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Señor

**DIRECTOR DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

E.

S.

D.

REF: Expediente No. **12 -029.506-** solicitud de patente de invención a favor de **GENENTECH, INC.** Título: **TERAPIA ANTI-ANGIOGÉNESIS PARA EL TRATAMIENTO DE CÁNCER DE MAMA PREVIAMENTE TRATADO.**

RECURSO DE REPOSICIÓN

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad solicitante, manifiesto a usted que debidamente notificado de la Resolución No. 76533 del 16 de Diciembre de 2014, interpongo contra ella en debido término, **RECURSO DE REPOSICIÓN**, para que sea revocada en su totalidad, y en su lugar se conceda el Privilegio de Patente, para el objeto de la solicitud en referencia.

Respaldo el RECURSO en los siguientes

HECHOS

1. La resolución No. 76533 arriba citada niega el Privilegio exclusivo de Patente de Invención para el objeto de la solicitud de la referencia, considerando que el capítulo reivindicatorio carece de nivel inventivo. Lo anterior, de acuerdo con las siguientes consideraciones.

i. Determinación del Estado de la Técnica

Consultadas las fuentes de información con que se cuenta se encontraron los siguientes documentos, que anticipan el objeto de esta solicitud.

No	Documento	Título	Fecha de publicación
D2	O'Shaughnessy & Brufsky 2008	<i>"RiBBON 1 and RiBBON 2: Phase III Trial of Bevacizumab with Standard Chemotherapy for Metastatic Breast Cancer"</i>	Agosto/2008

Considera el examinador que la presente invención no cumple con el requisito de nivel inventivo en vista del documento D2.

RESUELVE

ARTÍCULO SEGUNDO: Denegar la patente de invención a la creación titulada **"TERAPIA ANTI-ANGIOGÉNESIS PARA EL TRATAMIENTO DE CÁNCER DE MAMA PREVIAMENTE TRATADO"**.

FUNDAMENTOS

Nos permitimos mostrar nuestro total desacuerdo frente a todas y cada una de las objeciones de la Resolución No. 76533 toda vez que en dicho análisis no se demostró de manera concluyente que la invención carecía de nivel inventivo. A continuación, me permito desvirtuar todas y cada una de las afirmaciones de su Despacho en contra del nivel inventivo de la invención y expuestas en la Resolución No. 76533.

En primera instancia, consideramos pertinente reiterar que de acuerdo con la reivindicación 1 del actual pliego reivindicatorio, la presente invención corresponde a un kit de partes farmacéutico que comprende los siguientes elementos:

- una composición de **anticuerpo anti-VEGF**; e
- instrucciones para utilizar la composición de anticuerpo anti-VEGF en combinación con **quimioterapia como terapia de segunda línea**.

Por tanto, es evidente que la presente invención hace referencia a un kit que representa una combinación de fármacos con aplicaciones puntuales sobre una condición de cáncer de mama metastásico triple negativo, tal y como se enuncia en el encabezado de dicha reivindicación.

De esta manera, la invención reivindicada da a conocer la combinación de un anticuerpo anti-VEGF y un agente quimioterapéutico de segunda línea frente a una condición patológica determinada, la cual ha demostrado ser **eficaz** y por tanto simboliza un **beneficio real y tangible** en el campo técnico, hecho que solicitamos sea reconocido pertinentemente por su Despacho.

A este respecto, vale la pena señalar que contrario a lo que afirma el señor Examinador, la expresión "*como terapia de segunda línea*" refiriéndose a una quimioterapia no alude al momento de administración del tratamiento sino al **tipo de quimioterapia** indicada.

En este sentido, es de notar que si bien la expresión "*quimioterapia*" hace referencia a un amplio grupo de compuestos con utilidad terapéutica definida, al indicar que esta corresponde a una "*terapia de segunda línea*" se restringe el espectro o alcance de dicha expresión pues **no todas las quimioterapias son reconocidas como terapias de segunda línea**.

Dicho de otro modo, los agentes quimioterapéuticos de segunda línea no necesariamente hacen referencia a tratamientos que no han sido exitosos en una primera ocasión, sino que definen una categoría de medicamentos que se consideran únicamente en tal instancia, hecho que evidentemente constituye una **limitación o restricción al alcance** de la invención pues **reduce** la cantidad de compuestos activos que podrían combinarse con el anticuerpo anti-VEGF de acuerdo con la presente invención.

Así pues, reiteramos que la expresión "*como terapia de segunda línea*" constituye una **limitación técnica** de la invención que en efecto restringe el alcance de la expresión "*quimioterapia*" de forma adecuada y comprensible para cualquier persona

normalmente versada en la materia, razón por la que consideramos que los comentarios del señor Examinador carecen de todo fundamento.

Asimismo, teniendo en cuenta que en conjunto la expresión “*quimioterapia como terapia de segunda línea*” representa un grupo puntual de agentes terapéuticos con una finalidad específica, solicitamos respetuosamente sea reconsiderada tal objeción.

Por otra parte, considera el señor Examinador que el desarrollo del kit de partes aquí reivindicado no encuentra sustento en las divulgaciones del capítulo descriptivo, apreciación con la cual nos encontramos nuevamente en desacuerdo pues el capítulo descriptivo que acompaña la presente solicitud divulga abiertamente que la combinación de un anticuerpo anti-VEGF y un agente quimioterapéutico de segunda línea tiene un efecto **sobresaliente y clínicamente importante** sobre el parámetro de supervivencia libre de progresión medido en individuos tratados que han sido diagnosticados con cáncer de mama triple negativo, aspecto que será expuesto en profundidad más adelante.

Con la única intención de demostrar que el capítulo descriptivo sí soporta de manera adecuada la materia reivindicada, reproducimos a continuación la Tabla 2 del citado documento, en donde se observa claramente que el ensayo clínico de la invención comprendió pacientes diagnosticados con cáncer de mama triple negativo:

Tabla 2 Características de los pacientes, Población ITT

	Quimio/PL (n=225)	Quimio/BV (n=459)
Edad, años		
Media	55,0	55,0
Media (rango)	55 (23-90)	55,6 (25-86)
≥65, %	19,6	22,0
ECOG PS 1, %	50,9	50,2
Nº de sitios metastásicos		
Media (rango)	2,5 (0-6)	2,5 (0-6)
≥ 3 sitios, %	47,1	44,5
Enfermedad solamente ósea, %	9,8	6,8

Enfermedad visceral, %	25,3	26,8
HR positivo, %	73,3	71,7
Triple negativo, %	20,9	24,4
Intervalo desde diagnóstico de MBC hasta primer PE ≥6 meses, %	70,7	72,5
HER2-negativo, %	85,3	83,9
-desconocido, %	13,8	14,6
Enfermedad medible, %	79,6	78,9

BV=bevacizumab, HR=receptor hormonal, PE=progreso de la enfermedad, PL=placebo.

