

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

- ☒ Patente de invención
☐ Registro de Diseño Industrial
☐ Patente de Modelo de Utilidad

Esquema de Trazado de Circuitos Integrados

Número de expediente: 12-129-535

Solicitante: GENENTECH, INC, F. HOFFMANN-LA ROCHE AG.

Apoderado: JUAN PABLO CADENA SARMIENTO.

Título de la Nueva Creación: TERAPIA ANTI-ANGIOGENESIS PARA EL TRATAMIENTO DEL CANCER OVARICO.

Gaceta: 659 de 02 de enero de 2013, No. de publicación 2071.

2. Datos del Opositor

Persona Natural

☐

Persona Jurídica

☐

TECNOQUIMICAS S.A.

Nombre o denominación /Razón social completa

Documento de identificación: C.C. ☐ C.E. ☐ NIT ☒ Otro ☐ Cuál _____

Número 890 300 466-5

Dirección: Calle 23 No. 7-39 Ciudad Cali

Teléfono (092) 882.55.55 Fax: (092) 883.88.59 E-mail: _____

☐

Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del representante o apoderado:

REYES VILLAMIZAR JOSE LUIS

79'152.473

44655

Apellidos y Nombre

Documento de identificación

T.P. No.

Dirección del representante

Cra 17 No. 88-23 Of.205

Dirección electrónica

info@reyes-abogados.com

No. Fax

621.26.31

Número telefónico

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación

6. Fundamentos de la oposición

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000)

Justificación: VER ANEXO

Prórroga: SI ☒ NO ☐

7. Anexos

Comprobante de pago de la tasa para la presentación de la solicitud No. _____ Fecha: _____

☐ Poder, si fuera el caso con el que se acredita la representación.

☐ Pruebas de los fundamentos de la oposición

☐ Copias para traslado

8. Firma

JOSÉ LUIS REYES VILLAMIZAR

Nombre y apellidos

Firma

79.152.473

C.C.

44655

T.P.

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: EXPEDIENTE 12 129-535

TÍTULO SOLICITADO: “TERAPIA ANTI-ANGIOGENESIS PARA EL TRATAMIENTO DEL CANCER ÓVARICO”

PUBLICACIÓN: Gaceta 659 de 02 de enero de 2013, N° de publicación 2071.

PRIORIDAD:

US 61/307.095	23/02/2010
US 61/351.231	03/06/2010
US 61/360.059	30/06/2010
US 61/439.819	04/02/2011

**SOLICITANTE: GENENTECH, INC.
F.HOFFMANN-LA ROCHE A.G.**

APODERADO: JUAN PABLO CADENA SARMIENTO

TRÁMITE: PRESENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad TECNOQUÍMICAS S.A., en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente **12-129-535**, por no cumplir con lo dispuesto en la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUÍMICAS S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud colombiana en trámite **12-129-535** que se refiere al tratamiento de enfermedades y condiciones patológicas con anticuerpos anti-VEGF, no cumple los requisitos materiales para otorgársele el privilegio de patente de invención, tal como puede determinarse al valorar los siguientes argumentos:

En primer lugar me permito resumir lo reclamado por el solicitante como un método de tratamiento ya que la solicitud en trámite se caracteriza por someter al paciente a un régimen de tratamiento que combina quimioterapia con la administración de un anticuerpo anti-VEGF.

En este sentido, lo que se reivindica como invención en las primeras 19 reivindicaciones se encuentra específicamente excluido de patentabilidad por la Decisión 486 de la Comunidad Andina de Naciones en su Art. 20 literal (d) que dicta lo siguiente:

“No serán patentables:

... d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o animales”.

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De esta forma, la solicitud no cumple con los requisitos para ser aceptada, máxime cuando el método terapéutico se basa en la administración de medicamentos de uso común, como lo es un anticuerpo anti-VEGF tal como BEVACIZUMAB, el cual se conoce desde hace varios años, (fecha de publicación de la patente de Bevacizumab US 6054297: 25 de abril de 2000) y que incluso se reclama en la cláusula 22 de la presente solicitud.

Por otro lado, la solicitud incumple además con los requisitos de claridad al reivindicar un kit (como en las reivindicaciones 20 a 23) que comprende un envase que comprende una composición de anticuerpo e instrucciones para usar la composición, lo cual no solo no corresponde a características técnicas de un solo producto, o un solo proceso, sino que mezcla diferentes productos que ni siquiera pertenecen a la misma área técnica y los trata como si pudieran dar lugar un efecto técnico en su combinación.

De cualquier forma, las reivindicaciones que hacen alusión al kit, solo mencionan condiciones del tratamiento lo cual no es patentable, o revelan características del anticuerpo Bevacizumab, las cuales no cumplen adicionalmente con el criterio de novedad.

Por si fuera poco, los métodos reclamados y en especial lo revelado en las reivindicaciones 24 a 28 además de estar exentos de patentabilidad, no presentan aplicación industrial y no se encuentran dentro de los "productos o procesos", los cuales son las únicas categorías aceptables en esta jurisdicción.

Aunque los argumentos hasta aquí mencionados son suficientes para demostrar la violación flagrante a la Decisión 486, será además demostrada la falta de Novedad y Nivel Inventivo del objeto reclamado por la solicitud mediante la comparación con los documentos del estado de la técnica tal como consta a continuación:

- El documento del estado de la técnica Penson Richard T. *et al.*, "*Phase II study of carboplatin, paclitaxel, and Bevacizumab with maintenance Bevacizumab as first-line chemotherapy for advanced mullerian tumors*" publicado el 1 de enero de 2010 (en adelante Penson *et al.*), describe estudios de fase II donde un régimen comprendido por Carboplatino, Paclitaxel y Bevacizumab seguido de terapia de mantenimiento con Bevacizumab ha sido

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usado como quimioterapia de primera línea para el tratamiento de cáncer de ovario.

Dichas características reclamadas de igual manera por la solicitud pueden verse en la pagina 155, 1er párrafo de Penson *et al.*, tal como se mencionan en el siguiente aparte:

Paclitaxel, carboplatin, and bevacizumab have been combined in lung cancer, but it is unknown whether the feasibility of this regimen will be generalizable to other diseases. This is especially important because we know that bevacizumab by itself can cause GIP in recurrent ovarian cancer and can be life threatening. Thus, the full toxicity

Así mismo, el documento evidencia el mantenimiento de Bevacizumab en una terapia con Carboplatino, Paclitaxel y Bevacizumab como una combinación activa posible en pacientes con cáncer ovario avanzado y no tratado (ver página 159, segundo párrafo)

First-line carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab is a highly active combination that remains experimental but is feasible in patients with previously untreated advanced ovarian cancer. Randomized controlled trials are required to determine the efficacy of bevacizumab when used in combination with chemotherapy and as maintenance therapy in the treatment of ovarian cancer.

De acuerdo a lo observado, el documento de Penson *et al.*, anticipa todas las características técnicas reclamadas por la solicitud en trámite, estos es, el método de tratamiento y no solo éste sino que además indica la enfermedad a tratar y la expectativa de su implementación, con lo cual no cabe duda que la materia allí revelada y la anterioridad mencionada divulgan el mismo objeto, por lo tanto la solicitud no cumple con el criterio de Novedad.

- Por otra parte, el documento del estado de la técnica Richardson D. *et al.*, "Combination gemcitabine, platinum, and Bevacizumab for the treatment of recurrent ovarian cancer" publicado el 1 de diciembre de 2008 describe un régimen de quimioterapia que comprende la combinación de Gemcitabina,

cisplatino o carboplatino y Bevacizumab para el tratamiento de cáncer de ovario recurrente.

[22]. The addition of bevacizumab to gemcitabine and carboplatin for the treatment of non-small cell lung cancer was shown to significantly improve PFS as well as RR [23].

En este sentido, el documento de Richardson et al., menciona una mejora significativa en la supervivencia y en la tasa de respuesta en el tratamiento de cáncer de ovario mediante el tratamiento divulgado.

Esta anterioridad muestra además, que este régimen es altamente eficaz en el tratamiento de cáncer de ovario epitelial recurrente con una tasa de respuesta de 78% (ver el siguiente aparte que corresponde a la tabla 2, página 463, columna derecha)

Table 2

Response data (N=33)	Number (%) ^a			
Platinum sensitivity	CR	PR	Stable	Progressive
Platinum-sensitive ^b	13 (61)	6 (29)	2 (10)	0
Secondary platinum-resistant	1 (17)	3 (50)	1 (17)	1 (17)
Platinum-resistant/refractory	2 (33)	1 (17)	2 (33)	1 (17)
Total	16 (48)	10 (30)	5 (15)	2 (6)

^a Percentages may not add to 100 due to rounding.

