REYES & REYES
A B O G A D O S

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: **Expediente 11-143-266**

TÍTULO SOLICITADO: **"TERAPIA COMPLEMENTARIA CONTRA EL CANCER"**

PUBLICACIÓN: **Gaceta 645 de 31 de Mayo de 2012, Nº de publicación 651.**

PRIORIDAD: **US 61/171,008 DE 20/04/2009; US 61/171,318 DE 21/04/2009; US 61/181,195 DE 26/05/2009**

SOLICITANTE: **GENENTECH, INC.; NSABP FOUNDATION, INC**

APODERADO: **JUAN PABLO CADENA SARMIENTO**

TRÁMITE: **SUSTENTACIÓN DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUIMICAS S.A.,** en ejercicio de lo dispuesto por el artículo 42, inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 30 de Agosto de 2012, en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito insistir en los argumentos planteados en la oposición respectiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los

artículos 14 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

La mencionada solicitud colombiana en trámite en su capítulo reivindicatorio revela como eje central de sus reclamaciones un método de terapia complementaria farmacéutica donde solo se especifica que luego de la cirugía se administra una antagonista de VEGF tal como se menciona en la reivindicación 1:

> *Un método de terapia complementaria, que comprende la administración a un paciente con cáncer, luego de la cirugía definitiva, de una cantidad eficaz de un antagonista específico de VEGF, de manera de extender la sobrevida libre de enfermedad (DFS) o la sobrevida general (OS) en el paciente, donde el antagonista específico de VEGF se administra durante más de un año.*

Y la reivindicación independiente 4 también se refiere a un método de tratamiento en el cual se administra un antagonista específico de VEGF luego de una cirugía:

> *Un método de terapia complementaria, que comprende la administración a un paciente con cáncer, luego de la cirugía definitiva, de una cantidad eficaz de un antagonista específico de VEGF, donde se previene o demora el avance del cáncer durante el tratamiento activo con el antagonista específico de VEGF, y donde el tratamiento activo dura más de un año.*

De las anteriores reivindicaciones, se observa que el elemento clave de la solicitud es la administración del VEGF después de un tratamiento de cirugía en pacientes con cáncer, lo cual correspondería a un método de tratamiento, y como tal no puede ser patentado ya que es parte de una excepción de patentabilidad.

En este caso, para la reivindicación 4 el solicitante desea proteger un método de prevención de aparición del cáncer después de la cirugía, mientras que en las reivindicaciones 22 y 23 se encuentra que la presente solicitud de patente pretende patentar un método de prevención de cáncer únicamente, donde la amplitud de la cobertura de la materia reclamada es mayor, ya que no hay restricciones sobre la etapa de cirugía.

22. Un método de prevención de la recurrencia del cáncer en un paciente, que comprende la administración al paciente, de una cantidad eficaz de un antagonista específico de VEGF durante más de un año, donde dicha administración del antagonista específico de VEGF previene la recurrencia del cáncer

23. Un método para disminuir la probabilidad de recurrencia del cáncer en un paciente, que comprende la administración al paciente, de una cantidad eficaz de un antagonista específico de VEGF durante más de un año, donde dicha administración del anticuerpo anti-VEGF disminuye la probabilidad de recurrencia del cáncer.

De la lectura de las anteriores reivindicaciones, se observa que de manera contundente la solicitud busca la protección de los métodos de tratamiento mediante la administración de un anticuerpo anti-VEGF, los cuales a la fecha de prioridad reclamada ya habían sido revelados. Así mismo, en el resumen presentado por la solicitante se observa: *"En la presente solicitud, se revelan métodos y composiciones que comprenden anticuerpos anti-VEGF para el uso en la terapia complementaria del cáncer."*, de manera que es evidente que también el interés del solicitante está en la posibilidad de patentar las composiciones que contienen anticuerpos anti-VEGF.

Por lo tanto, frente a la posibilidad de llevar las reivindicaciones a la categoría de las composiciones es necesario aclarar que una composición con anticuerpos anti-VEGF ya es conocida de la forma en que se cita en los ejemplos de la solicitud, siendo que además todas las composiciones que puedan ser reclamadas deben cumplir con los criterios de soporte en la parte descriptiva de la solicitud. Esto en consecuencia, implica que las composiciones que contienen anticuerpos, que pueden ser reivindicadas por la solicitud anti-VEGF, no presentarían tampoco novedad y/o nivel inventivo.

En mi memorial de oposición presenté el documento del estado de la técnica:

- Publicación Intenacional WO 2008/077077 "VEGF-Specific Antagonists For Adjuvant And Neoadjuvant Therapy And The Treatment Of Early Stage Tumors" 26-06-2008

Dicho documento afecta los requisitos de patentabilidad de la presente solicitud dado que describe métodos para tratar el cáncer en un sujeto que involucran: la

reducción de un tumor, métodos para tratar un sujeto con cáncer operable, métodos de terapia con neo-adyuvantes (página 1, resumen) y adicionalmente, el documento enseña que el reconocimiento de VEGF como un regulador principal de la angiogénesis en condiciones patológicas ha llevado a muchos intentos para su bloqueo en las condiciones que envuelve la angiogénesis patológica.