En vista de la anterior evidencia, solicitamos respetuosamente sean reconsideradas las objeciones relacionadas con la supuesta falta de sustento de la presente invención, las cuales hemos demostrado carecen de total fundamento.

Ahora bien, centrándonos en el análisis de los requisitos de patentabilidad, es nuestra intención expresar que la novedad de la presente invención no se ve perjudicada por las divulgaciones del documento D2 dado que este no enseña en ningún momento un kit de partes farmacéutico destinado a una patología tan específica y puntual como lo es el **cáncer de mama metastásico triple negativo**, el cual es un tipo de cáncer de mama caracterizado porque las células tumorales no expresan los siguientes marcadores moleculares:

- (a) receptores de estrógenos (negativo para ER);
- (b) receptores de progesterona (negativo para PG); y
- (c) protooncogén HER2neu (negativo para HER2).

Debido a que el documento D2 guarda total silencio frente al desarrollo de un **kit** que comprenda un anticuerpo anti-VEGF en combinación con un agente quimioterapéutico orientado al **tratamiento de segunda línea** de pacientes diagnosticados con cáncer de mama metastásico triple negativo previamente tratado, afirmamos que este no constituye soporte documental a la objeción del señor Examinador y solicitamos, en consecuencia, esta sea reconsiderada.

Más allá de lo dicho, es oportuno mencionar que los cánceres de mama triple negativos constituyen un cuadro patológico mucho más agresivo en comparación con las demás variedades de cáncer de mama, lo cual se ve ratificado por la **alta tasa de recurrencia del cáncer y alta tasa de muertes** que padecen sus pacientes; circunstancia que ha sido ampliamente documentada y que por tanto, simboliza un campo de desafío para el desarrollo de nuevas y mejores alternativas terapéuticas, como la que propone la presente invención.

Tomando como referencia este contexto, nos permitimos mencionar que tal y como mencionamos anteriormente, la presente invención manifiesta un efecto **sobresaliente y clínicamente importante** sobre el parámetro de supervivencia libre de progresión medido en individuos tratados, hecho que ratifica sin lugar a dudas no sólo la novedad de la misma, sino su nivel inventivo.

Como muestra de lo dicho, reproducimos a continuación un fragmento del capítulo descriptivo en donde se define el parámetro de supervivencia libre de progresión (PFS) y se exponen los resultados alcanzados por la presente invención:

“En el estudio, PFS fue definida como el tiempo desde la aleatorización hasta el progreso de la enfermedad o la muerte según lo evaluado por los médicos intervinientes en el estudio (evaluado por el investigador). Los puntos de referencia secundarios incluyeron la tasa de respuesta objetiva, la duración de la respuesta, la tasa de supervivencia de un año, la supervivencia general, la evaluación de la PFS por tipo y seguridad de la quimioterapia. Los resultados indicaron una prolongación en la PFS, el criterio de valoración primario es una cohorte agrupada de pacientes que reciben avastin + quimioterapia (HR = 0,775; valor p (rango log) = 0,0072). La PFS promedio (95% CI) fue de 7,2 meses (6,5, 7,6) en el brazo de bevacizumab/quimioterapia (Brazo A de la Figura 1, n=459) contra 5,1 meses (4,1, 6,0) en el brazo de placebo/quimioterapia (Brazo B de la Figura 1 n=225). Ver la Tabla 3 Análisis Primario de Eficacia de PFS y Figura 2 (Criterio de valoración Primario de PFS) y Figura 3 (Análisis Específicos de Cohortes de PFS). Los resultados de PFS fueron generalmente consistentes a través de las cohortes de quimioterapia con la excepción del pequeño subgrupo

de vinorelbina. Otros subgrupos (edad, negativo triple, etc.) fueron en general consistentes con los resultados primarios de PFS.

Adaptado del capítulo descriptivo de la presente solicitud, página 94

Tal y como es posible apreciar, este fragmento reporta que la presente invención produjo una **prolongación del tiempo de supervivencia libre de progresión** determinada por la comparación de los resultados derivados del estudio de cohorte de pacientes que reciben Avastin + quimioterapia, en donde se observó lo siguiente:

- Los pacientes a quienes fue suministrado bevacizumab/quimioterapia presentaron PFS promedio de **7,2 meses**;
- Los pacientes a quienes fue suministrado placebo/quimioterapia presentaron PFS promedio de **5,1 meses**.

Con base en lo anterior, afirmamos que el kit reivindicado permite prolongar favorablemente el parámetro de supervivencia libre de progresión (PFS), lo cual además de constituir una clara **ventaja** de la invención, demuestra que la misma exhibe indicios adicionales de nivel inventivo dado dicho resultado sorprendente e inesperado.

En este contexto, nos permitimos aclarar que los resultados anteriormente expuestos no habrían podido ser previstos de ninguna manera pues, como es bien sabido en el campo técnico, la combinación de agentes para el tratamiento de cáncer suele categorizarse como una **terapia agresiva** que, aunque eficaz, podría causar deterioro de la condición inicial de los individuos tratados.

Del mismo modo, es oportuno agregar que la eficacia terapéutica de ambos agentes por separado no constituye garantía de que al ser empleados en combinación, como propone el kit de partes reivindicado, se alcance un efecto superior o al menos similar al inicial, hecho que es evidente para el versado en la materia y que sustenta además la patentabilidad de la presente invención.

Finalmente, como muestra definitiva del **aporte** que genera la presente invención al campo técnico, acudimos nuevamente al trabajo de Brufsky *et al.* (2012) –artículo anexo a este memorial–, el cual aborda el origen de la presente invención, tal y como resumimos enseguida:

“Un estudio en Fase III (RIBBON-2) de Avastin® (bevacizumab) en combinación con quimioterapia aumentó el tiempo de vida de mujeres con cáncer de mama HER-2 negativo metastásico cuya quimioterapia inicial había dejado de funcionar sin empeoramiento de la enfermedad (supervivencia libre de progreso o PFS), en comparación con la quimioterapia solamente. Los doctores que tratan a las mujeres en el estudio escogieron el tipo de quimioterapia empleada en combinación con Avastin y las quimioterapias fueron evaluadas en forma conjunta en el análisis primario de criterio de valoración. Los eventos adversos eran consistentes con aquellos previamente reportados para Avastin, y no se observó señal nueva de seguridad de Avastin alguna en el estudio.

RIBBON-2 fue un estudioclínico controlado con placebo, de doble ciego, aleatorizado, multicentral, internacional donde se inscribieron 684 pacientes con cáncer de mama HER-2-negativo metastásico quienes habían recibido previamente quimioterapia para su enfermedad metastásica.”

