담당의사가 주의 깊게 이러한 부작용이 발생하는지 관찰하고 필요한 처치를 시행할 것입니다. 치료 과정에 무엇이라도 이상한 점이 있으면, 담당 의사나 간호사에게 자유롭게 물어보시기 바랍니다.

다른 치료방법

만약 이 임상시험에 참여하지 않기로 한 경우, 다음과 같은 치료가 가능합니다. 수술 후에 시행하는 표준 치료법은 파클리탁셀과 카보플라틴을 3 주 간격으로 정맥 내로 투여하는 것입니다. 이 임상 시험에 참여하지 않더라도 표준 치료를 받을 수 있습니다. 다른 방법으로 시스플라틴과 도시탁셀을 이용한 치료는 알레르기나 다른 부작용이 발생한 경우 선택할 수 있습니다. 방사선 치료는 일반적으로 시행하지 않지만, 상태에 따라서 이용할 수 있습니다. 또한 면역 치료도 하나의 치료 선택사항이 될 수 있습니다.

임상시험에 참여하여 얻을 수 있는 잠재적인 이득 및 손해

이 임상 시험에 참여하는 것이 귀하에게 직접적인 도움이 될 지는 모릅니다. 귀하의 담당 의사는 이 치료로 큰 부작용 없이 질병의 진행과 재발을 막길 기대하고 있습니다. 하지만 그렇게 될지 약속할 수는 없습니다.

이 임상 시험에서 시행하는 두 가지 치료법 모두 장단점이 있습니다. 두 가지 약제를 정맥 내로 투여하는 것의 장점은, 더 많이 사용한 방법이기 때문에 어떤 종류의 부작용이 생길 지 예측하기가 더 쉽다는 점이 있습니다. 반면 복강내 투여법은 더 많은 부작용이 생길 수 있습니다. 하지만 이는 조절 가능할 것이며 치료 효과는 클 것으로 생각됩니다. 하지만 복강으로 투여하는 경우 정맥 내로 투여하는 것에서는 찾아볼 수 없는 (복통, 복막염과 같은) 부작용이 생길 수 있어 이것이 잠재적인 손해가 될 수 있습니다. 이것들은 소규모의 임상 연구와 과거 경험의 결과로 추측에 의한 가능성 정도 수준입니다. 이 임상시험은 이 치료법들의 이득과 손해의 균형을 확인하기 위해 시행됩니다. 현재 상황으로 이득을 확실히 보장할 수는 없습니다.

비용적인 측면에서 치료 II 군에 배정받을 경우 3 주 간격의 카보플라틴 복강내 투여와 일주일 간격의 파클리탁셀 정맥 투여는 아직 의료보험 적용이 되지 않은 치료법으로 II 군에 배정받은 피험자에 한해서 카보플라틴과 파클리탁셀을 무료로 제공받으실수 있습니다.

본 임상 시험으로 얻은 치료법의 효능 및 부작용에 대한 자료는 미래에 귀하와 같은 환자를 치료하는데 이용될 것입니다.

본 임상시험이 준수하는 지침은

본 임상시험은 의료 윤리 방침을 원리로 이루어진 헬싱키 선언에 입각하여 실시됩니다.
본 연구 역시 국가적 임상 연구를 위하여 관련된 윤리적 지침을 함께 준수합니다

연구 참여에 동의철회는 불이익을 초래하지 않습니다

본 연구에 귀하가 참여하는 것에 관하여, 귀하에게 자발적인 의사로 참여할 것을 설명할 것입니다. 귀하는 이 연구과제 참여에 동의하지 않더라도 앞으로 향후의 치료나 의료서비스에 어떠한 불이익을 받지 않을 것입니다. 만약 귀하가 연구 참여에 동의철회를 하여 충분한 치료를 받을 수 없다거나, 또는 연구 담당의사가 손해를 입히게 될 것을 염려할 수도 있습니다; 하지만, 그러한 사례는 없습니다.

만약 귀하가 본 연구 참여하지 않는 것을 선택하였을 경우, 귀하의 연구담당의사는 다른 치료방법에 대해 설명할 것입니다, 그러므로 귀하는 연구 담당의사와 충분히 상의하도록 하십시오.

