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Abogado(a)/Señor(a)

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Asunto:	Radicación:	12-29506- -11
	Trámite:	11
	Evento:	378
	Actuación:	519
	Oficio:	5486
	Folios:	21

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/US2010/045147				
Fecha de Presentación Internacional	11/08/2010				

Como resultado del examen de fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

Descripción:	Radicado No. 12-029506-00000	20/Febrero/2012
Reivindicaciones:	Radicado No. 12-029506-00000	20/Febrero/2012
	Radicado No. 12-029506-00008	13/Noviembre/2013
Dibujos:	Radicado No. 12-029506-00000	20/Febrero/2012
Secuencias:	Radicado No. 12-029506-00000	20/Febrero/2012
Oposiciones:	Radicado No. 12-029506-00004	Tecnoquímicas S.A. 02/Mayo/2013
	Radicado No. 12-029506-00005	LAFRANCOL S.A.S. 06/Mayo/2013
Respuesta del solicitante:	Radicado No. 12-029506-00008	13/Noviembre/2013
Prioridades:	US 61/234.281	15/Agosto/2009
	US 61/266.343	03/Diciembre/2009

Expediente 12-29506- -11

Se acepta la reivindicación de prioridad porque ésta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del capítulo primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada. Para la presente solicitud se estudió el capítulo reivindicatorio completo (Radicado No. 12-029506-00008-0000).

Título de la solicitud: "Terapia anti-angiogénesis para el tratamiento de cáncer de mama previamente tratado".

El problema planteado en esta solicitud consiste en la necesidad de desarrollar métodos para el tratamiento de cáncer de mama.

Para resolver este problema técnico la solicitud en estudio proporciona un kit para tratar un cáncer de mama metastásico previamente tratado en un paciente humano diagnosticado con cáncer de mama triple negativo que comprende un paquete que comprende una composición de anticuerpo anti-VEGF e instrucciones para utilizar la composición de anticuerpo anti-VEGF en combinación con quimioterapia, en donde las instrucciones indican que la supervivencia libre de progreso para pacientes que reciben quimioterapia y bevacizumab es de 7.2 meses con una relación de peligro de 0.775 y un valor p de 0.0072.

El objeto de la presente solicitud se relaciona con la clasificación internacional de patentes (CIP): A61K 39/395, A61P 35/00.

4. De la solicitud de patente

Título

De acuerdo con la materia reclamada el título de la presente invención se ha modificado y quedará de la siguiente manera: "COMPOSICIÓN DE ANTICUERPO ANTI-VEGF EN COMBINACIÓN CON QUIMIOTERAPIA PARA EL TRATAMIENTO DE CANCER DE MAMA PREVIAMENTE TRATADO".

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicaciones no cumplen con los requisitos de claridad y concisión de acuerdo con los siguientes puntos:

1). Un kit-de-partes debe estar caracterizado por una preparación farmacéutica o medicamento A y una preparación farmacéutica o medicamento B indicándose las cantidades o proporciones definidas de ambas preparaciones, sin incluirse instrucciones de preparación ni forma de administración de cada una de las preparaciones. Sin embargo, en el kit reclamado en la presente solicitud no se indica la preparación farmacéutica B, más allá que la mera mención de que se trata de la combinación con quimioterapia, y tampoco se mencionan cantidades o proporciones definidas de los elementos combinados. Asimismo, en el capítulo descriptivo no existe sustento de que dicha asociación de componentes, que provienen de preparaciones

individuales, formen una unidad funcional dirigida a un único propósito o efecto técnico sinérgico. Por tal motivo, la materia reclamada se entiende como una composición de anticuerpo anti-VEGF en combinación con quimioterapia, objeto que según el conocimiento del conjunto de la persona versada en la materia, se conoce como inmunoconjugado.

Por otra parte, una reivindicación independiente debe tener un preámbulo delimitado que permita tener claridad sobre el alcance de la invención, y la parte característica debe indicar aquellas características que la diferencian del estado de la técnica. En la reivindicación 1 de la presente solicitud, se emplean dos conectores que son: “que comprende un paquete”, 2) “que comprende una composición”; de manera que no resulta evidente cuál es la parte que caracteriza la reivindicación. Se sugiere hacer las aclaraciones necesarias.

Además, la reivindicación 1 se refiere a un paquete, definido por la composición que comprende, lo cual, aparte de carecer de claridad por el hecho de que un elemento contenedor no debe definirse por su contenido sino por sus características técnicas esenciales, corresponde a un campo técnico diferente.

Adicionalmente, la expresión *“en donde las instrucciones indican que la supervivencia libre de progreso para pacientes que reciben quimioterapia y bevacizumab es de 7.2 meses con una relación de peligro de 0.775 y un valor p de 0.0072”* es un resultado a alcanzar y no aporta características técnicas a la invención. Estos parámetros deben mencionarse en la memoria descriptiva pero no deben incluirse dentro de las reivindicaciones.

Por otra parte, la expresión *“...en un paciente humano diagnosticado con cancer de mama triple negativo...”* no corresponde a una característica técnica del objeto reivindicado, por el contrario se refiere a una característica de elegibilidad de los pacientes del método de tratamiento.

Por último, es importante que la solicitante advierta que a pesar de que el preámbulo de la reivindicación 1 se refiere a un kit para tratar un cáncer de mama metastásico previamente tratado en un paciente humano diagnosticado con cáncer de mama triple negativo, ésta no revela todas las características técnicas esenciales que logren diferenciarla del estado de la técnica, puesto que, como se mencionó anteriormente, no se describen las preparaciones farmacéuticas A y B ni sus proporciones que permitan lograr el efecto técnico descrito.

Se sugiere hacer las aclaraciones necesarias.

2). La reivindicación 2, la cual menciona las características técnicas del anticuerpo anti-VEGF, se refiere en su preámbulo al *“kit de acuerdo con cualquiera de las reivindicaciones 1”* lo cual carece de sentido puesto que es una reivindicación dependiente de la única reivindicación independiente 1. Además no es necesario incluir la estructura de polipéptido, puesto que es suficiente con nombrar el número de secuencia referido en el listado de secuencias (ej. SEQ ID No. 1).

3). Por último este Despacho considera que existe una inconsistencia entre la materia reclamada y la materia divulgada en la memoria descriptiva. En primer lugar, el término quimioterapia en sentido general, implica una serie de compuestos de naturaleza química diversa por lo que no se puede definir una combinación de agentes, encabezada en la forma de kit-de-partes, por referencia a la mención general que se hizo en la descripción (pág. 73), cuando en la realidad no hay sustento para una combinación en la que se evidencie la sinergia. Asimismo, la referencia al estudio de fase III (pág. 77) en el que se concluye la sobrevida de los pacientes no es evidencia de efecto inesperado, toda vez que podría anticiparse dicho efecto como consecuencia de la suma de los efectos de cada compuesto por separado: el

anticuerpo por un lado y la quimioterapia con taxanos por otro. Así las cosas, es el isoblograma el que da cuenta de una verdadera sinergia en términos de disminución de la dosis requerida y % de sobrevida de los pacientes.

En segundo lugar, hay que tener en cuenta que según la descripción hay al menos 4 quimioterapéuticos diferentes: taxanos, gemcitabina, capecitabina y vinorelbina y cada uno combinado con Bevacizumab sería una combinación diferente, para lo cual no se presentó sustento de un efecto inesperado. Además, no existe evidencia alguna del diseño de un kit puesto que la descripción contempla únicamente la divulgación de un método de tratamiento.

5. Unidad de invención (Art 25 D 486)

La solicitud no cumple con el requisito de unidad de invención porque se refiere a al menos 4 grupos inventivos diferentes:

Grupo inventivo 1: Bevacizumab combinado con taxanos (reivindicaciones 1 a 3).

Grupo inventivo 2: Bevacizumab combinado con gemcitabina (reivindicaciones 1 a 3).

Grupo inventivo 3: Bevacizumab combinado con capecitabina (reivindicaciones 1 a 3).

Grupo inventivo 4: Bevacizumab combinado con vinorelbina (reivindicaciones 1 a 3).

No hay unidad de invención entre los cuatro grupos inventivos ya que el elemento técnico particular para todos los grupos que define el concepto común inventivo para esta solicitud es Bevacizumab, un anticuerpo conocido en el estado de la técnica, y por lo tanto no cumple con el requisito de novedad de acuerdo con el documento D1 (Análisis de patentabilidad para la reivindicación 1).

Se le sugiere al solicitante restringir la materia a patentar en un solo concepto común inventivo especificando el avance tecnológico sobre el estado de la técnica. Esto se logra entre otras formas definiendo las características esenciales de la invención y mostrando las otras características particulares como dependientes, pero sin perjuicio de la concisión de las nuevas reivindicaciones tanto independientes como dependientes.

El solicitante también puede realizar una o más de las divisionales de acuerdo a los grupos de conceptos técnicos inventivos presentados en esta solicitud, esto claro, sin ampliar el objeto inicial de la invención.

6. Análisis de las Oposiciones

Argumentaciones de Tecnoquímicas S.A.