^b Platinum sensitive at time of treatment with gemcitabine, platinum, and bevacizumab.

Así las cosas, la anterioridad citada no solo menciona los componentes del método de tratamiento, sino que a su vez demuestra con datos las tasas de respuesta, indicando que el objeto de la solicitud ya había sido evaluado y demostrado su efecto técnico.

Por todo lo anterior y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo ya que el mismo carece de novedad y de nivel inventivo frente a las anterioridades aquí señaladas.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

IV PRUEBAS

Ruego que se tenga como tal, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- ❖ El documento Penson Richard T. *et al.*, "*Phase II study of carboplatin, paclitaxel, and Bevacizumab with maintenance Bevacizumab as first-line chemotherapy for advanced mullerian tumors*" publicado el 1 de enero de 2010. Todo el documento
- ❖ El documento Richardson D. *et al.*, "*Combination gemcitabine, platinum, and Bevacizumab for the treatment of recurrent ovarian cáncer*" publicado el 1 de diciembre de 2008. Todo el documento.

VI. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Certificado de existencia y representación legal de TECNOQUIMICAS S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
5. Copia para correr traslado al solicitante.
6. Las mencionadas en el acápite de pruebas

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A. las recibirá en sus oficinas localizadas en la Calle 23 N° 7-39 de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P.A. 44.655 de C.S.J.

AA 32867710
LIBRANZA RAMA
NOTARIA TERCERA
BOGOTÁ D.C.



ESCRITURA NUMERO CUATRO MIL QUINIENTOS -
TREINTA Y NUEVE (No.4.539) -----
En la ciudad de Cali, Capital del Depar-
tamento del Valle del Cauca, República de
Colombia, a los VEINTITRES (23) días -
del mes de OCTUBRE del año DOS MIL UNO --

(2.001), ante mí, JORGE ENRIQUE CAICEDO ZAMORANO, Notario
T E R C E R O (3o.) del Círculo de Cali, - - - - -

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali,
identificado con la cédula de ciudadanía número 14.949.561 de Cali, y dijo: ----

Como Notario Veintitres de este Círculo
hago constar que esta fotocopia coincide
con su fotocopia auténtica que he tenido
a la vista.
13 AGO 2007
WILLY VALEZ MORA
NOTARIO VEINTITRES
Bogotá D.C. - Colombia

MERO.- Que obra en su carácter de Representante Legal de en nombre y
representación de TECNOQUIMICAS S.A. sociedad comercial organizada y existente
conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida
por escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de
junio de 1957, reformada en distintas oportunidades, según consta en el certificado
expedido por la Cámara de Comercio de Cali -----

4539
OCT 23

SEGUNDO: Que en tal carácter, por este público instrumento, concede Poder Especial
pero amplio y suficiente a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de
Bogotá, identificado con C.C. # 79.152.473 Isaquén, abogado en ejercicio, portador
de la T.P 44655 del C.S.de la J., domiciliado en Bogotá, D.C., República de Colombia
con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante
con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad
industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos
represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente
ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo
concerniente a los siguientes asuntos: a) Obtención, formulación de observaciones y
oposición a patentes de invención, modelos y dibujos industriales y el registro de
licencias de uso de esos derechos; b) Las acciones de oposición, cancelación, nulidad,
medidas cautelares, concesión de licencias y en general los procesos civiles, penales,
administrativos o contencioso-administrativos relacionados con estos derechos u otros de
diferente naturaleza; acciones y procesos que promovamos o se nos promuevan; y c) para

LUZ MERY CORDEIRO
ELABORACION DE ESCRITURAS
Notaría 3ª de Cali

que en todos los asuntos arriba determinados, , tanto en los términos señalados por los artículos 42 y complementarios de la Decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.

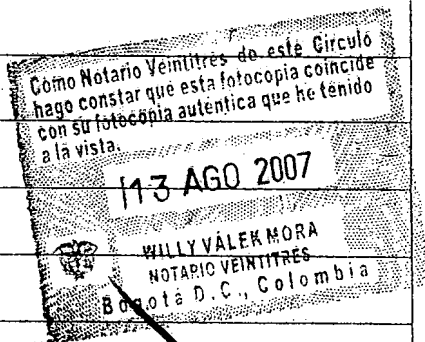
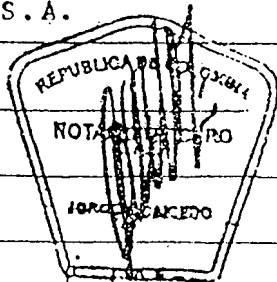
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.

Se agregan comprobantes. Derechos \$30.000.00 Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No.5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrió en la hoja número AA 3286877. ENMENDADO "OCTUBRE" VALE.

91 *Juan m Barberi*

JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO

Combination gemcitabine, platinum, and bevacizumab for the treatment of recurrent ovarian cancer

Debra L. Richardson, Floor J. Backes, Leigh G. Seamon, Vanna Zanagnolo, David M. O'Malley, David E. Cohn, Jeffrey M. Fowler, Larry J. Copeland*

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, The Ohio State University College of Medicine, Columbus, OH, USA

Received 11 June 2008

Available online 30 September 2008

Abstract

Objective. To describe the response rate (RR), progression-free survival (PFS), and toxicity profile of combination gemcitabine, platinum, and bevacizumab (GPB) for the treatment of recurrent epithelial ovarian cancer (EOC).

Methods. A chart review of all patients with recurrent EOC who were treated with D1, D15 GPB in a 28-day cycle at a single institution was performed. Standard doses were gemcitabine 1000 mg/m², cisplatin 30 mg/m² or carboplatin AUC 3, and bevacizumab 10 mg/kg. All patients were analyzed for toxicity. RR and PFS were assessed in all patients who received at least 2 cycles of GPB.

Results. Thirty-five patients were identified, and 33 received at least 2 cycles of GPB. The majority of patients (80%) were platinum sensitive. Patients received a median of 6 cycles of GPB (range 1–24). Sixteen patients (48%) had a complete response (CR), and 10 patients (30%) had a partial response (PR), for a total RR of 78%. An additional 5 patients (15%) had stable disease, and only 2 (6%) patients had progressive disease. The median overall PFS was 12 months (95% CI 7–15), with a median follow-up time of 10 months (2–22). Two patients (6%) had bowel perforations, and both survived. Hematologic toxicities were most common, with 29% and 14% of patients experiencing grade 3 or 4 neutropenia and thrombocytopenia respectively.

Conclusions. The combination of GPB demonstrated excellent efficacy for the treatment of recurrent EOC. However, serious toxicities occurred, and the safety profile of this combination requires further study.

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Keywords: Gemcitabine; Bevacizumab; Platinum; Recurrent epithelial ovarian cancer; Bevacizumab; Bowel perforation

Introduction

Ovarian cancer is the fourth leading cause of cancer death among women in the United States [1]. Every year about 22,000 women are diagnosed with ovarian cancer and approximately 15,000 women will die from the disease [2]. Although about 75% of patients with EOC will respond to first-line chemotherapy with platinum and paclitaxel, most patients with advanced stage EOC will recur. However, there are multiple active chemotherapeutic agents for the treatment of recurrent EOC. Because of this, the treatment of recurrent EOC can persist for many years. While chemotherapy in the recurrent setting is not

curative, the goal of therapy is to improve quality of life and possibly extend quantity of life while minimizing side effects [3].

Preclinical trials demonstrate synergism between platinum agents and gemcitabine, and gemcitabine may overcome platinum resistance [4,5]. Pfisterer et al. demonstrated that gemcitabine plus carboplatin improves PFS with acceptable toxicity compared to single-agent carboplatin in a randomized phase III trial (median PFS 8.6 months versus 5.8 months) [6]. RR of 16–64% have been achieved with combination gemcitabine plus platinum [5–9].

Angiogenesis is necessary for tumor growth and progression [10]. Angiogenesis is regulated by both positive and negative factors, the most potent of which is vascular endothelial growth factor (VEGF) [11]. Multiple reports have shown that angiogenesis, as measured by microvessel density, is associated with worse survival for ovarian cancer patients [12–16].