Incluso, en el documento se reclama el método para el tratamiento de cáncer que consiste en administrar una cantidad efectiva de un antagonista específico de VEGF (páginas 5 y 6) por lo que se entiende que el eje central de dicha anterioridad es precisamente la misma de la solicitud en trámite:

La anterioridad entonces destruye la novedad de la solicitud al reclamar el tratamiento de cáncer en diferentes estadios por medio de la administración de un antagonista VEGF (reivindicación 1), en donde dicho tratamiento puede realizarse después de una cirugía de retiro del tumor (reivindicación 11), y en donde dicho tratamiento se realiza con el anticuerpo monoclonal Bevacizumab (reivindicación 38).

II. COMPLEMENTO DE INFORMACION

En esta ocasión, sometemos a consideración de la Superintendencia de Industria y Comercio los siguientes documentos:

- Publicación Internacional WO 2005/000900 "Treatment with anti-VEGF antibodies" publicado el 6 de enero de 2005.
- Publicación Internacional WO 2008/094969 "Combination therapy with angiogénesis inhibitors" publicado el 07 de agosto de 2008

El documento **WO 2005/000900** se refiere a métodos para tratar enfermedades y condiciones patológicas con el uso de anticuerpos anti-VEGF preferiblemente en combinación con uno o más agentes antitumorales (ver abstract).

En este documento se menciona que el método corresponde a la administración de una cantidad efectiva de anti-VEGF donde la administración incrementa la duración de la sobrevida de un paciente con cáncer (ver el siguiente recuadro página 6 del documento WO 2005/000900):

In one aspect, the present invention provides a method for increasing the duration of survival of a human patient having cancer, comprising administering to the patient effective amounts of an anti-VEGF antibody composition and an anti-neoplastic composition, wherein said anti-neoplastic composition comprises at least one chemotherapeutic agent, whereby the co-administration of the anti-VEGF antibody and the anti-neoplastic composition effectively increases the duration of survival.

In another aspect, the present invention provides a method for increasing the progression free survival of a human patient having cancer, comprising administering to the patient effective amounts of an anti-VEGF antibody composition and an anti-neoplastic composition, wherein said anti-neoplastic composition comprises at least one chemotherapeutic agent, whereby the co-administration of the anti-VEGF antibody and the anti-neoplastic composition effectively increases the duration of progression free survival.

El documento no solo señala la terapia con antagonistas anti-VEGF sino que además describe a profundidad los anticuerpos con los cuales se relaciona, que de igual forma que la solicitud en estudio corresponden a aquellos como Bevacizumab (ver página 8, último párrafo), humanizados, quiméricos e incluso se evidencian los hibridomas de los cuales se obtienen dichos antagonistas, veamos:

An "anti-VEGF antibody" is an antibody that binds to VEGF with sufficient affinity and specificity. Preferably, the anti-VEGF antibody of the invention can be used as a therapeutic agent in targeting and interfering with diseases or conditions wherein the VEGF activity is involved. An anti-VEGF antibody will usually not bind to other VEGF homologues such as VEGF-B or VEGF-C, nor other growth factors such as PlGF, PDGF or bFGF. A preferred anti-VEGF antibody is a monoclonal antibody that binds to the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709. More preferably the anti-VEGF antibody is a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta et al. (1997) Cancer Res. 57:4593-4599, including but not limited to the antibody known as bevacizumab (BV; Avastin™).

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Los métodos de tratamiento y de administración obedecen a aquellos cubiertos por el ámbito de las reivindicaciones, los cuales permiten obtener una sobrevida mayor a la que presenta el paciente con la administración únicamente del agente quimioterapéutico (ver página 55):

In another embodiment, the present invention provides methods for increasing progression free survival of a human patient susceptible to or diagnosed with a cancer. Time to disease progression is defined as the time from administration of the drug until disease progression. In a preferred embodiment, the combination treatment of the invention using anti-VEGF antibody and one or more chemotherapeutic agents significantly increases progression free survival by at least about 2 months, preferably by about 2 to about 5 months, when compared to a treatment with chemotherapy alone.

En este caso se especifica el aumento de sobrevivencia de al menos 2 meses en comparación con el tratamiento con el agente quimioterapéutico solo, lo que no ocurre con la solicitud en estudio, la cual únicamente menciona el aumento de la sobrevida, pero no da un marco de referencia según lo cual se pueda medir ese aumento.

Este documento también objeta tanto la novedad como el nivel inventivo de la solicitud ya que describe los mismos componentes estructurales y esenciales de los productos y procedimientos, sabiendo además que su eje fundamental se encuentra en el método de tratamiento, no patentable.