1. Dice el opositor que esta solicitud pretende obtener patente para un método para tratar un paciente diagnosticado con cáncer de mama. Método que está exceptuado de patentabilidad por la Decisión 486 por no ser susceptible de aplicación industrial.
2. Adicional a esto, el opositor argumenta que los componentes que integran el método de tratamiento no cumplen con los criterios de novedad o nivel inventivo. En primer lugar, el anticuerpo empleado anti-VEGF corresponde al anticuerpo Bevacizumab (Avastin®), el cual se encuentra plenamente documentado en el estado de la técnica y su patente se encuentra próxima a expirar (<http://www.drugbank.ca/drugs/DB00112>). En segundo lugar, el opositor

traslada el documento científico Miller *et al.* 2005¹, el cual se anticipa por completo a lo revelado en la solicitud de estudio, ya que describe el tratamiento de pacientes con cáncer metastásico de seno con Bevacizumab y capecitabina. En tercer lugar, el opositor cita el documento científico Ramaswamy *et al.* 2006², con el cual también se objeta la falta de novedad de la solicitud en trámite, al incluir la administración de Bevacizumab y Docetaxel para el tratamiento de cáncer de seno metastásico. En último lugar, el opositor presenta el artículo científico Burstein *et al.* 2008³, el cual también describe el tratamiento de cáncer metastásico de seno con Bevacizumab, pero en este caso, con otro agente quimioterapéutico: Vinorelbina.

3. La compañía opositora concluye de esta manera que el método de tratamiento, sus componentes y sus características técnicas y funcionales ya han sido anticipados en el estado de la técnica, y como consecuencia la solicitud carece de novedad. Sumado a esto, afirma que la materia carece de nivel inventivo porque una persona versada en la materia tendría suficientes herramientas y motivaciones para sugerir un tratamiento como el que se pretende, haciendo uso de una terapia general con anti-VEGF y su combinación con otros agentes quimioterapéuticos.

Argumentaciones de LAFRANCOL S.A.S.

1. Afirma el opositor que las composiciones y combinaciones farmacéuticas que comprenden anticuerpos anti-VEGF en combinación con uno o más agentes terapéuticos antitumorales, útiles en el tratamiento del cáncer de mama metastásico, son totalmente conocidas en la industria farmacéutica, y por ello, no existe novedad sobre estos preceptos y mucho menos nivel inventivo en la solicitud en trámite.
2. Adicionalmente, dice el opositor que la solicitante no puede acceder a un beneficio de patente sobre composiciones y combinaciones farmacéuticas que comprenden moléculas descubiertas y plenamente identificadas en el sector químico-farmacéutico, como es el caso del Bevacizumab, el cual fue patentado en el año por la OMPI con No. WO9845331⁴.
3. En otro respecto, el opositor acota el hecho de que la materia reclamada en la solicitud está excluida del beneficio de patente en concordancia con la decisión 486, puesto que se refieren a un método de tratamiento.
4. Por último, el opositor presenta tres documentos que según argumenta, demuestran la falta de novedad y nivel inventivo de la solicitud. Dichos documentos son: Miller *et al.* 2007⁵; Ramaswamy *et al.* 2006²; y Burstein *et al.* 2008³.

Respuestas del Solicitante

En respuesta a los argumentos de la oposición presentada por Tecnoquímicas S.A., la solicitante presentó un nuevo capítulo reivindicatorio compuesto por 3 reivindicaciones, que según argumenta, en él se ha eliminado cualquier alusión a método de tratamiento, y en consecuencia se da cumplimiento a los requerimientos de la Decisión 486.

1 Miller, K, *et al.* 2005. Randomized Phase III Trial of Capecitabine compared with Bevacizumab plus Capecitabine in Patients with previously treated metastatic breast cancer. *Journal of Clinical Oncology* 23(4):792-799.

2 Ramaswamy *et al.* 2006. En línea: <http://clincancerres.aacrjournals.org/content/12/10/3124.long>

3 Burstein *et al.* 2008. En línea: <http://clincancerres.aacrjournals.org/content/14/23/7871.long>

4 En línea: http://www.lens.org/images/patent/WO/1998045331/A2/WO_1998_045331_A2.pdf

5 Miller *et al.* 2007. En línea: <http://www.ncbi.nlm.nih.gov/pubmed/18160686>

Con relación a la falta de novedad y nivel inventivo sustentada por la oposición, la solicitante afirma que las modificaciones al pliego reivindicatorio hacen énfasis en un kit que corresponde a una composición farmacéutica destinada al tratamiento de segunda línea de pacientes diagnosticados previamente con cáncer de mama triple negativo metastásico, y no como un tratamiento de primera línea. De este modo, ninguno de los documentos presentados por la oposición proporcionan un kit que permita el tratamiento de un subgrupo de pacientes que padezcan cáncer de mama triple negativo, y por lo tanto, dichas anterioridades no se relacionan con el alcance de la presente invención.

Para soportar la actividad inventiva relacionada con la presente invención, la solicitante presentó el artículo científico Brufsky *et al.* 2012⁶, con el cual, según la solicitante, se demuestra la existencia de un efecto sinérgico entre la quimioterapia y el Bevacizumab, al ser empleados como tratamiento de pacientes de cáncer de mama del subgrupo triple negativo metastásico.

Respuesta del Examinador Técnico

En primer lugar, las argumentaciones con relación al incumplimiento del Artículo 20 de la Decisión 486 fueron tenidas en cuenta para el presente examen, como fue expuesto en el numeral 4 del presente documento.

En segundo lugar, los documentos trasladados por ambas compañías opositoras, al desvirtuar el nivel inventivo del objeto de la presente solicitud, se considerarán dentro del examen de patentabilidad.

En tercer lugar, respecto al argumento de la solicitante según el cual los documentos trasladados por la oposición no proporcionan de manera alguna un kit que permita el tratamiento de un subgrupo de pacientes que padezcan de cáncer de mama triple negativo, se aclara que aunque la solicitante manifieste lo anterior como el propósito final del kit, las reivindicaciones no definen claramente las características técnicas esenciales del kit que permitan el logro de dicho propósito, y por ello, los documentos presentados por las compañías opositoras prosperan para sustentar la falta de nivel inventivo.

7. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: agosto 15 de 2009, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación
D1	WO98/45331	"Anti-VEGF antibodies"	15/Octubre/1998
D2	O'Shaughnessy & Brufsky 2008	"RiBBON 1 and RiBBON 2: Phase III Trial of Bevacizumab with Standard Chemotherapy for Metastatic Breast Cancer"	Agosto/2008
D3	Miller <i>et al.</i> 2005	"Randomized Phase III Trial of Capecitabine compared with Bevacizumab plus Capecitabine in Patients with previously treated metastatic breast cancer"	01/Febrero/2005
D4	Ramaswamy <i>et al.</i> 2006	"Phase II trial of bevacizumab in combination with weekly docetaxel in metastatic breast cancer patients"	15/mayo/2006
D5	Burstein <i>et al.</i> 2008	"VEGF as a marker for outcome among advanced breast cancer patients receiving anti-VEGF therapy with bevacizumab and vinorelbine chemotherapy"	01/Diciembre/2008

⁶ Brufsky *et al.* 2012. Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RiBBON-2 trial. Breast Cancer Res Treat. 133(3):1067-75.

El documento D1⁴ divulga anticuerpos anti-VEGF humanizados y uso de los mismos para la inhibición del crecimiento de tumores (resumen).

El documento D2⁷ presenta los ensayos clínicos RiBBON 1 y 2 que consisten en la combinación de Bevacizumab con quimioterapia estándar para el tratamiento de cáncer de mama metastásico (Pág. 371 Col. derecha).

El documento D3¹ revela un ensayo clínico de fase III en pacientes con cáncer de mama metastásico previamente tratados, que consiste en la combinación de bevacizumab con capecitabina (resumen).

El documento D4² divulga la administración de Bevacizumab y Docetaxel para el tratamiento de cáncer de seno metastásico (resumen).

El documento D5³ da a conocer el tratamiento de cáncer metastásico de seno con Bevacizumab en combinación con vinorelbina (resumen).

8. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en “un kit para tratar un cáncer de mama metastásico previamente tratado en un paciente humano diagnosticado...”.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D1
kit para tratar un cáncer de mama metastásico previamente tratado en un paciente humano que comprende	Kit para el tratamiento de cáncer de mama (Pág. 5 líneas 6 - 11; Pág. 44 líneas 7 - 9; Pág. 45 línea 4) que comprende
una composición de anticuerpo anti-VEGF en combinación con quimioterapia.	Una composición de anticuerpo anti-VEGF empaquetada e instrucciones de uso (Pág. 5 líneas 6 - 11; Pág. 44 líneas 7 - 9) en combinación con un agente quimioterapéutico (Pág. 32 líneas 27 - 30).

Las características esenciales de la combinación de la reivindicación 1 habian sido divulgadas previamente en el documento D1.

