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Bogotá, D.C.,

Abogado
ALICIA LLOREDA RICAURTE

ASUNTO	Radicación	09-79621
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	011

113081

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (Fase Nacional)	☐	Cap. I	☐
		Cap. II	☐

No. Solicitud Internacional PCT/US2008/055502
Fecha de Presentación Internacional 29 febrero 2008

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

1. Documentos estudiados

Descripción:	Folios 98 a 321	30 junio 2009
Reivindicaciones:	Folios 322 a 341	30 junio 2009
	Folios 422 a 441	29 septiembre 2009
	Folios 479 a 485	11 diciembre 2009
Dibujos:	Folios 342 a 397	30 junio 2009
Secuencias:	Folios 398 a 416	30 junio 2009
Oposiciones (Lafrancol S.A):	Folios 519 a 523	15 febrero 2011
Prioridad:	US 60/892.640	02 febrero 2007
	US 60/912.053	16 abril 2007
	US 61/029.748	19 febrero 2008

2. Análisis de la Prioridad

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

3. Objeto de la invención

Título de la solicitud: "Predicción de respuesta a un inhibidor de dimerización HER basado en expresión de HER3 bajo".

El problema planteado en esta solicitud consiste en la necesidad proporcionar métodos para seleccionar pacientes con cáncer de ovario en donde se presenten niveles relativos de tanto HER2 como HER3.

Para resolver este problema técnico la solicitud en estudio proporciona un método de selección de agentes quimioterapéuticos inhibidores de HER, para tratar pacientes con cáncer mediante el uso de HER3 bajo y HER alto.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K39/395; C12Q1/68; G01N33/574

4. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de las reivindicaciones 7 a 19 que hace referencia a un método de tratamiento y de diagnóstico no es patentable de acuerdo con el Art citado.

5. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 1 a 6 no es patentable, de acuerdo con el Art 14.

Se aclara al solicitante que a pesar de que la materia reivindicada en las clausulas 1 a 19 no es patentable, en el estado de la técnica se divulga en el documento D1 y D2, el uso de un antagonista de un inhibidor HER2/HER3 como medio para seleccionar pacientes con cáncer.

Ítem	Documento	Título	Fecha de Publicación
D1	US2004106161	Methods for identifying tumors that are responsive to treatment with anti-ErbB2 antibodies	03 junio 2004

D1 ¹(folios 548 a 550) divulga un método de identificación de tumores sensibles al tratamiento con anticuerpos anti-HER2 mediante la detección de la presencia de un complejo de proteínas HER2/HER3 en una muestra de células tumorales. Asimismo, se divulga un método de tratamiento con agentes quimioterapéuticos como pertuzumab (inhibidor de HER3), para pacientes que presentan tumores con heterodimeros HER/2/HER1 y / o HER2/HER3.

6. Análisis de la Oposición

Oposición de LaFranco S.A.

El opositor argumenta que el objeto de reivindicación no cumple con los requisitos de patentabilidad ya que las composiciones que comprenden administrar un inhibidor de dimerización HER y un agente quimioterapéutico para obtener método de tratamiento de un tipo de cáncer, son prácticas y eventos totalmente conocidos en la industria farmacéutica.

De igual manera el opositor argumenta que: "con respecto a las composiciones farmacéuticas de las cuales se hace referencia, donde se involucran agentes tales como Doxorubicina, Docetaxel, Trastuzumab, Gecitabina, Carboplatino, entre muchos otros, es imprescindible manifestar que no puede la solicitante acceder a un beneficio patentario sobre formulaciones farmacéuticas que comprenden moléculas que se encuentran descubiertas y plenamente identificadas en el sector químico-farmacéutico" y posteriormente cita los siguientes documentos de patente para cada una de las moléculas señaladas así:

1URL:http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=2004106161A1&KC=A1&FT=D&ND=&date=20040603&DB=&locale=en_EP

Doxorubicina: ZA6802378 / US3590028
Docetaxel: EP253738 / US4814470
Trastuzumab: WO8906692 / US5677171
Gemcitabina: GB2136425 / US4808614
Carboplatino: NL7307863 / US4140707

Por último el opositor expresa que la solicitud de la referencia pretende proteger objetos que no son considerados invenciones, tales como métodos de tratamiento y de diagnóstico aplicables al cuerpo humano, y adjunta como documentos prueba fichas técnicas del Merck Index (2006) de Doxorubicina, Docetaxel, Trastuzumab, Gemcitabina, Carboplatino (folios 524 a 528)

Respuestas del Solicitante

A los argumentos del opositor, el solicitante no dio ninguna respuesta.

Respuesta del Examinador Técnico

Teniendo en cuenta que el objeto reivindicado no es patentable y que no se reclama ningún tipo de composición, este despacho considera que los documentos presentados en la Oposición no desvirtúan la Novedad y el Nivel Inventivo del objeto de esta solicitud; por lo cual no se considerarán dentro del Examen de Patentabilidad.

Asimismo, esta de acuerdo con el opositor en cuanto a que el objeto reclamado relaciona materia no patentable como son: métodos de tratamiento y de diagnóstico aplicables al cuerpo humano.

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

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante y presentarla por escrito

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JESÚS FERNEL GARCÍA GARCÍA
Director de Nuevas Creaciones (E)

27 JUL. 2012

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

Elaborado por: Ana Delia Pinzón García
Revisado por: Consuelo Leguizamón Leguizamón
Aprobado por: Jesús Fernel García García



US 20040106161A1

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SSI

(19) **United States**

(12) **Patent Application Publication**

Bossenmaier et al.

(10) **Pub. No.: US 2004/0106161 A1**

(43) **Pub. Date: Jun. 3, 2004**

(54) **METHODS FOR IDENTIFYING TUMORS
THAT ARE RESPONSIVE TO TREATMENT
WITH ANTI-ERBB2 ANTIBODIES**

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(21) **Appl. No.: 10/619,754**

(22) **Filed: Jul. 14, 2003**

Related U.S. Application Data

(60) **Provisional application No. 60/396,290, filed on Jul.
15, 2002. Provisional application No. 60/480,043,
filed on Jun. 20, 2003.**

Publication Classification

(51) **Int. Cl.⁷ G01N 33/574; C07K 16/30**
(52) **U.S. Cl. 435/7.23; 530/388.8**

(57)

ABSTRACT

Tumors are identified as responsive to treatment with anti-HER2 antibodies by detecting the presence of a HER2/HER3 and/or HER2/HER1 protein complex or for HER2 phosphorylation in a sample of tumor cells. Patients suffering from a tumor comprising HER2/HER1 and/or HER2/HER3 heterodimers and/or HER2 phosphorylation are treated with anti-HER2 antibodies, such as rhuMAb 2C4.

US 2004/0106161 A1

Jun. 3, 2004

39

-continued

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 100 105

<210> SEQ ID NO 6
 <211> LENGTH: 119
 <212> TYPE: PRT
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<400> SEQUENCE: 6

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 35 40 45

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly Arg Val Gly Tyr Ser Leu Tyr Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

What is claimed is:

1. A method of identifying a tumor as responsive to treatment with an anti-HER2 antibody comprising:

- a) detecting the presence of a HER2/HER3 and/or HER2/HER1 protein complex in a sample of said tumor;
- c) identifying a tumor as responsive to treatment with anti-HER2 antibody when a complex is detected.

2. The method of claim 1 wherein the anti-HER2 antibody blocks ligand activation of an ErbB heterodimer comprising HER2.

3. The method of claim 1 wherein the anti-HER2 antibody is monoclonal antibody 2C4.

4. The method of claim 1 wherein the anti-HER2 antibody is rhuMab 2C4.

5. The method of claim 1 wherein the presence of a HER2/HER3 and/or HER2/HER1 protein complex is detected by:

- a) immunoprecipitating any protein complexes that comprise HER2 with an anti-HER2 antibody;
- b) contacting the immunoprecipitated complexes with an antibody selected from the group consisting of anti-HER3 antibodies and anti-HER1 antibodies; and
- c) determining if an anti-HER3 and/or anti-HER1 antibody binds to the immunoprecipitated complexes,

wherein a HER2/HER3 and/or HER2/HER1 complex is detected if it is determined that anti-HER3 and/or anti-HER1 antibodies bind to the immunoprecipitated complexes.