Por otro lado, el documento **WO 2008/094969** describe métodos para tratar tumores empleando terapia para angiogénesis con inhibidores tales como antagonistas de VEGF.

Al igual que en los documentos anteriores se emplea el anticuerpo Bevacizumab como el antagonista de VEGF preferible tal como se puede ver en el sumario de la invención (párrafo 0008)

Summary of the Invention

[0008] The present invention provides combination therapies for treating tumors, wherein a VEGF antagonist is combined with a protein kinase inhibitor having at least the PDGFR blocking activity, thereby producing anti-tumor activities. In certain embodiments, the VEGF antagonist is a compound that interferes with the binding of VEGF to a cellular receptor. Examples of such VEGF blocking antagonists include, but are not limited to, soluble VEGF receptors, apatmers or peptibodies that are specific to VEGF, and anti-VEGF antibodies. In one embodiment, the anti-VEGF antibody is bevacizumab.

El método de administración de dichos antagonistas anti-VEGF también es descrito por el documento WO 2008/094969 cuando menciona que es usual que se lleve a cabo la administración por un periodo definido de tiempo para prevenir o reducir la recurrencia de tumores (ver párrafos 0119 y 0120)

En vista de todo lo anterior, en el estado de la técnica ya se revelaban las características técnicas esenciales de lo reclamado por el solicitante, de manera tal que las reivindicaciones se dirigen hacia métodos de terapia con adyuvantes presentadas en el documento del estado de la técnica para tratar un paciente con un antagonista anti-VEGF como Bevacizumab y en consecuencia la solicitud en trámite no cumple con el criterio de Novedad y mucho menos puede atribuírsele Nivel Inventivo.

Para terminar, la solicitud se basa en resultados hipotéticos sin tener una clara definición de la estructura de las composiciones o las mejoras existentes definiendo una administración que depende de cada paciente y su progreso con relación a un compuesto de referencia para aumentar la sobrevida de los pacientes.

Ya que los documentos observados en el presente escrito mencionan todas las características técnicas esenciales de la composición, e incluso del método de tratamiento, la solicitud no cumple con los criterios de Novedad o Nivel inventivo.

III. ANEXOS

- ✓ Publicación Internacional WO 2005/000900 "Treatment with anti-VEGF antibodies" publicado el 6 de enero de 2005. Portada, páginas 1, 6, 8 55 y reivindicaciones.

- ✓ Publicación Internacional WO 2008/094969 "Combination therapy with angiogenesis inhibitors" publicado el 07 de agosto de 2008. Portada, páginas 1- 3, 38 y reivindicaciones.

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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— *with international search report*
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/000900 A1

(54) Title: TREATMENT WITH ANTI-VEGF ANTIBODIES

(57) Abstract: This invention concerns in general treatment of diseases and pathological conditions with anti-VEGF antibodies. More specifically, the invention concerns the treatment of human patients susceptible to or diagnosed with cancer using an anti-VEGF antibody, preferably in combination with one or more additional anti-tumor therapeutic agents.

combination chemotherapies are known in the art and described in, for example, Saltz et al. (1999) *Proc ASCO* 18:233a and Douillard et al. (2000) *Lancet* 355:1041-7.

In one aspect, the present invention provides a method for increasing the duration of survival of a human patient having cancer, comprising administering to the patient effective amounts of an anti-VEGF antibody composition and an anti-neoplastic composition, wherein said anti-neoplastic composition comprises at least one chemotherapeutic agent, whereby the co-administration of the anti-VEGF antibody and the anti-neoplastic composition effectively increases the duration of survival.

In another aspect, the present invention provides a method for increasing the progression free survival of a human patient having cancer, comprising administering to the patient effective amounts of an anti-VEGF antibody composition and an anti-neoplastic composition, wherein said anti-neoplastic composition comprises at least one chemotherapeutic agent, whereby the co-administration of the anti-VEGF antibody and the anti-neoplastic composition effectively increases the duration of progression free survival.

Furthermore, the present invention provides a method for treating a group of human patients having cancer, comprising administering to the patient effective amounts of an anti-VEGF antibody composition and an anti-neoplastic composition, wherein said anti-neoplastic composition comprises at least one chemotherapeutic agent, whereby the co-administration of the anti-VEGF antibody and the anti-neoplastic composition effectively increases the response rate in the group of patients.

In yet another aspect, the present invention provides a method for increasing the duration of response of a human patient having cancer, comprising administering to the patient effective amounts of an anti-VEGF antibody composition and an anti-neoplastic composition, wherein said anti-neoplastic composition comprises at least one chemotherapeutic agent, whereby the co-administration of the anti-VEGF antibody and the anti-neoplastic composition effectively increases the duration of response.

The invention also provides a method of treating a human patient susceptible to or diagnosed with colorectal cancer, comprising administering to the patient effective amounts of an anti-VEGF antibody. The colorectal cancer can be metastatic. The anti-VEGF antibody treatment can be further combined with a standard chemotherapy for colorectal cancer such as the Saltz (5-FU/LV/irinotecan) regimen described by Saltz et al. (1999).

