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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: **COMPOSICIÓN DE ANTICUERPO ANTI-VEGF EN COMBINACIÓN CON QUIMIOTERAPIA PARA EL TRATAMIENTO DE CANCER DE MAMA PREVIAMENTE TRATADO.**

RESPUESTA A EXAMEN DE FONDO

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad solicitante me permito dar respuesta al Oficio No. 5486 relacionado con la patentabilidad de la presente invención y notificado por fijación en lista el 13 de Mayo de 2014.

De manera atenta nos permitimos remitir a su Despacho un nuevo pliego reivindicatorio que consta de tres (3) reivindicaciones, las cuales mantienen pleno sustento en las divulgaciones del capítulo descriptivo y no exceden en ningún momento el alcance de la invención previamente reclamada.

Con relación a dicho nuevo pliego reivindicatorio, es nuestra intención destacar que el mismo fue objeto de modificaciones realizadas con el fin de superar todas y cada una de las objeciones emitidas por el señor Examinador en contra de su patentabilidad, y en base a lo cual solicitamos respetuosamente las mismas sean retiradas.

Como primera medida, para contextualizar el análisis que prosigue, consideramos oportuno presentar aquí la nueva reivindicación 1, la cual fue adecuada siguiendo las sugerencias manifestadas en el Oficio técnico:

"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 como terapia de segunda línea"

Tal y como es posible apreciar, las siguientes modificaciones fueron llevadas a cabo:

- Se eliminó 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"*, evitando de este modo hacer referencia a posibles resultados a alcanzar.
- Se incluyó la expresión *"como terapia de segunda línea"* en referencia al tipo de kit al cual hace referencia la presente invención, el cual difiere de las terapias de primera línea descritas en el estado de la técnica, aspecto que será comentado a profundidad más adelante.

Sin embargo, más allá de las anteriores modificaciones, consideramos pertinente mencionar que la expresión *"en un paciente humano diagnosticado con cáncer de mama triple negativo"* no corresponde en ningún momento a una "característica de elegibilidad de los pacientes del método de tratamiento" sino a una **limitación técnica** de la presente invención, la cual permite definir de manera concreta el **alcance** de la misma.

En este sentido, es de notar que la presente invención hace referencia a un kit que representa una combinación de fármacos orientados a un propósito particular, el cual se relaciona con la **eficacia** de tal combinación frente a una condición patológica determinada; es decir, con el hecho de que el kit reivindicado representa un **beneficio**

real y tangible que puede ser determinado mediante la supervivencia libre de progresión de los individuos diagnosticados con cáncer de mama triple negativo.

Así pues, afirmamos que la expresión "*en un paciente humano diagnosticado con cáncer de mama triple negativo*" no hace referencia a otra cosa distinta que a la población para cuya eficacia de la aplicación de la presente invención ha sido demostrada, lo cual constituye entonces una **limitación o restricción técnica** del **alcance** de la presente invención, y no a alguna "característica de elegibilidad" como afirma el señor Examinador.

Como sustento de lo anterior, anexamos al presente memorial el artículo científico de Brufsky *et al.* (2012), el cual proporciona evidencia documental sobre la eficacia y beneficio del kit de la presente invención asociados con su uso en la población de pacientes humanos diagnosticados con cáncer de mama triple negativo, tal y como se reivindica aquí.

De acuerdo con esto, solicitamos respetuosamente sean retiradas las objeciones que perjudican la claridad de la nueva reivindicación 1, la cual en vista de las modificaciones y argumentos previamente comentados, constituye una divulgación totalmente válida del objeto y alcance de la presente invención.

En cuanto a la reivindicación 2, nos permitimos destacar que tal y como sugirió el señor Examinador, (i) el preámbulo de la misma fue corregido y (ii) las secuencias de aminoácidos fueron explícitamente removidas permaneciendo únicamente la referencia a las SEQ ID NO. 1 y 2; a partir de lo cual se considera superado el inconveniente de claridad previamente denotado.