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Bevacizumab is a recombinant monoclonal antibody against VEGF, and prevents angiogenesis in animal models [17–19]. As such, it has a different mechanism of action than traditional chemotherapeutic agents. Bevacizumab has been studied extensively in patients with a variety of tumor types, including colorectal, breast, lung, and renal carcinoma [20,21]. Bevacizumab has previously been combined with other multi-drug regimens, such as 5-fluorouracil/irinotecan/leucovorin for metastatic colon cancer with significantly improved survival [22]. The addition of bevacizumab to gemcitabine and carboplatin for the treatment of non-small cell lung cancer was shown to significantly improve PFS as well as RR [23].

Recent reports have demonstrated bevacizumab is active in patients with recurrent EOC. RR of 16–21% have been reported for single-agent bevacizumab for the treatment of persistent or recurrent EOC [24–26]. A recently published phase II trial of bevacizumab with oral cyclophosphamide demonstrated a RR of 24% in patients with recurrent EOC [27]. Wright et al. reported a RR of 35% for bevacizumab in combination with a cytotoxic agent in platinum-refractory EOC patients [28]. In addition, bevacizumab in combination with taxane chemotherapy improves symptoms in patients with refractory EOC [29]. Thus, bevacizumab is an attractive candidate to add to cytotoxic chemotherapy regimens and is currently being investigated in randomized clinical trials as first-line treatment (GOG 218 and ICON 7). The objective of this study is to describe the RR, PFS, and toxicity profile of combination GPB for the treatment of recurrent EOC.

Materials and methods

A retrospective chart review was performed of all patients who initiated treatment with combination GPB (cisplatin or carboplatin) for recurrent EOC between October 2005 (the first time this regimen was used at our institution) and July 2007 at a single institution. Follow-up continued until March 2008. Institutional review board approval was obtained. Patients were identified by reviewing chemotherapy log books. Both platinum sensitive (recurrence >6 months after completing platinum-based chemotherapy) and platinum-resistant (recurrence <6 months after completing platinum-based chemotherapy) patients were included. Charts were abstracted for pertinent demographic information, as well as toxicities and treatment response. All patients were included in the toxicity analysis. RR and PFS were calculated for patients who received at least 2 cycles of this combination treatment.

The standard treatment dose was gemcitabine 1000 mg/m², bevacizumab 10 mg/m², and either carboplatin area under the curve (AUC) 3 mg/ml/min or cisplatin 30 mg/m² on days 1 and 15 in a 28-day cycle. The creatinine clearance for calculation of the carboplatin dose was calculated according to the Jelliffe method. Patients were pre-medicated with ondansetron, dexamethasone, and lorazepam, and metoclopramide, dexamethasone, and ativan were given to prevent delayed emesis. The use of granulocyte-colony stimulating factors (G-CSF) and erythropoietin stimulating agents (ESAs) was per physician discretion.

Measurable disease was defined as at least one lesion that was greater than 1cm on spiral CT, as defined by Response to

Treatment in Solid Tumors (RECIST) criteria [30]. In the absence of measurable disease, CA-125 levels were used to assess response per modified Rustin criteria [31]. Complete response was disappearance of gross evidence of disease, resolution of measurable disease on CT scan, or a normalization of CA-125 levels from an elevated level. Partial response was a 30% or greater reduction in measurement of longest dimension of each lesion, or >50% decrease in CA-125 levels. Progressive disease was a 20% or greater increase in measurement of longest dimension of each lesion or the appearance of any new lesion, or a doubling of CA-125 levels within 8 weeks of the start of chemotherapy. Stable disease was any condition which did not meet the above criteria. Best response was reported. CA-125 levels were routinely drawn with the standard pre-chemotherapy labs. CT scans were obtained as appropriate to follow measurable disease and at the physician's discretion. The NCI CTCAE Version 3.0 was used to evaluate toxicities. The worst grade toxicity in each category per patient was reported. PFS is the time from the date of first treatment with combination gemcitabine, platinum, and bevacizumab until disease progression or date of last contact.

Statistical analysis

Simple descriptive statistics were used to report response rates and frequency and severity of toxicities, including percentages, 95% confidence intervals, means, and medians as appropriate. Chi-square was used to calculate differences in proportions. Overall PFS was determined using the Kaplan Meier survival curve. Stata release 10 (College Station, Texas) was used to perform statistical calculations.

Results

Thirty-five subjects were identified, and all were included in the toxicity analysis. Seventeen of these patients are part of an ongoing prospective phase II trial of gemcitabine, carboplatin, and bevacizumab for the treatment of recurrent ovarian cancer. Ninety-four percent (33/35) of the subjects received at least 2 cycles and were analyzed for RR and PFS. The median age was 60 years, and the majority of the subjects were Caucasian. Eighty percent (28/35) of the patients were primarily platinum sensitive. Of these, 21% (6/28) had developed secondary platinum resistance (Table 1).

Patients had received a median of 2 prior chemotherapy regimens (range 1–11). All patients had been treated with platinum-based first-line chemotherapy. The median platinum-free interval was 13 months (range 0–50 months). Seven patients (20%) had received combination gemcitabine and platinum previously. Bevacizumab was added to combination gemcitabine and cisplatin after 4 cycles in 1 patient, and after 5 cycles in another. Seven patients (20%) had been treated with bevacizumab in the past. No patients were treated with combination GPB prior to this study.

Of the 33 patients analyzed for response and PFS, 21 patients received carboplatin while 12 patients were treated with cisplatin combined with gemcitabine and bevacizumab. Two patients had cisplatin substituted for carboplatin due to persistent neutropenia

Table 1

Baseline demographics (N=35)	Number (%) ^a
Median age (range), years	60 (41–77)
Race	
Caucasian	30 (86)
African-American	3 (9)
Unknown	2 (6)
Stage at diagnosis	
I	3 (9)
II	4 (11)
III	25 (71)
IV	2 (6)
Not staged	1 (3)
Histology	
Serous	24 (69)
Endometrioid	3 (9)
Mixed epithelial	3 (9)
Clear cell	1 (3)
Transitional	1 (3)
Unknown	3 (9)
Grade at diagnosis	
1	2 (6)
2	3 (9)
3	28 (80)
Unknown	2 (6)
Residual disease at primary surgery	
No gross residual	13 ^b (37)
Optimal (<1 cm)	20 (57)
Suboptimal (>1 cm)	1 (3)
Unknown	1 (3)
Platinum response	
Sensitive	28 (80)
Resistant/refractory	7 (20)
Secondary resistant	6
Measurable disease	20 (61)
Median platinum-free interval (range), months	13 (0–50)
Median number of previous chemotherapeutic regimens	2 (1–11)

^a Percentages may not add up to 100% due to rounding.
^b One patient received 4 cycles of neoadjuvant chemotherapy.

in one case and thrombocytopenia in the second case. There were several deviations from the standard regimen. The carboplatin doses ranged from AUC 2.5–3, cisplatin 25–30 mg/m², gemcitabine 600–1000 mg/m², and 1 patient was treated with bevacizumab 5 mg/kg. One patient was started on a 21 day cycle (omitting day 15), and three patients were changed to gemcitabine, platinum, and bevacizumab every 21 days for recurrent cycle delays. Eleven patients had the dose of gemcitabine reduced, usually by 20%.

Patients received a median of 6 cycles of combination GPB (range 1–24). Nineteen of the 35 patients (54%) experienced treatment delays. Ten percent (49/482) of treatments were delayed for a median of 1 week (range 1–8 weeks). Treatment delay was more common for patients who received carboplatin in addition to gemcitabine and bevacizumab, as compared to patients who received cisplatin. 36% (5/14) of the patients who were treated with cisplatin were delayed, versus 74% (17/23) of the patients treated with carboplatin (*p*=0.05). The most common reason for treatment delay was thrombocytopenia (cisplatin and carboplatin), followed by neutropenia (carboplatin). Sixteen patients (46%) received G-CSF, and 22 (63%) received erythropoiesis stimulating agents.