El documento D1 divulga un kit para el diagnóstico y el tratamiento de cáncer de mama el cual comprende un anticuerpo anti-VEGF. También da a conocer anticuerpos anti-VEGF conjugados con otros agentes quimioterapéuticos (Pág. 32 líneas 27 - 30). Del mismo modo, el documento D1 enseña las secuencias de las cadenas variables ligera y pesada del anticuerpo anti-VEGF (A.4.6.1) conocido como bevacizumab (<http://www.drugbank.ca/drugs/DB00112>). Dichas secuencias del anticuerpo divulgado tienen un 100% de identidad con las secuencias de aminoácidos del anticuerpo anti-VEGF del kit reclamado en la presente solicitud (figuras 1 y 2).

7 O’Shaughnessy, J & Brufsky, A. 2008. RiBBON 1 and RiBBON 2: Phase III Trial of Bevacizumab with Standard Chemotherapy for Metastatic Breast Cancer. Clinical Breast Cancer 8(4):370-373.

SEQ_125_HV_WO1998045331

Sequence ID: lcl|103827 Length: 123 Number of Matches: 1

Range 1: 1 to 123 [Graphics](#)

▼ Next Match ▲ Previous Match

Score	Expect	Method	Identities	Positives	Gaps
255 bits(652)	3e-93	Compositional matrix adjust.	123/123(100%)	123/123(100%)	0/123(0%)
Query 1	EVQLVESGGGLVQPGGSLRLS	CAASGYTF	TNYGMNWVRQAPGKGLEWVGWINTYTGEPTY		60
Sbjct 1	EVQLVESGGGLVQPGGSLRLS	CAASGYTF	TNYGMNWVRQAPGKGLEWVGWINTYTGEPTY		60
Query 61	AADFRRFTFSLDTSKSTAYLQ	MNSLRAEDTAVYYCAKYPHYGSSHWYFDVWGQGT	LVT		120
Sbjct 61	AADFRRFTFSLDTSKSTAYLQ	MNSLRAEDTAVYYCAKYPHYGSSHWYFDVWGQGT	LVT		120
Query 121	VSS	123			
Sbjct 121	VSS	123			

Figura 1. Porcentaje de identidad del 100% entre las secuencias de la cadena variable pesada del anticuerpo anti-VEGF divulgado en el documento D1 y el divulgado en la presente solicitud. Alineamiento (Blastp) entre la secuencia SEQ ID No. 125 (sbjct) y la secuencia SEQ ID No. 1 (query).

SEQ_124_LV_WO1998045331

Sequence ID: lcl|35177 Length: 108 Number of Matches: 1

Range 1: 1 to 108 [Graphics](#)

▼ Next Match ▲ Previous Match

Score	Expect	Method	Identities	Positives	Gaps
221 bits(563)	3e-80	Compositional matrix adjust.	108/108(100%)	108/108(100%)	0/108(0%)
Query 1	DIQMTQSPSSLSASVGD	RVTITCSASQDISNYLNWYQQKPGKAPKVL	IYFTSSLHSGVPS		60
Sbjct 1	DIQMTQSPSSLSASVGD	RVTITCSASQDISNYLNWYQQKPGKAPKVL	IYFTSSLHSGVPS		60
Query 61	RFSGSGSGTDFTLTIS	SLQPEDFATYYCQQYSTVPWTFGQGTKVEIKR		108	
Sbjct 61	RFSGSGSGTDFTLTIS	SLQPEDFATYYCQQYSTVPWTFGQGTKVEIKR		108	

Figura 2. Porcentaje de identidad del 100% entre las secuencias de la cadena variable ligera del anticuerpo anti-VEGF divulgado en el documento D1 y el divulgado en la presente solicitud. Alineamiento (Blastp) entre la secuencia SEQ ID No. 124 (sbjct) y la secuencia SEQ ID No. 1 (query).

Por lo tanto, la reivindicación 1 no se considera nueva. Las reivindicaciones dependientes 2 a 3 tampoco cumplen con el requisito de novedad.

Grupos inventivos 1 a 4:

Entiéndase la reivindicación 1 como una composición de anticuerpo anti-VEGF en combinación con taxanos, gemcitabina, capecitabina y vinorelbina, para tratar un cáncer de mama metastásico previamente tratado.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D2
Bevacizumab en combinación con quimioterapia para el tratamiento de pacientes con cáncer de mama metastásico tratados previamente	Tratamiento de pacientes con cáncer de mama metastásico tratados previamente (Pág. 372 Col. derecha, primer párrafo). que consiste en la administración de bevacizumab en combinación con quimioterapia estándar (Pág. 372 Col. derecha, primer párrafo).

Las características esenciales de la reivindicación 1 habían sido divulgadas previamente por el documento D2 porque divulga la combinación con quimioterapia de una composición de anticuerpo anti-VEGF (bevacizumab) para aumentar el tiempo hasta el progreso de la enfermedad en pacientes con cáncer de mama recurrente, dando a conocer un ensayo clínico de segunda línea (Ribbon 2) que evalúa la eficacia

y seguridad de bevacizumab en combinación con regímenes de quimioterapia estándar, como paclitaxel, docetaxel, gemcitabina, vinorelbina y capecitabina, en pacientes con cáncer de mama metastásico tratados previamente (Pág. 372 Col. derecha, primer párrafo). Dicho ensayo clínico consideró dentro de los criterios de exclusión a pacientes KER2-positivos (Pág. 372 Col. derecha, tercer párrafo).

La reivindicación 1 carece de novedad de acuerdo con la información divulgada en el documento D2. Las reivindicaciones dependientes 2 a 3 tampoco cumplen con el requisito de novedad.

Vale la pena mencionar que el grupo inventivo 1 también carece de novedad frente a las enseñanzas del documento D4, el cual combina bevacizumab con docetaxel (resumen).

El grupo inventivo 3 también carece de novedad puesto que sus características esenciales habían sido divulgadas con anterioridad en el documento D3, el cual combina bevacizumab con capecitabina (resumen).

El grupo inventivo 4 tampoco es nuevo puesto que sus características esenciales se enseñaban previamente en el documento D5, el cual demuestra la efectividad de la combinación bevacizumab y vinorelbina (resumen).

En consecuencia, los grupos inventivos 1 – 4 carecen de novedad.

Como se evidenció en el presente examen, en el estado de la técnica es ampliamente conocido el empleo de bevacizumab en combinación con quimioterapia para el tratamiento de cáncer de mama, como también puede consultarse en la revisión Lorusso (2008)⁸, que discute la efectividad de bevacizumab en el tratamiento de cáncer de mama HER2-negativo y los diferentes ensayos empleados hasta su fecha de publicación.

9. Conclusión

Los requisitos de Patentabilidad de la presente solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO98/45331	1 - 3	Nivel inventivo
D2	O'Shaughnessy & Brufsky 2008	1 - 3	Nivel inventivo
D3	Miller <i>et al.</i> 2005	1 - 3	Nivel inventivo
D4	Ramaswamy <i>et al.</i> 2006	1 - 3	Nivel inventivo
D5	Burstein <i>et al.</i> 2008	1 - 3	Nivel inventivo

⁸ Lorusso, V. 2008. Bevacizumab in the treatment of HER2-negative breast cancer. *Biologics* 2(4): 813–821. En línea: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2727886/>

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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JOSÉ LUIS SALAZAR LÓPEZ
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El anterior requerimiento fue notificado por fijación en lista, de fecha 2014-05-13

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RiBBON 1 and RiBBON 2: Phase III Trials of Bevacizumab with Standard Chemotherapy for Metastatic Breast Cancer

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Introduction

Despite advances in detection and therapy, recurrent or metastatic disease will develop in approximately 30% of women with breast cancer.¹ The clinical course of metastatic breast cancer (MBC) is heterogeneous, owing to large differences in the growth rate and responsiveness to systemic therapy.² Many patients with MBC respond to their first treatment with endocrine or chemotherapy agents, but the disease nearly always progresses and the probability of a response decreases with each course of treatment.² Average survival in patients with MBC is 2 years to 4 years after diagnosis.³⁻⁶

Antiangiogenesis is a new strategy for treating breast cancer. The invasion and metastasis of breast cancer and other solid tumors depend on angiogenesis, a process that is stimulated by the release of proangiogenic peptides, including vascular endothelial growth factor (VEGF).^{7,8} Bevacizumab is a humanized monoclonal antibody that binds to and neutralizes the VEGF-A ligand, thereby inhibiting the development of new tumor vasculature and the maintenance of existing vasculature.⁹ Bevacizumab also induces vascular normalization, as evidenced by greater tumor uptake of chemotherapy agents after anti-VEGF therapy in pre-clinical colon xenograft models.¹⁰ Antiangiogenesis therapy has been studied in phase 1, 2, and 3 clinical trials in more than 5000 patients with advanced carcinomas,¹¹ and the efficacy of bevacizumab-containing regimens has been shown in first-line trials in MBC,¹² colorectal cancer,¹³ and non-small-cell lung cancer (NSCLC),¹⁴ as well as in later lines of therapy for colorectal cancer,¹⁵ ovarian cancer,¹⁶ and NSCLC.¹⁷

Rationale for First- and Second-Line Treatment

In the first-line treatment of colorectal cancer (CRC), the addition of bevacizumab to irinotecan, fluorouracil, and leucovorin resulted in a median survival benefit of 4.7 months (20.3 months vs 15.6 months).¹³ In second-line treatment, overall survival (OS) was 12.5 months with bevacizumab in combination with FOLFOX-4 and 10.7 months with FOLFOX-4 alone.¹⁵ The efficacy of bevacizumab has also been shown in NSCLC. Overall survival in patients treated with first-line paclitaxel, carboplatin, and bevacizumab was 12.3 months and in patients treated with paclitaxel and carboplatin alone was 10.3 months.¹⁴ A phase 1-2 study of bevacizumab in combination with erlotinib in patients with NSCLC suggests that this regimen has antitumor activity in recurrent disease.¹⁷

Bevacizumab-related adverse events (AEs) include hypertension, arterial thromboembolic events, hemorrhage, and wound healing complications.¹⁸ Bevacizumab has been associated with gastrointestinal perforation in patients with CRC and with pulmonary hemorrhage in patients with NSCLC. Pulmonary hemorrhage has been associated with predominantly squamous cell histology, so patients with NSCLC must be selected carefully for treatment with bevacizumab.