Figures 3A-3C provide analysis of duration of survival by different subgroups of patients divided by baseline characteristics.

Figure 4 represents Kaplan-Meier estimates of survival comparing the group given 5-FU/LV plus placebo vs. the group given 5-FU/LV plus bevacizumab (BV).

Figure 5 represents Kaplan-Meier estimates of progression-free survival comparing the group given 5-FU/LV plus placebo vs. the group given 5-FU/LV plus bevacizumab (BV).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. DEFINITIONS

The terms "VEGF" and "VEGF-A" are used interchangeably to refer to the 165-amino acid vascular endothelial cell growth factor and related 121-, 189-, and 206- amino acid vascular endothelial cell growth factors, as described by Leung *et al. Science*, 246:1306 (1989), and Houck *et al. Mol. Endocrin.*, 5:1806 (1991), together with the naturally occurring allelic and processed forms thereof. The term "VEGF" is also used to refer to truncated forms of the polypeptide comprising amino acids 8 to 109 or 1 to 109 of the 165-amino acid human vascular endothelial cell growth factor. Reference to any such forms of VEGF may be identified in the present application, e.g., by "VEGF (8-109)," "VEGF (1-109)" or "$VEGF_{165}$." The amino acid positions for a "truncated" native VEGF are numbered as indicated in the native VEGF sequence. For example, amino acid position 17 (methionine) in truncated native VEGF is also position 17 (methionine) in native VEGF. The truncated native VEGF has binding affinity for the KDR and Flt-1 receptors comparable to native VEGF.

An "anti-VEGF antibody" is an antibody that binds to VEGF with sufficient affinity and specificity. Preferably, the anti-VEGF antibody of the invention can be used as a therapeutic agent in targeting and interfering with diseases or conditions wherein the VEGF activity is involved. An anti-VEGF antibody will usually not bind to other VEGF homologues such as VEGF-B or VEGF-C, nor other growth factors such as PlGF, PDGF or bFGF. A preferred anti-VEGF antibody is a monoclonal antibody that binds to the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709. More preferably the anti-VEGF antibody is a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta et al. (1997) Cancer Res. 57:4593-4599, including but not limited to the antibody known as bevacizumab (BV; Avastin™).

effectively increased as compared to a chemotherapy alone. For example, patient group treated with the anti-VEGF antibody combined with a chemotherapeutic cocktail of at least two, preferably three, chemotherapeutic agents may have a median duration of survival that is at least about 2 months, preferably between about 2 and about 5 months, longer than that of the patient group treated with the same chemotherapeutic cocktail alone, said increase being statistically significant. Duration of survival can also be measured by stratified hazard ratio (HR) of the treatment group versus control group, which represents the risk of death for a patient during the treatment. Preferably, a combination treatment of anti-VEGF antibody and one or more chemotherapeutic agents significantly reduces the risk of death by at least about 30% (i.e., a stratified HR of about 0.70), preferably by at least about 35% (i.e., a stratified HR of about 0.65), when compared to a chemotherapy alone.

In another embodiment, the present invention provides methods for increasing progression free survival of a human patient susceptible to or diagnosed with a cancer. Time to disease progression is defined as the time from administration of the drug until disease progression. In a preferred embodiment, the combination treatment of the invention using anti-VEGF antibody and one or more chemotherapeutic agents significantly increases progression free survival by at least about 2 months, preferably by about 2 to about 5 months, when compared to a treatment with chemotherapy alone.

In yet another embodiment, the treatment of the present invention significantly increases response rate in a group of human patients susceptible to or diagnosed with a cancer who are treated with various therapeutics. Response rate is defined as the percentage of treated patients who responded to the treatment. In one aspect, the combination treatment of the invention using anti-VEGF antibody and one or more chemotherapeutic agents significantly increases response rate in the treated patient group compared to the group treated with chemotherapy alone, said increase having a Chi-square p-value of less than 0.005.

In one aspect, the present invention provides methods for increasing duration of response in a human patient or a group of human patients susceptible to or diagnosed with a cancer. Duration of response is defined as the time from the initial response to disease progression. In a combination treatment of the invention using anti-VEGF antibody and one or more chemotherapeutic agents, a statistically significant increase of at least 2 months in duration of response is obtainable and preferred.

WHAT IS CLAIMED IS:

1. A method of treating cancer in a human patient, comprising administering to the patient effective amounts of an anti-VEGF antibody and an anti-neoplastic composition, wherein said anti-neoplastic composition comprises at least one chemotherapeutic agent.

2. The method of claim 1, wherein the cancer is selected from the group consisting of breast cancer, colorectal cancer, rectal cancer, non-small cell lung cancer, non-Hodgkins lymphoma (NHL), renal cell cancer, prostate cancer, liver cancer, pancreatic cancer, soft-tissue sarcoma, kaposi's sarcoma, carcinoid carcinoma, head and neck cancer, melanoma, ovarian cancer, mesothelioma, and multiple myeloma.