Response data (Table 2)

Twenty patients (61%) had measurable disease, while the other 13 patients were followed with CA-125 levels only for response (Table 2). Forty-eight percent (16/33) of patients had a CR (95% CI 31 to 66%), and 30% (10/33) had a PR (95% CI 16 to 49%), for a total RR of 78% (95% CI 61 to 91%). In addition, 5 patients (15%) had stable disease, and only 2 patients (6%) had progressive disease. Ninety percent (19/21) of the patients who were platinum sensitive at the time of treatment with this combination had either a CR or PR, and none had progressive disease. Sixty-seven percent (4/6) of the patients who had developed secondary platinum resistance prior to this treatment responded, and only 1 patient progressed. Of the 6 patients who were primarily platinum-resistant/refractory and evaluable for response, there were 2 (33%) complete responders and 1 (17%) partial responder (see Table 3). Seventy percent of patients with measurable disease were responders (8 CR and 6 PR), compared to 93% of patients followed with CA-125 levels for best response (8 CR and 4 PR). Both patients with progressive disease had measurable disease.

The median overall PFS was 12 months (95% CI 7–15 months), with a median follow-up time of 15 months (range 6–26 months) (see Fig. 1). One patient was lost to follow-up after 7 cycles with stable disease. Two patients were still undergoing treatment with combination GPB at the end of this study. Ten (30%) patients had combination GPB discontinued due to complete CR. Eight patients had this treatment stopped due to progressive disease. Treatment with this combination was stopped in 14 patients due to side effects, 6 who had no evidence of disease, and 8 who had evidence of disease. At last follow-up, 10 subjects had died of disease, 19 subjects were alive with disease, and 6 subjects had no evidence of disease.

Toxicity data (Table 3)

The most common Grade 3 and 4 toxicities were hematologic. Twenty-nine percent (10/35) of subjects had Grade 3 or 4 neutropenia. Grade 3 and 4 anemia occurred in 11% (4/35) and thrombocytopenia in 14% (5/35) of subjects. Grade 3 and 4 non-hematologic toxicities were uncommon (<10%). However, 2 patients (one with no history of hypertension) developed malignant hypertension requiring hospitalization. Carboplatin was discontinued in 3 patients for hypersensitivity reactions, and cisplatin in 1 patient for a reaction. While three patients had grade

Table 2

Response data (N=33)	Number (%) ^a			
Platinum sensitivity	CR	PR	Stable	Progressive
Platinum-sensitive ^b	13 (61)	6 (29)	2 (10)	0
Secondary platinum-resistant	1 (17)	3 (50)	1 (17)	1 (17)
Platinum-resistant/refractory	2 (33)	1 (17)	2 (33)	1 (17)
Total	16 (48)	10 (30)	5 (15)	2 (6)

^a Percentages may not add to 100 due to rounding.
^b Platinum sensitive at time of treatment with gemcitabine, platinum, and bevacizumab.

3 neuropathies, 1 of these was a pre-existing grade 3 neuropathy, and 1 occurred in a patient with a pre-existing grade 2 neuropathy. In total, sixteen patients (46%) had pre-existing neuropathy from previous chemotherapy, the majority (56%) of which was grade 2.

Thirteen subjects were hospitalized for a total of 17 hospital stays during treatment with this combination therapy. Reasons for hospitalization were as follows: placement of VP shunt (unrelated to chemotherapy), anti-coagulation for deep venous thrombosis, failure to thrive, dehydration due to diarrhea, malignant hypertension, hypercalcemia secondary to bone metastases, hyponatremia, fever (no identified source), rectal bleeding, small bowel obstruction, carboplatin administration for hypersensitivity, streptococcal bacteremia, enterovaginal fistula, and bowel perforation.

There were 3 serious gastrointestinal complications. Two patients were diagnosed with bowel perforation, and 1 patient developed an enterovaginal fistula while on treatment. The first bowel perforation occurred after cycle #2 in a platinum sensitive patient who had a CR. An abdominal CT scan revealed an anastomotic leak from the site of her ileo-cecal anastomosis which was performed 15 months prior, with an associated abscess. Of note, the patient had only received one previous chemotherapy regimen. The second bowel perforation occurred after 5 cycles of triple combination chemotherapy in a platinum sensitive subject with a CR. This patient had no prior history of bowel surgery, and had received 2 previous chemotherapy regimens. She was diagnosed with a perforated diverticular

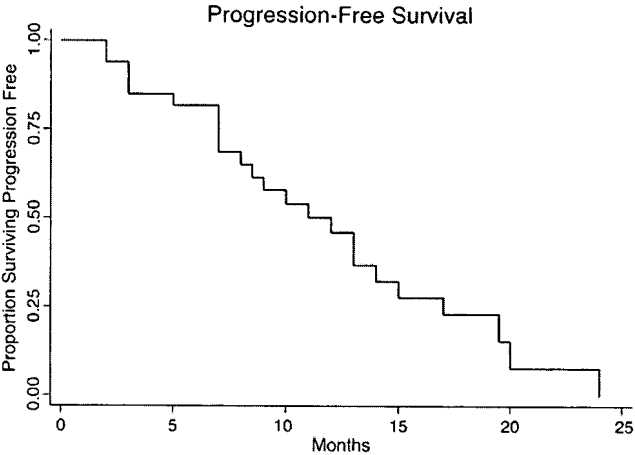


Fig. 1. Kaplan–Meier curve for time to progression. Median PFS was 12 months (95% CI 7–15), with a median follow-up time of 10 months.

abscess. The enterovaginal fistula occurred after 3 cycles of GPB in a patient with stable disease.

There was one death while on treatment with combination GPB (cisplatin). This 52 year old patient with a history of well-controlled hypertension and lupus had received 7 cycles of GPB when she was hospitalized for work-up and treatment of hypercalcemia. The patient was noted to have progressive disease, including bone metastases with spinal cord compression. She underwent a neurosurgical procedure for management of the spinal cord compression and spine stabilization, and had a massive cerebrovascular accident on post-operative day (POD) #11. After discussion with the family, the patient was changed to comfort care status and expired POD #14.

Discussion

The combination of GPB is highly active in the treatment of recurrent EOC, with a RR of 78% and a median PFS of 12 months. While single-agent bevacizumab has demonstrated modest activity (RR 16–21%) in patients with platinum-resistant/refractory disease, the addition of bevacizumab to cytotoxics has resulted in a reported RR of 35% [24–26,28]. The higher RR in this study compared to previously published studies incorporating bevacizumab may be attributable to the inclusion of platinum sensitive patients, although the CR in 2 platinum-resistant patients is noteworthy. The RR in this study compares favorably to published RR (16–64%) for combination gemcitabine and platinum, with a longer PFS in the present study [5–9]. The low rate of progressive disease is notable, as 20% of patients had received combination gemcitabine and platinum previously and 20% had been treated with bevacizumab in the past.

While the RR and duration of response are promising, significant toxicities were noted. The occurrence of bowel perforations in ovarian cancer patients treated with bevacizumab has been reported to be 0–15% [24–29,32]. In fact, a phase II trial of bevacizumab in platinum-resistant EOC patients was halted early because of a higher than expected gastrointestinal perforation rate [25]. A recent paper suggested that careful

Table 3
Toxicity data

	Patients, N (%)			(N=35)	
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Leukopenia	9 (26)	11 (31)	7 (20)	0	0
Neutropenia	5 (14)	8 (23)	8 (23)	2 (6)	0
Anemia	10 (29)	14 (40)	4 (11)	0	0
Thrombocytopenia	11 (31)	7 (20)	4 (11)	1 (3)	0
Fatigue	8 (23)	20 (57)	3 (9)	0	0
Pain	4 (11)	10 (29)	3 (9)	0	0
Headache	3 (9)	0	0	0	0
Constipation	16 (46)	2 (6)	0	0	0
Diarrhea	4 (11)	1 (3)	1 (3)	0	0
Nausea	10 (29)	6 (17)	3 (9)	0	0
Fistula, enterovaginal	0	0	1 (3)	0	0
Perforation, GI	0	0	2 (6)	0	0
Neuropathy					
Cranial	0	1 (3)	0	0	0
Sensory	7 (20)	15 (43)	3 (9)	0	0
Creatinine	1 (3)	1 (3)	0	0	0
Proteinuria	4 (11)	10 (29)	0	0	0
Hemorrhage	6 (17)	3 (9)	0	0	0
Thromboembolic	0	0	1 (3)	0	0
Hypertension	1 (3)	3 (9)	1 (3)	2 (6)	0
Liver function tests	4 (11)	1 (3)	0	0	0
Dyspnea	0	2 (6)	0	0	0
CNS ischemia	–	0	1 (3)	0	1 (3)
Allergy	1 (3)	2 (6)	3 (9)	0	0
Mucositis	4 (11)	1 (3)	0	0	0
Rash	0	1 (3)	0	0	0

patient selection may reduce the risk of bowel perforation, by avoiding bevacizumab in patients with clinical symptoms of bowel obstruction, pelvic exam consistent with rectosigmoid involvement, or bowel involvement on CT scan [33]. However, these risk factors were not present in our 2 patients who developed gastrointestinal perforation. Wright et al. suggest that bevacizumab should be incorporated earlier in treatment, as the 2 patients in their paper who suffered from bowel perforation were heavily pretreated [34]. Our patients who experienced gastrointestinal perforation were not heavily pretreated, having received 1 and 2 prior chemotherapy regimens respectively. In addition to bowel perforations, there have been 4 reported fistulas in EOC patients treated with bevacizumab. Further study is required to understand the mechanisms underlying bowel perforation and fistula formation in EOC patients treated with bevacizumab, and to determine if this complication is avoidable by patient selection.