A randomized phase 3 trial (AVF2119g) evaluated second-line treatment with bevacizumab plus capecitabine and treatment with capecitabine alone in patients with MBC who had been treated with anthracyclines and taxanes.¹⁹ The overall response rate in this heavily treated population was higher in those treated with the combination (19.8% vs. 9.1%), but median progression-free survival (PFS; 4.9 months vs. 4.2 months) and OS (15.1 months vs. 14.5 months) were not significantly greater. The investigators suggested that the lack of a survival benefit could be explained by the fact that the optimal time to intervene with an antiangiogenesis agent might be earlier in the course of the disease. As a result, bevacizumab was subsequently evaluated in the first-line setting. In the pivotal phase 3 E2100 trial in the first-line treatment of MBC, PFS was significantly longer in the patients treated with weekly paclitaxel plus bevacizumab than in those treated with paclitaxel alone

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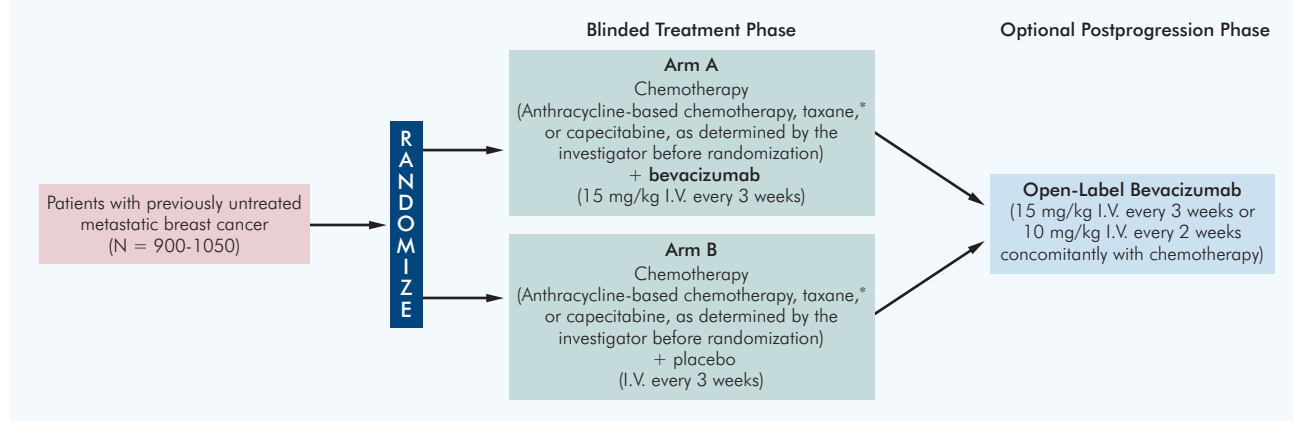
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Figure 1 RiBBON 1 Study Schema



*Docetaxel or paclitaxel–protein-bound particles.
Abbreviation: I.V. = intravenous

(11.4 months vs. 6.1 months; hazard ratio, 0.50) and the response rate was twice as great (28.2% vs. 14.2%).¹² There was no significant difference in survival between the 2 arms. Bevacizumab appears to be more efficacious in first-line treatment, and the differences in the efficacy of bevacizumab in combination with chemotherapy might be dependent on the choice of chemotherapy agent and the line of treatment. Direct comparisons of efficacy in the AVF2119g and E2100 studies cannot be made because the chemotherapy agents were different, as was the degree of chemotherapy pretreatment in the 2 studies.

The XCALIBr trial evaluated capecitabine/bevacizumab in the first-line treatment of patients with MBC.^{20,21} Median time to progression (TTP; N = 106) was 5.7 months (95% confidence interval [CI], 4.9-8.4 months); patients with estrogen receptor–positive disease (n = 57) had a superior outcome, with a median TTP of 8.9 months (95% CI, 7.5-13.6 months), compared with 4 months (95% CI, 3-4.9 months) in patients with estrogen receptor–negative disease. Further, overall response rate was 38% (47% in the estrogen receptor–positive population and 27% in the estrogen receptor–negative population), and median OS was > 16 months (> 16.6 months in patients with estrogen receptor–positive disease and > 7.5 months in patients with estrogen receptor–negative disease).²¹ Capecitabine/bevacizumab was well tolerated in this previously untreated population; the majority of AEs were mild or moderate. Thirteen percent of patients reported grade 3 palmar-plantar erythrodysesthesia, 10% reported grade 3 pain, and (in the first phase of the study) 2% reported grade 4 pulmonary embolism.

A number of questions about the role of bevacizumab in breast cancer and the optimal combination of chemotherapy agents, line of treatment, and duration of treatment are yet to be answered. The safety profile of bevacizumab in breast cancer also requires more study. Bevacizumab has been well tolerated in patients with breast cancer, but cardiotoxicity has been reported in one study in which patients had been or were being treated with concomitant anthracyclines. In the AVF2119g trial in patients with extensive previous cytotoxic therapy, congestive heart failure (CHF) occurred in 3.1% of the patients treated with bevacizumab and capecitabine and in 0.9% of those treated with capecitabine alone.¹⁹ In contrast,

a higher incidence of CHF was not observed in the E2100 trial of bevacizumab with paclitaxel in patients with previously untreated MBC. Further analysis of the safety of bevacizumab in patients treated with previous or concomitant anthracyclines is therefore warranted.

Patients with central nervous system (CNS) metastases have been ineligible for clinical studies of bevacizumab because of the risk of cerebrovascular bleeding. The use of bevacizumab in combination with irinotecan in 32 patients with malignant gliomas, however, has shown that bevacizumab might be safe in patients with CNS tumors.²² No CNS hemorrhages or ≥ grade 2 systemic hemorrhages had occurred in any patient.

Because antiangiogenic therapy has the potential to improve the clinical outcomes in patients with MBC, there is a need to optimize its use, particularly early in the course of metastatic disease. The ongoing RiBBON studies are large, multicenter, randomized placebo-controlled phase 3 trials that are evaluating the efficacy and safety of bevacizumab in combination with standard-of-care chemotherapy regimens in patients with previously untreated (RiBBON 1) or previously treated (RiBBON 2) MBC. Because investigators are given the choice of which chemotherapy regimen to use, the RiBBON trials might provide data to support the use of bevacizumab in combination with various standard-of-care chemotherapy agents, including capecitabine. The capecitabine arm in this study is adequately powered for a statistically significant difference in capecitabine versus capecitabine/bevacizumab to be demonstrated. Another unique feature is that RiBBON 2 is a purely second-line study, in contrast with the AVF2119g trial, in which approximately 40% of patients had been treated with ≥ 2 chemotherapy regimens for MBC.¹⁹

RiBBON 1 (AVF3694g)

Treatment

Patients are being randomized in a 2:1 ratio of chemotherapy plus bevacizumab or chemotherapy plus placebo (Figure 1). The primary objective of the RiBBON 1 trial is to evaluate the clinical benefit of the addition of bevacizumab 15 mg/kg intravenous (I.V.) on day 1 every 3 weeks versus a placebo to standard first-line chemotherapy

regimens in patients with MBC, as measured by PFS. The standard first-line regimen options that physicians and patients can choose from in this study are 3-week cycles of taxanes (docetaxel 75-100 mg/m² I.V. or paclitaxel protein-bound particles 260 mg/m² I.V.), anthracycline-based regimens (FEC: 5-fluorouracil 500 mg/m² I.V., epirubicin 90-100 mg/m² I.V., and cyclophosphamide 500 mg/m² I.V. on day 1; FAC: 5-fluorouracil 500 mg/m² I.V., doxorubicin 50 mg/m² I.V., and cyclophosphamide 500 mg/m² I.V. on day 1; AC: doxorubicin 50-60 mg/m² I.V. and cyclophosphamide 500-600 mg/m² I.V. on day 1; EC: epirubicin 90-100 mg/m² I.V. and cyclophosphamide 500-600 mg/m² I.V. on day 1), and capecitabine 1000 mg/m² orally twice a day on days 1-14. Investigator assessments based on Response Evaluation Criteria in Solid Tumors (RECIST) are being used to determine progression. Secondary endpoints are PFS in the 3 primary study cohorts (taxane-based, anthracycline-based, and capecitabine therapy), 1-year survival, OS, overall response, best response assessed by the investigator using RECIST, and safety. Patients are treated with placebo or bevacizumab, which can be continued for up to 2 years in the absence of disease progression or unacceptable toxicity. Patients who complete the study or who discontinue treatment (regardless of their participation in the optional post-progression phase) are followed up every 4 months for survival. Subjects in whom there is disease progression during the blinded treatment phase might be eligible for treatment with open-label bevacizumab in combination with a second-line chemotherapy agent of choice during the optional unblinded post-progression phase on both study arms.

