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Señor

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

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REF: Expediente No. **12-029506**– solicitud de patente de invención a favor de **GENENTECH, INC.** Título **TERAPIA ANTI-ANGIOGÉNESIS PARA EL TRATAMIENTO DE CÁNCER DE MAMA PREVIAMENTE TRATADO**

RESPUESTA A OPOSICIÓN

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 a la oposición presentada por **LAFRANCOL S.A.S**, relacionada con la patentabilidad de la presente invención y notificado por fijación en lista el 20 de Agosto de 2013.

Como primera medida nos permitimos presentar un nuevo pliego reivindicatorio con el fin de dar cumplimiento a los requerimientos de la Decisión 486, en el cual se ha eliminado cualquier alusión a un método de tratamiento. De esta manera, el pliego reivindicatorio en mención comprende un total de tres (3) reivindicaciones que son plenamente patentables.

En este sentido, la nueva reivindicación 1 establece lo siguiente:

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, 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.*

Lo cual es abiertamente aceptado por el **Instructivo para Examen de Solicitudes de Patentes de Invención y Modelo de Utilidad** en el numeral 2.15, el cual hace mención a lo largo de su contenido de la información incluida a continuación:

“El kit-de-partes está conformado por preparaciones combinadas de componentes individuales, donde tales componentes forman una unidad funcional (combinación verdadera) dirigida a un único propósito. Sin embargo, la sola asociación de componentes en sí no la convierte en una unidad funcional en la cual una interacción directa entre los componentes es necesaria para el propósito final. Por lo tanto, la solicitud de protección mediante patente de un kit-de-partes debe ser considerada cuando el centro de la invención es una combinación nueva de dos o más compuestos conocidos para una finalidad terapéutica específica y el producto será comercializado en forma de kit (denominado también como envase médico, estuche o empaque).”

Un kit o empaque médico puede estar conformado por:

- Una composición farmacéutica o medicamento A*
- Una composición farmacéutica o medicamento B*
- Forma de administración de cada composición farmacéutica o medicamento.*
- Instrucciones para la administración de cada una de las composiciones farmacéuticas para conseguir un efecto deseado y la cantidad de la forma”*

Por tanto, a partir de las modificaciones en mención damos por superada cualquier falencia en relación con la reclamación de materia considerada como no patentable.

Ahora bien, notamos que la sociedad opositora establece que la materia divulgada por la presente invención carece de novedad y de nivel inventivo a la luz del arte previo, toda vez que las composiciones farmacéuticas que comprenden anticuerpos anti-VEGF son ampliamente conocidas para el tratamiento del cáncer de mama metastásico, para lo cual incluye a lo largo del documento de oposición las referencias D1 (Miller et al.), D2 (Ramaswamy et al.) y D4 (Burstein et al.). Al respecto, nos permitimos incluir los siguientes argumentos que defienden la patentabilidad del nuevo pliego reivindicatorio.

La nueva reivindicación 1 ha sido modificada con el fin de hacer énfasis en que el kit revelado es apto para el tratamiento de cáncer de mama metastásico previamente tratado en un paciente humano diagnosticado con **cáncer de mama triple negativo**, lo cual se constituye como el propósito final del kit, y es logrado mediante la debida combinación del anticuerpo anti-VEGF y quimioterapia a partir de instrucciones específicas para dicha combinación.

De esta manera, es fundamental llamar la atención de la sociedad opositora frente al hecho relacionado con que el kit objeto de la presente invención corresponde a una combinación farmacéutica destinada al tratamiento de **segunda línea** de pacientes diagnosticados previamente con cáncer de mama triple negativo metastásico tratado.

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En contraste con lo anterior, notamos que la referencia **D1 (Miller et al.)** citada por el señor Opositor centra sus enseñanzas en el tratamiento inicial de cáncer de mama metastásico con la combinación bevacizumab/paclitaxel, en donde es fundamental hacer énfasis en el hecho de que los pacientes objeto del tratamiento en mención **no son seleccionados mediante el estado de Her2, el estado ER (receptor de estrógeno) o el estado PgR (receptor de progesterona)**.