Hematologic toxicities are common when gemcitabine and platinum are combined for the treatment of recurrent EOC. Grade 3 and 4 neutropenia ranges from 28–77% in patients treated with D1, D8 gemcitabine and platinum, depending on the usage of G-CSF support and dose of gemcitabine used [5,6,8,9,35,36]. Oxaliplatin has been combined with gemcitabine in a biweekly treatment schedule, with less hematologic toxicity [37,38]. Bozas et al. demonstrated a significant reduction in grade 3 and 4 neutropenia by using a D1, D15 regimen of combination cisplatin and gemcitabine. The rates of grade 3 and 4 hematologic toxicity in the present study are similar to those reported by Bozas et al [7]. The degree of neuropathy was not surprising, considering almost half of the patients had pre-existing neuropathy. One patient died while on treatment from an arterial thromboembolic event, possibly related to treatment, though the patient had recently undergone a neurosurgical procedure.

There are several limitations to this study. It is retrospective, and therefore subject to the inherent biases of retrospective studies, including selection bias. The treatment doses varied somewhat, but this is probably reflective of real world practice. There is no control group, so the effect that bevacizumab had on the RR cannot be directly measured. The patients were heterogeneous and included platinum sensitive and platinum-resistant patients. Because of the pre-clinical and clinical data suggesting synergism between gemcitabine and platinum, and the high response rates in platinum-resistant patients, we decided to include platinum-resistant patients [4,5,7,8].

In conclusion, combination GPB is highly efficacious in the treatment of recurrent EOC, with an overall response rate of 78%. However, serious adverse events from the addition of bevacizumab to gemcitabine and platinum occurred, especially hypertension and gastrointestinal complications. Currently, the dilemma for the clinician is when to incorporate bevacizumab in the treatment of recurrent EOC. The optimal timing of incorporation of bevacizumab in the treatment of recurrent EOC, the ideal patient, and the appropriate dose is unknown. The risk/benefit profile of the addition of bevacizumab to current cytotoxic regimens has to be carefully weighed. Further studies of the safety profile of this combination are warranted.

In addition, prospective comparisons of combination chemotherapy with and without bevacizumab (GOG 213 and the OCEANS trial) will help to better define the risk/benefit profile of the addition of bevacizumab to cytotoxic chemotherapy for recurrent EOC treatment.

Conflict of interest statement

Some of the patients included in this retrospective study are part of an ongoing prospective phase II trial at The Ohio State University. Funding is provided by Genentech, Inc and Eli Lilly, Corporation. Their funding is evenly distributed by patient enrollment. The funding is not granted until patients are enrolled onto the trial. None of the investigators have any conflicts to disclose.

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Phase II Study of Carboplatin, Paclitaxel, and Bevacizumab With Maintenance Bevacizumab As First-Line Chemotherapy for Advanced Müllerian Tumors

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ABSTRACT

Purpose

New strategies are needed to improve outcomes for patients with advanced ovarian cancer. Bevacizumab is a recombinant humanized monoclonal antibody that neutralizes vascular endothelial growth factor but is associated with GI perforations (GIPs) in patients with recurrent disease.

Patients and Methods

An open-label, phase II clinical trial was conducted in newly diagnosed patients with stage $\geq$ IC epithelial müllerian tumors. Patients received intravenous (IV) carboplatin (area under the curve = 5), paclitaxel (175 mg/m² IV), and bevacizumab (15 mg/kg IV) for six to eight cycles on day 1 every 21 days. Bevacizumab was omitted in the first cycle and continued as a single agent for 1 year.

Results

Sixty-two women participated in this study. Fifty-one patients (82%) were optimally surgically cytoreduced before treatment. The median age was 58 years (range, 18 to 77 years). Forty-five women (73%) had ovarian cancer, 10 (16%) had peritoneal cancer, four (6%) had fallopian tube cancers, and three (5%) had uterine papillary serous tumors. The majority of patients (90%) had stage III or IV disease. A median of 17 maintenance cycles (range, 0 to 25+ cycles) of bevacizumab (556 cycles) were administered with mild toxicity. Treatment was associated with two pulmonary embolisms and two GIPs, all occurring during the chemotherapy phase of treatment (364 total cycles). No grade 4 toxicities were seen during maintenance bevacizumab treatment. Radiographic responses were documented in 21 (75%) of 28 women with measurable disease (11 complete responses and 10 partial responses), with CA-125 responses in 76% of patients (11 complete responses, 21%; and 35 partial responses, 55%). The progression-free survival rate at 36 months was 58%.

Conclusion

The regimen of carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab is feasible, safe, and worthy of future study in advanced ovarian cancer.

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INTRODUCTION

Ovarian cancer is diagnosed in approximately 22,400 American women each year, and 15,000 women with ovarian cancer die, making it the leading cause of death from gynecologic malignancies in the United States.¹ Difficult to detect, the disease typically presents with symptoms only when advanced.² However, ovarian cancer is among the most sensitive of solid tumors to chemotherapy. The combination of carboplatin and paclitaxel is widely considered to be standard first-line therapy.³ Survival has improved little since the introduction of platinum, and taxane and biologics combined with this regimen are being explored in the hope of improving outcomes.⁴

Ovarian cancers secrete large amounts of vascular endothelial growth factor (VEGF) in vitro and in vivo. VEGF seems to play a crucial role in angiogenesis and tumor-induced immunosuppression in ovarian cancer patients⁵ and has been confirmed as an independent prognostic indicator by multivariate analysis of survival.⁶

Bevacizumab (Avastin; Genentech, South San Francisco, CA) is a recombinant humanized monoclonal antibody directed to VEGF⁷ that binds to and neutralizes the biologic properties of human VEGF.⁸ A phase II study conducted by the Gynecologic Oncology Group (GOG) evaluated bevacizumab monotherapy in women with recurrent platinum-resistant ovarian cancer and demonstrated a

response rate of 21% and a 6-month progression-free survival (PFS) rate of 40%.⁹ A separate consortium study of the combination of bevacizumab with daily, low-dose, oral cyclophosphamide demonstrated similar findings.¹⁰ However, a company-sponsored study was halted prematurely with a high rate (11%) of GI perforation (GIP).¹¹

Paclitaxel, carboplatin, and bevacizumab have been combined in lung cancer, but it is unknown whether the feasibility of this regimen will be generalizable to other diseases. This is especially important because we know that bevacizumab by itself can cause GIP in recurrent ovarian cancer and can be life threatening. Thus, the full toxicity of bevacizumab cannot always be extrapolated from one disease to another. Furthermore, it has been proposed that the earlier use of bevacizumab, when there is less bulky disease, especially after chemical debulking with one cycle of chemotherapy, might be better tolerated, with less risk of GIP. Therefore, the present study was designed to test the feasibility of the regimen in newly diagnosed ovarian cancer to determine whether the toxicity profile, especially with respect to GIP, would be acceptable enough to justify moving it into a phase III trial. The results of the present study provide a firm basis for the ongoing phase III trial (GOG218), which also tests the hypothesis tested in this study that protracted bevacizumab may impact PFS.

PATIENTS AND METHODS

The primary objectives of this multi-institutional phase II study were to examine the toxicity of this treatment when administered in adjuvant fashion and estimate the objective response rate and PFS of carboplatin, paclitaxel, and bevacizumab followed by single-agent bevacizumab as consolidation for advanced müllerian tumors.