Key Inclusion Criteria

RiBBON 1 is being conducted in patients with histologically or cytologically confirmed breast carcinoma with measurable or nonmeasurable locally recurrent or metastatic disease. Locally recurrent disease must not be resectable with curative intent. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and adequate cardiac, hematologic, renal, and liver function.

Key Exclusion Criteria

Patients are excluded from RiBBON 1 if they have human epidermal growth factor receptor (HER)2-positive disease; if they have been treated with chemotherapy for locally recurrent or metastatic disease; if they have been treated with hormone therapy within 7 days before study entry; if they have been treated with adjuvant or neoadjuvant chemotherapy within a year before study entry; if they have had a major surgical procedure, investigational therapy, open biopsy, or significant traumatic injury within 28 days before study entry; if they have been treated with radiation therapy within 14 days before study entry; or if they have CNS metastases.

Statistical Considerations

Approximately 900 to 1050 subjects will be enrolled at ≤ 250 centers worldwide in order to achieve a power of 80% with a 5% significance level to see significantly greater PFS with bevacizumab added to chemotherapy than with chemotherapy alone. A 2-step hierarchical primary analysis will be performed at the interim and the final analysis.

RiBBON 2 (AVF3693g)

Treatment

The primary objective of the RiBBON 2 trial is to evaluate whether the addition of bevacizumab to standard chemotherapy can increase PFS in the second-line treatment of patients with MBC. Secondary endpoints include OS, overall response, duration of response, and the incidence of AEs. Patients are being randomized in a 2:1 ratio to chemotherapy plus bevacizumab or chemotherapy plus placebo, in which the chemotherapy is at the discretion of the investigator and is determined before randomization (Figure 2). The chemotherapy may be given in accordance with the recommendations in the prescribing information, in accordance with institutional guidelines, or as follows: paclitaxel 90 mg/m² I.V. every week for 3 weeks followed by 1 week of rest or 175 mg/m² I.V. every 3 weeks; paclitaxel protein-bound particles 260 mg/m² I.V. every 3 weeks; docetaxel 75-100 mg/m² I.V. every 3 weeks; gemcitabine 1250 mg/m² I.V. on days 1 and 8 of each 3-week cycle; vinorelbine 30 mg/m² I.V. every week; capecitabine 1000 mg/m² orally twice a day on days 1-14 of each 3 week cycle. Treatment with bevacizumab or placebo will continue until disease progression, unacceptable toxicity, or death, or for a maximum of 2 years.

Key Inclusion Criteria

RiBBON 2 is being conducted in patients with histologically confirmed breast carcinoma with measurable or nonmeasurable metastatic disease that has progressed during or after treatment with 1 (noninvestigational) chemotherapy regimen, defined as single-agent chemotherapy given before or during disease progression or a specified combination or sequence of cytotoxic agents given in the first-line setting. Patients must have an ECOG PS of 0 or 1 and adequate cardiac, hematologic, renal, and liver function.

Key Exclusion Criteria

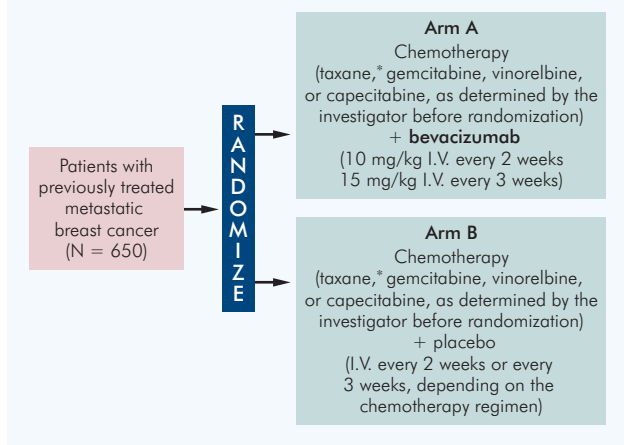
Patients are excluded from RiBBON 2 if they have been treated with > 1 cytotoxic regimen for MBC; if they have HER2-positive disease or unknown estrogen receptor or progesterone receptor status; if they have been treated with radiation therapy other than for palliation, hormone therapy, biologic therapy, or chemotherapy for MBC within 21 days before study entry; if they have been treated with bevacizumab or other VEGF-targeted agents; or if they have CNS metastases.

Statistical Considerations

Approximately 650 patients will be enrolled at ≤ 400 centers worldwide in order to achieve a power of 80% with a 5% significance level to see significantly greater median PFS with second-line bevacizumab plus chemotherapy than with chemotherapy alone. An interim analysis is planned after 260 events have occurred.

Conclusion

Delaying disease progression, extending survival, and preserving quality of life are important goals in the treatment of MBC. The RiBBON trials are designed to evaluate the efficacy and safety of bevacizumab in combination with several chemotherapy agents and regimens for MBC in the first-line (RiBBON 1) and second-line (RiBBON 2) settings. These trials should provide important data

Figure 2 RiBBON 2 Study Schema

*Docetaxel, paclitaxel, or paclitaxel-protein-bound particles.
Abbreviation: I.V. = intravenous

on the safety and efficacy of the long-term use of bevacizumab and the use of antiangiogenesis therapy in combination with standard-of-care regimens for MBC.

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Randomized Phase III Trial of Capecitabine Compared With Bevacizumab Plus Capecitabine in Patients With Previously Treated Metastatic Breast Cancer

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose

This randomized phase III trial compared the efficacy and safety of capecitabine with or without bevacizumab, a monoclonal antibody to vascular endothelial growth factor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane.

Patients and Methods

Patients were randomly assigned to receive capecitabine (2,500 mg/m²/d) twice daily on day 1 through 14 every 3 weeks, alone or in combination with bevacizumab (15 mg/kg) on day 1. The primary end point was progression-free survival (PFS), as determined by an independent review facility.

Results

From November 2000 to March 2002, 462 patients were enrolled. Treatment arms were balanced. No significant differences were found in the incidence of diarrhea, hand-foot syndrome, thromboembolic events, or serious bleeding episodes between treatment groups. Of other grade 3 or 4 adverse events, only hypertension requiring treatment (17.9% v 0.5%) was more frequent in patients receiving bevacizumab. Combination therapy significantly increased the response rates (19.8% v 9.1%; $P = .001$); however, this did not result in a longer PFS (4.86 v 4.17 months; hazard ratio = 0.98). Overall survival (15.1 v 14.5 months) and time to deterioration in quality of life as measured by the Functional Assessment Of Cancer Treatment—Breast were comparable in both treatment groups.

Conclusion

Bevacizumab was well tolerated in this heavily pretreated patient population. Although the addition of bevacizumab to capecitabine produced a significant increase in response rates, this did not translate into improved PFS or overall survival.

J Clin Oncol 23:792-799. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Metastatic breast cancer (MBC) remains a devastating disease, claiming the lives of more than 40,000 women in the United States each year.¹ Though an expanding array of active agents has become available for the treatment of metastatic disease, overall survival has changed little in the last half century.² While response rates $\geq 30\%$ are routinely achieved in previ-

ously untreated patients, response rates decrease significantly in patients previously exposed to chemotherapy.³

Further therapeutic advances require new strategies that are based on an understanding of breast cancer biology. Invasion and metastasis of breast cancer depends on angiogenesis, the formation of new blood vessels that nourish the tumor.^{5,6} Extensive laboratory data suggest that angiogenesis plays an essential role in breast cancer

development, invasion, and metastasis.⁷⁻¹⁰ Clinicopathologic correlations confirm this role. Breast cancer vascularity, quantified by tumor microvessel density, predicts tumor shedding at the time of surgery,¹¹ bone marrow micrometastases,¹² recurrence, and overall survival.¹³⁻¹⁵ This nascent vascular network provides a unique opportunity for therapeutic intervention.