6. The method of claim 1 wherein the presence of a HER2/HER3 and/or HER2/HER1 protein complex is detected by:

- a) contacting the tumor sample with an anti-HER2 antibody that comprises a fluorophore;
- b) contacting the tumor sample with an antibody selected from the group consisting of anti-HER3 and anti-HER1 antibodies, wherein said antibody comprises a second fluorophore;
- c) determining if the first fluorophore and the second fluorophore are in close proximity by measuring the fluorescence resonance energy transfer, wherein the presence of a HER2/HER3 and/or HER2/HER1 protein complex is detected if the first and second fluorophore are determined to be in close proximity.

7. The method of claim 1 wherein the presence of a HER2/HER3 and/or HER2/HER1 protein complex is detected by:

- a) contacting the tumor sample with a first binding compound, wherein said first binding compound comprises a first target binding moiety that specifically binds HER2 and further comprises a detectable moiety linked to the first target binding moiety by a cleavable linker;
- b) contacting the tumor sample with a second binding compound, wherein the second binding compound comprises a second target binding moiety that specifically binds HER3 or HER1 and an activatable cleaving agent;

- c) activating the cleaving agent such that if the first binding compound and the second binding compound are in close proximity the second binding compound cleaves the cleavable linker in the first binding compound to produce a free detectable moiety; and
 - d) identifying the presence of the free detectable moiety, wherein the presence of a HER2/HER3 or HER2/HER1 protein complex is detected when free detectable moiety is identified.
8. The method of claim 7 wherein the first target binding moiety comprises an anti-HER2 antibody or antibody fragment.
9. The method of claim 7 wherein the first target binding moiety comprises a HER2 receptor ligand.
10. The method of claim 7 wherein the second target binding moiety comprises an anti-HER3 antibody or antibody fragment.
11. The method of claim 7 wherein the second target binding moiety comprises a HER3 receptor ligand.
12. The method of claim 7 wherein the second target binding moiety comprises an anti-HER1 antibody or antibody fragment.
13. The method of claim 7 wherein the second target binding moiety comprises a HER1 receptor ligand.
14. The method of claim 7 wherein the sample is obtained from a patient suffering from the tumor.
15. The method of claim 14 wherein the sample is obtained by a biopsy of the tumor.
16. The method of claim 14 wherein the sample is obtained by purifying circulating tumor cells from the patient's blood.
17. The method of claim 14 wherein the sample is obtained during surgery to remove the tumor from the patient.
18. The method of claim 1 wherein the sample of the tumor is obtained from a mouse.
19. The method of claim 18 wherein the tumor is a xenografted tumor.
20. The method of claim 19 wherein the xenografted tumor is produced by transplanting a fragment of a human tumor into a mouse.
21. The method of claim 1 wherein the tumor is a lung tumor.
22. The method of claim 1 wherein the tumor is a mammary tumor.
23. A method for identifying tumor cells as responsive to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family comprising:
- (a) providing a biological sample comprising HER2-positive tumor cells; and
 - (b) detecting the phosphorylation of an ErbB receptor in said biological sample, wherein said phosphorylation indicates that said tumor cells are responsive to treatment with said antibody.
24. The method of claim 23 wherein the phosphorylation of an ErbB2 (HER2) receptor is detected.
25. The method of claim 23 wherein the other member is selected from the group consisting of HER3, HER1 and HER4.
26. The method of claim 23 wherein the antibody binds HER2.
27. The method of claim 26 wherein the anti-HER2 antibody blocks ligand activation of an ErbB heterodimer comprising HER2.
28. The method of claim 27 wherein the antibody is rhuMAb 2C4.
29. The method of claim 25 wherein the antibody binds HER3.
30. The method of claim 25 wherein the antibody binds HER1.
31. The method of claim 25 wherein the antibody binds HER4.
32. The method of claim 23 additionally comprising detecting the presence of at least one protein complex selected from the group consisting of HER2/HER3, HER2/HER1, and HER2/HER4 in the sample.
33. The method of claim 32 wherein the presence of said protein complex or complexes is detected by:
- a) immunoprecipitating any protein complex that comprises HER2 with an anti-HER2 antibody;
 - b) contacting the immunoprecipitated complex with at least one antibody selected from the group consisting of anti-HER3, anti-HER1, and anti-HER4 antibodies; and
 - c) determining if said anti-HER3 and/or anti-HER1 and/or anti-HER4 antibody binds to the immunoprecipitated complex, wherein a HER2/HER3 and/or HER2/HER1 and/or HER2/HER4 complex is detected if it is determined that anti-HER3 and/or anti-HER1 and/or anti-HER4 antibodies bind to the immunoprecipitated complex.
34. The method of claim 32 wherein the presence of said protein complex or complexes is detected by:
- a) contacting the tumor sample with an anti-HER2 antibody that comprises a fluorophore;
 - b) contacting the tumor sample with an antibody selected from the group consisting of anti-HER3, anti-HER1 and anti-HER4 antibodies, wherein said antibody comprises a second fluorophore;
 - c) determining if the first fluorophore and the second fluorophore are in close proximity by measuring the fluorescence resonance energy transfer,
- wherein the presence of a HER2/HER3 and/or HER2/HER1 and/or HER2/HER4 protein complex is detected if the first and second fluorophore are determined to be in close proximity.
35. The method of claim 32 wherein the presence of said protein complex or complexes is detected by:
- a) contacting the tumor sample with a first binding compound, wherein said first binding compound comprises a first target binding moiety that specifically binds HER2 and further comprises a detectable moiety linked to the first target binding moiety by a cleavable linker;
 - b) contacting the tumor sample with a second binding compound, wherein the second binding compound comprises a second target binding moiety that specifically binds HER3 or HER1 or HER4 and an activatable cleaving agent;
 - c) activating the cleaving agent such that if the first binding compound and the second binding compound

D2
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Clinical Activity of Pertuzumab (rhuMAB 2C4), a HER Dimerization Inhibitor, in Advanced Ovarian Cancer: Potential Predictive Relationship With Tumor HER2 Activation Status

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ABSTRACT

Purpose

Ovarian cancers (OCs) frequently have HER2 activation in the absence of HER2 overexpression. Pertuzumab, a humanized antibody that prevents HER2 dimerization and inhibits multiple HER-mediated pathways, was studied in a phase II, multicenter trial in advanced, refractory OC.

Patients and Methods

Sixty-one patients (cohort 1) with relapsed OC received a loading dose of 840 mg pertuzumab intravenously followed by 420 mg every 3 weeks; 62 patients (cohort 2) received 1,050 mg every 3 weeks. Response rate was the primary end point. Fresh tumor biopsies were obtained in cohort 1 to assay for phosphorylated HER2 (pHER2).

Results

Median age was 57 years and median number of prior chemotherapy regimens was five. Fifty-five patients in cohort 1 and 62 patients in cohort 2 were assessable for efficacy. There were five partial responses (response rate [RR] = 4.3%; 95% CI, 1.7% to 9.4%), eight patients (6.8%) with stable disease (SD) lasting at least 6 months, and 10 patients with CA-125 reduction of at least 50% (includes two partial responses and four patients with SD $\geq$ 6 months; total clinical activity, 14.5%). Median progression-free survival (PFS) was 6.6 weeks. Eight of 28 tumor biopsies (28.6%) were pHER2+ by enzyme-linked immunosorbent assay (ELISA; without gene amplification). Median PFS for pHER2+ patients was 20.9 weeks ($n = 8$) versus 5.8 weeks for pHER2- ($n = 20$; $P = .14$) and 9.1 weeks for unknown pHER2 status ($n = 27$). Pertuzumab was well tolerated with diarrhea in 69.1% (11.4% grade 3, no grade 4). Five patients had asymptomatic left ventricular ejection fraction decreases to less than 50% (one confirmed by central facility).

Conclusion

Pertuzumab is well tolerated with a RR of 4.3% in heavily-pretreated OC patients. Further studies on pHER2 as a diagnostic are warranted.