연구 참여 동의 후에도 언제든지 철회할 수 있습니다

귀하는 본 연구 참여 동의를 언제라도 중단할 수 있습니다. 임상시험 치료가 시작된 후의 경우라도, 귀하는 연구 참여 동의를 어떤 사유에서든지(이상반응을 견딜 수 없을 것 같은 경우) 철회할 수 있습니다.

귀하가 연구 담당의사에게 연구 참여 중단에 대해 말하는 것을 주저하지 마십시오.

만약 임상시험이 중단되는 경우라면, 다른 적합한 치료를 귀하에게 제공할 것입니다.

그러나 귀하가 임상시험 치료와 지정된 병원 방문일정을 지속할 수 없게 된다면, 이전에 수집된 데이터는 중단된 시점까지 이용될 것입니다.

또한, 치료가 중단되면, 귀하는 암의 재발하는 것에 있어 추적 관찰조사를 위해 병원 내원이 필요합니다.

연구에 관한 정보

본 연구에서 사용되는 약물 양쪽 모두는 이미 시판되고 있습니다. 만약 새롭고 중요한 정보가 귀하가 연구에 참여하는 동안에 얻어지면, 귀하가 연구 참여를 유지하는 동안 확인된 정보를 귀하에게 제공할 것입니다. 임상시험의 최종결과는 향후 몇 년 이후 이용될 수 있을 것입니다.

그 결과가 완료되었을 때, 귀하의 연구 담당의사는 임상시험의 최종 결과에 관한 설명을 귀하에게 제공할 것입니다.

개인 정보의 보호

귀하의 의무기록 중 일부는 iPocc Trial Coordinating Center(Kitasato 대학 임상약리학연구센터, 임상시험센터 : 5-9-1 Shirokane, Minato-ku, Tokyo, Japan)에 보내질 것입니다. Coordinating Center 의 연구자는 귀하의 의료 정보를 포함하고 있는 의무기록을 열람할 수 있습니다; 그러나, 그 보고서는 귀하의 개인 정보를 포함하지 않습니다.

본 임상시험을 적절하게 수행하고 있는지 점검하기 위해, 지정된 연구의사, 예를 들면

임상시험 실사 요원과 모니터요원은 의무기록을 열람할 수 있습니다.
대신에, 연구에 정부기관, 예를 들어 보건부 장관, 노동부와 복지부[Welfare(일본후생성 MHLW)]장관 등에 의해 임상시험이 검토될 수도 있습니다. 이런 모든 사례에서, 귀하의 개인정보와 신분을 보장하여 최대한에 의료서비스를 제공할 것입니다.
본 연구에서 얻어지는 결과는 시행된 치료의 안전성과 유효성을 확인하기 위해 이용될 것입니다. 우리는 연구결과를 의학세미나와 학회 저널에서 발표하는 것을 계획하고 있습니다. 그러나, 연구 결과는 대략 685명의 환자들의 종합한 보고될 것이므로 귀하의 개인정보에 관한 것(예를 들어 귀하의 성명)은 발표되지 않을 것입니다..

이상반응의 사례

임상시험치료는 신중하게 시행할 것입니다; 그러나, 귀하가 연구에 참여하는 동안 또는 귀하가 임상시험치료를 받은 것을 고려하여 연구 종료 후에 건강상 장해가 발생할 가능성이 있습니다. 귀하는 원칙상 금전적인 보상은 받지 않을 것입니다. 다만 어떤 다른 임상시험과 같이 항암제의 효과가 나타나게 될 것입니다. 그러나, 어떠한 부작용이 발생하게 되더라도, 적합한 치료를 제공할 것입니다.
본 임상시험계획서와 인과관계가 있는 부작용이나 부작용 처치과정에서 발생된 신체상의 손상이 있는 경우, 직접적인 원인이 되어 발생된 신체상의 손상에 대하여 대한부인종양연구회가 체결한 보험에 의거하여 보상을 할 것입니다.
귀하가 단지 연구에 참여하는 동안뿐만 아니라 연구의 종료 후에도 역시 연구의 전반적 부분에 대해 귀하가 부당한 대우를 받은 적이 있다고 느꼈다면, 귀하의 연구담당의사에게 그 부분에 대해 말하는 것이 중요합니다.