Por tanto, es evidente que la referencia D1 no se relaciona de manera alguna con un kit que permita el tratamiento de un subgrupo de pacientes que padezcan de una condición triple negativa, y por tanto, las divulgaciones de la anterioridad en mención no se relacionan con el alcance de la presente invención.

De manera similar, al hacer lectura de las divulgaciones de la referencia **D2 (Ramaswamy et al.)** es posible identificar que la anterioridad en mención se encuentra relacionada con el tratamiento del cáncer de mama metastásico con la combinación bevacizumab/docetaxel, **sin considerar la selección de pacientes mediante el estado de Her2, el estado ER o el estado PgR**. Así las cosas, la referencia D2 tampoco se relaciona con un kit que permita el tratamiento de un subgrupo de pacientes que padezcan de una condición triple negativa.

En consecuencia, las divulgaciones de D2 tampoco anticipan las divulgaciones de la presente invención.

Ahora bien, en lo que concierne a la referencia **D4 (Burstein et al.)** notamos que la misma revela a lo largo de su contenido los aspectos relacionados con el tratamiento de cáncer de mama avanzado mediante la combinación de bevacizumab y vinorelbina, el cual se lleva a cabo sin la previa selección de los pacientes tomando como punto de partida sus estados Her2, ER o PgR; es decir, dicha referencia es igualmente silenciosa frente a un kit para el tratamiento de pacientes que diagnosticados con cáncer de mama triple negativo.

En este sentido, ninguna de las referencias citadas por la sociedad opositora anticipa el concepto inventivo que caracteriza a la presente invención, y por tanto, esta última cumple con el requisito de novedad a la luz del arte previo.

Una vez demostrada la novedad de la presente invención a la luz del arte previo citado por el señor Opositor, nos permitimos incluir como parte del presente memorial un artículo científico debidamente publicado (Brufsky et al.), el cual soporta la actividad inventiva relacionada con la presente invención, tal como se expone a continuación.

En este sentido, la presente invención surgió de los resultados del ensayo clínico RIBBON-2, tal como se evidencia en el ejemplo 1, el cual establece en resumen lo siguiente:

“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 HER2-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 HER2-negativo metastásico quienes habían recibido previamente quimioterapia para su enfermedad metastásica."

De esta manera, el artículo *Brufsky et al.* se relaciona con un análisis detallado del subgrupo triple negativo del ensayo RIBBON-2, en el cual se evidencia que cuando los resultados del subgrupo triple negativo se comparan con el resto de grupos de pacientes, los efectos del tratamiento son sustancialmente marcados en términos de la mediana de los valores PFS y ORR, como se evidencia en la tabla 2, incluida a continuación:

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

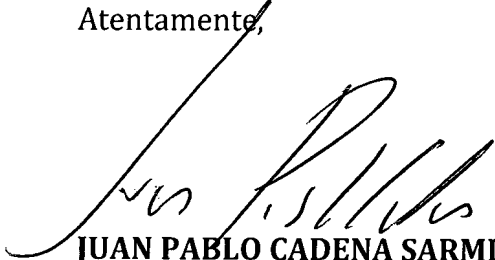
Lo anterior demuestra de manera contundente que existe un efecto sinérgico marcado entre la quimioterapia y el bevacizumab al ser empleados como tratamiento del subgrupo triple negativo, y de esta manera, dicha combinación propicia una mejora sustancial de la sobrevida de los pacientes diagnosticados con cáncer de mama triple negativo.

En consecuencia, al tener en cuenta que las referencias D1, D2 y D4 citadas por su Despacho son completamente ajenas al alcance de la presente invención, dichas anterioridades no sugieren de manera alguna el desarrollo del kit reivindicado, ni el efecto superior suscitado por la aplicación del mismo sobre los pacientes diagnosticados con cáncer de mama triple negativo.