J Clin Oncol 24:4324-4332. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Ovarian cancer is the fourth most common cause of cancer mortality among women in the United States.¹ Novel therapies with better efficacy and less toxicity, particularly for patients with platinum-resistant disease, are needed.²

The human epidermal growth factor family of receptors (HER1/EGFR, HER2, HER3, and HER4) mediate cell growth and are dysregulated in many types of cancer.³ Receptor dimerization is essential for HER pathway activation leading to receptor phosphorylation and downstream signal transduc-

tion.³ Unlike HER1, -3 and -4, HER2 has no known ligand and assumes an open conformation, with its dimerization domain permanently exposed for interaction with other ligand-activated HER receptors.⁴ HER2 is the preferred partner for dimer formation,⁵⁻⁷ and preclinical studies have shown that HER2-containing heterodimers are the most mitogenic and have the highest transformation potential of all the HER complexes.³

The HER pathway is involved in ovarian cancer pathogenesis.⁸⁻¹² Many ovarian tumor samples express all members of the HER family.⁸ Coexpression of HER1 and HER2 is seen more

frequently in ovarian cancer than in normal ovarian epithelium,⁹ and overexpression of both receptors correlates with poor prognosis.¹⁰⁻¹² Preferred dimerization with HER2 (HER1/HER2, HER2/HER3) and subsequent pathway activation via receptor phosphorylation have also been shown to drive ovarian tumor cell proliferation, even in the absence of HER2 overexpression.^{13,14}

(trhuMab 2C4, Onnitarg; Genentech Inc, South San Francisco, CA) is the first in a new class of targeted anticancer agents termed *HER2 tyrosine kinase inhibitors*.¹⁵ Pertuzumab is a recombinant, humanized monoclonal antibody that targets an epitope within the HER2 dimerization domain.¹⁶ Once bound, pertuzumab inhibits ligand-activated HER dimerization with HER2, independent of HER2 expression levels.^{17,18} Pertuzumab has demonstrated growth inhibition in ovarian, lung, breast, and prostate tumor cells without HER2 overexpression.^{19,17,18} In a phase I clinical study, two of 21 patients with advanced cancer had confirmed partial responses (PRs). Of these, one patient demonstrated a confirmed PR that lasted 11 months in a platinum-resistant ovarian cancer with absence of HER2 gene amplification.¹⁹

The primary objectives of this phase II, open-label, multicenter study were to determine the overall response rate and investigate the safety and tolerability of two dose levels of pertuzumab in patients with advanced, refractory or recurrent ovarian cancer. As a secondary objective, HER2 activation was investigated as a predictor of outcome.

Patient Population

Patients with advanced, histologically documented epithelial ovarian cancer that had recurred despite platinum-based chemotherapy were eligible. All patients gave written informed consent, and the protocol and consent form were approved by institutional review boards. Measurable disease was defined according to Response Evaluation Criteria in Solid Tumors (RECIST).²⁰ Nonmeasurable disease patients were also eligible and defined as clinically or radiologically detectable disease (eg, ascites, mesenteric thickening) plus two consecutive elevations in pretreatment serum CA-125 measurements more than 40 IU/mL.

All patients were at least 18 years old with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and a life expectancy of at least 12 weeks. Other eligibility criteria included progression within 12 months with initial platinum or recurrence after re-treatment with platinum-based chemotherapeutic regimen (no limit to the number of prior therapies), and adequate cardiac, hematologic, hepatic, and renal function. Patients in cohort 1 had to be willing to undergo a tumor biopsy. Key exclusion criteria included prior treatment with any experimental anticancer agent within 4 weeks of day 1; treatment with any HER-targeted agent; history of any CNS or brain metastases; left ventricular ejection fraction (LVEF) less than 50%; and prior exposure to more than 360 mg/m² doxorubicin or liposomal doxorubicin, more than 120 mg/m² mitoxantrone, or more than 90 mg/m² idarubicin.

Study Design and Treatment Schedule

The primary objective of this study was to determine the best overall response and safety and tolerability of single agent pertuzumab. The secondary objective was to determine time to disease progression, duration of response and survival in the overall population and with regards to the presence or absence of detectable HER2 phosphorylation.

This open-label, multicenter study enrolled two sequential cohorts of approximately 60 patients each. Cohort 1 received a loading dose of 840 mg pertuzumab (Genentech Inc, South San Francisco, CA) on day 1 of cycle 1 and 420 mg pertuzumab on day 1 of each 3-week cycle thereafter by intravenous infusion for up to 1 year. Cohort 2 received 1,050 mg pertuzumab on day 1 of each 3-week cycle (up to 1 year). The dose and schedule selected for cohort 1 was based on pharmacodynamic data from preclinical studies¹⁸

and a phase I study that showed that 420 mg (or 6 mg/kg for a 70-kg patient) should result in steady-state serum concentrations shown to be efficacious in animal models (5 to 25 µg/mL).²¹ A loading dose of 840 mg was used to achieve steady-state concentrations rapidly in cohort 1. A higher pertuzumab dose was used for cohort 2 because preclinical studies suggested a dose-dependent increase in efficacy.^{17,18}

Pertuzumab infusion was interrupted if a patient developed dyspnea or clinically significant hypotension. Therapy was discontinued for recurrent National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 3.0) grade 3 or grade 4 rash, diarrhea, or major organ toxicity; grade 4 hematologic toxicity; grade 3 or 4 allergic reaction; symptomatic congestive heart failure with a drop in LVEF; any other subjectively intolerable toxicity, or progressive disease.

Efficacy Determinations

Tumor burden was evaluated at baseline by clinical and image based evaluation, including a computed tomography scan of the chest, abdomen, and pelvis. Investigator-determined best overall response was defined using RECIST for measurable tumors and Gynecologic Cancer Intergroup CA-125 response criteria for nonmeasurable tumors.²² CA-125 measurements were obtained from all patients on day 1 of each cycle. Objective response was assessed before cycles 3, 5, 7, 9, 13, and 17, and confirmed by repeat assessment at least 4 weeks later.

Efficacy-assessable patients received at least one dose of pertuzumab and underwent at least one response assessment. Three efficacy-assessable subgroups were considered: (1) all patients; (2) patients with detectable tumor HER2 phosphorylation; and (3) patients with no detectable tumor HER2 phosphorylation before therapy.

Best overall response, duration of response, progression-free survival (PFS), and survival were determined for all subgroups in cohort 1 and efficacy-assessable patients in cohort 2. Disease progression was defined as progressive disease or death, whichever occurred first. Duration of PFS was defined as the time from day 1 of study to the time of documented disease progression or death. Duration of survival was defined as the time from day 1 of study to the time of death. Duration of response was defined as the time from the initial complete response or PR to the time of disease progression or death.

Total HER2 and HER2 Phosphorylation Assessment

Twenty ovarian tumor samples from a commercial source (ILS Bio, Chestertown, MD) and fresh frozen tumor samples from patients in cohort 1 (obtained within 42 days before day 1 of treatment) were analyzed for HER2 expression and phosphorylation. Tumor lysates were quantitatively analyzed for total HER2 and HER2 phosphorylation status by Western blotting and phosphorimager assay (Fig 1A). Tumor samples were classified as positive if signals were detected above the lower limit of quantitation (LOQ) of the assay and negative if beneath the LOQ. Lysates also were analyzed by immunoprecipitation using an anti-HER2 antibody followed by Western blotting for HER2 or phosphotyrosine. Full details of the assay methods are presented in the Appendix (online only).

Fluorescence *in situ* hybridization (FISH) analysis for HER2 gene copy number was performed on frozen and formalin-fixed tumor sections using the PathVysion HER2 DNA Probe Kit (Vysis, Downers Grove, IL). FISH results were manually scored in a blinded fashion, and amplification was defined as a HER2/CEP17 ratio more than 2.0. Where possible, HER2 phosphorylation was also assessed by immunohistochemistry (IHC) using a phospho-specific anti-HER2 antibody (P-Tyr 1248; clone PN2A) on frozen tumor sections (Appendix).