Ahora bien, encontramos que el señor Examinador levanta una objeción por unidad de invención porque en su concepto, la descripción de la presente solicitud da a conocer cuatro grupos quimioterapéuticos diferentes que originarían, a partir de la combinación de cada uno de ellos con bevacizumab, cuatro posibles grupos inventivos.

Frente a ello, es pertinente mencionar que el alcance de la presente invención se encuentra definido única y exclusivamente por la materia reivindicada, es decir, por la materia que hace parte explícita de las reivindicaciones y que define de manera puntual las características técnicas y limitaciones de la presente invención.

En este orden de ideas, nos permitimos recordar que a lo largo del pliego reivindicatorio no se hace referencia a los cuatro grupos de agentes quimioterapéuticos que menciona el señor Examinador, sino a **“quimioterapia”** en general, término que evidentemente se encuentra sustentado por las divulgaciones del capítulo descriptivo.

Así las cosas, afirmamos que el nuevo pliego reivindicatorio hace referencia a un único concepto inventivo y que, por tanto, no recae en ningún conflicto de unidad de invención, sobre todo teniendo en cuenta que las actuales reivindicaciones no hacen referencia en ningún momento a **“taxanos”**, **“gemcitabina”**, **“capecitabina”** o **“vinorelbina”** sino a **“quimioterapia”**, expresión que constituye una justa generalización de tales subcategorías.

De la mano con lo anterior, es nuestra intención destacar que no existe inconsistencia alguna entre la materia reclamada en el actual pliego reivindicatorio y aquella divulgada en el capítulo descriptivo ya que precisamente la expresión **“quimioterapia”** engloba de manera clara y apropiada los agentes farmacológicos conocidos como **“taxanos”**, **“gemcitabina”**, **“capecitabina”** y **“vinorelbina”**, a partir de lo cual la invención reclamada guarda estrecha concordancia con las divulgaciones del capítulo descriptivo.

Consecuentemente, solicitamos sea retirada la objeción por unidad de invención que perjudica al actual pliego reivindicatorio toda vez que la misma carece de validez y fundamentos a la luz de la materia que se reivindica.

En conexión con este hecho, consideramos pertinente expresar nuestro total desconcierto frente al enfoque y manejo del señor Examinador ya que, en lugar de

ceñirse de manera fiel a la materia reivindicada, establece interpretaciones propias de la presente invención, así como evidencia el siguiente fragmento:

“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.”

Nuevamente, nos permitimos reiterar que la invención reivindicada no hace referencia a la combinación del anticuerpo anti-VEGF con taxanos, gemcitabina, capecitabina y vinorelbina sino a la combinación de dicho anticuerpo con **quimioterapia**, evidenciando de este modo el enfoque altamente subjetivo bajo el cual su Despacho emite un concepto respecto a la patentabilidad de la invención.

Habiendo aclarado este hecho, reiteramos que el actual pliego reivindicatorio no recae en ninguna falta al requisito de unidad de invención, razón por la cual solicitamos sea reconocida la entera validez del mismo mediante el retiro de la respectiva objeción.

Novedad y Nivel inventivo

En cuanto a los requisitos de patentabilidad, considera el señor Examinador que la presente invención carece de novedad a la luz de las enseñanzas de los siguientes documentos:

Tabla 1. Estado de la técnica concerniente a la presente invención.