3. The method of claim 1, wherein the cancer is metastatic.

4. The method of claim 1, wherein the patient is previously untreated.

5. The method of claim 1, wherein the chemotherapeutic agent is selected from the group consisting of alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodopyyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitor, interferons, platinum cooridnation complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroides, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog.

6. The method of claim 5, wherein the chemotherapeutic agent is selected from the group consisting of 5-fluorouracil (5-FU), leucovorin, irinotecan, oxaliplatin, capecitabine , paclitaxel and doxetaxel.

7. The method of claim 1, wherein the anti-neoplastic composition comprises a combination of at least two chemotherapeutic agents.

8. The method of claim 7, wherein the anti-neoplastic composition comprises 5-FU and leucovorin.

9. The method of claim 7, wherein the anti-neoplastic composition comprises 5-FU, leucovorin and irinotecan.

10. The method of claim 1, wherein upon completing treatment with the anti-VEGF antibody and the anti-neoplastic composition, the patient receives further chemotherapeutic treatment with at least one chemotherapeutic agent.

11. The method of claim 10, wherein the chemotherapeutic agent used in further chemotherapeutic treatment is selected from the group consisting of 5-FU, leucovorin, irinotecan, oxaliplatin, capecitabine, paclitaxel and doxetaxel.

12. The method of claim 11, wherein the chemotherapeutic agent is oxaliplatin.

13. The method of claim 1, wherein said anti-VEGF antibody binds the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709.

14. The method of claim 1, wherein the anti-VEGF antibody is a human antibody.

15. The method of claim 1, wherein the anti-VEGF antibody is a humanized antibody.

16. The method of claim 15, wherein the anti-VEGF antibody is a humanized A4.6.1 antibody or fragment thereof.

17. The method of claim 1, wherein the anti-VEGF antibody is administered intravenously.

18. The method of claim 1, wherein the anti-VEGF antibody is administered to the patient at about 5mg/kg every 2 to 3 weeks.

19. The method of claim 1, whereby the co-administration of the anti-VEGF antibody and the anti-neoplastic composition effectively increases the duration of survival of the human patient.

20. The method of claim 19, wherein the duration of survival of the patient is increased by at least about 2 months when compared to another patient treated with the anti-neoplastic composition alone.

21. The method of claim 1, whereby the co-administration of the anti-VEGF antibody and the anti-neoplastic composition effectively increases the duration of progression free survival of the human patient.

22. The method of claim 21, wherein the progression free survival of the patient is increased by at least about 2 months when compared to another patient treated with the anti-neoplastic composition alone.

23. The method of claim 1, whereby the co-administration of the anti-VEGF antibody and the anti-neoplastic composition effectively increases the response rate in a group of human patients.

24. The method of claim 23, wherein the response rate of the group of human patients is significantly increased with a Chi-square p-value of less than 0.005 when compared to another group of patients treated with the anti-neoplastic composition alone.

25. The method of claim 1, whereby the co-administration of the anti-VEGF antibody and the anti-neoplastic composition effectively increases the duration of response of the human patient.

26. The method of claim 25, wherein the duration of response of the patient is increased by at least about 2 months when compared to another patient treated with the anti-neoplastic composition alone.

27. A method of treating a human patient susceptible to or diagnosed with colorectal cancer, comprising administering to the patient effective amounts of an anti-VEGF antibody.

28. The method of claim 27, wherein the colorectal cancer is metastatic.

29. The method of claim 27, wherein said anti-VEGF antibody binds the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709.

30. The method of claim 27, wherein the anti-VEGF antibody is a human antibody.

31. The method of claim 27, wherein the anti-VEGF antibody is a humanized antibody.

32. The method of claim 31, wherein the anti-VEGF antibody is a humanized A4.6.1 antibody or fragment thereof.

33. The method of claim 27, wherein the anti-VEGF antibody is administered by intravenous infusion.

34. The method of claim 27, wherein the anti-VEGF antibody is administered to the patient at about 5mg/kg every 2 to 3 weeks.

35. The method of claim 27, further comprising administering to the patient one or more chemotherapeutic agents.

36. The method of claim 35, wherein the chemotherapeutic agent is selected from the group consisting of alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodopyyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitor, interferons, platinum cooridnation complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroides, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog.

37. The method of claim 35, wherein the chemotherapeutic agent is selected from the group consisting of 5-fluorouracil, leucovorin, irinotecan, oxaliplatin, capecitabine, paclitaxel and doxetaxel.

38. A method of treating a human patient or a group of human patients having metastatic colorectal cancer, comprising administering to the patient effective amounts of an anti-VEGF antibody composition and an anti-neoplastic composition, wherein said anti-neoplastic composition comprises a fluorouracil based combination of chemotherapeutic agents, whereby the co-administration of the anti-VEGF antibody and the anti-neoplastic composition results in statistically significant and clinically meaningful improvement of the treated patient as measured by the duration of survival, progression free survival, response rate or duration of response.