Por tanto, no existen herramientas técnicas que permitan al normalmente versado en la materia llegar a las divulgaciones de la presente invención, lo cual nos lleva a concluir que la oposición de la sociedad LAFRANCOL S.A.S carece del sustento y del análisis requerido para afectar la patentabilidad del kit acá reivindicado, ya que se ha demostrado que el mismo cumple con la totalidad de disposiciones de la Decisión 486.

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,



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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, 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.
2. El kit de acuerdo con cualquiera de las reivindicaciones 1, en donde el anticuerpo anti-VEGF tiene una región variable de cadena pesada que comprende la siguiente secuencia de aminoácidos:

EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWVRQA PGKGLEWVGW
INTYTGEPTY AADFKRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCAKYP
HYYGSSHWYF DVWGQGT LVT VSS (SEC ID NO. 1)

y una región variable de cadena ligera que comprende la siguiente secuencia de aminoácidos:

DIQMTQSPSS LSASVGDRVIT ITCSASQDIS NYLNWYQQKP GKAPKVLIIYF
TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ
GTKVEIKR (SEC 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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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).

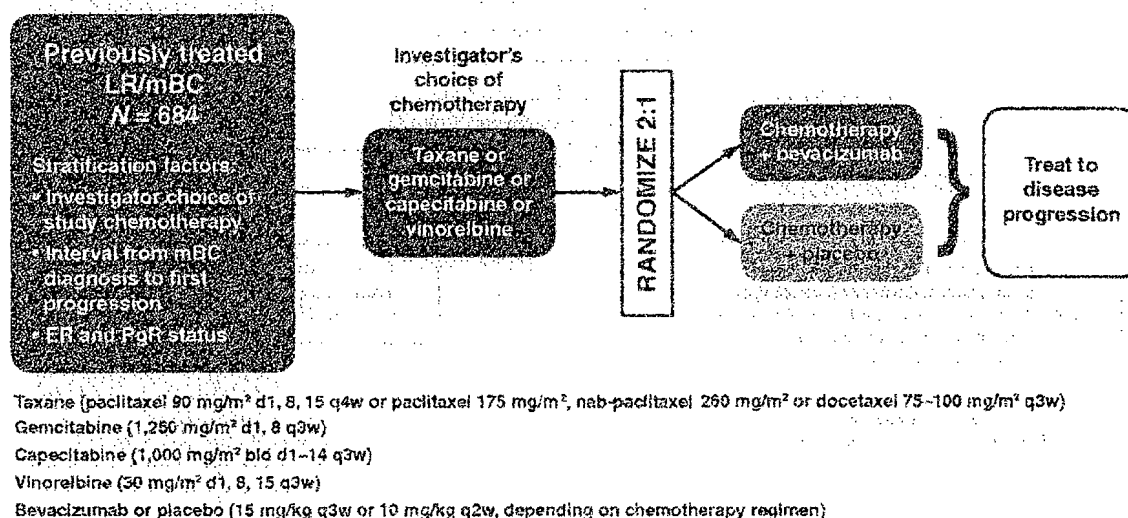


Fig. 1 Study design of RIBBON-2. ER estrogen receptor, LR locally recurrent, mBC metastatic breast cancer, nab nanoparticle albumin-bound, PgR progesterone receptor