Tolerability and Safety Assessment

Adverse events were assessed on day 1 of each cycle and graded according to NCI-CTC version 2. Cardiac function was monitored at baseline and before cycles 3, 5, 7, 9, 13, and 17 by two-dimensional echocardiogram. Serum markers of cardiac damage (troponin T) were assayed at the beginning of each cycle.

Statistical Analysis

Demographic and baseline characteristics were summarized using means ($\pm$ standard deviation) or medians (with ranges) for continuous variables, and proportions for categorical variables. Three efficacy subgroups were

considered, as described above. For cohort 1, the 95% Blyth-Still-Casella exact CIs were calculated for all three subgroups; 95% Blyth-Still-Casella exact CIs were calculated for efficacy-assessable and all treated patients in cohort 2. Median PFS and duration of survival were calculated using Kaplan-Meier methodology. With 40 patients in each cohort, rate of best response could be estimated with an SE not greater than 0.08. The target response rate (RR) for cohort 1 was at least 30%. With an assumed 13 of the 40 assessable patients in cohort 1 pHER2+, rate of best response for this subgroup could be estimated with an SE of not greater than 0.14. If the true RR was 30%, there would be an 80% probability of observing three or more responses in this subgroup. To obtain 40 assessable patients with sufficient assessable tissue biopsies and/or archival tissue, 60 patients were enrolled in each cohort.

RESULTS

HER2 Expression and Activation in an Unselected Series of Ovarian Carcinomas

HER2 expression and activation in ovarian carcinomas was assessed in an anonymized series of 20 banked tumor samples, separate from the clinical trial. By immunoprecipitation and Western blotting, HER2 protein expression was demonstrated in all 20 tumors (Fig 1). This was confirmed quantitatively by HER2 ELISA. Two of the samples displayed *HER2* gene amplification by FISH, whereas the others were FISH-negative (data not shown). By ELISA, HER2 phosphorylation was detected in nine of 20 tumors (45%). The two FISH-positive tumors had very high levels of HER2 protein overexpression, as well as high amounts of phosphorylated protein compared with the other FISH-negative tumors. IHC for phosphorylated HER2 (pHER2) using the HER2 P-Tyr 1248 monoclonal antibody (mAb) clone PN2A was positive in the two FISH-positive tumors, but was insufficiently sensitive to detect the lower levels of pHER2 present in the other seven ELISA-positive tumors (data not shown). These data support the use of ELISA for assaying HER2 activation in the fresh tumor biopsies.

Patients

One hundred twenty-nine patients were enrolled (65 in cohort 1, 64 in cohort 2). One hundred twenty-three patients were treated with pertuzumab (61 in cohort 1, 62 in cohort 2). Patient characteristics (Table 1) were similar between cohorts. All patients had received a platinum-based therapy and had progressed, and it was approximated that 87% patients had progressed less than 6 months from their last platinum-containing regimen (as determined by start/stop of prior regimens) before entry to the study. A median of two cycles of pertuzumab was administered. Fifty-five patients in cohort 1

Characteristic	No.	%
No. of Patients	123	
Age, years		
Median	57	
Range	35-83	
Race/ethnicity		
White	106	86.2
Black	3	2.4
Asian or Pacific Islander	3	2.4
Hispanic	7	5.7
Other	4	3.3
ECOG PS		
0	65	52.8
1	56	45.5
2-3	2	1.6
Histology		
Epithelial	121	98.4
Other*	2	1.6
Duration of cancer, months		
Median	38.6	
Range	3.3-143.7	
Measurable disease	112	91.1
Prior surgery	122	99.2
Prior radiotherapy	16	13.4
Prior chemotherapy	123	100.0
Prior chemotherapy regimens		
Median	5.0	
Range	1-13	
Response to first platinum		
Platinum refractory†	66	54.1
Platinum sensitive	57	46.3

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.
 *Other included small cell of the ovary and mesothelioma.
 †Recurrence during or within 6 months of last platinum-containing regimen.

and 62 patients in cohort 2 were assessable for response by either RECIST or CA-125.

Efficacy by Dose of Pertuzumab

The best overall response for all patients is listed in Table 2. Two of 55 patients (3.6%) in cohort 1 and three of 62 patients (4.8%) in cohort 2 demonstrated objective PRs, for an overall RR of 4.3% (95% CI, 1.7% to 9.4%), which is below the targeted response rate of 30%. The median duration of response was 18.6 weeks (95% CI, 13.1 to 29.1). In addition, eight patients (6.8%) had stable disease (SD) lasting

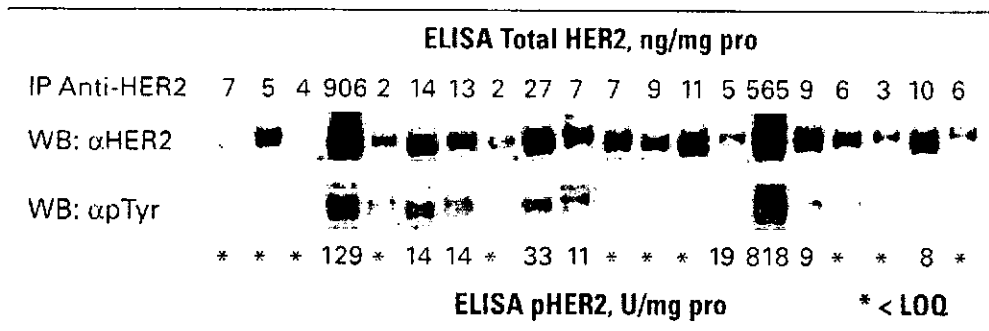


Fig 1. Total HER2 and phosphorylated HER2 (pHER2) protein detected in 20 unselected ovarian tumors by immunoprecipitation (IP)/WB and by enzyme-linked immunosorbent assay (ELISA). WB, Western blot; LOQ, limit of quantitation.

Table 2. Clinical Activity by Cohort and by Date Received (cohort 1, 420 mg; cohort 2, 1,050 mg)

	Cohort 1 n = 57		Cohort 2 n = 62		Total n = 119	
	n	%	n	%	n	%
PR	7	12.3	3	4.8	10	8.4
SD $\geq$ 6 months	4	7.0	4	6.5	8	6.7
SD $\geq$ 6 months, CA-125 drops $\geq$ 50%	3	5.5	1	1.6	4	3.4
Other SD	2	3.6	1	1.6	3	2.5
Other SD	15	27.3	18	29.0	33	28.2
PD	71	124.1	33	53.2	104	87.3
Unable to evaluate response	2	3.6	2	3.2	4	3.4
Median PFS, weeks	46.7		52.7		52.7	
95% CI	30 to 66.6		38.9 to NYR		38.9 to 66.7	
Median PFS, weeks	7.6		6.1		6.6	
95% CI	6.0 to 11.4		5.9 to 11.4		6.0 to 10.9	

NOTE: Clinical activity was defined as PR = SD $\geq$ 6 months + SD with CA-125 drop $\geq$ 50%. Clinical activity was achieved in nine patients (16.4%) in cohort 1, and in four patients (6.5%) in cohort 2. At least seven patients (14.5%) overall.

Abbreviations: pHER2, phosphorylated HER2; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; NYR, not yet reached. Five patients had CA-125 drops $\geq$ 50% (one in cohort 1, three in cohort 2); thus there were a total of eight (6.8%) CA-125 responses with SD.

at least 6 months—four in each cohort. Ten patients also had CA-125 decrease of at least 50% with at least an SD at the first response evaluation (these patients were measurable by RECIST, and so CA-125 was not used and confirmed for response); two were in the PR group, four were in the SD of at least 6 months group, and four had SD of 6 months or less. Overall rate of clinical activity of the 17 of 117 patients (PR, SD $\geq$ 6 months, CA-125 decrease) was therefore 14.5%, although this was not a prespecified end point.

Two patients enrolled in cohort 2 had SD for 1 year and were subsequently enrolled into a rollover study to allow continued treatment with single agent pertuzumab. Since enrolling in the extension study one patient has been treated for an additional eight cycles (total 76 weeks), and continues to be treated, and the other patient progressed after four additional cycles (total 64 weeks).