De esta manera, Brufsky *et al.* (2012) relata la ejecución del ensayo clínico RIBBON-2 practicado para un subgrupo triple negativo de la condición patológica cáncer de mama metastásico, en el cual se evidencia que cuando los resultados de dicho subgrupo se comparan con el resto de grupos de pacientes, los efectos del tratamiento son sustancialmente superiores en términos de la mediana de los valores PFS y ORR, como evidencia la Tabla 2 de dicho documento, la cual se incluye a continuación:

Table 2 Summary of efficacy

Characteristic	TNBC population		Overall population	
	Bevacizumab + chemotherapy (N = 112)	Placebo + chemotherapy (N = 47)	Bevacizumab + chemotherapy (N = 459)	Placebo + chemotherapy (N = 225)
Progression-free survival				
Events, N (%)	94 (84)	42 (89)	372 (81)	184 (82)
Median, months	6.0	2.7	7.2	5.1
HR* (95% CI)	0.494 (0.33–0.74)		0.78 (0.64–0.93)	
P value (log-rank)	0.0006		0.0072	
Overall survival (OS)				
Events, N (%)	52 (46)	29 (62)	206 (45)	109 (48)
Median, months	17.9	12.6	18.0	16.4
HR* (95% CI)	0.624 (0.39–1.007)		0.90 (0.71–1.14)	
P value (log-rank)	0.0534 ^b		0.3741 ^b	
1-year OS rate, % (95% CI)	63 (52–72)	50 (34–64)	70 (65–74)	66 (59–72)
Difference in rates, % (95% CI)	13 (–6 to 31)		3.3 (–5 to 11)	
P value*	0.1758 ^b		0.426	
Objective response				
Objective response rate, % (95% CI)	41 (31–51)	18 (8–34)	40 (34–45)	30 (23–37)
Difference, % (95% CI)	23 (7–39)		10 (2–18)	
P value*	0.0078		0.0193 ^b	

CI confidence interval, HR hazard ratio, TNBC triple-negative breast cancer

* Stratified analysis (chemotherapy regimen and disease-free interval)

^b Not significant

Tales resultados ratifican que, contrario a la insistente posición del señor Examinador, existe un marcado **efecto sinérgico** entre la quimioterapia y el anticuerpo bevacizumab al ser empleados como tratamiento del subgrupo triple negativo, y de esta manera, dicha combinación propicia una mejora sustancial y apreciable de la sobrevida de los pacientes diagnosticados con dicha condición.

Consecuentemente, dado que el documento D2 citado por su Despacho es completamente ajeno al alcance de la presente invención, resulta imposible atribuirle obviaidad alguna a la misma ya que este no sugiere, motiva ni contempla de manera alguna el desarrollo del kit que aquí se reivindica, y mucho menos el **efecto superior e inesperado** suscitado por la aplicación del mismo sobre tal población.

Dicho esto, solicitamos respetuosamente se reconozca en esta instancia la plena patentabilidad de la presente invención dado el cabal cumplimiento de los requisitos de novedad y nivel inventivo por su parte, además de la existencia de un claro **beneficio** asociado con un **efecto superior inesperado** que, como tal, constituye un indicio adicional de nivel inventivo.

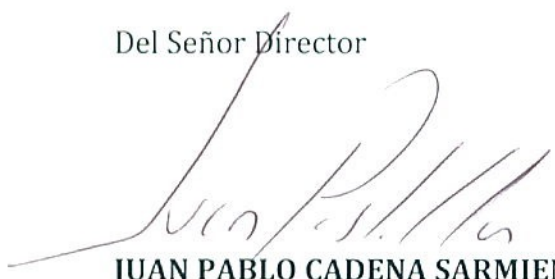
PETICIÓN

Por las razones anteriormente expuestas, solicito a ese despacho **REVOCAR** la decisión tomada mediante la Resolución No. 76533 del 16 de Diciembre de 2014 y tendiente a obtener la concesión del Privilegio de Patente de conformidad con los artículos 14 y 48 de la Decisión 486 de la comunidad Andina.

NOTIFICACIONES

Recibiré notificaciones en la Secretaría General de la Superintendencia de Industria y Comercio, o en su defecto, en mi oficina de Abogado, situada en la Calle 70ª No. 4-41 de esta ciudad de Bogotá.

Del Señor Director



JUAN PABLO CADENA SARMIENTO

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CLINICAL TRIAL

Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial

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Abstract Patients with metastatic triple-negative breast cancer (TNBC) typically have a poor prognosis and limited treatment options. To determine the impact of combining bevacizumab with second-line chemotherapy in patients with metastatic TNBC, we performed an exploratory subgroup analysis of the randomized phase 3 RIBBON-2 trial. RIBBON-2 enrolled patients with metastatic breast cancer that had progressed on first-line non-bevacizumab-containing chemotherapy. After selection of chemotherapy (taxane, gemcitabine, capecitabine, or vinorelbine), patients were randomized 2:1 to receive chemotherapy with either bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) or placebo. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), and safety. Of 684 patients treated in RIBBON-2, 159 (23%) had TNBC. Baseline characteristics were reasonably balanced in the two

treatment groups. The majority received taxane chemotherapy. The hazard ratio (HR) for PFS was 0.494 [95% confidence interval (CI) 0.33–0.74; $P = 0.0006$]. Median PFS was 6.0 months with bevacizumab–chemotherapy versus 2.7 months with chemotherapy alone. Median OS was 17.9 versus 12.6 months, respectively (HR 0.624, 95% CI 0.39–1.007; $P = 0.0534$). ORR was 41 versus 18%, respectively ($P = 0.0078$). The safety profile was consistent with the overall study population and previous phase 3 trials of bevacizumab. Patients with metastatic TNBC derived significant PFS and response benefits from the combination of bevacizumab with second-line chemotherapy. Despite the small sample size and immature data, there was a trend toward improved OS.

Keywords Angiogenesis · Bevacizumab · Metastatic breast cancer · Second-line chemotherapy · Triple-negative breast cancer · Vascular endothelial growth factor

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2

Introduction

In the past decade, triple-negative breast cancer (TNBC) has attracted attention as a particularly challenging situation in metastatic breast cancer (MBC) due to patients' poor prognosis and limited treatment options [1, 2]. TNBC is a heterogeneous subgroup defined by a lack of human epidermal growth factor receptor 2 (HER2) overexpression or amplification and low estrogen receptor (ER) and progesterone receptor (PgR) expression [1, 3]. There is no standard treatment for patients with TNBC, and prospective randomized data in this setting are limited. Platinum-based regimens are often selected but no randomized data indicate significant efficacy in TNBC [1]. Results of a randomized phase 2 trial in 123 patients with TNBC suggested that combining the investigational agent iniparib with gemcitabine–carboplatin significantly improved efficacy versus chemotherapy alone [4]. However, this effect was not observed in the subsequent randomized phase 3 trial ($N = 519$) with a similar design [5]. Neither progression-free survival (PFS) nor overall survival (OS)—the co-primary endpoints—was significantly improved with the addition of iniparib to gemcitabine–carboplatin.