39. The method of claim 38, wherein the anti-neoplastic composition comprises 5-FU, leucovorin and irinotecan.

40. The method of claim 39, wherein the anti-neoplastic composition comprises the regimen having 500 mg/m^2 5-FU, 20mg/m^2 leucovorin and 125 mg/m^2 irinotecan and is administered to the patient in repeating 6-week cycles consisting of weekly administrations for 4 weeks followed by 2 weeks of rest, and wherein the anti-VEGF antibody is administered to the patient at 5 mg/kg every other week.

41. The method of claim 38, wherein the anti-neoplastic composition comprises 5-FU and leucovorin.

42. The method of claim 41, wherein the 5-FU and leucovorin are administered to the patient at 500 mg/m^2 each in repeating 8 week cycles consisting of weekly administrations for

4 weeks followed by 2 weeks of rest, and wherein the anti-VEGF antibody is administered to the patient at 5 mg/kg every other week.

43. The method of claim 41 for human patients considered non-optimal candidates for first-line irinotecan therapy.

44. The method of claim 38, wherein the anti-neoplastic composition comprises 5-FU, leucovorin and oxaliplatin.

45. An article of manufacture comprising a container, a composition within the container comprising an anti-VEGF antibody and a package insert instructing the user of the composition to administer to a cancer patient the anti-VEGF antibody composition and an anti-neoplastic composition comprising at least one chemotherapeutic agent.

46. A kit for treating cancer in a human patient comprising a package comprising an anti-VEGF antibody composition and instructions for using the anti-VEGF antibody composition and an anti-neoplastic composition comprising at least one chemotherapeutic agent for treating cancer in a patient.

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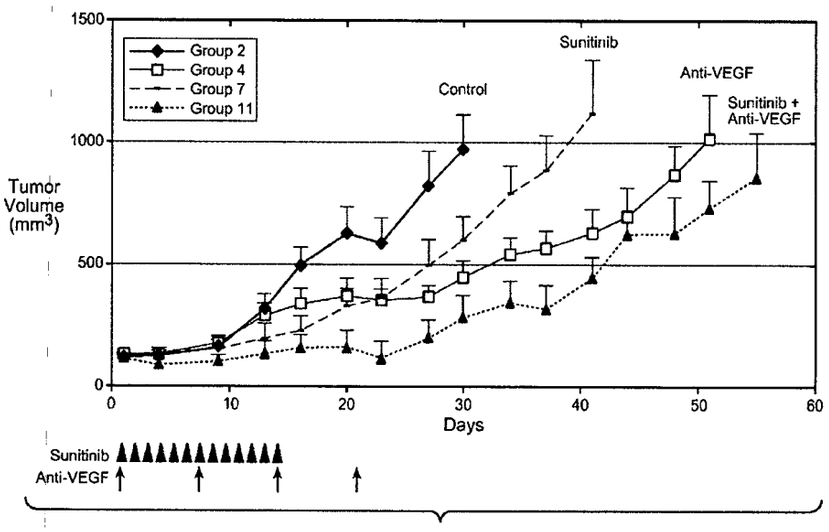

(57) Abstract: Disclosed herein are methods of treating tumors using a combination therapy with angiogenesis inhibitors.

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COMBINATION THERAPY WITH ANGIOGENESIS INHIBITORS

Cross-Reference to Related Application

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 60/887,688, filed 1 February 2007, the disclosure of which is incorporated herein by reference in its entirety.

Background of the Invention

[0002] Development of a vascular system is a fundamental requirement for many physiological and pathological processes. Actively growing tissues such as embryos and tumors require adequate blood supply. They satisfy this need by producing pro-angiogenic factors, which promote new blood vessel formation via a process called angiogenesis. Vascular tube formation is a complex but orderly biological event involving all or many of the following steps: a) Endothelial cells (ECs) proliferate from existing ECs or differentiate from progenitor cells; b) ECs migrate and coalesce to form cord-like structures; c) vascular cords then undergo tubulogenesis to form vessels with a central lumen d) existing cords or vessels send out sprouts to form secondary vessels; e) primitive vascular plexus undergo further remodeling and reshaping; and f) peri-endothelial cells are recruited to encase the endothelial tubes, providing maintenance and modulatory functions to the vessels; such cells including pericytes for small capillaries, smooth muscle cells for larger vessels, and myocardial cells in the heart. Hanahan, D. *Science* 277:48-50 (1997); Hogan, B. L. & Kolodziej, P. A. *Nature Reviews Genetics.* 3:513-23 (2002); Lubarsky, B. & Krasnow, M. A. *Cell.* 112:19-28 (2003).