No	Documento	Título
D1	W098/45331	<i>“Anti-VEGF antibodies”</i>
D2	O’Shaughnessy & Brufsky 2008	<i>“RiBBON 1 and RiBBON 2: Phase III Trial of Bevacizumab with Standard Chemotherapy for Metastatic Breast Cancer”</i>
D3	Miller et al. 2005	<i>“Randomized Phase III Trial of Capecitabine compared with Bevacizumab plus Capecitabine in Patients with previously treated metastatic breast cancer”</i>
D4	Ramaswamy et al. 2006	<i>“Phase II trial of bevacizumab in combination with weekly docetaxel in metastatic breast cancer patients”</i>
D5	Burstein et al. 2008	<i>“VEGF as a marker for outcome among advanced breast cancer patients receiving anti-VEGF therapy with bevacizumab and vinorelbine chemotherapy”</i>

Partiendo de nuestro desacuerdo frente a la posición del señor Examinador y la objeción derivada de su análisis, procedemos a demostrar el cabal cumplimiento de los requisitos de novedad y nivel inventivo por parte de la presente invención, muy a pesar de las divulgaciones de las referencias citadas.

Como primera medida, nos permitimos llamar la atención sobre la modificación realizada a la reivindicación 1, mediante la cual se incorporó la expresión “*como terapia de segunda línea*” en referencia a la aplicación terapéutica que define a la presente invención, la cual constituye como tal una **limitación técnica** que además de restringir su alcance, establece una clara diferencia entre el estado de la técnica y la misma.

Así pues, es posible notar que el kit objeto de la presente invención corresponde a una combinación farmacéutica destinada al tratamiento de **segunda línea** de pacientes diagnosticados con **cáncer de mama triple negativo previamente tratado** que, como tal, demuestra ser eficaz –aspecto que será abordado más adelante– y que por tanto implica un claro beneficio que además de ello, permite visualizar de mejor manera la diferencia existente entre esta y el arte previo.

En lo que respecta a las anterioridades citadas por su Despacho, nos permitimos señalar que las mismas fallan completamente en anticipar todas y cada una de las características técnicas que caracterizan y dan origen a la presente invención, hecho que demostramos a continuación:

- El documento D1 se limita únicamente a divulgar el anticuerpo anti-VEGF bevacizumab, fallando abiertamente en sugerir o proponer el desarrollo de un **kit** que, además de dicho anticuerpo, comprenda un agente quimioterapéutico orientado al tratamiento de segunda línea de pacientes diagnosticados con cáncer de mama triple negativo previamente tratado.
- 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 triple negativo previamente tratado, por lo cual tampoco desvirtúa la patentabilidad de la presente invención.

- El documento D3 se relaciona con el **tratamiento inicial** de cáncer de mama metastásico, por lo que es evidente que sus enseñanzas no abarcan en ningún momento el tratamiento de segunda línea de pacientes diagnosticados con cáncer de mama triple negativo previamente tratado, siendo esta una condición terapéutica mucho más específica.
- El documento D4 se limita a dar a conocer una combinación aleatoria para el tratamiento de cáncer de mama metastásico, por lo que este falla igualmente en proponer un **kit** para el tratamiento de segunda línea de una población que padece cáncer de mama triple negativo previamente tratado.
- El documento D5, de manera similar, se enfoca en proporcionar una terapia combinada que no es selectiva como tratamiento de segunda línea para pacientes cuyo cuadro clínico corresponda a cáncer de mama triple negativo previamente tratado, por lo cual sus enseñanzas tampoco son comparables con la presente invención.

De acuerdo con lo anterior, asumimos demostrado que ninguna de las referencias citadas por el señor Examinador anticipa el concepto inventivo que da lugar a la presente invención, razón por la cual insistimos en que esta cumple de manera satisfactoria con el requisito de novedad en vista del arte previo.

Ahora bien, habiendo ratificado la novedad de la presente invención, es necesario ahora mencionar que la misma cuenta también con la debida altura inventiva, para lo acudimos al trabajo de Brufsky *et al.* (2012), 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 estudio clínico 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 ^a (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 ^a (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 ^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)	
P 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

Tales resultados ratifican que, contrario a la apreciación 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** de la sobrevida de los pacientes diagnosticados con dicha condición.

Consecuentemente, dado que las referencias D1 a D5 citadas por su Despacho son completamente ajenas al alcance de la presente invención, resulta imposible atribuirle obviedad alguna a la misma ya que estas no sugieren, motivan ni contemplan 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.