Figure 2A shows a Kaplan-Meier curve of PFS for efficacy-assessable patients in cohorts 1 and 2. Median PFS for the overall population was 6.6 weeks (95% CI, 6.0 to 10.9) and was similar between cohorts 1 and 2 (7.6 weeks [95% CI, 6.0 to 11.4] versus 6.1 weeks [95% CI, 5.9 to 11.4], respectively). Figure 3A shows a Kaplan-Meier curve of overall survival for efficacy-assessable patients in cohorts 1 and 2. Median survival for the overall population was 52.7 weeks (95% CI, 38.9 to 66.7). Median survival was 46.7 weeks (95% CI, 30.4 to 66.6) for patients in cohort 1, but has not yet been reached in cohort 2. Of the five patients in cohort 2 with a PR, only one has died, at 26 weeks, with follow-up from the remaining from 56 to 93 weeks). Of the eight patients who had SD lasting at least 6 months, none have died (with follow-up from 51 to 105 weeks). Finally, of the 50 patients who had PD, 40 have died with a median survival of 33.1 weeks (the 20 censored having follow-up of 49 to 96 weeks).

Efficacy by pHER2 Status

Because many of the tumors did not meet the minimal requirement to be assayed by ELISA ($\geq$ 99 ng sample with $\geq$ 30% tumor content), only 34 of the 65 tumor biopsies obtained from patients in cohort 1 were adequate for evaluation by ELISA. All assessable samples had detectable levels of HER2 protein (median, 6.7 ng/mg; range, 1.4

to 21.7 ng/mg). No tumor biopsies were found to have HER2 overexpression levels comparable with those seen in the two FISH-positive banked tumor samples from the unselected series (906 and 565 ng/mg protein). FISH assays of the fresh tumor biopsies and/or archival tumor samples from patients in either cohort did not demonstrate *HER2* gene amplification in any of the assessable patient tumors.

Of the 34 fresh tumor specimens that were adequate for evaluation, 10 (29.4%) were found to have detectable levels of phosphorylated HER2 (pHER2+). Of the 34 assessable biopsies, 28 patients were also assessable for clinical efficacy; eight (28.6%) of 28 patients had pretreatment tumor samples that were pHER2+, whereas 20 (71.4%) of 28 were pHER2-.

The best overall response according to pHER2 status for efficacy-assessable patients in cohort 1 is listed in Table 3. PR was observed in one (12.5%) of eight patients with pHER2+ tumors, but in none of the patients with pHER2- tumors. A higher proportion of patients with pHER2+ tumors had SD at the first response evaluation compared with patients with pHER2- tumors (75% v 25%, respectively). Overall rate of clinical activity (PR, SD $\geq$ 6 months, or CA-125 decrease with SD) was 25.0% for pHER2+ patients, 10% for pHER2- patients, and 18.5% for patients with unknown pHER2 status.

The Kaplan-Meier curve of PFS for efficacy-assessable patients in cohort 1 (Fig 2B) shows that median PFS for patients with pHER2+ tumors was 20.9 weeks (95% CI, 11.1 to 24.6) compared with 5.8 weeks (95% CI, 5.3 to 10.6) for patients with pHER2- tumors ($P = .14$) and 9.1 weeks (95% CI, 6.1 to 12.1) for patients with pHER2-unknown tumors. The Kaplan-Meier curve of overall survival for efficacy-assessable pHER2+ patients was 74.6 weeks (95% CI, 28.4 to not yet reached), 37.0 weeks (95% CI, 18.6 to not yet reached) for pHER2- patients, and 48.4 weeks (95% CI, 21.6 to 82.1) for pHER2-unknown tumors. The log-rank test showed a trend toward improved survival for pHER2+ versus pHER2- tumors ($P = .365$).

Safety

Table 4 lists all adverse events irrespective of relatedness that occurred in at least 10% of treated patients. The most common

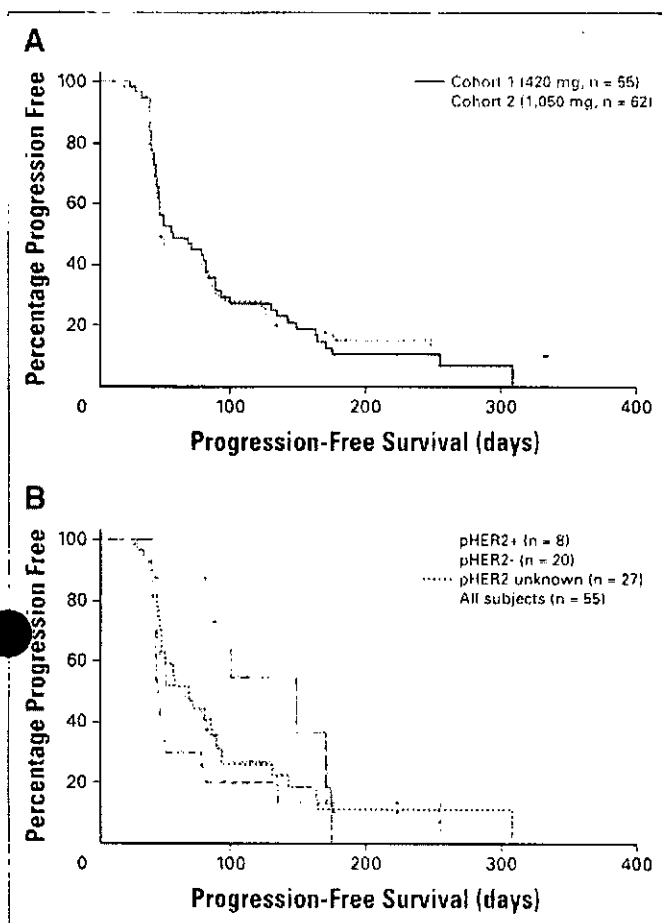


Fig 2. Progression-free survival (PFS) of efficacy-assessable patients. (A) PFS for Cohorts 1 and 2 and (B) PFS by phosphorylated HER2 (pHER2) status (cohort 1 only).

adverse event considered related to pertuzumab by investigators was diarrhea (predominantly grade 1-2). Adverse events led to study drug discontinuation in six patients (two small bowel obstructions, one grade 3 diarrhea, one grade 3 edema, one grade 3 vomiting, one grade 3 elevated creatinine). There were no major differences in the incidence and nature of adverse events between the two cohorts.

There were 44 serious adverse events (SAEs) reported and six (4.9%) were considered treatment-related (one case each of diarrhea, abdominal pain, LVEF decrease, atrial fibrillation, pericardial effusion, and pneumonia). Death not resulting from progressive disease occurred in one patient who experienced respiratory arrest before receiving pertuzumab, and another who died 9 months after her last dose of pertuzumab.

Due to reports of cardiotoxicity associated with HER2 inhibition, cardiac function has been monitored carefully in all pertuzumab clinical trials. One patient (1.6%) in cohort 1 and four (6.5%) in cohort 2 had a decrease in LVEF to less than 50%. All patients were asymptomatic, and only one decrease was confirmed by a central facility. To place this cardiac safety data in context, of 167 assessable patients with cardiac monitoring across three phase II studies of single-agent pertuzumab in the United States (non-small-cell lung cancer [NSCLC], prostate cancer, and the current study), nine (5.4%) have had a decrease in LVEF to less than 50%. All patients were asymptomatic, and only two (1.2%) were confirmed by a central facility.

DISCUSSION

Our initial analysis of banked ovarian tumor samples demonstrated that HER2 activation was detectable in a subset of tumors, including tumors with nonamplified *HER2* genes and lower levels of HER2 protein expression, as well as tumors with *HER2* gene amplification and highly overexpressed HER2 protein. We hypothesized that targeting HER2 pathway activation with pertuzumab would inhibit the growth of these tumors.

This study demonstrates that single-agent pertuzumab has clinical activity in heavily-pretreated patients with advanced ovarian cancer. A low number of responses were seen, and the primary end point of response rate was not met; however, a larger proportion of patients achieved CA-125 responses and prolonged SD. In retrospect, a 30% response rate is a high bar for activity from a biologic agent. Despite differences in eligibility criteria, median survival after pertuzumab was comparable to the median survival of platinum-resistant patients reported by Gordon et al²³ in a phase III trial with liposomal doxorubicin and topotecan (35.6 weeks and 41.3 weeks, respectively).

