation in an amount that is approximately the same or less of the initial dose, wherein the subsequent doses are separated in time from each other by at least one week.

[0013] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION

[0014] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0015] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus for example, a reference to "a method" includes one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0016] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

[0017] General Description

[0018] The invention is based on the findings that administration of a VEGF trap capable of binding and inhibiting the biological activity of VEGF, for example the VEGF trap VEGFR1 R2-FcΔC1 (a) (SEQ ID NOs:3-4), in combination with radiation therapy (including ionizing radiation and/or therapeutic radiopharmaceuticals, results in a significant inhibition of tumor growth. The effect of the combination of a VEGF trap and radiation therapy on tumor growth provides a promising therapeutic approach to the treatment of human cancer. For a description of VEGF-receptor-based antagonist VEGF traps Flt1D2, Flk1D3, FcΔC1(a) (SEQ ID NOs:1-2) and VEGFR1R2-FcΔC1(a) (SEQ ID NOs:3-4), see PCT WO/0075319, the contents of which is incorporated in its entirety herein by reference.

[0019] Methods of Administration

[0020] The invention provides methods of treatment comprising administering to a subject an effective amount of a pharmaceutical composition comprising a VEGF trap, in combination with radiation therapy. Various delivery systems are known and can be used to administer the composition of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction can be enteral or parenteral and include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, intraocular, and oral routes. The compounds may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. Administration can be acute or chronic (e.g. daily, weekly, monthly, etc.) or in combination with other agents. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0021] In another embodiment, the active agent can be delivered in a vesicle, in particular a liposome, in a controlled release system, or in a pump. In another embodiment where the active agent of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see, for example, U.S. Pat. No. 4,980,286), by direct injection, or by use of microparticle bombardment, or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see e.g., Joliet et al., 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0022] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved, for example, and not by way of limitation, by local

infusion during surgery, topical application, e.g., by injection, by means of a catheter, or by means of an implant, the implant being of a porous, non-porous, or gelatinous material, including membranes, such as silastic membranes, fibers, or commercial skin substitutes.

[0023] A composition useful in practicing the methods of the invention may be a liquid comprising an agent of the invention in solution, in suspension, or both. The term "solution/suspension" refers to a liquid composition where a first portion of the active agent is present in solution and a second portion of the active agent is present in particulate form, in suspension in a liquid matrix. A liquid composition also includes a gel. The liquid composition may be aqueous or in the form of an ointment.

[0024] An aqueous suspension or solution/suspension useful for practicing the methods of the invention may contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers and water-insoluble polymers such as cross-linked carboxyl-containing polymers. An aqueous suspension or solution/suspension of the present invention is preferably viscous or muco-adhesive, or even more preferably, both viscous and mucoadhesive. Radiation Therapy and Therapeutic Radiopharmaceuticals

[0025] Radiation is used as a therapeutic treatment for many types of cancers and is delivered in various ways, depending on the disease, its location, and its stage. Such therapy may include cesium, iridium, iodine, or cobalt radiation. The radiation therapy may be whole body irradiation, or may be directed locally to a specific site or tissue in or on the body. Typically, radiation therapy is administered in pulses over a period of time from about 1 to about 2 weeks. The radiation therapy may, however, be administered over longer periods of time. Optionally, the radiation therapy may be administered as a single dose or as multiple, sequential doses. Examples of radiation therapies include conformal radiation therapy, coronary artery brachytherapy, fast neutron radiotherapy, intensity modulated radiotherapy (IMRT), interoperative radiotherapy, interstitial brachytherapy, interstitial breast brachytherapy, organ preservation therapy, and stereotactic radiosurgery. The use of therapeutic radiopharmaceuticals is also encompassed by the invention. Examples of therapeutic radiopharmaceuticals include, for example, P32 chromic phosphate colloid, P32 sodium chromate, Sr89 chloride, 5 ml53 EDTMP leixidronam, 1131 sodium iodide, Y90 ibritumomab tiuxetan, 1 nl1 tositumomab, and Y90 microspheres. The VEGF trap is administered to the patient concurrently or sequentially of treatment with radiation and/or a therapeutic radiopharmaceutical compound. Following administration of the VEGF trap and radiation, the patient's cancer and physiological condition can be monitored in various ways well known to the skilled practitioner. For instance, tumor mass may be observed physically, by biopsy or by standard x-ray imaging techniques.

[0026] Pharmaceutical Compositions

[0027] The present invention provides pharmaceutical compositions comprising a VEGF trap and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals,

and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin.