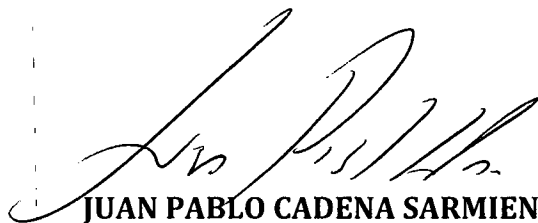
Dicho esto, solicitamos respetuosamente se reconozca la plena patentabilidad de la presente invención dado el cabal cumplimiento de los requisitos de novedad y nivel inventivo por su parte, además de la existencia de un claro **beneficio** asociado con un **efecto superior inesperado** que, como tal,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

Por último, a raíz de los comentarios del señor Examinador respecto a la patentabilidad de la presente invención, consideramos necesario aclarar según el Artículo 14 de la Decisión 486, la patentabilidad de una invención se ve definida por el cumplimiento de los requisitos de novedad, nivel inventivo y aplicabilidad industrial; y aunque la existencia de un efecto técnico sorprendente sea considerado como un indicio adicional de nivel inventivo (Instructivo de Patentabilidad, Numeral 2.13.5.3.1 Indicios de la existencia de nivel inventivo, página 74) la ausencia de dicho efecto técnico sorprendente no implica necesariamente la ausencia de nivel inventivo.

De este modo, insistimos en que la patentabilidad de la presente invención se ha llevado a cabo desde un enfoque subjetivo y carente de fundamentos que, de uno u otro modo, demuestra la falta de validez de las objeciones manifestadas por su Despacho, hecho que solicitamos sea debidamente reconocido mediante el análisis y consideración de los argumentos y evidencias aquí expuestas en favor de la concesión del privilegio de patente a la presente invención.

En vista de lo anteriormente expuesto, respetuosamente solicitamos el retiro de las objeciones de la presente solicitud y la concesión del privilegio solicitado, ya que en opinión del solicitante cumple con todos los requisitos establecidos en la Decisión 486.

Atentamente,



JUAN PABLO CADENA SARMIENTO

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REIVINDICACIONES

1. 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 como terapia de segunda línea.

2. El kit de acuerdo con la reivindicación 1, en donde el anticuerpo anti-VEGF tiene una región variable de cadena pesada que comprende la secuencia de aminoácidos SEQ ID NO. 1 y una región variable de cadena ligera que comprende la secuencia de aminoácidos SEQ ID NO. 2.

3. El kit de acuerdo con la reivindicación 1, en el cual el anticuerpo anti-VEGF es bevacizumab.

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

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Shaker Dakhil · Arija Brize · Hope S. Rugo · Ragene Rivera ·
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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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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).