Vascular endothelial growth factor (VEGF) is among the most potent stimulators of angiogenesis. In addition to endothelial cell mitogenesis and migration, VEGF inhibits endothelial cell apoptosis and supports maintenance of the newly formed tumor vasculature. VEGF produces other biologic effects, including induction of proteinases that remodel extracellular matrix, increased vascular permeability, vasodilation, and inhibition of antigen-presenting dendritic cells.¹⁶

Bevacizumab (Avastin; Genentech, South San Francisco, CA), a humanized monoclonal antibody (mAb) directed against all isoforms of VEGF-A, inhibits growth of human tumors in animal models.¹⁷ A phase II study of bevacizumab monotherapy in 75 patients with previously treated MBC reported a 9.3% objective response rate, with 17% of patients responding or stable at 22 weeks; four patients continued therapy without progression for more than 12 months.¹⁸ Bevacizumab, alone and in combination with chemotherapy, was well tolerated, with hypertension, proteinuria, thrombosis, and bleeding being the most commonly reported toxicities.¹⁹⁻²² Given the efficacy and minimal toxicity in the phase II studies, this randomized phase III study was initiated to compare capecitabine monotherapy with the combination of capecitabine plus bevacizumab in patients with previously treated MBC.

PATIENTS AND METHODS

Patient Eligibility

Women with histologically or cytologically confirmed MBC were eligible if they had received prior therapy with both an anthracycline and a taxane, and at least one, but no more than two, prior chemotherapy regimens for metastatic disease. If relapse occurred within 12 months of completing adjuvant anthracycline and taxane therapy, patients were eligible without intervening chemotherapy. Patients with HER2-positive disease (3+ protein expression by immunohistochemistry or gene amplification by fluorescence in situ hybridization) must have progressed following trastuzumab. Additional inclusion criteria included bidimensionally measurable disease with at least one lesion measuring ≥ 2 cm; Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate renal, hepatic, and hematologic function.

Patients were excluded if they had any history or radiographic evidence of CNS disease; screening head computed tomography or brain magnetic resonance image was required. Patients could not have other primary malignancy except basal cell carcinoma of the skin or in situ cervical cancer within 5 years, major surgery within 4 weeks, other antitumor therapy within 21 days, nonhealing wound or fracture, infection requiring parenteral

antibiotics, or clinically significant cardiovascular disease. Therapeutic anticoagulation, regular nonsteroidal anti-inflammatory medication, and aspirin (> 325 mg/d) were prohibited, but prophylactic anticoagulants to maintain a vascular access device were permitted. Concurrent administration of bisphosphonates was allowed if initiated at least 21 days before study entry. Women of reproductive potential were required to use effective contraception.

Local institutional review boards approved the protocol, and patients provided written informed consent before screening.

Treatment Plan

All patients received capecitabine 2,500 mg/m²/d (1,875 mg/m²/d if creatinine clearance 30 to 50 mL/min), orally twice daily for 14 days followed by a 7-day rest period. Capecitabine was interrupted for grade 2 or 3 toxicity and resumed at a reduced dose (75% starting dose for first occurrence, 50% at second occurrence) on resolution to less than grade 2. Capecitabine was discontinued if toxicity $\geq$ grade 2 recurred after two dose reductions, and for grade 4 toxicity.

Patients randomized to the combination arm received bevacizumab (15 mg/kg) intravenously on day 1 of each 3-week cycle. Initially, bevacizumab was infused over 90 minutes. If no infusion-related reactions occurred, subsequent infusions were reduced to 60, then 30 minutes. Premedication was optional. Treatment was interrupted for proteinuria $\geq 2,000$ mg per 24 hours and resumed on resolution to less than 2,000 mg per 24 hours. Blood pressure was monitored before and immediately after each bevacizumab infusion; antihypertensive therapy was given at the investigator's discretion. Bevacizumab therapy was not withheld or discontinued for capecitabine-related toxicities.

Patients continued therapy for a maximum of 35 cycles or until disease progression or prohibitive toxicity. Patients without progression at the completion of 35 cycles could continue the same treatment on an extension study. Patients randomized to the combination arm could continue bevacizumab, either alone or with other therapies, after initial disease progression. Patients randomly assigned to capecitabine monotherapy could not receive bevacizumab at any time.

Safety and Efficacy Assessments

Patients were evaluated before each treatment cycle. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. Disease status was assessed at baseline, every 6 weeks until 24 weeks, then every 9 weeks until progression. Contrast-enhanced spiral computed tomography of the chest, abdomen, and pelvis was required at each evaluation. In patients with known bone involvement, bone scans were performed at baseline and were repeated as clinically indicated. Visible cutaneous lesions were photographed. All images and clinical information were forwarded to an independent review facility (IRF; RadPharm, Princeton, NJ) for evaluation by radiologists and oncologists blinded to treatment assignment and local response designation. Response was characterized according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria,²³ with the following minor modifications: target lesions were required to be ≥ 2 cm in diameter; unequivocal progression of nontarget lesions required the lesion to be measured at baseline when possible; if measurable, the lesion diameter must have doubled to at least 2 cm; target lesions measured by physical examination had to be clearly visible in good-quality photographs containing a ruler. All patients were monitored for survival every 4 months.

Pharmacokinetics

Pharmacokinetics (PK) were assessed in a subset of patients. For patients in the combination arm, serum samples measured bevacizumab during cycles 1, 3, 5, 7, and 9 (predose and 10 minutes following completion of infusion). Samples to measure capecitabine and its metabolites 5'-deoxy-5-fluorouridine (5-DFUR) and fluorouracil (FU) were drawn during cycles 1 and 3 (predose and 90, 150, and 240 minutes postdose). Exposure to chemotherapy (area under the curve [AUC], 0 to 240 minutes) was assessed for each of the three analytes (capecitabine, FU, and 5-DFUR) and was normalized to capecitabine dose.

Quality of Life

Quality of life (QOL) was assessed using the Functional Assessment Of Cancer Treatment—Breast (FACT-B) questionnaire at baseline, every 6 weeks until 24 weeks, and then every 9 weeks. Time to deterioration in QOL (TDQ) as measured by the Trial Outcome Index (TOI; the sum of the physical well-being, functional well-being, and breast cancer-specific questions in the FACT-B) was the primary end point.²⁴ A decline in TOI of more than five points from baseline, disease progression, or death was considered a clinically meaningful deterioration in QOL. Formal comparison of TDQ used the unstratified log-rank test.

Statistical Analysis

The primary end points were progression-free survival (PFS) as determined by the IRF, and safety of the combination in this patient population. PFS was defined as time from randomization to the date of IRF-documented disease progression or death. The investigator (INV) assessment was used for three patients lacking an IRF assessment. Patients without an event were treated as censored at the time of the last tumor assessment. Secondary end points included PFS based on INV assessment, objective response rate and duration as determined by both IRF and INV, and QOL and survival.

Sample size calculations assumed a two-sided log-rank test, 90% power at the 5% significance level, a hazard ratio of bevacizumab versus control of 0.667 (improvement in median PFS from 4 to 6 months), and one interim analysis at 50% information time, which required 265 events. Enrollment of 400 patients would allow analysis when 66% of patients had progressed. The study would stop at the interim analysis if the hazard ratio for PFS was less than 0.5 (1-sided $P < .0001$) or greater than 1, corresponding to an asymmetric stopping boundary (the efficacy interim analysis was later cancelled due to delayed availability of IRF assessments). An independent data monitoring committee reviewed all deaths, and serious and targeted adverse events (grade 3 and 4 diarrhea, grade 3 hand-foot syndrome, grade 3 and 4 bleeding, and any thrombosis) monthly until December 2001. The protocol was extended to enroll approximately 50 additional patients for PK assessment. Data cutoff for this analysis was 28 June 2002—3 months after the last patient was randomly assigned.

Random assignment was stratified for Eastern Cooperative Oncology Group performance status (0 or 1), number of prior chemotherapy regimens for metastatic disease (0 or ≥ 1), and study site. All randomly assigned patients were included in the efficacy (intent-to-treat) analysis. Safety analyses included only treated patients (analyzed as treated). A two-sided stratified log-rank test was performed at the 0.0498 level to determine whether PFS was prolonged for the bevacizumab plus capecitabine group compared with the capecitabine-alone group (type I error of 0.01% was allocated for both the safety and can-

celled efficacy interim analyses). An estimate of the hazard ratio $\lambda_{\text{bevacizumab} + \text{capecitabine}} / \lambda_{\text{capecitabine}}$ with 95% CIs was determined using a stratified Cox regression model with an indicator variable for treatment group. Median PFS in each treatment group was estimated using the Kaplan-Meier method. Because patients in the bevacizumab treatment arm were permitted to remain on study if capecitabine was discontinued for toxicity, tumor assessments more than 42 days after discontinuation of capecitabine were censored. Objective response rates were compared using the χ^2 test; overall survival comparisons used an unstratified log-rank test. Exploratory analyses to gauge the impact of potential prognostic factors on PFS were conducted using Cox regression to estimate treatment effect within various subgroups.