[0028] The composition of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0029] The amount of the composition of the invention that will be effective for its intended therapeutic use can be determined by standard clinical techniques based on the present description. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. Generally, suitable dosage ranges for intravenous administration are generally about 20-500 micrograms of active compound per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

[0030] For systemic administration, a therapeutically effective dose can be estimated initially from in vitro assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Initial dosages can also be estimated from in vivo data, e.g., animal models, using techniques that are well known in the art. One having ordinary skill in the art could readily optimize administration to humans based on animal data.

[0031] Dosage amount and interval may be adjusted individually to provide plasma levels of the compounds that are sufficient to maintain therapeutic effect. In cases of local administration or selective uptake, the effective local concentration of the compounds may not be related to plasma concentration. One having skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation.

[0032] The amount of compound administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician. The therapy may be repeated intermittently while symptoms are detectable or even when they are not detectable. The therapy may be provided alone or in combination with other drugs.

Specific Embodiments

[0033] Example 1 describes experiments in which tumors grown in mice from U-87 glioblastoma cells were treated with a combination of low or high doses of the VEGF trap of SEQ ID NOs:3-4 with or without a single dose of radiation. The results showed enhanced suppression and delay of tumor growth with the combination of VEGF inhibitor and radiation therapy.

[0034] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

[0035] The following example is put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1

Improvement of Tumor Control by Combining a VEGF Trap and Radiation Therapy

[0036] Materials and Methods: U-87 cells, a clinically relevant human glioblastoma cell line, were injected subcutaneously into the right hind limb (5×10^5 cells in 0.1 ml PBS) of athymic NCR NUM mice and allowed to grow until reaching a diameter of 4-5 mm before treatment. Tumor growth delay (TGD) was determined using time in days for the tumor to grow to 1000 mm^3 . In one experiment, a VEGF trap (SEQ ID NOs:3-4) was used at two doses, high (25 mg/kg) and low (2.5 mg/kg) given every three days for up to three weeks, using the same schedule with and without a single dose of radiation of 10 Grays (Gy).

[0037] In a second experiment, VEGF trap was used at either mid (10 mg/kg) or low (2.5 mg/kg) dose, and treatment was initiated one week prior to the single dose of radiation, following the radiation treatment, VEGF trap treatment was continued for an additional 21 days, again being administered every third day.

[0038] Results: In the first study, control tumors had an average TGD of 10 days whereas low dose VEGF trap increased TGD an additional 10 days. A single dose of radiation of 10 Gy increased TGD 10 days over that of control whereas radiation plus low dose VEGF trap increased TGD 20-25 days over that of control. High dose VEGF trap increased TGD 40 days over that of control but did not show any increased benefit when combined with radiation. In the second study, when VEGF Trap at either 10 mg/kg or 2.5 mg/kg was combined with radiation therapy, enhanced tumor suppression was observed. As seen in Table 1, average tumor size at an interim point in the study, Study Day 35, is reduced when VEGF trap (VEGFT) is combined

with radiation. Additionally, fewer tumors reach the specified study endpoint by this time when combination therapy is given. The results show that suppression and delay in tumor growth is achieved by the combined treatments.

[0039] It is concluded that VEGF trap alone is an effective inhibitor of tumor growth in the U-87 glioblastoma model and that low or mid dose VEGF trap in combination with single dose radiation has an enhanced effect on tumor cell killing. These results have important implications for the treatment of human cancer.

TABLE 1

Study Day 35		
Treatment Group	Tumor Volume (mm ³) ± SEM	# Mice Still in Study
Control	1854 ± 276	1/8
Radiation Only	2243 ± 104	0/8

TABLE 1-continued

Study Day 35		
Treatment Group	Tumor Volume (mm ³) ± SEM	# Mice Still in Study
VEGFT 2.5 mg/kg	1751 ± 174	1/9
VEGFT 10 mg/kg	1357 ± 205	6/10
VEGFT 2.5 mg/kg + Radiation	1400 ± 206	5/8
VEGFT 10 mg/kg + Radiation	668 ± 347	5/6