연구에 참여한 피험자에게 요구되는 사항

연구 기간 동안에, 귀하에게 필요한 검사를 시행하는 데 협조를 부탁할 것입니다, 왜냐하면 그것은 귀하의 안전뿐만 아니라 치료의 적합한 평가를 위해 필요하기 때문입니다.
또한 귀하가 어떤 비정상적 신체 상태를 경험하게 된다면, 귀하의 연구담당의사에게 가능한 즉시 조치를 취하도록 알려주십시오.
귀하가 다른 병원에 내원해야 한다면, 귀하가 임상시험에 참여하고 있다는 것 그리고 귀하가 외적으로 의사를 만난 적이 있는 기관의 연구담당의사에게 조언을 듣고 있다고 다른 병원 의사에게 알려 주십시오. 만약 귀하가 다른 약물들(일반용 의약품과 보조제 포함)을 복용하는 것에 대해서는 반드시 연구 담당의사에게 말해 주십시오.
귀하가 본 임상시험에 관해서 어떤 질문이 있다면, 연구 담당의사에게 언제든지 물어보는 것을 주저하지 마십시오.

삽입된 복막 저장 기구를 착용한 피험자에게 요구되는 사항

상당히 드문 예로, 귀하는 공항 게이트와 같은 곳에 설치된 금속 탐지기에 멈춰야 할 수도 있습니다. 귀하가 삽입된 복막 저장기구를 착용한 것을 나타내는 진료카드뿐만 아니라 진단서를 가지고 다닐 것을 권고해 드립니다.
저장기구가 삽입된 동안 귀하는 X선/MRI/CT와 같은 검사를 시행하는 것이 안전할 것입니다.

본 임상시험의 윤리적 평가

본 임상시험은 많은 의료전문가에 의해 충분히 실시되었습니다. 또한, 본 임상시험은 피험자의 권리, 안전, 복지를 보호할 책임이 있는 임상시험윤리심의위원회 (IRB)에 의해 승인되었습니다. 임상시험에 관련된 기관책임자는 그 사항들을 보호하기 위해 또한 조치를 취할 것입니다..
귀하가 피험자 권리에 관하여 문의사항이 생긴다면, 아래 기재된 세부사항으로 연락하십시오.

본 임상시험 심의위원회 관한 정보:
한국원자력의학원 원자력병원 임상연구심의위원회
전화번호: 02-970-1389

임상시험책임자의 상세 정보는 아래와 같습니다.
임상시험책임자 성명: 유상영
연락처(소속): 산부인과 (직위) 과장
연구간호사(연구담당자):
전화번호.

공식화된 연구정보

본 연구는 일본 UMIN (University Hospital Medical Information Network) 임상시험 등록사이트 http://www.umin.ac.jp/ctr/index-j.htm 에 등록되었습니다. 뿐만 아니라 연구 정보를 대중적으로 이용할 수 있게 할 목적으로 영국에 clinical.gov 사이트http://clinicaltrials.gov/ 에 등록되었습니다. 정보는, 예를 들면 연구방법, 연구진행, 연구 결과를 인터넷을 통하여 누구든지 정보를 얻을 수 있도록 하였습니다.

최종 정리

본 연구에 참여를 하는 것은 귀하의 선택입니다. 귀하가 연구 참여를 동의하지 않거나 연구 참여를 동의하는 것 어느 쪽이든 선택할 수 있습니다.
만약 본 임상시험에 참여하는 것을 신중하게 고려하여 결정하였다면, 다음 페이지 동의서에 날짜와 서명을 기입해 주시고 연구담당의사에게 동의서를 전달해 주십시오.
동의서 사본은 귀하가 간직하도록 할 것입니다.

피험자 동의서

연구 기관(병원명칭) **원자력병원**
날짜기입(_____/_____/_____)
임상시험 정보를 제공한 담당의사
성명란_____
서명란(자필서명)_____

본인은 이 동의서의 모든 _____(페이지의 전체 수를 삽입) 페이지의 사본을 받았습니다.
본인은 삶의 질(QOL)을 포함하여 연구 정보를 읽었습니다. 또는 연구 담당자로부터 연구설명을 들었습니다.
본인은 연구정보와 문의하는 내용에 대한 답변에 대해 이해하였습니다.
본인은 본 연구에 참여하는 것을 동의합니다,