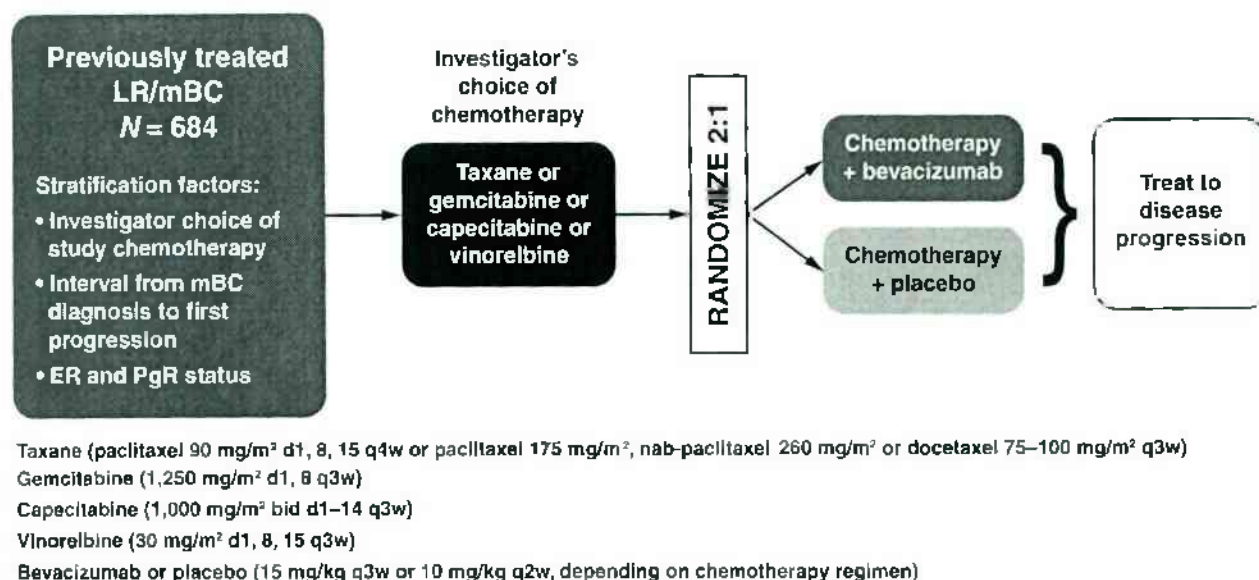


Fig. 1 Study design of RIBBON-2. ER estrogen receptor, LR locally recurrent, mBC metastatic breast cancer, nab nanoparticle albumin-bound, PgR progesterone receptor

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

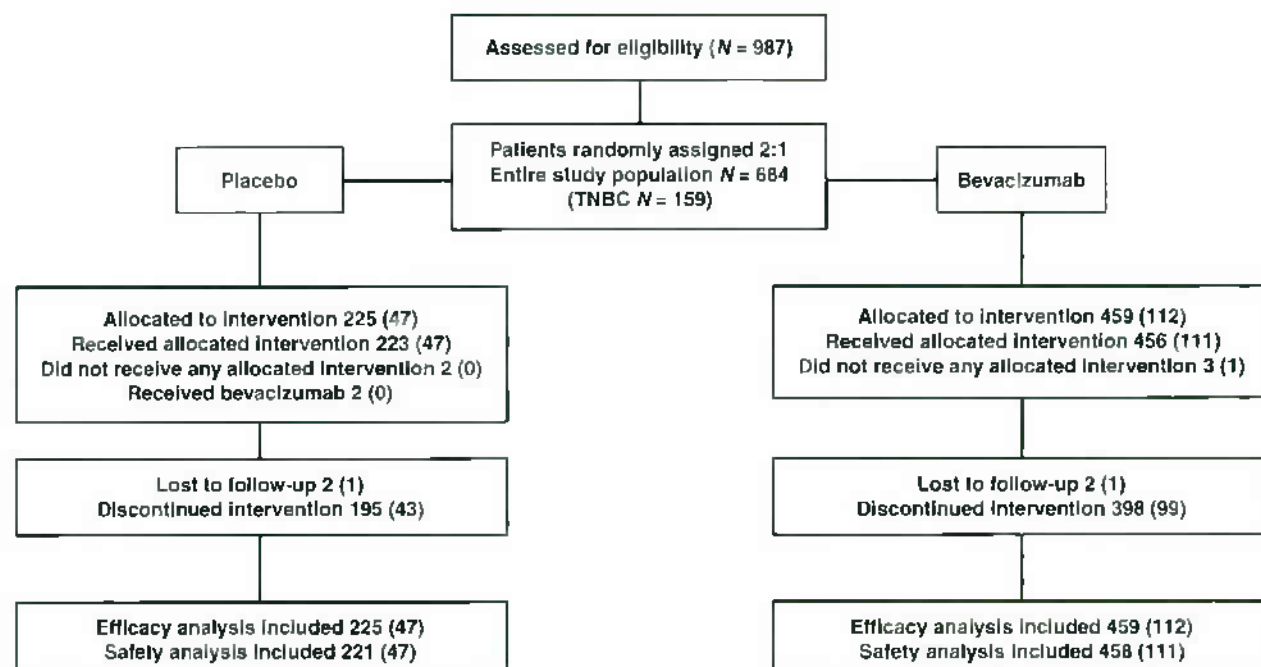


Fig. 2 Trial profile showing the entire study population (TNBC subgroup data shown in *parentheses*). TNBC triple-negative breast cancer