Taxane therapy is frequently used in TNBC and appears active in this disease subtype, demonstrating median PFS of approximately 5 months as first-line therapy for metastatic TNBC [6]. Combining bevacizumab with a taxane or other standard chemotherapy significantly improved PFS (the primary endpoint) in three randomized phase 3 trials in the first-line setting (E2100, AVADO, RIBBON-1) [7–9] and a fourth phase 3 trial in the second-line setting (RIBBON-2) [10]. Subpopulation analyses have failed to identify any subset of patients deriving a particularly large or small benefit from bevacizumab-containing therapy. Furthermore, extensive translational research has not yet identified a biomarker enabling selection of patients gaining the most substantial effect from bevacizumab.

The rationale for the use of bevacizumab in this setting includes high levels of vascular endothelial growth factor (VEGF), enhanced angiogenesis supporting rapid growth and early metastases [11], and the prognostic role of VEGF receptor 2 [12] in TNBC. In subgroups of patients with TNBC treated in the first-line setting, the hazard ratio (HR) for PFS ranged from 0.49 in E2100 (median 10.6 months with bevacizumab–paclitaxel vs. 5.3 months with paclitaxel alone) to 0.78 in the taxane/anthracycline cohort of RIBBON-1 [6]. In the ATHENA study, median time to progression was 7.2 months and median OS was 18.3 months among 585 patients receiving first-line bevacizumab-containing therapy for TNBC [13].

To gain insight into the effect of second-line bevacizumab in patients with TNBC, we performed an exploratory analysis of data from the subpopulation of

patients with TNBC treated in the RIBBON-2 trial. We believe that the lack of progress and limited treatment options for this patient population justify exploratory analyses, particularly when supported by consistent results from pre-specified planned analyses in very similar populations.

Patients and methods

Patients

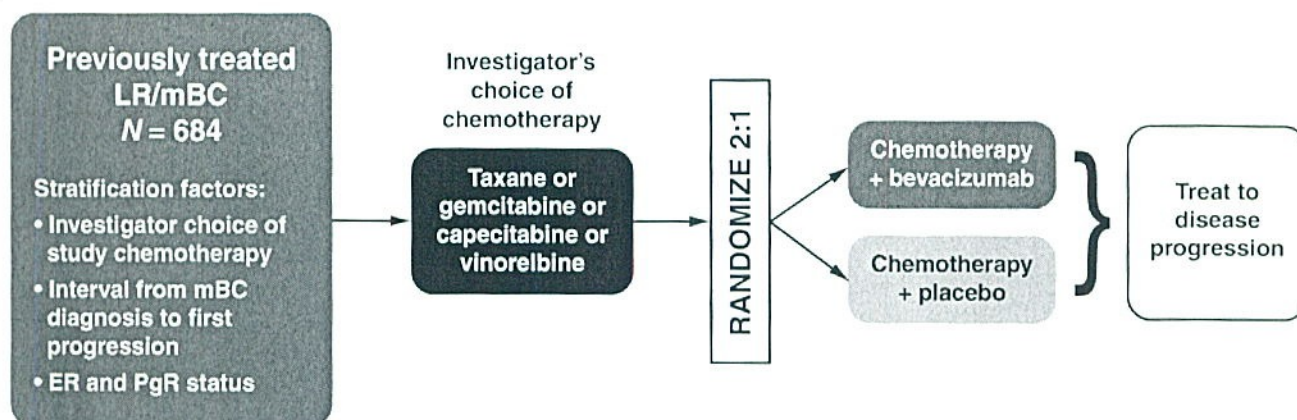
Eligible patients had histologically confirmed MBC that had progressed on previous non-bevacizumab-containing first-line chemotherapy. The design of the RIBBON-2 trial has been described in detail previously and is summarized in Fig. 1 [10]. RIBBON-2 was conducted in accordance with US Food and Drug Administration Good Clinical Practice, International Conference on Harmonisation E6 Guideline for Good Clinical Practice, and national and local ethical and legal requirements. All patients provided written informed consent before study-specific screening.

Randomization and masking

After selection of chemotherapy from a pre-specified list (taxane, capecitabine, gemcitabine, or vinorelbine), patients were stratified according to study chemotherapy choice, interval from MBC diagnosis to first progression, and ER and PgR status (both negative vs. other). ER and PgR status was defined by the investigator, with no pre-defined cut-off, reflecting clinical practice at each participating center. Patients were then randomized 2:1 to receive either bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks, depending on the selected chemotherapy regimen) or placebo with their chemotherapy. Patients and clinicians were masked to treatment assignment. Treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal. All patients were allowed to receive bevacizumab after progression on study therapy.

Statistics

This analysis of patients with TNBC was exploratory. An exploratory P value is provided for each result. The sensitivity analysis in patients with ER- and PgR-negative disease (a stratification factor) was pre-specified in the statistical analysis plan. The data included in this analysis are from the protocol-specified primary data cut-off for PFS and interim OS. As defined in the protocol, the final OS analysis will be performed after 557 events have occurred in the entire study population (anticipated in spring 2012).



Taxane (paclitaxel 90 mg/m² d1, 8, 15 q4w or paclitaxel 175 mg/m², nab-paclitaxel 260 mg/m² or docetaxel 75–100 mg/m² q3w)
 Gemcitabine (1,250 mg/m² d1, 8 q3w)
 Capecitabine (1,000 mg/m² bid d1–14 q3w)
 Vinorelbine (30 mg/m² d1, 8, 15 q3w)
 Bevacizumab or placebo (15 mg/kg q3w or 10 mg/kg q2w, depending on chemotherapy regimen)

Fig. 1 Study design of RIBBON-2. *ER* estrogen receptor, *LR* locally recurrent, *mBC* metastatic breast cancer, *nab* nanoparticle albumin-bound, *PgR* progesterone receptor

Results

Patient population

The overall population of patients from RIBBON-2 included 459 patients receiving bevacizumab-containing therapy and 225 receiving chemotherapy with placebo (Fig. 2), recruited between February 2006 and June 2008. Of these, 112 (24%) and 47 (21%), respectively, had TNBC.

Baseline characteristics are shown in Table 1. The bevacizumab and placebo arms in the TNBC subgroup were generally reasonably well balanced, although a larger proportion of patients in the bevacizumab arm than the placebo arm were post-menopausal at diagnosis and/or had at least three organs with metastatic disease. Patients in the TNBC subgroup generally had a shorter time to first progression than those in the overall study population.