Recent data suggest that tumor response rate may not be the optimal end point for assessing the clinical benefit of biologic agents like pertuzumab. Erlotinib, a small-molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase,²⁴ produced a 7.4% RR in

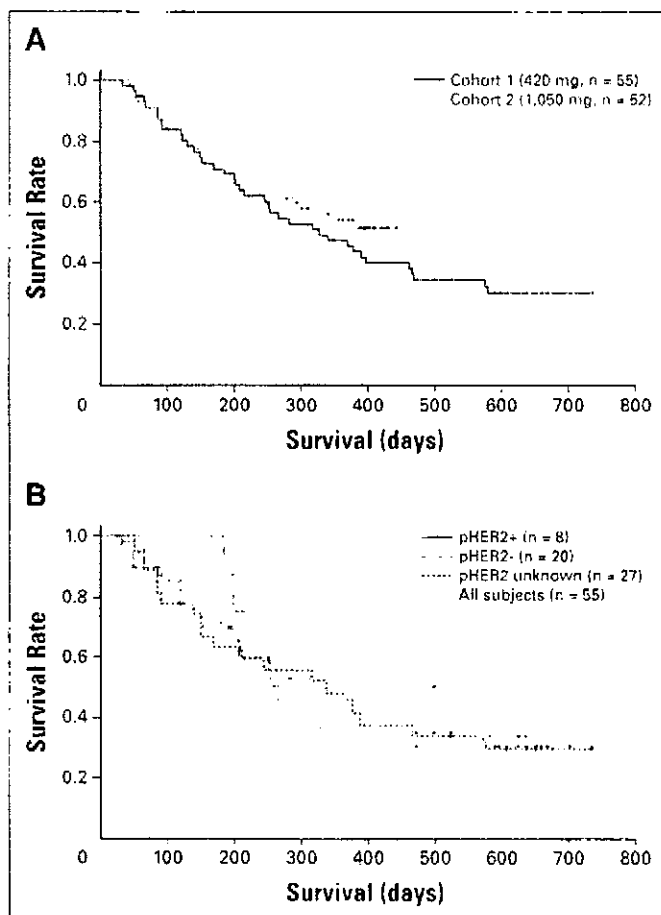


Fig 3. Overall survival of efficacy-assessable patients. (A) Overall survival for cohorts 1 and 2 and (B) overall survival by phosphorylated HER2 (pHER2) status (cohort 1 only).

Table 3. Clinical Efficacy of Pertuzumab in Patients in Cohort 1 by Tumor pHER2 Status

	pHER2		pHER2+		Unknown		All Patients	
	No.	%	No.	%	No.	%	No.	%
Total	8	100.0	20	100.0	27	100.0	55	100.0
≤ 6 months	1	12.5	0	0	1	3.7	2	3.6
6 to < 12 months	0	0	2*	10.0	2	7.4	4	7.3
12 to < 24 months	0	0	0	0	2	7.4	3	5.5
≥ 24 months	0	0	0	0	2	7.4	2	3.6
Median	5	62.5	5	25.0	7	25.9	8	27.3
95% CI	1	12.5	13	65.0	13	48.1	27	49.1
Unknown	0	0	2	10.0	0	0	2	3.6
Survival, weeks								
Median		74.6		37.0		48.4		46.7
95% CI		28.4 to NYR		18.6 to NYR		21.5 to 82.1		39.4 to 66.6
Unknown		NYR		5.8		9.1		7.0
95% CI		1.0 to 24.6		5.3 to 10.6		5.1 to 12.1		6.0 to 11.4

[illegible]

second-line metastatic NSCLC patients with wild-type EGFR. Though few tumor regressions were observed, erlotinib demonstrated significant improvement in PFS and overall survival in NSCLC.²⁴

A key aspect of therapy with targeted agents is accurate selection of patients most likely to benefit from treatment. Our data and other studies suggest that ovarian cancer has a low incidence of *HER2* gene amplification and protein overexpression.²⁵ In a study of ovarian cancer patients treated with trastuzumab, the overall incidence of both *HER2* 2+ and 3+ expression was only 1.4% of tumors (95 of 837 tumors screened by IHC) and only 4.1% were *HER2* 3+.²⁶ Conversely in this study, none of the patients' tumors had *HER2* amplification; however 29.4% had evidence of activated *HER2* (p*HER2* +). The prevalence of p*HER2* + observed in the study of banked ovarian samples was 45%. This is well within the range of a useful diagnostic tool for patient selection. *HER2* amplification was not required for any clinical activity associated with pertuzumab in this study, reflecting results obtained in the preclinical setting.²⁷ These results lend further support for the use of markers of *HER2* activation and not overexpression as the appropriate diagnostic for selection in ovarian cancer.

Consistent with the mechanism of action of pertuzumab, the efficacy results for cohort 1 suggest that patients with HER2 phosphorylation showed better outcome following pertuzumab therapy, compared to patients with pHER2⁻ tumors. However, it remains unknown whether the presence of pHER2 specifically predicts outcome to pertuzumab or is simply a good prognostic marker in ovarian cancer. Randomized trials are needed to confirm the utility of pHER2 as a diagnostic marker. Additionally, the assessment of HER2 phosphorylation status in formalin-fixed pathology specimens presents technical challenges for routine diagnostic testing. Because fresh-frozen tissue is required for the pHER2 assay, alternative predictive markers of HER2 activation are being investigated as

potential diagnostic tests moving forward. Data from microarray expression profiling of the present tumor series indicate that higher coexpression of HER2, EGFR, IER3 and certain IER ligands may correlate with pHER2 status.¹⁷

Other HER targeting agents have been studied in ovarian cancer. Erlotinib produced a 6% RR in EGFR+ advanced ovarian cancer patients.²⁶ Trastuzumab produced a response rate of 7.3% in HER2 2+ and 3+ patients.²⁶ Treatment with gefitinib in 26 assessable recurrent ovarian cancer patients resulted in four patients with SD for at least 6 months with one of them (3.8%) having a PR.²⁹ In the current study, pertuzumab had a comparable low response rate although, of note, patients were not preselected. Given that pertuzumab blocks all HER2-mediated signaling, in contrast to targeted blockade of EGFR1 or HER2 overexpression, pertuzumab may result in higher rates of clinical activity in an appropriately selected population. It will be interesting to observe the clinical activity of the dual EGFR and HER2 inhibitor lapatinib, currently under investigation in unselected ovarian cancer patients progressing within 12 months of a platinum regimen, with 6-month PFS as the primary end point.

In addition to further exploring HER2 activation as a marker for patient selection, future development of pertuzumab will evaluate the drug in combination with other chemotherapies and targeted agents. Multiple trials have shown that the clinical effect of chemotherapy is maximized when combined with targeted drugs (ie, trastuzumab in breast cancer; bevacizumab in breast cancer, colorectal cancer, and NSCLC; cetuximab in colorectal cancer¹⁶⁻³⁷). Furthermore, preliminary preclinical data suggest that combining pertuzumab with other agents leads to additive activity.³⁸ Given these data and its tolerable safety profile, combination studies with pertuzumab are warranted and are ongoing.