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

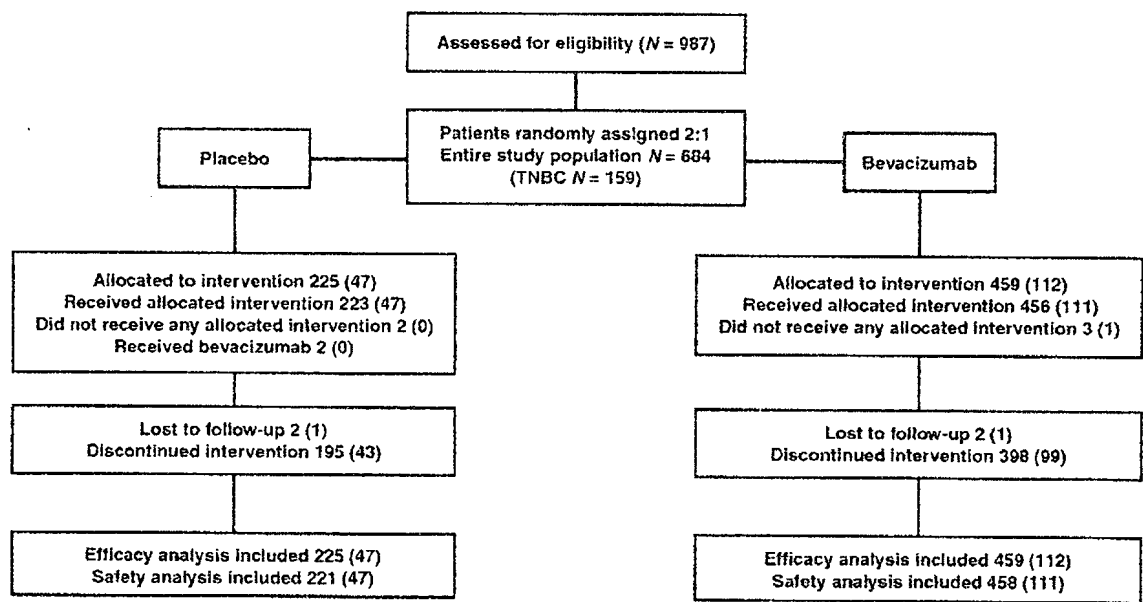


Fig. 2 Trial profile showing the entire study population (TNBC subgroup data shown in parentheses). TNBC triple-negative breast cancer

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

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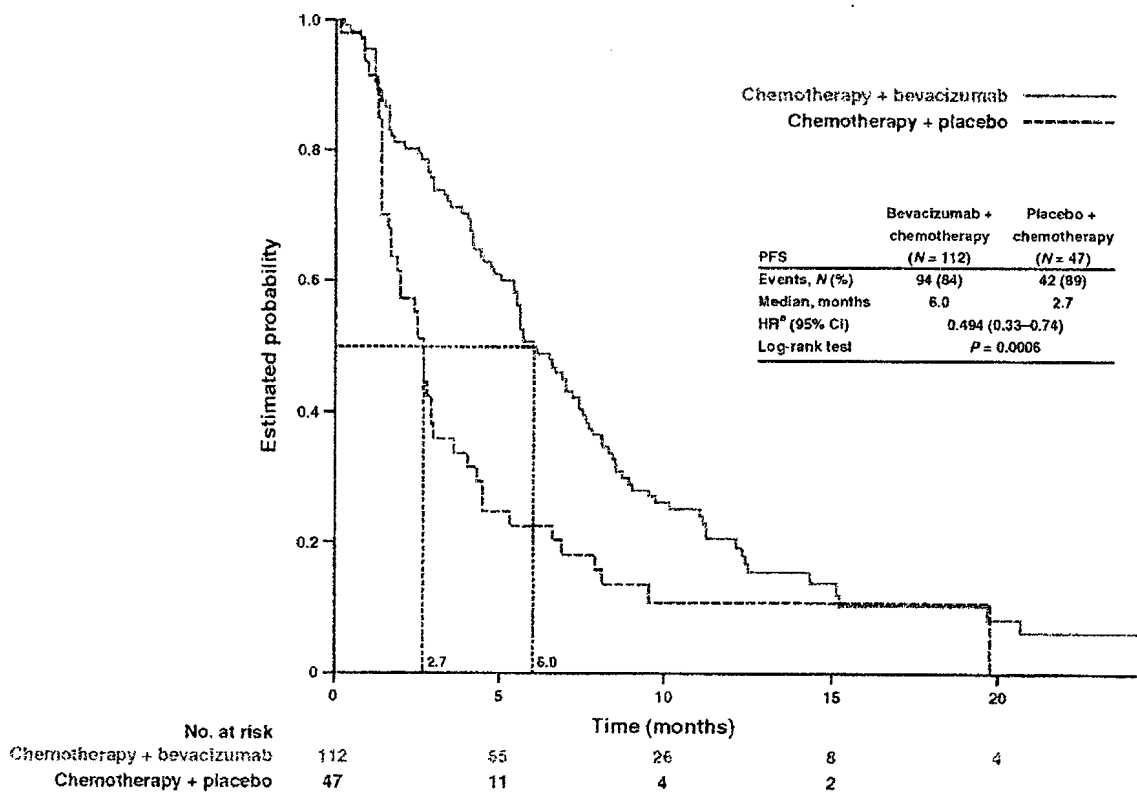