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

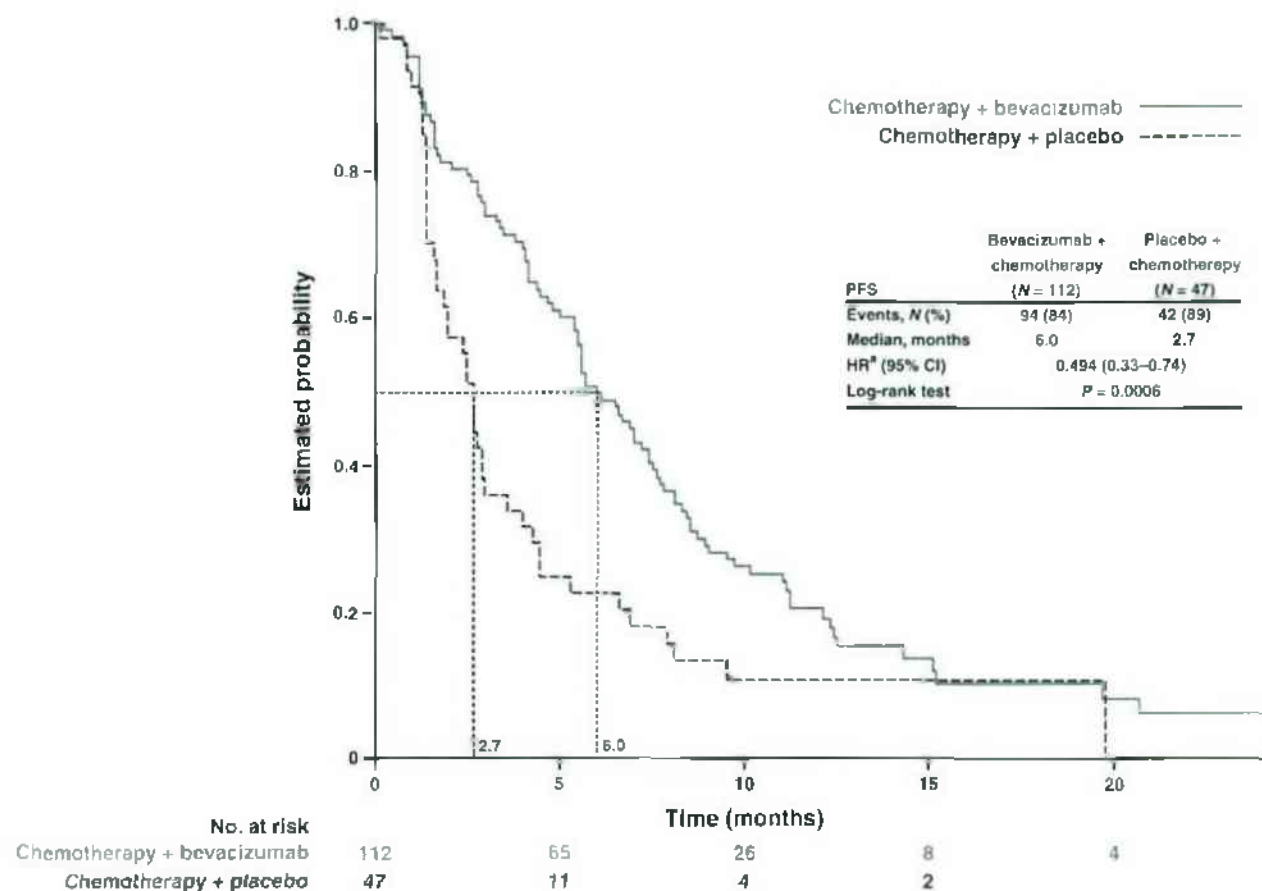


Fig. 3 Progression-free survival: triple-negative breast cancer subgroup. ^aStratified analysis (chemotherapy regimen, interval from locally recurrent/metastatic breast cancer diagnosis to first progression). HR hazard ratio, PFS progression-free survival

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-I [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 (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 ^a (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 ^a (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 ^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)	
P 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.