Table 4. Incidence of Adverse Events Regardless of Causality Occurring in $\geq 10\%$ of Treated Patients (grade 3/4 in any cohort*)

	Cohort 1 (n = 61)						Cohort 2 (n = 62)						All Patients (N = 123)					
	All Grades		Grade 3		Grade 4		All Grades		Grade 3		Grade 4		All Grades		Grade 3		Grade 4	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Any adverse events	61	100.0	26	42.6	9	14.8	61	98.4	25	40.3	8	12.9	122	99.2	51	41.5	17	13.8
Diarrhea	40	65.6	7	11.5	0	0	45	72.6	7	11.3	0	0	55	69.1	14	17.9	0	0
Fatigue	21	34.4	2	3.3	0	0	34	54.8	2	3.2	0	0	55	44.7	4	3.3	0	0
Rash/dermatitis, various†	18	29.5	0	0	0	0	23	37.1	1	1.6	0	0	41	33.3	1	0.8	0	0
Nausea	25	41.0	5	8.2	1	1.6	22	35.5	4	6.5	0	0	47	38.2	9	7.3	1	0.8
Abdominal pain	26	42.6	3	4.9	1	1.6	21	33.9	3	4.8	0	0	47	38.2	6	4.9	1	0.8
Vomiting	25	41.0	10	16.4	1	1.6	17	27.4	3	4.8	0	0	42	34.1	12	10.6	1	0.8
Constipation	17	27.9	3	4.9	1	1.6	11	17.7	1	1.6	0	0	28	22.8	4	3.3	1	0.8
Anorexia	15	24.6	1	1.6	1	1.6	12	19.4	2	3.2	0	0	27	22.0	3	2.4	1	0.8
Peripheral edema	13	21.3	0	0	0	0	14	22.6	0	0	0	0	27	22.0	0	0	0	0
Ejection fraction decreased	11	18.0	0	0	0	0	14	22.6	1	1.6	0	0	25	20.3	1	0.8	0	0
Dehydration	13	21.3	4	6.6	0	0	8	12.9	2	3.2	0	0	21	17.1	6	4.9	0	0
Abdominal distention	13	21.3	0	0	0	0	8	12.9	1	1.6	0	0	21	17.1	1	0.8	0	0
Dyspnea	10	16.4	2	3.3	0	0	10	16.1	4	6.5	1	1.6	20	16.3	6	4.9	1	0.8
Cough	9	14.8	0	0	0	0	11	17.7	0	0	0	0	20	16.3	0	0	0	0
Weight decrease	10	16.4	2	3.3	0	0	9	14.5	1	1.6	0	0	19	15.4	3	2.4	0	0
Dyspepsia	6	9.8	0	0	0	0	13	21.0	1	1.6	0	0	19	15.4	1	0.8	0	0
Anemia	9	14.8	0	0	0	0	10	16.1	1	1.6	0	0	19	15.4	1	0.8	0	0
Headache	10	16.4	0	0	0	0	6	9.7	0	0	0	0	16	13.0	0	0	0	0
Small intestinal obstruction	9	14.8	5	8.2	3	4.9	6	9.7	2	3.2	3	4.8	15	12.2	7	5.7	6	4.9
Hypokalemia	6	9.8	2	3.3	0	0	9	14.5	1	1.6	1	1.6	15	12.2	3	2.4	0	0
Insomnia	10	16.4	0	0	0	0	5	8.1	0	0	0	0	15	12.2	0	0	0	0
Pruritus	8	13.1	0	0	0	0	7	11.3	0	0	0	0	15	12.2	0	0	0	0
Urinary tract infection	6	9.8	0	0	0	0	8	12.9	0	0	0	0	14	11.4	0	0	0	0
Dizziness	7	11.5	0	0	0	0	6	9.7	0	0	0	0	13	10.6	0	0	0	0
Dysuria	7	11.5	0	0	0	0	6	9.7	0	0	0	0	13	10.6	0	0	0	0

*Cohorted from MEDRA terms "rash," "erythema," "rash erythematous," "rash maculo-papular," "dermatitis acneiform," "dermatitis allergic," "drug eruption," "rash papular," "rash pruritic," and "rash scaly."

REFERENCES

- Jemal A, Murray T, Ward E, et al: Cancer statistics, 2005. *CA Cancer J Clin* 55:10-30, 2005
- Armstrong DK: Relapsed ovarian cancer: Challenges and management strategies for a chronic disease. *Oncologist* 5:20-28, 2002 (suppl)
- tk3Yarden Y, Slivkowski MX: Untangling the ErbB signaling network. *Nat Rev Mol Cell Biol* 2:127-137, 2001
- Garrett TP, McKern NM, Lou M, et al: The crystal structure of a truncated ErbB2 ectodomain reveals an active conformation, poised to interact with other ErbB receptors. *Mol Cell* 11:495-505, 2003
- Tzahar E, Waterman H, Chen X, et al: A hierarchical network of interreceptor interactions determines signal transduction by Neu differentiation factor/neuregulin and epidermal growth factor. *Mol Cell Biol* 16:5276-5287, 1996
- Graus-Porta D, Beery RR, Daly JM, et al: ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling. *Embo J* 16:1647-1655, 1997
- Sundaresan S, Roberts PE, King KL, et al: Biological response to ErbB ligands in nontransformed cell lines correlates with a specific pattern of receptor expression. *Endocrinology* 139:4756-4764, 1998
- Campiglio M, Ali S, Knyazev PG, et al: Characteristics of EGFR family-mediated HRG signals in human ovarian cancer. *J Cell Biochem* 73:522-532, 1999
- Bast RC Jr, Pusztai L, Kerns BJ, et al: Coexpression of the HER-2 gene product, p185HER-2, and epidermal growth factor receptor, p170EGFR, on epithelial ovarian cancers and normal tissues. *Hybridoma* 17:313-321, 1998
- Bartlett JM, Langdon SP, Simpson BJ, et al: The prognostic value of epidermal growth factor receptor mRNA expression in primary ovarian cancer. *Br J Cancer* 73:301-306, 1996
- Berchuck A, Kamel A, Whitaker R, et al: Overexpression of HER-2/neu is associated with poor survival in advanced epithelial ovarian cancer. *Cancer Res* 50:4087-4091, 1990
- Slamon DJ, Godolphin W, Jones LA, et al: Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 244:707-712, 1989
- Xu F, Yu Y, Le XF, et al: The outcome of heregulin-induced activation of ovarian cancer cells depends on the relative levels of HER-2 and HER-3 expression. *Clin Cancer Res* 5:3653-3660, 1999
- Totpal K, Balter I, Akita RW: Targeting ErbB2/HER2's role as a coreceptor with rhuMab2C4 inhibits ErbB/HER ligand-dependent signaling and proliferation of ovarian tumor cell lines. *Proc Am Assoc Cancer Res* 44:151, 2003 (abstr 776)
- Adams CW, Allison DE, Flagella K, et al: Humanization of a recombinant monoclonal antibody to produce a therapeutic HER dimerization inhibitor, pertuzumab. *Cancer Immunol Immunother* 55:717-727, 2006
- Franklin MC, Carey KD, Vajdos FF, et al: Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. *Cancer Cell* 5:317-328, 2004
- Agus DB, Akita RW, Fox WD, et al: Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. *Cancer Cell* 2:127-137, 2002
- Malik S, Totpal K, Balter I: Dose-response studies of recombinant humanized monoclonal antibody 2C4 in tumor xenograft models. *Proc Am Assoc Cancer Res* 44:150, 2003 (abstr 773)
- Agus DB, Gordon MS, Taylor C, et al: Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer. *J Clin Oncol* 23:2534-2543, 2005
- Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92:205-216, 2000
- Allison DE, Malik M, Qureshi F, et al: Pharmacokinetics of HER2-targeted rhuMab 2C4 (pertuzumab) in patients with advanced solid malignancies: Phase Ia results. *Proc Am Soc Clin Oncol* 22:197, 2003 (abstr 790)
- Rustin GJ: Use of CA-125 to assess response to new agents in ovarian cancer trials. *J Clin Oncol* 21:187-193, 2003
- Gordon AL, Flagella JT, Guthrie D, et al: Recurrent epithelial ovarian carcinoma: A randomized phase