Patients

The study was an investigator-initiated study approved by the Dana-Farber/Harvard Cancer Center (DF/HCC; Boston, MA) Scientific Review Committee and Institutional Review Board. The study was conducted at four sites in compliance with institutional and federal guidelines. Patients were eligible if they met the following criteria and signed written informed consent: ≥ 18 years old; histologic diagnosis of epithelial ovarian carcinoma, fallopian tube cancer, primary peritoneal carcinoma, or papillary serous müllerian carcinoma; a previous attempt at surgical debulking; stage $\geq 1C$; Eastern Cooperative Oncology Group performance status of 0 to 2; peripheral neuropathy less than grade 2; and life expectancy ≥ 6 months. Patients meeting any of the following criteria were not eligible for the trial: a history of serious systemic disease, myocardial infarction within the last 6 months, uncontrolled hypertension, unstable angina, New York Heart Association grade 2 or greater congestive heart failure, unstable symptomatic arrhythmia requiring medication (patients with chronic atrial arrhythmia, ie, atrial fibrillation or paroxysmal supraventricular tachycardia, were eligible), or peripheral vascular disease (grade ≥ 2); prior history of thrombotic events or stroke; prior chemotherapy or radiotherapy; bleeding diathesis, therapeutic anticoagulation (prophylactic low-dose warfarin was allowed; 1 mg orally every day with international normalized ratio < 1.2), or any active bleeding; evidence of tumor involving major blood vessels on computed tomography (CT) scan; a surgical wound that had failed to close; prior treatment with an antiangiogenic agent; active psychiatric disease or neurologic symptoms requiring treatment (grade 1 sensory neuropathy was allowed); CNS or brain metastases; proteinuria or clinically significant impairment of renal function (patients unexpectedly discovered to have $> 1+$ proteinuria at baseline had to have < 1 g of protein/24 hours); dementia or significantly altered mental status that would prohibit the understanding and/or giving of informed consent; hypersensitivity to polyethoxylated castor oil (Cremophor EL; BASF, Ludwigshafen, Germany); active bacterial, viral, or fungal infections; or receiving other investigational therapy. Neutrophil count had to be more than 1,500/ μ L,

and platelet count had to be more than 100,000/ μ L. Alkaline phosphatase and bilirubin had to be less than 1.5 $\times$ the upper limit of normal, AST had to be less than 5 $\times$ the upper limit of normal, and calculated creatinine clearance had to be more than 50 mL/min. Patients could not be included if the initial surgical cytoreduction was such that interval cytoreductive surgery might materially improve prognosis because patients were not permitted to have interval cytoreductive surgery on study.

All patients were registered with the Quality Assurance for Clinical Trials group at DF/HCC who also managed all the data in a Health Insurance Portability and Accountability Act-compliant format. Patients were required to have a medical history and physical examination, with evaluation of performance status, CBC with differential and platelets, serum creatinine, total bilirubin, AST, ALT, and urinalysis before each cycle of treatment. Tumor response was evaluated using CA-125 and at least abdominopelvic CT every three cycles and every 3 months during maintenance until completion of study. The study competed with a DF/HCC study investigating intraperitoneal chemotherapy preferentially enrolling patients with optimally resected disease.

Treatment and Dose Modifications

Carboplatin and paclitaxel were administered concurrently with bevacizumab after surgery for six to eight cycles every 21 days. Bevacizumab was obtained directly from Genentech. Bevacizumab was omitted in the first cycle and immediately postoperatively and was continued for 1 year of maintenance therapy. Bevacizumab was suspended for 4 to 6 weeks before major surgery and 2 weeks before minor elective surgery.

Bevacizumab was diluted in 0.9% sodium chloride and administered initially over 90 minutes, with the rate subsequently increased as tolerated (minimum, 30 minutes). Patients received paclitaxel premedication with dexamethasone 20 mg orally 14 and 7 hours before paclitaxel administration, using an in-line filter with a microporous membrane not greater than 0.22 μ m over 3 hours. All sites used 12- and 7-hour dexamethasone premedication. Carboplatin was infused intravenously over 1 hour, with the dose calculated using the Calvert formula based on calculated creatinine clearance (Jelliffe formula). Carboplatin (area under the curve = 5) is an institutional standard and may allow the future incorporation of novel agents that have hematologic toxicity, but it was not anticipated that bevacizumab would exacerbate hematologic toxicity. Standard supportive care was used without primary growth factor prophylaxis.

Dose modifications for hematologic toxicities were based on blood counts at the time of re-treatment (re-treatment required absolute neutrophil count [ANC] $\geq 1,000/\mu$ L and platelets $\geq 100,000/\mu$ L). For an ANC of 750 to 1,000/ μ L, granulocyte colony-stimulating factor was added; drugs were held for ANC less than 750/ μ L. For a platelet count of 60,000 to 99,000/ μ L, carboplatin was reduced to area under the curve of 4; drugs were held for a platelet count of less than 60,000/ μ L, with bevacizumab held for a platelet count of less than 75,000/ μ L. Patients were removed from protocol if hematologic toxicity lasted more than 35 days. For nonhematologic toxicity, dose reductions of paclitaxel were sequentially allowed to 135 mg/m² and 100 mg/m² for neuropathy grade ≥ 2 , and one dose reduction of paclitaxel to 135 mg/m² was allowed for grade 2 liver toxicity. Bevacizumab infusion-related events were managed with premedication and slower infusions, and the drug was discontinued for any grade ≥ 3 toxicity and all arterial thromboembolic events.

Patients with grade 3 liver toxicity could have drug held until recovery to $\leq$ grade 1, with the drug discontinued if grade 3 liver function test elevations recurred with re-treatment. Proteinuria had to be less than 3+ to allow treatment with bevacizumab, and 2+ dipstick proteinuria required a 24-hour collection and drug to be held until proteinuria improved to less than 2 g of protein in a 24-hour urine collection. If this did not happen within 2 months or nephrotic syndrome developed (grade 4), bevacizumab was discontinued. Patients were taken off study for other grade 3 or 4 toxicity, and all arterial thromboembolic events. Patients who developed venous thromboembolism on study were allowed to continue with full anticoagulation if all of the following criteria were met: a stable in-range international normalized ratio (2 to 3), no prior grade 3 or 4 hemorrhagic event, and no tumor involving major blood vessels on any prior CT scan.

Toxicity

Toxicity was evaluated using Common Terminology Criteria for Adverse Events version 3. Serious adverse events were submitted to the US Food and Drug Administration, Genentech Drug Safety, and all participating investigators.

Response

PFS was estimated with CT scans and CA-125 blood tests every 3 months and measured from study registration. Response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST),¹² and CA-125 response was evaluated by Rustin criteria requiring two 50% reductions in CA-125.¹³

Statistical Considerations

Accrual was set at 62 patients. The study initially recruited 17 patients and was temporarily halted for evaluation of deaths as a result of thromboembolism, arterial complications, and GIPs. The study was to be terminated if five or more of these toxicities were observed. The probability of missing these toxicities was $P = .025$ when the true rate would have been 50% and was $P = .126$ when the true rate would have been 40%. The overall survival and PFS times were estimated using the Kaplan-Meier method, and 95% CIs were estimated using the exact binomial distribution.

Table 1. Patient Demographics and Clinical Characteristics		
Characteristic	Patients (N = 62)	
	No.	%
Age, years		
Median	58	
Range	18-77	
Follow-up, months		
Median	17	
Range	1-26	
Performance status		
1	42	68
2	20	32
Stage		
Early	6	10
III	43	69
IV	13	21
Site		
Ovary	45	73
Primary peritoneal	10	16
Fallopian tube	4	8
UPSC	3	5
Histology		
Papillary serous	43	69
MMMT	7	11
Mixed	6	10
Endometrioid	3	5
Clear cell	3	5
Grade		
3	50	81
2	7	11
1	3	5
Unknown	2	3
Cytoreduction*		
Optimal	49	79
Suboptimal	13	21

Abbreviations: UPSC, uterine papillary serous carcinoma; MMMT, malignant mixed Müllerian tumor.
*Suboptimal includes patients who did not get surgery because of stage IV disease (n = 3).