Efficacy

At the time of data cut-off, PFS events had occurred in 84% of patients with TNBC receiving bevacizumab and in 89% of those receiving placebo. PFS—the primary endpoint of the trial—was significantly longer with bevacizumab-containing therapy than with chemotherapy alone [HR 0.494 (95% CI 0.33–0.74); $P = 0.0006$] in this subgroup analysis. Median PFS was 6.0 months in the bevacizumab arm versus 2.7 months in the placebo arm (Fig. 3). The overall response rate was also significantly higher with bevacizumab than with placebo (41 vs. 18%, respectively; $P = 0.0078$ for the 23% difference between arms). Table 2 summarizes efficacy

by treatment arm in the TNBC subgroup and overall population.

At the time of this analysis, 52 patients (46%) had died in the bevacizumab arm versus 29 (62%) in the placebo arm. The most common cause of death was disease progression (43 vs. 55%, respectively). The HR for OS was 0.624 (95% CI 0.39–1.007; $P = 0.0534$) (Fig. 4). The median OS was 17.9 versus 12.6 months for bevacizumab versus placebo, respectively. Subgroup analyses of PFS and OS by age, body weight, and race did not reveal any subgroup with a particularly large or small benefit, although patient numbers in each subgroup were very small and limit interpretation.

While the present analysis in TNBC was exploratory, subgroup analyses according to stratification factors were pre-specified in the statistical analysis plan. As patients with known HER2-positive status were ineligible for the trial, the TNBC population was broadly similar to the ER- and PgR-negative population. However, 31 patients from the ER- and PgR-negative population were excluded from the TNBC analyses because their HER2 status was unknown (16 patients in the bevacizumab arm and 11 in the placebo arm) or positive (two patients in each arm). Inclusion of these patients in the RIBBON-2 trial was due in part to a protocol amendment changing the definition of HER2 status from fluorescence in situ hybridization (FISH) positive or immunohistochemistry (IHC) 3+ to FISH positive or IHC 2+ or 3+ if FISH was unavailable.

The analysis of patients with ER- and PgR-negative disease, irrespective of HER2 status, included 130 patients receiving bevacizumab and 60 receiving placebo. The HR

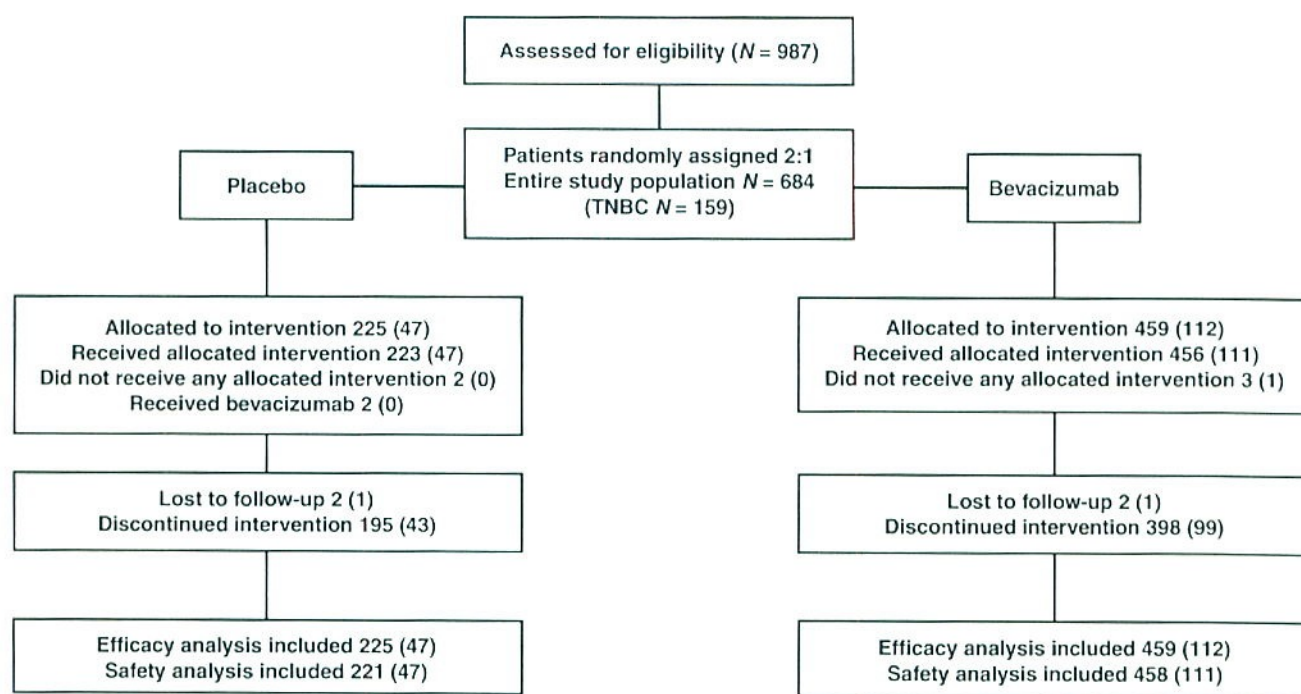


Fig. 2 Trial profile showing the entire study population (TNBC subgroup data shown in *parentheses*). *TNBC* triple-negative breast cancer

for PFS (stratified analysis) was 0.525 (95% CI 0.368–0.750; $P = 0.0004$). Median PFS was 6.5 months with bevacizumab versus 2.8 months with placebo—similar to the values observed in the TNBC analysis. Analysis of OS demonstrated a HR of 0.629 (95% CI 0.409–0.967; $P = 0.0351$). Median OS was 17.9 versus 11.2 months for bevacizumab versus placebo, respectively.

In the subgroup of 67 patients with TNBC who received taxane chemotherapy, the HR for PFS was 0.458 (95% CI 0.25–0.85). Median PFS was 7.2 months in the bevacizumab arm ($N = 47$) versus 3.0 months in the placebo arm ($N = 20$). The HR for OS was 0.549 (95% CI 0.24–1.26); median OS was 19.9 versus 12.6 months for bevacizumab versus placebo, respectively.

Safety

Collection of safety data in RIBBON-2 focused on typical bevacizumab adverse events observed in previous clinical trials and adverse events leading to study drug discontinuation. This approach was adopted because of the extensive safety data available from four earlier randomized phase 3 trials of bevacizumab in MBC [7–9, 14]. The safety profile in the TNBC subgroup was almost identical to that reported in the overall study population, except for the absence of grade ≥ 3 bleeding in the TNBC subgroup (Table 3).

There were two treatment-related deaths in each arm [2% in the bevacizumab arm (one case each of pneumonia

and altered state of consciousness) versus 4% in the placebo arm (one patient with tachycardia and metabolic acidosis; one sudden death)]. The three remaining deaths not attributable to disease progression were from multiple organ failure ($N = 1$) and neutropenic sepsis ($N = 1$) in the bevacizumab arm and intracranial hemorrhage ($N = 1$) in the placebo arm.