Fig. 3 Progression-free survival: triple-negative breast cancer subgroup. *Stratified analysis (chemotherapy regimen, interval from locally recurrent/metastatic breast cancer diagnosis to first progression). HR hazard ratio, PFS progression-free survival

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 ceruximab–cisplatin [15]; EndoTAG™-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

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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)	0.0334 ^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.

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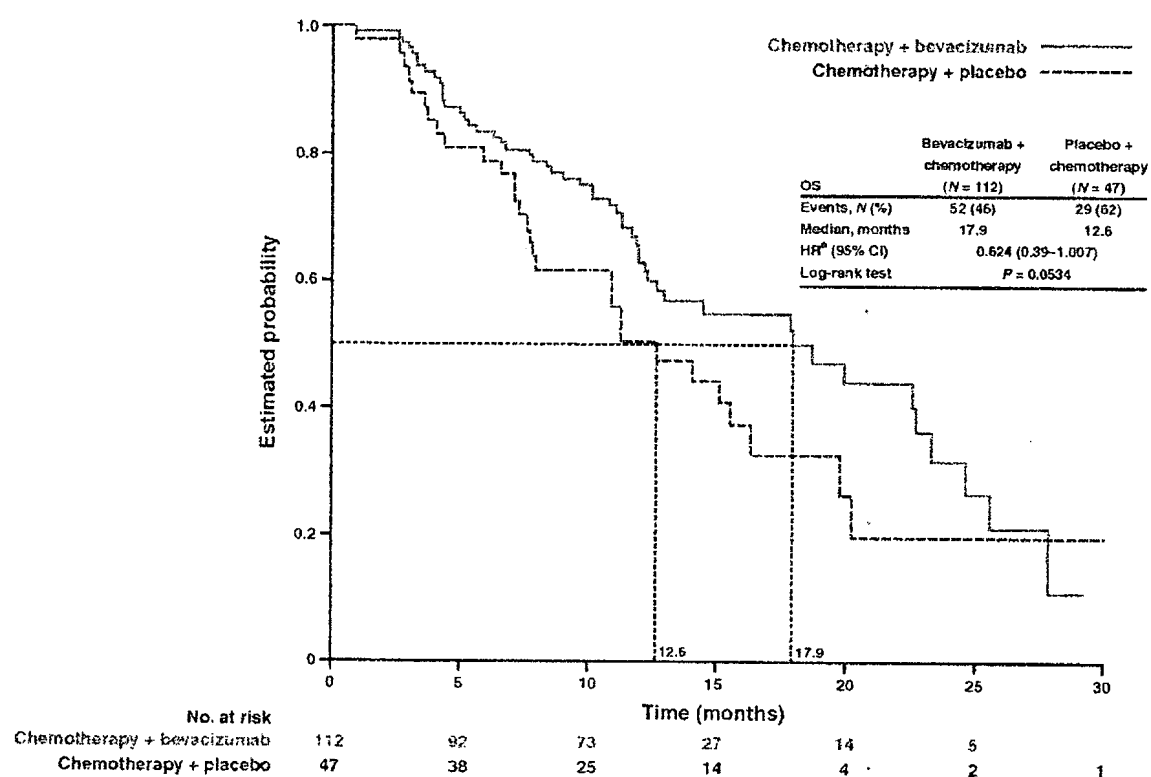


Fig. 4 Overall survival: triple-negative breast cancer subgroup. *Stratified analysis (chemotherapy regimen, interval from locally recurrent/metastatic breast cancer diagnosis to first progression). HR hazard ratio, OS overall survival

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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