[0040] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 4

<210> SEQ ID NO 1

<211> LENGTH: 1453

<212> TYPE: DNA

<213> ORGANISM: homo sapiens

<400> SEQUENCE: 1

```

aagcttgggc tgcaggtcga tcgactctag aggatcgatc cccgggagag ctgcaattcg      60
caaccacccat ggtcagctac tgggacaccg gggctcctgct gtgcgcgctg ctgagctgtc     120
tgctttctcac aggatctagt tccggaggta gacctttcgt agagatgtac agtgaatatcc     180
ccgaaattat acacatgact gaaggaaggg agctcgtcat tccctgccgg gttacgtcac      240
ctaacatcac tgttacttta aaaaagtttc cacttgacac ttgatccct gatggaaaac      300
gcataatctg ggacagtaga aagggttca tcatatcaaa tgcaacgtac aaagaaatag      360
ggcttctgac ctgtgaagca acagtcaatg ggcatttgta taagacaaac tatctcacac      420
atcgacaaac caatacaatc atagatgtgg ttctgagtcg gtctcatgga attgaactat      480
ctgttgagga aaagcttgtc ttaaattgta cagcaagaac tgaactaaat gtggggattg      540
acttcaactg ggaataccct tcttcgaagc atcagcataa gaaacttgta aaccgagacc      600
taaaaaccca gtctgggagt gagatgaaga aatttttgag caccttaact atagatgggtg      660
taacccggag tgaccaagga ttgtacacct gtgcagcatc cagtgggctg atgaccaaga      720
agaacagcac atttgtcagg gtccatgaaa agggcccggg cgacaaaact cacacatgcc      780
cacctgccc agcacctgaa ctctggggg gaccgtcagt ctctctcttc ccccaaaac      840
ccaaggacac cctcatgac tcccgaccc ctgaggtcac atgcgtggtg gtggacgtga      900
gccacgaaga cctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg      960
ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca     1020
ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag     1080
ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac     1140

```

-continued

```

aggtgtacac cctgccccca tcccgggatg agctgaccaa gaaccaggtc agcctgacct 1200
gcctgggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc aatgggcagc 1260
cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc ttcttcctct 1320
atagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg 1380
tgatgcataa ggctctgcac aacctacta cgcagaagag cctctccctg tctccgggta 1440
aatgagcggc cgc 1453

```

<210> SEQ ID NO 2

<211> LENGTH: 458

<212> TYPE: PRT

<213> ORGANISM: homo sapiens

<400> SEQUENCE: 2

```

Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1             5             10             15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Gly Arg Pro Phe Val Glu
      20             25             30
Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu Gly Arg Glu
      35             40             45
Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr Val Thr Leu
      50             55             60
Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile
      65             70             75             80
Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu
      85             90             95
Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys
      100            105            110
Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile Asp Val Val
      115            120            125
Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu Lys Leu Val
      130            135            140
Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile Asp Phe Asn
      145            150            155            160
Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu Val Asn Arg
      165            170            175
Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe Leu Ser Thr
      180            185            190
Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu Tyr Thr Cys
      195            200            205
Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr Phe Val Arg
      210            215            220
Val His Glu Lys Gly Pro Gly Asp Lys Thr His Thr Cys Pro Pro Cys
      225            230            235            240
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
      245            250            255
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
      260            265            270
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
      275            280            285
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
      290            295            300

```

-continued

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 305 310 315 320
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 325 330 335
 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 340 345 350
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
 355 360 365
 Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 370 375 380
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 385 390 395 400
 Asn Tyr Lys Thr Thr Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 405 410 415
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 420 425 430
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 435 440 445
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 450 455

<210> SEQ ID NO 3

<211> LENGTH: 1377

<212> TYPE: DNA

<213> ORGANISM: homo sapiens

<400> SEQUENCE: 3

```

atggtcagct actgggacac cgggggtcctg ctgtgcgcgc tgctcagctg tctgcttctc   60
acaggatcta gttccggaag tgataccggt agacctttcg tagagatgta cagtgaatc   120
cccgaaatta tacacatgac tgaaggaagg gagctcgtca ttcctgccg ggttacgtca   180
cctaacaatca ctgttacttt aaaaaagttt ccaactgaca ctttgatccc tgatgaaaa   240
cgcataatct gggacagtag aaagggtctt atcatatcaa atgcaacgta caaagaaata   300
gggcttctga cctgtgaagc aacagtcaat gggcatttgt ataagacaaa ctatctcaca   360
catcgacaaa ccaatacaat catagatgtg gttctgagtc cgtctcatgg aattgaacta   420
tctgttgagg aaaagcttgt cttaaattgt acagcaagaa ctgaactaaa tgtggggatt   480
gacttcaact ggaatacccc ttcttcgaag catcagcata agaaacttgt aaaccgagac   540
ctaaaaaccc agtctgggag tgagatgaag aaatttttga gcaccttaac tatagatggt   600
gtaaccggga gtgaccaagg attgtacacc tgtgcagcat ccagtgggct gatgaccaag   660
aagaacagca catttgtcag ggtccatgaa aaggacaaaa ctcacacatg cccaccgtgc   720
ccagcacctg aactcctggg gggaccgtca gtcttctctt tcccccaaa acccaaggac   780
acctcatga tctcccgga cctgaggttc acatgcgtgg tgggtggacgt gagccacgaa   840
gacctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca   900
aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg   960
caccaggact ggctgaatgg caaggagtac aagtgcgaag tctccaacaa agccctccca  1020
gcccccatcg agaaaacat ctcaaagcc aaagggcagc cccgagaacc acaggtgtac  1080
acctgcccc catcccgga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc  1140