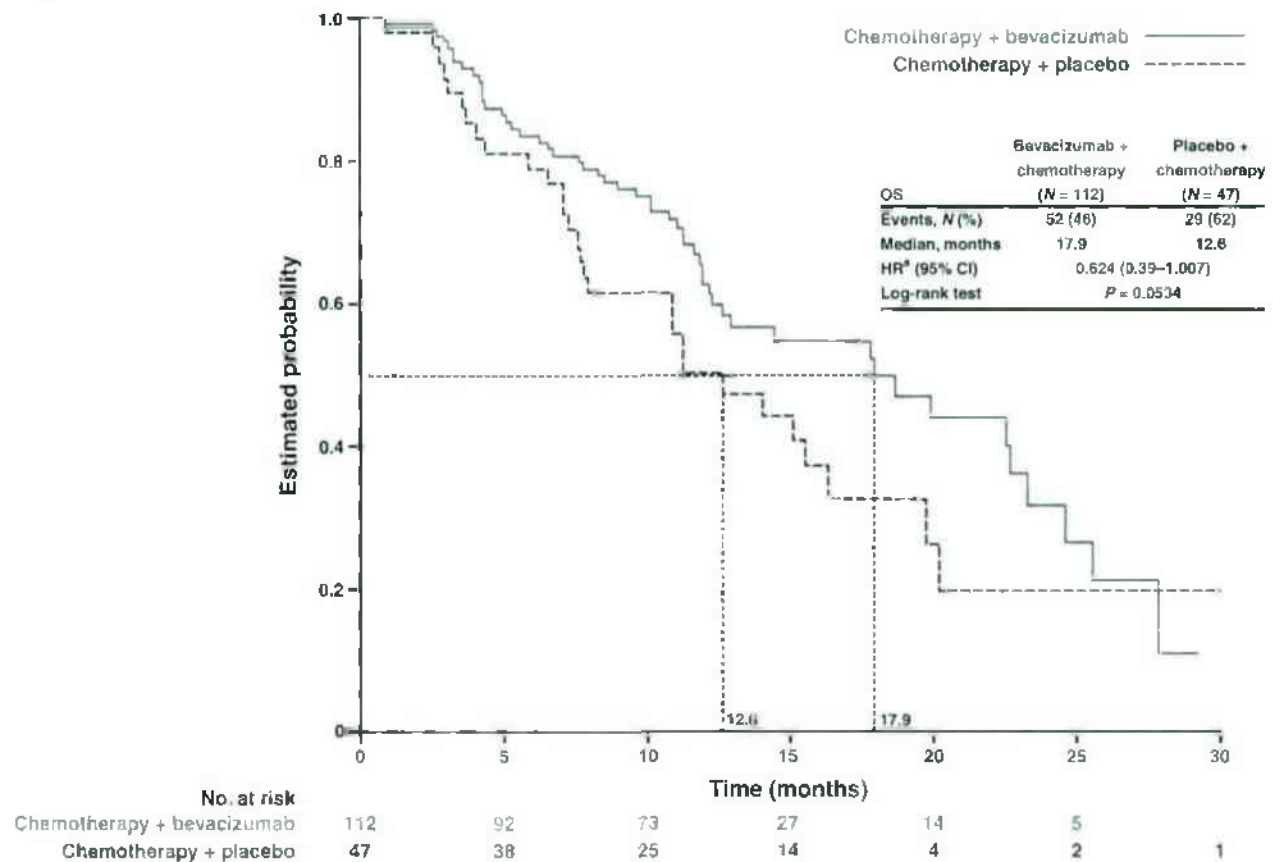


Fig. 4 Overall survival: triple-negative breast cancer subgroup. ^aStratified analysis (chemotherapy regimen, interval from locally recurrent/metastatic breast cancer diagnosis to first progression). HR hazard ratio, OS overall survival

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.