[0003] It is now well established that angiogenesis is implicated in the pathogenesis of a variety of disorders. These include solid tumors and metastasis, atherosclerosis, retrolental fibroplasia, hemangiomas, chronic inflammation, intraocular neovascular diseases such as proliferative retinopathies, e.g., diabetic retinopathy, age-related macular degeneration (AMD), neovascular glaucoma, immune rejection of transplanted corneal tissue and other tissues, rheumatoid arthritis, and psoriasis. Folkman et al., *J. Biol. Chem.*, 267:10931-10934 (1992); Klagsbrun et

al., *Annu. Rev. Physiol.* 53:217-239 (1991); and Garner A., "Vascular diseases", In: Pathobiology of Ocular Disease. A Dynamic Approach, Garner A., Klintworth GK, eds., 2nd Edition (Marcel Dekker, NY, 1994), pp 1625-1710.

[0004] In the case of tumor growth, angiogenesis appears to be crucial for the transition from hyperplasia to neoplasia, and for providing nourishment for the growth and metastasis of the tumor. Folkman *et al.*, *Nature* 339:58 (1989). Neovascularization allows the tumor cells to acquire a growth advantage and proliferative autonomy compared to the normal cells. A tumor usually begins as a single aberrant cell which can proliferate only to a size of a few cubic millimeters due to the distance from available capillary beds, and it can stay 'dormant' without further growth and dissemination for a long period of time. Some tumor cells then switch to the angiogenic phenotype to activate endothelial cells, which proliferate and mature into new capillary blood vessels. These newly formed blood vessels not only allow for continued growth of the primary tumor, but also for the dissemination and recolonization of metastatic tumor cells. Accordingly, a correlation has been observed between density of microvessels in tumor sections and patient survival in breast cancer as well as in several other tumors. Weidner *et al., N. Engl. J. Med* 324:1-6 (1991); Horak *et al., Lancet* 340:1120-1124 (1992); Macchiarini *et al., Lancet* 340:145-146 (1992). The precise mechanisms that control the angiogenic switch is not well understood, but it is believed that neovascularization of tumor mass results from the net balance of a multitude of angiogenesis stimulators and inhibitors (Folkman, 1995, *Nat Med* 1(1):27-31).

[0005] The process of vascular development is tightly regulated. To date, a significant number of molecules, mostly secreted factors produced by surrounding cells, have been shown to regulate EC differentiation, proliferation, migration and coalescence into cord-like structures. For example, vascular endothelial growth factor (VEGF) has been identified as the key factor involved in stimulating angiogenesis and in inducing vascular permeability. Ferrara et al., Endocr. Rev. 18:4-25 (1997). The finding that the loss of even a single VEGF allele results in embryonic lethality points to an irreplaceable role played by this factor in the development and differentiation of the vascular system. Furthermore, VEGF has been shown to be a key mediator of neovascularization associated with tumors and intraocular disorders. Ferrara et al., Endocr. Rev. supra. The VEGF mRNA is overexpressed by the majority of human

tumors examined. Berkman et al., J. Clin. Invest. 91:153-159 (1993); Brown et al., Human Pathol. 26:86-91 (1995); Brown et al., Cancer Res. 53:4727-4735 (1993); Mattern et al., Brit. J. Cancer 73:931-934 (1996); Dvorak et al., Am. J. Pathol. 146:1029-1039 (1995).

[0006] Anti-VEGF neutralizing antibodies suppress the growth of a variety of human tumor cell lines in nude mice (Kim *et al., Nature* 362:841-844 (1993); Warren *et al., J. Clin. Invest.* 95:1789-1797 (1995); Borgström *et al., Cancer Res.* 56:4032-4039 (1996); Melnyk *et al., Cancer Res.* 56:921-924 (1996)) and also inhibit intraocular angiogenesis in models of ischemic retinal disorders. Adamis *et al., Arch. Ophthalmol.* 114:66-71 (1996). Therefore, anti-VEGF monoclonal antibodies or other inhibitors of VEGF action are promising candidates for the treatment of tumors and various intraocular neovascular disorders. Such antibodies are described, for example, in EP 817,648 published January 14, 1998; and in WO98/45331 and WO98/45332, both published October 15, 1998.

[0007] Despite the significant advancement in the treatment of cancer achieved by angiogenesis inhibitors such as anti-VEGF antibody, improved therapies are still being sought, especially those that further enhance the overall efficacy.

Summary of the Invention

[0008] The present invention provides combination therapies for treating tumors, wherein a VEGF antagonist is combined with a protein kinase inhibitor having at least the PDGFR blocking activity, thereby producing anti-tumor activities. In certain embodiments, the VEGF antagonist is a compound that interferes with the binding of VEGF to a cellular receptor. Examples of such VEGF blocking antagonists include, but are not limited to, soluble VEGF receptors, apatmers or peptibodies that are specific to VEGF, and anti-VEGF antibodies. In one embodiment, the anti-VEGF antibody is bevacizumab.