```

-continued

```

aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagAAC 1200
aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttctc ctacagcaag 1260
ctcaccgtgg acaagagcag gtggcagcag gggaaactct tctcatgctc cgtgatgcat 1320
gaggctctgc acaaccacta cagcagaag agcctctccc tgtctccggg taaatga 1377

```

```

<210> SEQ ID NO 4
<211> LENGTH: 458
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

```

```

<400> SEQUENCE: 4

```

```

Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1             5             10             15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
      20             25             30
Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
      35             40             45
Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
      50             55             60
Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
      65             70             75             80
Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
      85             90             95
Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
      100            105            110
Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
      115            120            125
Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
      130            135            140
Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
      145            150            155            160
Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
      165            170            175
Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
      180            185            190
Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
      195            200            205
Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
      210            215            220
Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Cys Pro Pro Cys
      225            230            235            240
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
      245            250            255
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
      260            265            270
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
      275            280            285
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
      290            295            300
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
      305            310            315            320

```

-continued

His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn
				325					330					335	
Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly
			340					345					350		
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu
		355					360					365			
Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr
	370					375					380				
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn
385					390					395					400
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe
			405						410					415	
Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn
		420						425					430		
Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr
	435						440					445			
Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys						
	450					455									

What is claimed:

1. A method of treating cancer in a subject in need thereof, comprising administering to the subject a vascular endothelial growth factor (VEGF) trap in combination with radiation therapy such that the cancer is treated.

2. The method of claim 1, wherein the VEGF trap is VEGFR1R2-FcΔC1(a) or Flt1D2.Flk1D3.FcΔC1(a).

3. The method of claim 2, wherein the VEGF trap comprises the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:3.

4. The method of claim 1, wherein administration of a VEGF trap and radiation is concurrent or sequentially.

5. The method of claim 4, wherein radiation is ionizing radiation therapy and/or a therapeutic radiopharmaceutical.

6. The method of claim 1, wherein radiation therapy is administered as a single dose or in multiple doses.

7. The method of claim 1, wherein the subject is a human subject.

8. The method of claim 3, wherein administration of a VEGF trap and radiation is concurrent or sequentially.

9. The method of claim 8, wherein radiation is ionizing radiation therapy and/or a therapeutic radiopharmaceutical.

10. The method of claim 9, wherein radiation therapy is administered as a single dose or in multiple doses.

11. The method of claim 3, wherein the VEGF trap is administered at a high dose of at least 2.5 mg/kg.

12. The method of claim 3, wherein the VEGF trap is administered at a low dose of about or less than 1.0 mg/kg.

13. The method of claim 3, wherein the subject is a human subject.

14. The method of claim 1, wherein administration of the VEGF trap is subcutaneous, intramuscular, intradermal, intraperitoneal, intravenous, intranasal, epidural, or oral.

15. A method of reducing tumor growth in a subject in need thereof, comprising administering to the subject a vascular endothelial growth factor (VEGF) trap and radiation therapy, wherein the growth of the tumor is reduced.

16. The method of claim 15, wherein the VEGF trap is VEGFR1R2-FcΔC1(a) or Flt1D2.Flk1D3.FcΔC1(a).

17. The method of claim 16, wherein the VEGF trap comprises the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:3.

18. The method of claim 15, wherein the VEGF trap is administered concurrently or sequentially with radiation therapy.

19. The method of claim 15, wherein the radiation therapy is ionizing radiation therapy and/or a therapeutic radiopharmaceutical.

20. The method of claim 15, wherein the subject is a human subject.

21. The method of claim 15, wherein the VEGF trap administration is subcutaneous, intramuscular, intradermal, intraperitoneal, intravenous, intranasal, epidural, or oral.

22. A method of treating a human patient suffering from cancer, comprising administering an effective amount of a vascular endothelial growth factor (VEGF) trap and radiation to the human patient, the method comprising administering to the patient an initial dose of ≤ 1.0 mg/kg of the VEGF trap with radiation therapy.

23. The method of claim 22, wherein the VEGF trap is VEGFR1R2-FcΔC1(a) or Flt1D2.Flk1D3.FcΔC1(a).

24. The method of claim 22, wherein the VEGF trap is administered concurrently or sequentially with radiation therapy.

25. The method of claim 22, wherein the radiation therapy is ionizing radiation therapy and/or a therapeutic radiopharmaceutical.

26. The method of claim 22, wherein the VEGF trap administration is subcutaneous, intramuscular, intradermal, intraperitoneal, intravenous, intranasal, epidural, or oral.

27. An article of manufacture, comprising:

(a) packaging material; and

(b) a pharmaceutical agent contained within the packaging material, wherein the pharmaceutical agent comprises at least one dose of a vascular endothelial growth

factor (VEGF) trap, and the packaging material indicates that the VEGF trap can be used in the treatment of cancer or for reducing tumor growth in combination with radiation therapy.

* * * * *