RESULTS

Patient Population

A total of 462 patients were randomly assigned between November 2000 and March 2002 at 96 US centers: 230 to capecitabine alone and 232 to combination treatment. Fifteen patients randomly assigned to capecitabine alone and three patients randomized to combination treatment never received study treatment and were not included in the safety analysis. Overall, 93 (20%) of the treated patients failed to meet one or more of the eligibility criteria; major reasons for ineligibility included prior therapy within 21 days ($n = 27$), more than two regimens for metastatic disease ($n = 19$), CNS involvement ($n = 10$), laboratory values out of range ($n = 10$), no chemotherapy for metastatic disease with relapse more than 12 months from adjuvant therapy ($n = 4$), and no prior anthracycline or taxane ($n = 3$). Analysis of major end points excluding ineligible patients did not affect the outcome (data not shown); therefore, results presented include all randomized patients. Baseline demographic and tumor characteristics were well balanced between treatment groups (Table 1).

Efficacy

The objective response rate (ORR) significantly improved with addition of bevacizumab, as determined by both the IRF (19.8% [95% CI, 14.7% to 25.0%]) ν 9.1% [95% CI, 5.4% to 12.9%]; $P = .001$) and the investigators (30.2% [95% CI, 24.3% to 36.1%]) ν 19.1% [95% CI, 14.1% to 24.2%]; $P = .006$). The IRF and investigator disagreed on disease progression in 105 patients (22.7%); investigator-determined progression was not confirmed by the IRF in 79 patients, most commonly when progression was determined by physical examination. In 26 patients, progression was determined by IRF review but not investigator review. The combination of capecitabine and bevacizumab did not increase PFS as determined by the IRF (hazard ratio, 0.98 [95% CI, 0.77 to 1.25]; $P = .857$; Figure 1A) or the investigator (data not shown). The median duration of response and the proportion of subjects with responses of

Table 1. Patient Characteristics

Characteristic	Capecitabine (n = 230)		Capecitabine + Bevacizumab (n = 232)	
	No.	%	No.	%
Age, years				
Mean	52		51	
Range	30-77		29-78	
Race				
Black	25	10.9	30	12.9
White	185	80.4	187	80.6
Other	20	8.7	15	6.5
ECOG PS				
0	115	50.0	117	50.4
1	115	50.0	114	49.1
2	0	0	1	0.4
Estrogen receptor-positive	119	51.7	97	41.8
Progesterone receptor-positive	96	41.7	75	32.3
HER2-positive*	47	20.4	61	26.3
Duration of metastatic disease, years				
Median	1.3		1.0	
Range	0-19.3		0-13.2	
Visceral disease	184	80.0	180	77.6
≥ 3 sites of disease	116	50.4	114	49.1
Prior chemotherapy regimens for MBC				
0	37	16.1	35	15.1
1	98	42.6	107	46.1
2	87	37.8	79	34.1
3-5	8	3.5	11	4.7

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MBC, metastatic breast cancer.

*HER2-positive = 3+ by immunohistochemistry or amplification by fluorescence in situ hybridization.

more than 4 months' duration were similar in the two treatment groups (Fig 1B).

At data cutoff, 38% of patients had died. The majority of deaths (95.2%) were due to progressive disease. Two patients in the capecitabine-alone group died while on therapy: one patient suffered a cardiopulmonary arrest shortly after initiating treatment, and a second died from a presumed pulmonary embolus during cycle 2. No treatment-related deaths occurred during initial therapy in the combination arm. Median overall survival was similar in the two treatment groups (Fig 1C).

Safety

The addition of bevacizumab did not affect the frequency or severity of capecitabine toxicities (Table 2). Diarrhea (grade 3; 10.7% in the capecitabine-alone treatment group v 11.8% in the capecitabine plus bevacizumab treatment group), hand-foot syndrome (grade 3; 24.2% in the capecitabine alone v 27.5% in the combination therapy group), and need for dose modifications were similar in the two treatment groups. The mean delivered dose-intensity for capecitabine (80%) was similar to the combination therapy of capecitabine plus bevacizumab (75%). A total of 140 (65%) of

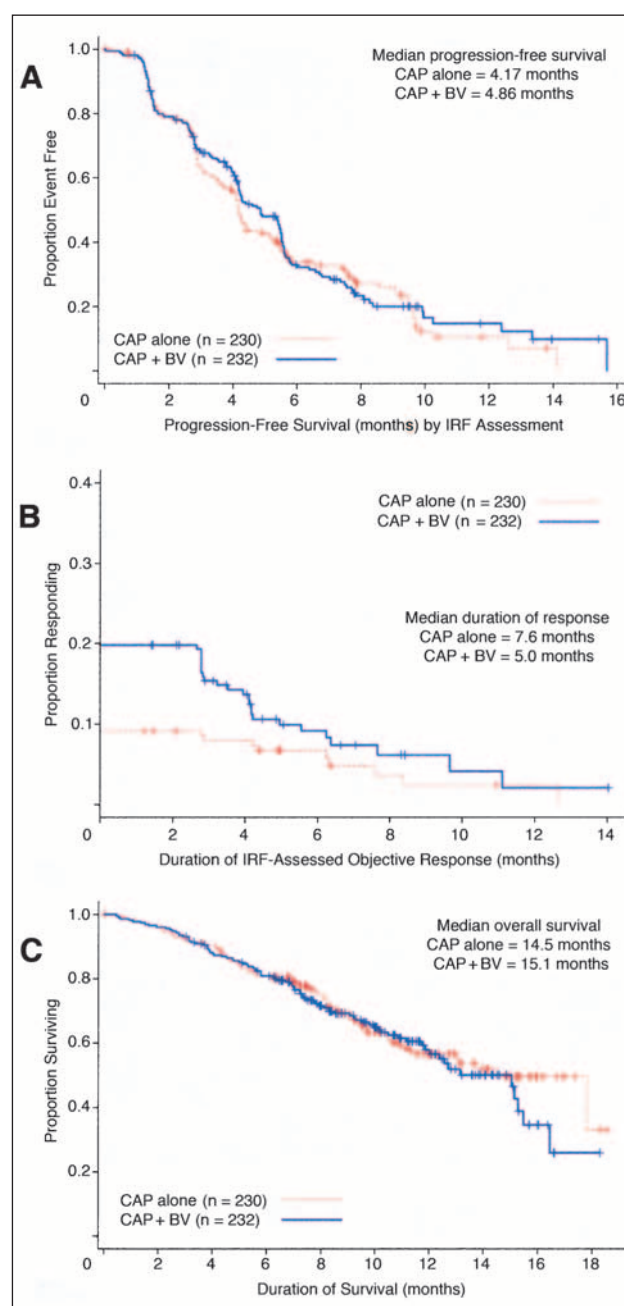


Fig 1. (A) The median progression-free survival by independent review facility (IRF) assessment, (B) median duration of IRF-assessed objective response, and (C) median duration of overall survival in both treatment groups. The investigator assessment was used for three patients lacking an IRF assessment. CAP, capecitabine; BV, bevacizumab.

215 patients in the capecitabine group required drug dose reduction, while 181 (79%) of 229 patients in the combination therapy group had their drug dose lowered. Twenty-nine patients (12.6%) in the capecitabine group and 28 patients (12.2%) in the combination group discontinued treatment due to toxicity. Eleven patients (4.8%) in the combination arm discontinued capecitabine but continued bevacizumab alone

Table 2. Common Capecitabine Toxicities

Toxicity	Capecitabine (n = 215)						Capecitabine + Bevacizumab (n = 229)					
	Grade 2		Grade 3		Grade 4		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Diarrhea	34	15.8	23	10.7	0	0	37	16.2	27	11.8	0	0
Stomatitis	11	5.1	0	0	1	0.5	16	7.0	4	1.7	0	0
Hand-foot syndrome	77	35.8	52	24.2	0	0	97	42.4	63	27.5	0	0

NOTE. National Cancer Institute Common Toxicity Criteria worst grade experienced per patient.

for at least two cycles. There were no clinically significant infusion reactions.

Hypertension was more common in the combination arm but was generally managed with medical therapy; no patient experienced grade 4 hypertension (Table 3). Four patients discontinued bevacizumab because of hypertension. Changes in preinfusion mean systolic and diastolic blood pressure were -2.6 and -0.7 mmHg, respectively, in the capecitabine alone group, compared with $+5.5$ and $+4.6$ mmHg in the combination group. The risk for developing hypertension correlated only with bevacizumab treatment; no relationship was observed with duration of therapy or pre-existing hypertension.

Proteinuria was more common in patients receiving combination therapy but was rarely clinically significant. Two patients discontinued treatment because of grade 3 proteinuria. One patient subsequently developed nephrotic syndrome; renal biopsy revealed collapsing glomerulopathy. She had mild renal insufficiency at baseline (creatinine clearance 41 mL/min) and had received pamidronate, a drug known to be associated with collapsing glomerulopathy,^{25,26} for nearly 2 years. The incidence of proteinuria in patients receiving concurrent bevacizumab and pamidronate was 33.9%, compared with 18.5% in patients receiving bevacizumab without pamidronate ($P = .026$). Additionally, patients on the combination arm with proteinuria were more likely to report hypertension (47.1% ν 16.9%). Proteinuria was rare in patients receiving capecitabine monotherapy, and there was no increase with pamidronate treatment.

abine monotherapy, and there was no increase with pamidronate treatment.