[0009] In one aspect, the protein kinase inhibitor is specific to PDGFR. In other aspects, the protein kinase inhibitor targets multiple RTKs including PDGFR and VEGFR-2, thereby blocking both PDGF and VEGF pathways. In one embodiment, the protein kinase inhibitor is sunitinib (SUTENT®).

[0010] Methods of the invention can be used for treating different cancers, both solid tumors and soft-tissue tumors alike. Non-limiting examples of cancers

[0118] For example, if the VEGF antagonist is an antibody, the antibody is administered by any suitable means, including parenteral, subcutaneous, intraperitoneal, intrapulmonary, and intranasal, and, if desired for local immunosuppressive treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. In addition, the antibody is suitably administered by pulse infusion, particularly with declining doses of the antibody. In one embodiment, the dosing is given by injections. In another embodiment, the dosing is given by intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic.

[0119] In another example, the VEGF antagonist compound is administered locally, e.g., by direct injections, when the disorder or location of the tumor permits, and the injections can be repeated periodically. The VEGF antagonist can also be delivered systemically to the subject or directly to the tumor cells, e.g., to a tumor or a tumor bed following surgical excision of the tumor, in order to prevent or reduce local recurrence or metastasis.

[0120] Administration of the therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). Combination therapy is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner.

[0121] The therapeutic agent can be administered by the same route or by different routes. For example, the VEGF antagonist in the combination may be administered by intravenous injection while the protein kinase inhibitor in the combination may be administered orally. Alternatively, for example, both the therapeutic agents may be administered orally, or both therapeutic agents may be administered by intravenous injection, depending on the specific therapeutic agents. The sequence in which the therapeutic agents are administered also varies depending on the specific agents.

[0122] Depending on the type and severity of the disease, about 1 μg/kg to

What is claimed is:

1. A method of treating tumor in a subject, comprising administering to said subject a VEGF antagonist and a protein kinase inhibitor,

wherein said VEGF antagonist interferes the binding of VEGF to a cellular receptor,

wherein said protein kinase inhibitor is capable of inhibiting at least the PDGF receptor tyrosine kinase, and

wherein said administering is for a time and in an amount sufficient to treat or prevent said tumor in said subject.

2. The method of claim 1, wherein said VEGF antagonist is an aptamer capable of specifically binding to VEGF.

3. The method of claim 1, wherein said VEGF antagonist is a soluble VEGF receptor protein, or VEGF binding fragment thereof, or a chimeric VEGF receptor protein.

4. The method of claim 3, wherein said chimeric VEGF receptor protein comprises at least the extracellular domain 2 from Flt-1 or KDR.

5. The method of claim 1, wherein said VEGF antagonist is an anti-VEGF antibody.

6. The method of claim 5, wherein said anti-VEGF antibody is a monoclonal antibody.

7. The method of claim 6, wherein said monoclonal antibody is a chimeric, fully human, or humanized antibody.

8. The method of claim 7, wherein said anti-VEGF antibody is bevacizumab, G6 series antibody, B20 series antibody, or VEGF binding fragments thereof.

9. The method of claim 8, wherein said anti-VEGF antibody is bevacizumab.

10. The method of claim 1, wherein said protein kinase inhibitor is capable of inhibiting both PDGF receptor tyrosine kinase and VEGF receptor tyrosine kinase.

11. The method of claim 10, wherein said protein kinase inhibitor is sunitinib or a pharmaceutically acceptable salt form thereof.

12. The method of claim 1, wherein the tumor is selected from the group consisting of breast cancer, colorectal cancer, rectal cancer, non-small cell lung cancer, non-Hodgkins lymphoma (NHL), renal cell cancer, prostate cancer, liver cancer, pancreatic cancer, soft-tissue sarcoma, Kaposi's sarcoma, carcinoid carcinoma, head and neck cancer, melanoma, ovarian cancer, mesothelioma, and multiple myeloma.

13. The method of claim 12, wherein the tumor is non-small cell lung cancer.

14. The method of claim 12, wherein the cancer is metastatic.

15. The method of claim 12, wherein the patient is previously untreated.

16. The method of claim 1, wherein the VEGF antagonist is bevacizumab and the protein kinase inhibitor is sunitinib.

17. The method of claim 16, wherein bevacizumab is administered intravenously to the subject at 10 mg/kg every other week or 15 mg/kg every three weeks, and wherein sunitinib is administered orally to the subject at a daily dose of 25 mg for 2, 3 or 4 weeks followed by 1 or 2 weeks off.

18. The method of claim 17, wherein bevacizumab is administered intravenously to the subject at 15 mg/kg every three weeks, and wherein sunitinib is administered orally to the subject at a daily dose of 25 mg for 2 weeks followed by 1 week off.

19. The method of claim 1 or 16, further comprising administering to the subject one or more chemotherapeutic agent(s).

20. The method of claim 19 wherein the chemotherapeutic agent administered is paclitaxel.

21. The method of claim 19 wherein the chemotherapeutic agents administered are carboplatin and paclitaxel.