RESULTS

Patient Characteristics

Between March 2005 and February 2007, 62 eligible and evaluable patients were enrolled. All patients have completed all planned cycles of chemotherapy. A total of 364 cycles of chemotherapy and 556 cycles of consolidation were administered. Thirteen patients (21%) received more than six cycles of chemotherapy (five received seven cycles, and eight received eight cycles) for a persistently elevated but decreasing CA-125, with poor prognostic features.

Patient characteristics are listed in Table 1. Although in concept, the study was designed for suboptimally cytoreduced patients and there was a competing phase II study of intraperitoneal chemotherapy, many of the patients (79%) had optimally cytoreduced disease, reflecting the typical optimal cytoreduction rate of the institutions (approximately 80%) and thus a likely selection bias. However, CT scan was required before commencing chemotherapy, and the operative evaluation significantly underestimated residual disease, with many patients (45%) having baseline CT scans with measurable disease (> 1 cm on spiral CT) and thus suboptimal disease.

All patients were evaluable for toxicity, and 28 were evaluable for response (Fig 1). Two women (3%) withdrew consent; one patient, with a prior history of problematic diverticulitis, withdrew when the information about GIP became available, and the other patient wished to discontinue maintenance for an overdue hip replacement. Only two patients had second-look laparotomies, which were both negative and uncomplicated.

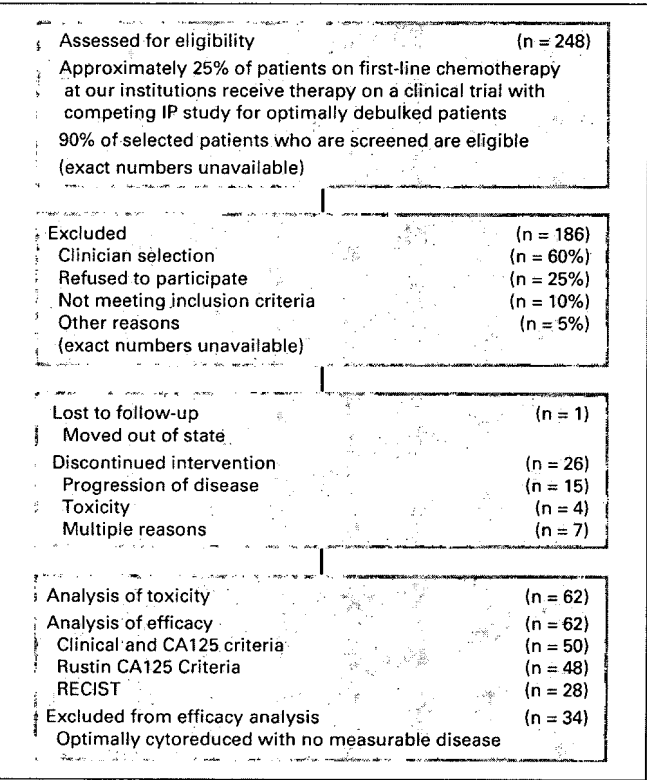


Fig 1. CONSORT diagram. RECIST, Response Evaluation Criteria in Solid Tumors.

Toxicity

Toxicities for the two phases (chemotherapy and single-agent bevacizumab treatment) of the study are listed in Tables 2 and 3. As expected, the combination of paclitaxel and carboplatin was generally well tolerated. There were no apparent excess chemotherapy toxicities because of the concurrent administration of bevacizumab.

Four women (6%) were removed for toxicity with autonomic neurotoxicity, hypertension, bilateral pulmonary embolism complicating a wound infection and empyema, and a nasal perforation. There were two wound healing delays, with both wounds not healing until the completion of chemotherapy, no arterial thromboses, no serious hemorrhages, and no treatment-related deaths. Allergic reactions were caused by bevacizumab (three grade 1 reactions in one patient) and paclitaxel (n = 11; five grade 3, two grade 2, and four grade 1 reactions in six patients) but not carboplatin.

On chemotherapy, eight patients required dose delays. Paclitaxel dose was reduced nine times in four patients, and carboplatin dose was reduced four times in three patients. During maintenance, there were 20 doses held in 14 patients.

Although hematologic toxicity was common, it was rarely complicated, and only two patients had fever and neutropenia. Granulocyte colony-stimulating factor was not proscribed in the protocol, which mandated dose delays and dose reductions, but five patients were administered filgrastim (n = 1) or pegfilgrastim. The episodes of severe thrombocytopenia with bevacizumab alone were late hematologic toxicity from carboplatin. Thromboses were documented in

Table 3. Consolidation Toxicity During 556 Cycles of Bevacizumab

Toxicity	Maximum Grade of Toxicity per Patient (No. of patients)				Total No. of Patients
	1	2	3	4	
Hematologic					
Neutropenia	3	1	1	0	5
Anemia	12	0	0	0	12
Thrombocytopenia	4	0	1	1	6
Nonhematologic					
Musculoskeletal pain*	25	14	3	0	42
Metabolic*	24	6	2	0	32
Bleeding	31	0	0	0	31
Fatigue	33	7	0	0	40
Rash or edema	9	2	0	0	11
Dysphonia	10	0	1	0	11
Hypertension	9	7	5	0	21
Proteinuria	4	5	2	0	11
Constitutional	3	0	0	0	3
Palpitations	2	0	0	0	1
Allergic reaction	1	0	0	0	1
Thromboembolism	0	0	0	0	0
GI perforation	0	0	0	0	0

NOTE. Additional grade 3 or 4 adverse events occurring in at least one instance were infection (grade 3, n = 1) and syncope (grade 3, n = 1). Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (version 3).

*Cumulative from various regions or sources.

Table 2. Chemotherapy Toxicity During 364 Cycles of Chemotherapy

Toxicity	Maximum Grade of Toxicity per Patient (No. of patients)				Total No. of Patients
	1	2	3	4	
Hematologic					
Neutropenia	7	4	4	10	25
Anemia	36	5	2	0	43
Thrombocytopenia	7	2	2	2	13
Febrile neutropenia	0	1	1	0	2
Nonhematologic					
Musculoskeletal pain*	34	12	3	0	49
Metabolic*	18	16	8	0	42
Hemorrhage	46	1	0	0	47
Alopecia	8	45	0	0	53
Neuropathy	31	6	4	0	41
Abnormal liver function tests	18	1	0	1	20
Cough or shortness of breath	18	2	0	0	20
Vomiting	13	5	2	0	20
Allergic reaction†	1	1	4	0	6
Hypertension	1	3	6	0	10
Thromboembolism	0	0	0	2	2
Palpitations	3	0	0	0	3
Proteinuria	5	1	0	0	6
GI perforation	1	0	0	1	2

NOTE. Additional grade 3 or 4 adverse events occurring in at least one instance were dehydration (grade 3, n = 1), fatigue (grade 3, n = 1), mucositis (grade 3, n = 1), and rash (grade 3, n = 1). Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (version 3).

*Cumulative from various regions or sources.

†All of the allergic reactions were to paclitaxel.

10% of patients but were readily managed with anticoagulation. Within months of starting the study, an amendment was filed to allow and encourage patients to take prophylactic aspirin during the consolidation phase of the study.

There were two GIPs. One patient presented with a pulmonary embolism, and on CT scan, a focus of gas was incidentally identified within mesenteric fat thought to be secondary to evolving infection or, less likely, an anastomotic leak, with no clinical sequelae. The other patient had a catastrophic GIP with surgery and received intensive care with pressor support for more than a week. No clear site of perforation was identified at laparotomy, with no persisting tumor identified by biopsy. Neither patient died. Patients with GIP and nephrotic syndrome were not kept on study.

Twenty-seven patients (44%) required antihypertensives (first-line lisinopril), but only two patients required multiple agents. One patient developed transient, fully reversible nephrotic syndrome. No patient developed reversible hypertensive leukoencephalopathy syndrome.

Patients discontinued or were removed from maintenance therapy for progressive disease (n = 15; 24%), toxicity (n = 4; 6%), or multiple other reasons (n = 7; 11%), with the most common reason cited being intolerable myalgias because they were moderate but continual (reported in 10% of patients).