References

- Gluz O, Liedtke C, Gotschalk N et al (2009) Triple-negative breast cancer—current status and future directions. *Ann Oncol* 20:1913–1927
- Dent R, Trudeau M, Pritchard KI et al (2007) Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res* 13(15 Pt 1):4429–4434
- Lehmann BD, Bauer JA, Chen X et al (2011) Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest* 121:2750–2767
- O'Shaughnessy J, Osborne C, Pippen JE et al (2011) Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med* 364:205–214
- O'Shaughnessy J, Schwartzberg LS, Danso MA et al. (2011) A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC). *J Clin Oncol* 29(Suppl): Abstract 1007
- O'Shaughnessy J, Dieras V, Glaspy J et al. (2009) Comparison of subgroup analyses of PFS from three phase III studies of bevacizumab in combination with chemotherapy in patients with HER2-negative metastatic breast cancer (MBC). *Cancer Res* 69(Suppl):512s (Abstract 207)
- Gray R, Bhattacharya S, Bowden C et al (2009) Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 27:4966–4972
- Miles DW, Chan A, Dirix LY et al (2010) Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol* 28:3239–3247
- Robert N, Dieras V, Glaspy G et al (2011) RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of HER2-negative locally-recurrent or metastatic breast cancer. *J Clin Oncol* 29:1252–1260
- Brufsky AM, Hurvitz S, Perez E et al (2011) RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol* 29:4286–4293
- Greenberg S, Rugo H (2010) Triple-negative breast cancer: role of antiangiogenic agents. *Cancer J* 16:33–38
- Ryden L, Jirstrom K, Haglund M, Stål O, Fernö M (2010) Epidermal growth factor receptor and vascular endothelial growth factor receptor 2 are specific biomarkers in triple-negative breast cancer. Results from a controlled randomized trial with long-term follow-up. *Breast Cancer Res Treat* 120:491–498
- Smith IE, Pierga J-Y, Biganzoli L et al (2011) Final overall survival results and effect of prolonged (≥ 1 year) first-line bevacizumab-containing therapy for metastatic breast cancer in the ATHENA trial. *Breast Cancer Res Treat* 130:133–143
- Miller KD, Chap LI, Holmes FA et al (2005) Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol* 23:792–799
- Baselga J, Stemmer SM, Pego A et al. (2010) Cetuximab + cisplatin in estrogen receptor-negative, progesterone receptor-negative, HER2-negative (triple-negative) metastatic breast cancer: results of the randomized phase II BALI-1 trial. *Cancer Res* 70(24 Suppl):95s (Abstract PD01-01)
- Awada A, Bondarenko IN, Tarasova O et al. (2010) Results of the first randomized phase II study of cationic liposomal paclitaxel (EndoTAG-1) targeting tumor endothelial cells in advanced triple-negative breast cancer (TNBC). *Ann Oncol* 21(Suppl 8):viii5 (Abstract LBA12)
- Roché HH, Sparano J, Valero V et al. (2010) Ixabepilone (IXA) and capecitabine (C) in patients (pts) with triple-negative breast cancer (TNBC): a retrospective analysis of phase 2 and phase 3 clinical studies. *Ann Oncol* 21(Suppl 8):viii103 (Abstract 299P)
- Irvin WY, Carey LA (2008) What is triple-negative breast cancer? *Eur J Cancer* 44:2799–2805
- Prat A, Parker JS, Karginova O et al (2010) Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. *Breast Cancer Res* 12:R68