24. Gosselin M, Friboulet A, Dizeu C, et al: Phase II study of the combination of paclitaxel and carboplatin in recurrent ovarian cancer. *Gynecol Oncol* 119:341-347, 2005
25. Therasse P, Vergier J, Castaigne S, et al: Phase II study of paclitaxel and carboplatin in recurrent ovarian cancer: A Gynecologic Intergroup study. *J Clin Oncol* 23:4696-4702, 2005 (suppl abstr 5059)
26. Vergier J, Therasse P, Konecny A, et al: Phase II study of paclitaxel and carboplatin in recurrent ovarian cancer: A Gynecologic Intergroup study. *J Clin Oncol* 23:792-799, 2005 (suppl abstr 3556)
27. Averbuch SD, Konecny A, Vergier J, et al: Phase II study of paclitaxel and carboplatin in recurrent ovarian cancer: A Gynecologic Intergroup study. *J Clin Oncol* 23:792-799, 2005 (suppl abstr 3556)
28. Gosselin M, Friboulet A, Dizeu C, et al: Phase II study of the combination of paclitaxel and carboplatin in recurrent ovarian cancer. *Gynecol Oncol* 119:341-347, 2005
29. Schacter RJ, Kohn E, S. M., et al: Phase II study of paclitaxel and carboplatin in recurrent ovarian cancer. *Gynecol Oncol* 119:341-347, 2005
30. Pritchard NW, Buzdar A, Scher H, et al: Phase II study of gemtuzumab plus paclitaxel in recurrent ovarian cancer. *J Clin Oncol* 23:792-799, 2005 (suppl abstr 3556)
31. Miller KD, Gosselin M, Holmes FA, et al: Randomized phase II trial of capecitabine compared with paclitaxel plus carboplatin in patients with previously treated metastatic breast cancer. *J Clin Oncol* 23:2696-2703, 2005 (suppl abstr 3556)
32. Hochster HS, Wenzel E, Hart J, et al: Safety and efficacy of bevacizumab (BoV) when added to cyclophosphamide (Cy) regimens as first-line treatment of metastatic colorectal cancer (CRC): TREE 1 & 2 Studies. *J Clin Oncol* 23:2495, 2005 (suppl abstr 3556)
33. Fernandez N, Yu D, Morse M, et al: A phase II study of paclitaxel, carboplatin, and bevacizumab in the treatment of metastatic colorectal cancer. *J Clin Oncol* 23:2696, 2005 (suppl abstr 3556)
34. Gosselin M, Friboulet A, Dizeu C, et al: Phase II study of the combination of paclitaxel and carboplatin in recurrent ovarian cancer. *Gynecol Oncol* 119:341-347, 2005
35. Vergier J, Therasse P, Konecny A, et al: Phase II study of paclitaxel and carboplatin in recurrent ovarian cancer: A Gynecologic Intergroup study. *J Clin Oncol* 23:4696-4702, 2005 (suppl abstr 5059)
36. Vergier J, Therasse P, Konecny A, et al: Phase II study of paclitaxel and carboplatin in recurrent ovarian cancer: A Gynecologic Intergroup study. *J Clin Oncol* 23:792-799, 2005 (suppl abstr 3556)
37. Salts LB, Gosselin M, Holmes FA, et al: Randomized phase II trial of capecitabine compared with paclitaxel plus carboplatin in patients with previously treated metastatic breast cancer. *J Clin Oncol* 23:2696-2703, 2005 (suppl abstr 3556)
38. Fries T, Jurek R, Schneider W, et al: Additive antitumor activity by combined treatment with the combi-antagonist humanized monoclonal antibody 29.4 and standard chemotherapeutic agents in NSCLC xenografts is independent of HER2 overexpression. *Proc Am Soc Clin Oncol* 22:238, 2003 (abstr 953)

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

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GLOSSARY

Pertuzumab: A humanized monoclonal antibody, pertuzumab (also referred to as Omnitarg), binds to HER-2 at a site used by the receptor to form dimers with other receptors (the "dimerization site") belonging to this family. Signaling via all HER-2 dimers is, therefore, inhibited.

HD1 (HER dimerization inhibitor): HD1 inhibits tumor growth and survival by inhibiting HER dimerization.

HER-2/neu (human epithelial growth factor receptor-2): Also called ErbB2, HER-2/neu belongs to the EGFR family and is overexpressed in several solid tumors. Like EGFR, it is a tyrosine kinase receptor whose activation leads to proliferative signals within the cells. On activation, the HER family of receptors are known to form homodimers and heterodimers, each with a distinct signaling activity. Because HER-2 is the preferred dimerization partner when heterodimers are formed, it is important for signaling through ligands specific for any members of the family. It is typically overexpressed in several epithelial tumors.

pHER2: Phosphorylated (activated) form of HER-2.

HER1/EGFR: Also known as ErbB1, HER belongs to the epidermal growth factor receptor (EGFR) receptor family.

HER-1/EGFR (ErbB1), HER-2 (ErbB2), HER-3 (ErbB3), and HER-4 (ErbB4) are the four members that comprise this receptor family.

HER3: Also known as ErbB3, HER belongs to the EGFR receptor family. HER-1/EGFR (ErbB1), HER-2 (ErbB2), HER-3 (ErbB3), and HER-4 (ErbB4) are the four members that comprise this receptor family.

HER4: Also known as ErbB4, HER belongs to the EGFR receptor family. HER-1/EGFR (ErbB1), HER-2 (ErbB2), HER-3 (ErbB3), and HER-4 (ErbB4) are the four members that comprise this receptor family.

ELISA (enzyme-linked immunosorbent assay): ELISA is used to detect the presence of an antibody or an antigen in a sample.

Gene amplification: The presence of multiple copies of a gene or genes that leads to overexpression of that gene or gene.

FISH (fluorescence in situ hybridization): In situ hybridization is a sensitive method that is generally used to detect specific gene sequences in tissue sections or cell preparations by hybridizing the complementary strand of a nucleotide probe to the sequence of interest. FISH uses a fluorescence probe to increase the sensitivity of in situ hybridization.

ERRATA

The September 10, 2006, article by Gordon et al entitled, "Clinical Activity of Pertuzumab (rhuMab 2C4), a HER Dimerization Inhibitor, in Advanced Ovarian Cancer: Potential Predictive Relationship With Tumor HER2 Activation Status" (*J Clin Oncol* 24:4324-4332, 2006) contained errors.

In Table 3, the data were incorrectly given for Survival and Progression Free Survival. The corrected table is reprinted below in its entirety. The online version has been corrected in departure from the print.

	pHER2+		pHER2 -		Unknown		All Patients	
	No.	%	No.	%	No.	%	No.	%
Total	8	100.0	20	100.0	27	100.0	55	100.0
PR	1	12.5	0	0	1	3.7	2	3.6
SD $\geq$ 6 months	0	0	2*	10.0	2	7.4	4	7.3
SD $\geq$ 6 months, CA-125 drops $\geq$ 50%	1	12.5	0	0	2	7.4	3	5.5
SD $\geq$ 6 months, CA-125 drops $\geq$ 25% but $<$ 50%	0	0	0	0	2	7.4	2	3.6
Other SD	6	62.5	3	15.0	7	25.9	15	27.3
PD	1	12.5	13	65.0	13	48.1	27	49.1
Unable to evaluate response	0	0	2	10.0	0	0	2	3.6
Survival, weeks								
Median	74.6		37.0		48.4		46.7	
95% CI	28.4 to NYR		18.6 to NYR		21.6 to 82.1		30.4 to 65.6	
PFS, weeks								
Median	20.9		5.6		9.1		7.6	
95% CI	11.1 to 24.6		5.3 to 10.6		6.1 to 12.1		6.0 to 11.1	

NOTE: Clinical activity was defined as PR + SD $\geq$ 6 months + SD with CA-125 drop $\geq$ 50%. Non-patients (10.0%) in cohort 1 achieved clinical activity. Of the 20 pHER2+ patients, 13 had PD (65.0%), whereas the incidence of PR + pHER2+ patients was only 12.5% (eight). The overall incidence of pHER2+ in 34 E. ISA assessive tumors was 29.4% (10 of 34), but only eight of 10 pHER2+ patients were assessed after clinical efficacy.

Abbreviations: pHER2+, over-expressed HER2; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression free survival.

*One patient had CA-125 drop $\geq$ 50%.

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The February 10, 2008, review article by Rastogi et al entitled, "Preoperative Chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27" (*J Clin Oncol* 26:778-785, 2008) contained errors. In Figure 1 and Figure 4, the abscissas (x-axes) were labeled as "Time After Surgery (years)," whereas they should have been labeled as "Time After Random Assignment (years)." The online version has been corrected in departure from the print.

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