Bevacizumab clearly increased minor mucosal bleeding. There were no grade 3 or 4 episodes of epistaxis in either patient group. However, a difference between treatment arms did occur for grades 1 or 2 epistaxis, with three events (1.4%) in the capecitabine treatment arm and 36 events (15.7%) in the capecitabine plus bevacizumab arm. Grade 3 or serious bleeding was rare and not different between treatment groups. Grade 4 hemorrhage was not reported. The incidence of thromboembolic events was infrequent and similar in the two treatment groups.

Nine patients in the study developed grade 3 or 4 congestive heart failure or cardiomyopathy: two in the capecitabine-alone group and seven in the combination group (Table 4). Baseline left ventricular ejection fraction (LVEF) was measured in 418 patients. Mean LVEF and number of patients with baseline LVEF less than 50% (14.9% capecitabine alone ν 12.2% combination) were similar in the two treatment groups. LVEF was less than 50% at baseline in three of six bevacizumab-treated patients who developed congestive heart failure or cardiomyopathy (baseline LVEF not measured in one), and in one of two control patients. Cardiac symptoms improved with medical management in all but one patient. Two of seven affected patients continued to receive bevacizumab therapy.

Seventy patients continued bevacizumab, either alone or in combination with other therapies, after initial pro-

Table 3. Common Bevacizumab Toxicities

Toxicity	Capecitabine (n = 215)								Capecitabine + Bevacizumab (n = 229)							
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hypertension	4	1.9	0	0	1	0.5	0	0	9	3.9	4	1.7	41	17.9	0	0
Proteinuria	14	6.5	2	0.9	0	0	0	0	42	18.3	7	3.1	2	0.9	0	0
Bleeding	19	8.8	4	1.9	1	0.5	0	0	60	26.2	5	2.2	1	0.4	0	0
Thrombotic event	0	0	4	1.9	5	2.3	3	1.4	1	0.4	3	1.3	9	3.9	4	1.7
Pulmonary embolism	0	0	0	0	0	0	3	1.4	0	0	0	0	0	0	3	1.3

NOTE. National Cancer Institute Common Toxicity Criteria worst grade experienced per patient.

Table 4. Other Common Toxicities

Toxicity	Capecitabine (n = 215)						Capecitabine + Bevacizumab (n = 229)					
	Grade 2		Grade 3		Grade 4		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematologic												
Anemia	8	3.7	1	0.5	0	0	12	5.2	4	1.7	0	0
Leukopenia	10	4.7	3	1.4	3	1.4	15	6.6	6	2.6	0	0
Thrombocytopenia	2	0.9	1	0.5	0	0	4	1.7	3	1.3	1	0.4
Gastrointestinal												
Nausea	30	14.0	4	1.9	0	0	33	14.4	6	2.6	0	0
Anorexia	17	7.9	5	2.3	0	0	25	10.9	2	0.9	0	0
Constipation	11	5.1	0	0	0	0	14	6.1	1	0.4	0	0
Cardiac												
Congestive heart failure	0	0	0	0	1	0.5	0	0	5	2.2	0	0
Cardiomyopathy	0	0	0	0	1	0.5	0	0	1	0.4	1	0.4
Infectious												
Infection	24	11.2	1	0.5	0	0	27	11.8	2	0.9	0	0
Fever	6	2.8	2	0.9	0	0	3	1.3	1	0.4	0	0
Miscellaneous												
Asthenia	35	16.3	10	4.7	4	1.9	58	25.3	14	6.1	3	1.3
Headache	9	4.2	1	0.5	0	0	26	11.4	4	1.7	0	0
Pain	20	9.3	4	1.9	0	0	24	10.5	7	3.1	0	0

NOTE. National Cancer Institute Common Toxicity Criteria worst grade experienced per patient.

gression. There were no new toxicities observed or safety issues that emerged in any of the patients.

PK

Bevacizumab PK parameters were estimated in 35 patients. Consistent with prior studies, bevacizumab had a long terminal half-life (23.1 day) and a mean clearance value of 2.08 mL/kg/d. Concentration increased with multiple doses and reached steady-state by week 18. Capecitabine AUC was determined in approximately 20 patients per arm. Dose-normalized AUCs for the three capecitabine-related moieties were similar in the two groups.

QOL

A total of 370 subjects completed baseline, and at least one subsequent QOL assessment (176 controls, 194 combination therapy subjects). Time to deterioration in QOL did not differ between treatment groups (2.86 v 2.92 months; $P = .633$). Detailed QOL analysis will be reported separately.

DISCUSSION

We report the first completed phase III trial of antiangiogenic therapy in patients with MBC. The patients enrolled had received prior anthracycline and taxane therapy; most had visceral involvement. Treatment was based on capecitabine, the only US Food and Drug Administration–approved chemotherapeutic in this refractory population.

The addition of bevacizumab to capecitabine therapy was generally well tolerated, with no significant increase in capecitabine-related toxicities. Though the majority of patients required capecitabine dose modification, excellent dose-intensity was maintained. The incidence of grade 3 hand-foot syndrome in our study (approximately 25%) is higher than in previous reports (approximately 10% to 13%).^{4,27} This difference may be attributed to increased investigator awareness of hand-foot syndrome and the different toxicity grading scales used. We assessed toxicity according to NCI-CTC criteria, which defines skin changes with pain interfering with function as a grade 3 toxicity. In contrast, previous studies used the NCIC-CTC (National Cancer Institute of Canada CTC) scale, which defines pain interfering with function as a grade 2 toxicity.

Bevacizumab-associated toxicities were well predicted by the phase II experience and rarely limited therapy.^{18,22,28} Hypertension requiring initiation or adjustment of prior antihypertensive therapy occurred in 18% of patients. Proteinuria developed in 22% of patients (predominantly grade 1). An apparent association between hypertension and proteinuria was noted in the combination arm: patients with proteinuria were more likely to develop hypertension (47.1% v 16.9%; $P < .001$) than patients who did not develop proteinuria. Thromboembolic events were infrequent and similar in the two treatment arms. Bleeding was primarily limited to minor mucosal oozing that did not require medical

intervention; serious hemorrhage was rare and was not increased in bevacizumab-treated patients.

An apparent increase (two v seven cases) in congestive heart failure and cardiomyopathy occurred in the bevacizumab-treatment arm, but the small number of events makes this association uncertain. All patients had prior anthracycline exposure, three of seven had received left chest wall radiation, and three had an LVEF less than 50% at study entry. In a previous phase II study, two of 75 breast cancer patients treated with bevacizumab monotherapy also developed congestive heart failure. Both had received prior anthracyclines and chest wall radiation; one had metastatic involvement of the pericardium.¹⁸ The association between the cardiac dysfunction, prior anthracycline exposure, and bevacizumab therapy is unclear.

The addition of bevacizumab to capecitabine clearly increased response rates, whether assessed by the IRF or the investigators, without significantly adding to the overall toxicity of the treatment regimen. Despite improvement in ORR, the duration of the responses was short with respect to PFS, and the proportion of long-term responders was similar in the two groups. The challenge now is to better understand how to exploit this activity. While it is possible that a negative interaction occurred between bevacizumab and capecitabine, the increased ORR and absence of augmented capecitabine toxicity makes this an unlikely explanation.

There are several possible explanations why the study did not meet its primary end point. This study used bevacizumab as a general therapy given on a population basis, rather than as a targeted therapy given to patients with a specific molecular phenotype. Methods to select those patients most likely to benefit from VEGF-directed therapies need to be developed. Analysis of primary tumor samples for pathologic factors correlating with response to bevacizumab is ongoing. Initial results were limited by the small number of patients contributing samples, and did not clearly identify a patient subset more likely to benefit from combined therapy.²⁹ Full results of correlative pathology studies will be reported separately.

The results of this study suggest that the optimal time to intervene with an antiangiogenic agent may be earlier in the course of disease. Angiogenic pathways become more numerous and redundant as breast cancer progresses.³⁰ Thus, it is unlikely that inhibition of a single factor or pathway would produce a sustained clinical effect in patients with previously treated, highly refractory disease. It is

also unlikely that advanced breast cancer is VEGF-independent, but increased expression of other angiogenic factors render VEGF less critical for continued tumor growth. As such, future trials should focus on patients with less advanced disease when fewer redundant angiogenic pathways exist. In a recently completed study, addition of bevacizumab to first-line chemotherapy (irinotecan, FU/leucovorin) in patients with metastatic colorectal cancer increased ORR, extended the duration of response, and prolonged PFS and overall survival.³¹ The increased ORR in our study and the results of the metastatic colorectal cancer trial further support the investigation of bevacizumab in patients with less refractory breast cancer. A phase III trial evaluating bevacizumab in combination with paclitaxel in chemo-naïve MBC patients (E2100) completed accrual in May 2004.

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