Efficacy

Clinical outcomes are listed in Tables 4 and 5, and overall survival and PFS are illustrated in Figure 2. At the completion of chemotherapy, 96% (95% CI, 90% to 99%) of patients had achieved at least a partial response by clinical and radiologic criteria and had a normal CA-125 (< 35 U/mL). Combining RECIST and formal Rustin criteria, the overall response rate was 76% (95% CI, 69% to 87%), with a

Table 4. Response to Chemotherapy Including All Patients Who Completed More Than Two Cycles of Chemotherapy

Response	Patients		
	No.	%	95% CI
Clinical and CA-125 response (N = 62)	50	81	71 to 92
Rustin criteria (n = 50)			
Overall response	48	94	86 to 99
Complete response	38	75	62 to 87
Partial response	10	20	10 to 34
Stable disease	2	4	1 to 14
Progressive disease	0	0	0 to 7
RECIST (n = 60)			
Overall response	45	75	62 to 85
Complete response	14	23	13 to 36
Partial response	31	52	38 to 65
Stable disease	15	25	15 to 37
Progressive disease	0	0	0 to 6

NOTE. The upper clinical response rate reflects the number of patients in remission at the end of chemotherapy (no clinical evidence of disease and a normal CA-125; intent-to-treat analysis for the whole cohort). The stricter criteria for response (RECIST and Rustin criteria [two 50% reductions in CA-125]) are shown with the denominator. Two patients withdrew consent but are included in the intent-to-treat analysis despite not receiving bevacizumab because they agreed to be observed, 12 patients had initially normal CA-125 levels, and two patients did not get scans for evaluation because they withdrew from the study as a result of toxicity (pulmonary embolism and neuropathy).
Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumors.

complete response documented in 13 patients (21%), partial response in 34 patients (55%), and stable disease in 13 patients (21%). No patient had progressive disease on chemotherapy.

Median PFS estimate is 29.8 months, and its lower 95% CI is 17.3 months, with the upper CI not yet estimable. Median overall survival has not yet been reached.

DISCUSSION

As the leading cause of death from gynecologic malignancies in the United States, ovarian cancer remains a silent killer of too many women, and the development of more effective therapy is the highest priority in gynecologic oncology. With increasing evidence that anti-

Table 5. Outcome on Maintenance Therapy (n = 58)

Response	No. of Patients	%
Removed from study prior to maintenance	4	6
Completed 18 cycles of maintenance therapy	29	47
Completed with increasing CA-125	2	3
Reason for removal from maintenance therapy		
Progressive disease	16	26
Multiple reasons*	7	11
Toxicity	4	6

NOTE. Percentages are based on the entire study population. Median progression-free survival estimate is 29.8 months, and its lower 95% CI is 17.3 months, with the upper CI not yet estimable. Median overall survival has not yet been reached.

*Five patients were removed from maintenance therapy at their or their clinician's discretion with stable disease, one patient was removed for a dental procedure, and one patient was lost to follow-up.

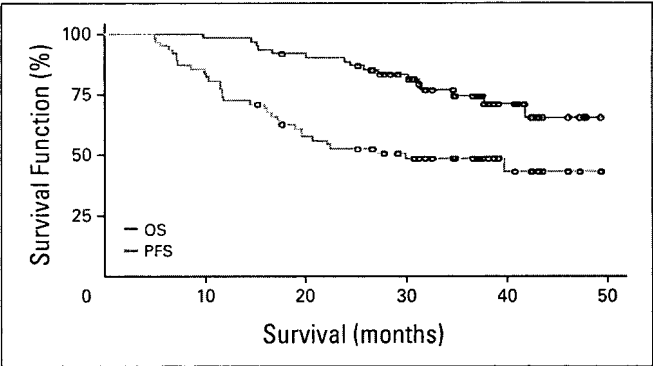


Fig 2. Overall survival (OS) and progression-free survival (PFS). Analysis includes all evaluable patients; two patients withdrew consent, 12 patients had initially normal CA-125 levels, and two patients did not get scans for evaluation.

angiogenic agents may be particularly potent in ovarian cancer, we have investigated the addition of bevacizumab with standard chemotherapy. We show here that the combination of carboplatin, paclitaxel, and bevacizumab is well tolerated and associated with a high remission rate. Although the intraperitoneal administration of chemotherapy is associated with better overall survival in carefully selected patients, in patients destined to experience relapse, intravenous carboplatin plus paclitaxel represents a convenient, well-tolerated regimen with a predictable toxicity profile that ideally lends itself to the integration of novel biologics.

In addition to the incorporation of bevacizumab with chemotherapy, we incorporated a maintenance phase of treatment using bevacizumab as a single agent. There are four main reasons to investigate protracted exposure to bevacizumab, despite the unproven benefit in this disease, extra risk, and cost. The first reason is mechanistic; the agent, although inducing apoptosis, is considered a biologic, and protracted exposure is thought to be necessary to maintain tumor dormancy. The second reason is preclinical; in the preclinical studies of ovarian cancer (SKOV-3 intraperitoneal murine model), the function-blocking VEGF antibody A4.6.1 significantly inhibited subcutaneous SKOV-3 tumor growth approximately 20-fold compared with controls ($P < .05$), and within 2 to 3 weeks of cessation of A4.6.1, mice developed severe ascites and tumor burden.¹⁴ The third reason is a clinical paradigm; studies in other solid tumors have treated patients until tumor progression, and it is now widely accepted that continual rather than intermittent palliative chemotherapy translates into a better quality of life.¹⁵ Finally, GOG178, a single prematurely closed but provocative randomized controlled trial, reported a large improvement in PFS.¹⁶ PFS is considered one of the most important end points in patients with advanced ovarian cancer. Despite these contentions, maintenance therapy should not be considered standard with supporting data from definitive randomized controlled trials.

Avoiding the risk of GIP remains a major priority for clinical investigations of bevacizumab in ovarian cancer. Our observed GIP rate (3%) approaches that observed in patients with metastatic colorectal cancer (2.4%).^{11,17-19} For patients with recurrent disease a number of strategies were identified to try and reduce the risk of GIP, including limiting the number of prior lines and excluding bowel involvement.²⁰ However, transmural metastases are common in recurrent disease, and the optimal and safest time to impact the clinical course of the disease may be during first-line therapy.

Micha et al²¹ report a similar overall response rate (80%) with an identical regimen of paclitaxel, carboplatin, and bevacizumab primary induction therapy in 20 similar patients, with similar toxicity. Traditionally, first-line clinical trials in ovarian cancer have not reported response rates because, after surgery, patients are considered to not have measurable disease. However, it is increasingly recognized that there is often evaluable and measurable disease in many patients who are surgically considered to have been optimally cytoreduced (< 1 cm disease at the end of surgery) if CT scans are performed before adjuvant chemotherapy. The outcomes of our study compare favorably with GOG158, which showed that carboplatin plus paclitaxel was not inferior to cisplatin plus paclitaxel in 792 patients.²²

First-line carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab is a highly active combination that remains experimental but is feasible in patients with previously untreated advanced ovarian cancer. Randomized controlled trials are required to determine the efficacy of bevacizumab when used in combination with chemotherapy and as maintenance therapy in the treatment of ovarian cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest

policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Richard T. Penson, Genentech (C) **Consultant or Advisory Role:** Richard T. Penson, AstraZeneca (C); Don S. Dizon, Bristol-Myers Squibb (C), Genentech (C); Ursula A. Matulonis, Genentech (C) **Stock Ownership:** None **Honoraria:** Don S. Dizon, Genentech **Research Funding:** Richard T. Penson, Genentech, DARA BioSciences, MGI Pharma, Bayer Pharmaceuticals, CuraGen, PDL BioPharma, Endocyte; Don S. Dizon, Genentech; Neil S. Horowitz, Genentech; Ursula A. Matulonis, Genentech; Susana M. Campos, Genentech **Expert Testimony:** Richard T. Penson, Aventis Pharma v Apotex (C) **Other Remuneration:** None

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Administrative support: Richard T. Penson, Maria R. Roche

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Final approval of manuscript: Richard T. Penson, Don S. Dizon, Stephen A. Cannistra, Maria R. Roche, Carolyn N. Krasner, Suzanne T. Berlin, Neil S. Horowitz, Paul A. DiSilvestro, Ursula A. Matulonis, Hang Lee, Modjule A. King, Susana M. Campos

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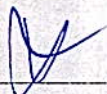
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SON: **TRESCIENTOS VEINTICINCO MIL PESOS MONEDA CORRIENTE**

Responsable: 

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*** Conceptos Pagados ***

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			\$103.000.00

SON: **CIENTO TRES MIL PESOS MONEDA CORRIENTE**

Responsable: _____

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