Discussion

Results of this exploratory analysis of 159 patients with TNBC demonstrate significantly improved PFS, higher overall response rate, and a trend toward longer OS for bevacizumab versus placebo, despite immature data. Subgroup data for OS were not reported in the primary paper and are a new and interesting finding in the present analysis. The findings from this exploratory analysis are supported by consistent results from the pre-specified subgroup analysis of patients with ER- and PgR-negative disease (irrespective of HER2 status), which demonstrated significantly improved PFS, overall response rate, and OS with the addition of bevacizumab to chemotherapy.

The likelihood of showing a substantial effect on OS is greater in the second-line setting than in the first-line setting. It is also greater in patients with TNBC than in general populations because of the poorer prognosis and, in general, the smaller number of lines of therapy possible.

Table 1 Summary of baseline characteristics

Characteristics	TNBC population		Overall population	
	Bevacizumab + chemotherapy (<i>N</i> = 112)	Placebo + chemotherapy (<i>N</i> = 47)	Bevacizumab + chemotherapy (<i>N</i> = 459)	Placebo + chemotherapy (<i>N</i> = 225)
Age (years)	55 (28–86)	49 (33–79)	55 (25–86)	55 (23–90)
Median (range)				
18–40, <i>N</i> (%)	10 (9)	6 (13)	39 (9)	20 (9)
41–64, <i>N</i> (%)	79 (71)	32 (68)	319 (70)	161 (72)
≥65, <i>N</i> (%)	23 (21)	9 (19)	101 (22)	44 (20)
Menopausal status at diagnosis, <i>N</i> (%) ^a				
Pre-menopausal	28 (25)	21 (45)	137 (30)	76 (34)
Peri-menopausal	5 (4)	3 (6)	28 (6)	17 (8)
Post-menopausal	73 (65)	23 (49)	276 (60)	127 (56)
Unknown	6 (5)	0	18 (4)	5 (2)
Race, <i>N</i> (%)				
White	77 (69)	31 (66)	360 (78)	175 (78)
Asian or Pacific Islander	15 (13)	8 (17)	55 (12)	29 (13)
Black	15 (13)	4 (9)	29 (6)	14 (6)
Hispanic	2 (2)	1 (2)	12 (3)	2 (1)
Other	3 (3)	3 (6)	3 (1)	5 (2)
ECOG PS, <i>N</i> (%) ^b				
0	47 (42)	26 (55)	228 (50)	110 (49)
1	64 (57)	21 (45)	230 (50)	114 (51)
Measurable disease at baseline, <i>N</i> (%)	100 (89)	39 (83)	362 (79)	179 (80)
Time to first progression				
Median, months	7.7	6.8	11.6	12.0
<6 months, <i>N</i> (%)	37 (33)	18 (38)	126 (27)	66 (29)
Metastatic sites, <i>N</i> (%)				
≥3 ^c	58 (48)	15 (32)	204 (44)	106 (47)
Visceral	83 (74)	29 (62)	341 (74)	159 (71)
Receptor status, <i>N</i> (%)				
ER and/or PgR positive	0	0	329 (72)	165 (73)
HER2 negative	112 (100)	47 (100)	385 (84)	192 (85)
HER2 status unknown	0	0	67 (15)	31 (14)
TNBC	112 (100)	47 (100)	112 (24)	47 (21)
Chemotherapy partner in RIBBON-2, <i>N</i> (%)				
Taxane	47 (42)	20 (43)	201 (44)	103 (46)
Gemcitabine	26 (23)	13 (28)	108 (24)	52 (23)
Capecitabine	18 (16)	10 (21)	97 (21)	47 (21)
Vinorelbine	21 (19)	4 (9)	53 (12)	23 (10)

ECOG PS Eastern Cooperative Oncology Group performance status, ER estrogen receptor, HER2 human epidermal growth factor receptor 2, PgR progesterone receptor, TNBC triple-negative breast cancer

^a Chi-squared *P* = 0.0358 for the difference between treatment arms in the TNBC subgroup

^b Missing in one patient in the bevacizumab arm

^c Chi-squared *P* = 0.0585 for the difference between treatment arms (<3 vs. ≥3 metastatic sites) in the TNBC subgroup

Clinically, the relevance of improved OS is arguably greater in TNBC, as these patients are notoriously difficult to treat and have poor clinical outcomes and limited

treatment options. Therefore, the median OS of almost 18 months in this analysis of the RIBBON-2 trial, conducted exclusively in the second-line setting, represents a

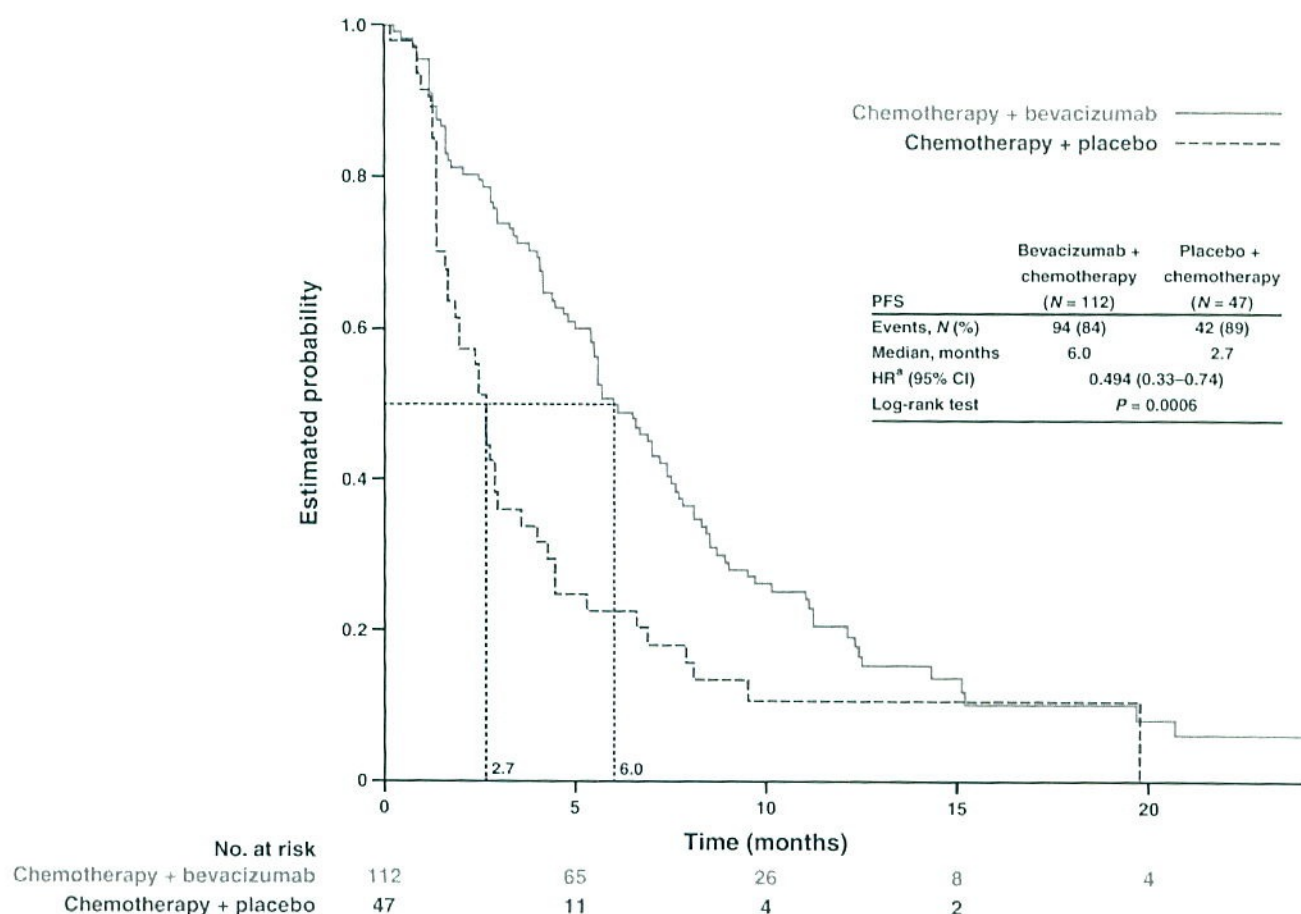


Fig. 3 Progression-free survival: triple-negative breast cancer subgroup. ^aStratified analysis (chemotherapy regimen, interval from locally recurrent/metastatic breast cancer diagnosis to first progression). HR hazard ratio, PFS progression-free survival

meaningful clinical achievement, especially when compared with median OS of less than 1 year with gemcitabine–carboplatin plus iniparib. Nevertheless, such cross-trial comparisons must be treated with caution because of differences between populations, definitions of TNBC, and tumor assessment schedules. The median PFS of 6.0 months in the present analysis is also encouraging and, within the limitations of cross-trial comparison, compares favorably with previously reported data in TNBC in the first-line or later settings (median PFS of approximately 4 months with cetuximab–cisplatin [15]; EndoTAGTM-1 [16]; ixabepilone–capecitabine [17]; and capecitabine alone [6]).

A major weakness of the TNBC trials described above, including the present subgroup analysis, is the heterogeneity of TNBC populations. Defining TNBC by a lack of particular characteristics (HER2-, ER-, and PgR-positive status), rather than the presence of clinical or molecular features, results in an artificial and often heterogeneous population of patients. TNBC broadly overlaps with basal-like breast

cancer but the terms are not synonymous [18]. Only approximately 10% of TNBC cases have *BRCA* mutations, whereas more than half of *BRCA* mutation-positive breast cancers are triple negative. This heterogeneity has been suggested as a possible explanation for the failure of the iniparib phase 3 trial, in which approximately one-quarter of patients had basal-like breast cancer, one-quarter had normal-like breast cancer, and one-fifth had luminal B subtype [5]. To further complicate subtyping of TNBC, our understanding of the biology of breast cancer continues to evolve, exemplified by the relatively recent identification of a new subtype—claudin-low breast cancer [19]. The study period for the RIBBON-2 trial pre-dated widespread molecular subtyping of breast cancer. However, careful selection of patients based on these biological differences is essential for future trials of new agents in TNBC if progress is to be made in this field.

Another limitation is the exploratory nature of the present analysis, an issue that is also relevant to several of the other TNBC data sets reported in the literature. In the

Table 2 Summary of efficacy

Characteristic	TNBC population		Overall population	
	Bevacizumab + chemotherapy (<i>N</i> = 112)	Placebo + chemotherapy (<i>N</i> = 47)	Bevacizumab + chemotherapy (<i>N</i> = 459)	Placebo + chemotherapy (<i>N</i> = 225)
Progression-free survival				
Events, <i>N</i> (%)	94 (84)	42 (89)	372 (81)	184 (82)
Median, months	6.0	2.7	7.2	5.1
HR ^a (95% CI)	0.494 (0.33–0.74)		0.78 (0.64–0.93)	
<i>P</i> value (log-rank)	0.0006		0.0072	
Overall survival (OS)				
Events, <i>N</i> (%)	52 (46)	29 (62)	206 (45)	109 (48)
Median, months	17.9	12.6	18.0	16.4
HR ^a (95% CI)	0.624 (0.39–1.007)		0.90 (0.71–1.14)	
<i>P</i> value (log-rank)	0.0534 ^b		0.3741 ^b	
1-year OS rate, % (95% CI)	63 (52–72)	50 (34–64)	70 (65–74)	66 (59–72)
Difference in rates, % (95% CI)	13 (–6 to 31)		3.3 (–5 to 11)	
<i>P</i> value ^a	0.1758 ^b		0.426	
Objective response				
Objective response rate, % (95% CI)	41 (31–51)	18 (8–34)	40 (34–45)	30 (23–37)
Difference, % (95% CI)	23 (7–39)		10 (2–18)	
<i>P</i> value ^a	0.0078		0.0193 ^b	

CI confidence interval, HR hazard ratio, TNBC triple-negative breast cancer

^a Stratified analysis (chemotherapy regimen and disease-free interval)

^b Not significant

present analysis, this resulted in some imbalances in baseline characteristics between the treatment arms. While these imbalances limit conclusions that can be drawn from the analysis, the consistent and supportive findings from the planned subgroup analysis of patients with ER- and PgR-negative disease strengthen the findings from the TNBC analysis. There is a strong rationale to try to understand the efficacy of agents in TNBC because of the high unmet clinical need for better treatment for these patients. The apparently greater benefit in the TNBC subset of the present trial raises the intriguing hypothesis that it is the effect of bevacizumab in TNBC that drives the overall impact in the full study population. In the 498 patients with non-TNBC (i.e., positive status for at least one of ER or PgR and/or HER2), the HR for PFS was 0.89 (95% CI 0.71–1.10; median 7.4 months with bevacizumab-containing therapy vs. 6.0 months with non-bevacizumab-containing therapy). The remaining 27 patients had unknown status for at least one receptor; the HR for PFS in this small subgroup was 0.65 (95% CI 0.22–1.87). None of the other subgroups analyzed in the overall population, defined according to clinical characteristics and disease and treatment history, showed such a

pronounced benefit for bevacizumab, although almost all favored bevacizumab.

No prospective trial has been conducted to evaluate bevacizumab specifically in patients with metastatic TNBC or in a specific molecular subtype. However, the findings from our analysis support the use of bevacizumab in patients with metastatic TNBC, who continue to have few treatment options. Bevacizumab has been evaluated prospectively in TNBC in the adjuvant BEATRICE trial (NCT00528567), in which patients with early TNBC were randomized to standard adjuvant chemotherapy either alone or in combination with bevacizumab, with bevacizumab continued as a single agent for a total bevacizumab treatment duration of 1 year. Results are anticipated in the near future and will provide the first randomized data for bevacizumab specifically in TNBC, as well as the first randomized data for adjuvant bevacizumab therapy for breast cancer.

In conclusion, data from this analysis suggest that chemotherapy in combination with anti-VEGF therapy has the potential to be an important second-line treatment option, demonstrating substantial activity in patients with TNBC who have not received first-line bevacizumab.

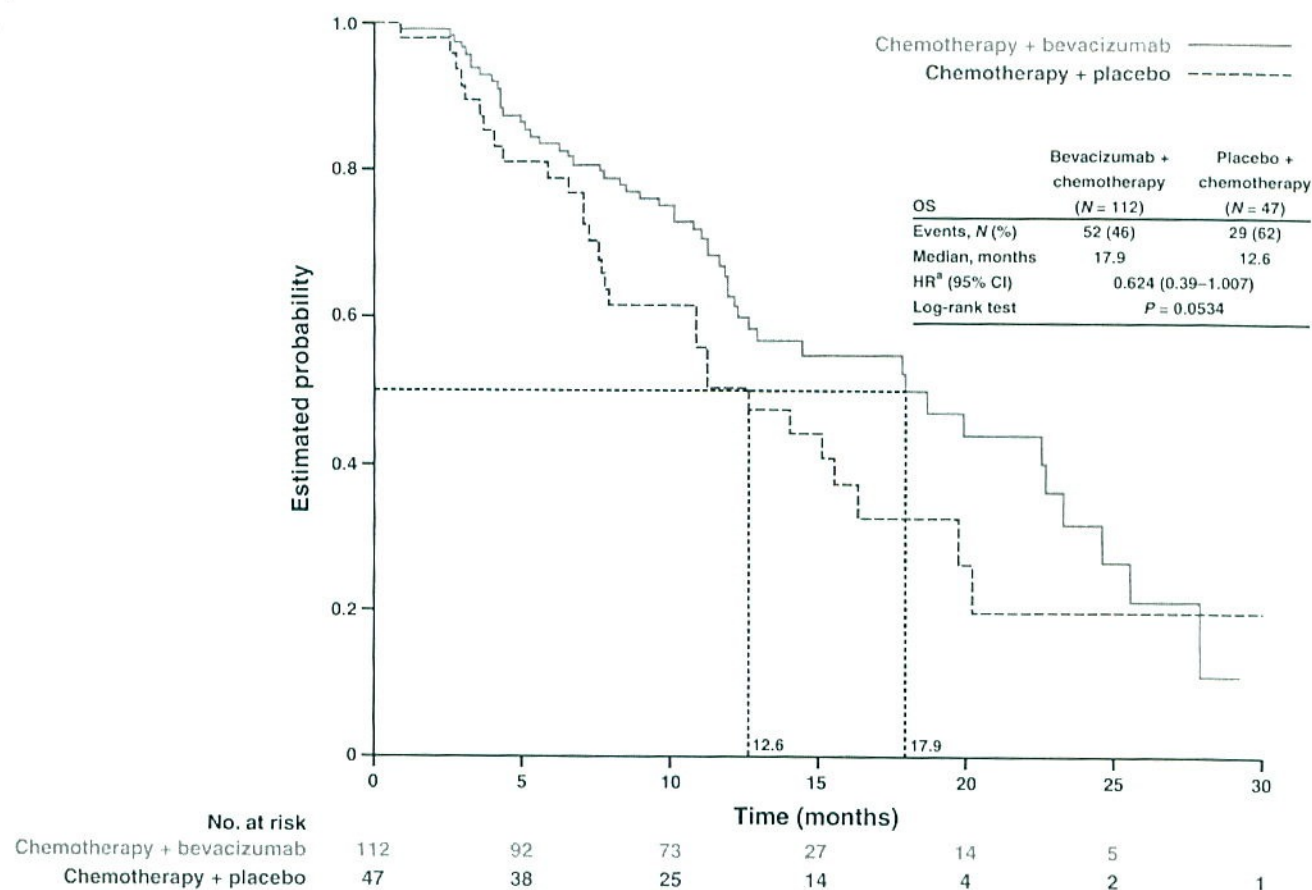


Fig. 4 Overall survival: triple-negative breast cancer subgroup. ^aStratified analysis (chemotherapy regimen, interval from locally recurrent/metastatic breast cancer diagnosis to first progression). *HR* hazard ratio, *OS* overall survival

Table 3 Summary of adverse events of special interest: TNBC subgroup

Adverse events of special interest, N (%)	TNBC population				Overall population	
	Bevacizumab + chemotherapy (N = 112)		Placebo + chemotherapy (N = 47)		Bevacizumab + chemotherapy (N = 459)	Placebo + chemotherapy (N = 225)
	All grades	Grade 3–5	All grades	Grade 3–5	Grade 3–5	Grade 3–5
Neutropenia	22 (19.6)	21 (18.8)	5 (10.6)	5 (10.6)	80 (17.4)	33 (14.7)
Febrile neutropenia	1 (0.9)	1 (0.9)	0	0	9 (2.0)	7 (3.1)
Hypertension	14 (12.5)	12 (10.7)	2 (4.3)	0	41 (8.9)	1 (0.4)
Proteinuria	6 (5.4)	6 (5.4)	1 (2.1)	0	15 (3.3)	1 (0.4)
Wound-healing complications	2 (1.8)	2 (1.8)	0	0	3 (0.7)	0
Bleeding	1 (0.9)	0	0	0	8 (1.7)	1 (0.4)
Thromboembolic events	5 (4.5)	3 (2.7)	2 (4.3)	2 (4.3)	15 (3.3)	7 (3.1)
CHF	1 (0.9)	1 (0.9)	0	0	4 (0.9)	2 (0.9)
Cardiac disorders (excluding CHF and ATEs)	1 (0.9)	1 (0.9)	2 (4.3)	2 (4.3)	2 (0.4)	4 (1.8)

ATE arterial thromboembolic event, CHF congestive heart failure, TNBC triple-negative breast cancer

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Conflict of interest A. Brufsky has a Consultant/advisory role with Genentech. V. Valero has received research funding and honoraria from Genentech/Roche. H.S. Rugo's institution has received research funding from Genentech/Roche and Lilly/Imclone. A. Duenne is an employee of F. Hoffmann-La Roche Ltd. N. Bousfoul was formerly a contractor for F. Hoffmann-La Roche Ltd. The other authors have no conflict of interest to declare.

Ethical standards RIBBON-2 was conducted in accordance with US Food and Drug Administration Good Clinical Practice, International Conference on Harmonisation E6 Guideline for Good Clinical Practice, and national and local ethical and legal requirements. All patients provided written informed consent before study-specific screening.

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