"상피성 난소암, 난관암, 또는 일차성 복막암 여성에서 파클리탁셀 매주 정맥 투여 및 카보플라틴 3주 간격 정맥 투여 요법과 파클리탁셀 매주 정맥 투여 및 카보플라틴 3주 간격 복강내 투여 요법에 대한 무작위 2상/3상 임상시험"

- ☐ **본인은 삶의 질(QOL)을 포함한 연구에 참여할 것입니다.**
- ☐ **본인은 삶의 질(QOL)을 제외하고 연구에 참여할 것입니다.**

_____

피험자 성명(서명) 날짜

_____

법정 대리인 성명[필요시] 날짜
피험자와의 관계
*요구될 경우에만 기입 (서명)

본인은 위와 같이 연구에 대해 충분한 설명을 제공하였습니다, 피험자로부터 동의가 얻어 졌는지 그리고 본인이 피험자 정보와 동의서 사본을 전달한 것을 확인하였습니다.

_____

연구담당의사(서명) 날짜

Ⅳ．先進医療申請書

関厚発０２２８第１３６号
平成２６年２月２８日

順天堂大学医学部附属順天堂医院
開設者　殿

関東信越厚生局長

「既に第３項先進医療として先進医療告示に定められている
医療技術（先進医療Ｂ）に係る届出」の受理について（通知）

貴保険医療機関から届出のありました先進医療について、施設基準に適合していることが認められるため、下記のとおり先進医療施設届出書を受理しましたので通知します。

記

１．受理番号	（先１７７）第６０６号
２．受付年月日	平成２６年　２月２７日
３．届出受理年月日	平成２６年　２月２７日
４．算定開始年月日	平成２６年　３月　１日
５．受理内容	先進医療 （技術名：パクリタキセル静脈内投与（一週間に一回投与するものに限る。）及びカルボプラチン腹腔内投与（三週間に一回投与するものに限る。）の併用療法　上皮性卵巣がん、卵管がん又は原発性腹膜がん）

（連絡先　関東信越厚生局東京事務所審査課　電話 03－6692－5119）

近厚発０７３１第８５号
平成２６年　７月３１日

姫路赤十字病院

開　　設　　者　様

近畿厚生局長

先進医療の届出の受理について（通知）

さきに届出のありましたこのことについて、下記のとおり受理したので通知します。

記

受　理　番　号	（先１７７）第４号
受 付 年 月 日	平成２６年　７月２８日
算定開始年月日	平成２６年　８月　１日
該当先進医療	パクリタキセル静脈内投与（一週間に一回投与するものに限る。）及びカルボプラチン腹腔内投与（三週間に一回投与するものに限る。）の併用療法　上皮性卵巣がん、卵管がん又は原発性腹膜がん

収受
26.8.07
第1532号
（複本）

四厚愛発１２２６第１２号
平成２６年１２月２６日

愛媛大学医学部附属病院
開　　設　　者　殿

四国厚生支局長

先進医療の届出の受理について（通知）

さきに届出のありましたこのことについて、下記のとおり受理したので通知します。

記

受　理　番　号	（先１７７）第２号
算定開始年月日	平成２７年　１月　１日
該当先進医療	パクリタキセル静脈内投与（一週間に一回投与するものに限る。）及びカルボプラチン腹腔内投与（三週間に一回投与するものに限る。）の併用療法　上皮性卵巣がん、卵管がん又は原発性腹膜がん

東北厚発０２０３第１４号
平成２７年２月３日

弘前大学医学部附属病院　開設者　殿

東北厚生局長

先進医療の届出の受理について

さきに届出のありましたこのことについて、下記のとおり受理したので通知します。

記

1	受理番号	（先－１７７）第１号
2	受付年月日	平成２７年１月２９日
2	算定開始年月日	平成２７年２月１日
3	該当先進医療	パクリタキセル静脈内投与（一週間に一回投与するものに限る。）及びカルボプラチン腹腔内投与（三週間に一回投与するものに限る。）の併用療法　上皮性卵巣がん、卵管がん又は原発性腹膜がん

（連絡先　東北厚生局青森事務所審査課　電話　017-724-9200）

弘大病経
第　　号
平 27.2.-4
弘前大学医学部
附属病院

V. 文 献

Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial

Bradley J Monk, Andrés Poveda, Ignace Vergote, Francesco Raspagliesi, Keiichi Fujiwara, Duk-Soo Bae, Ana Oaknin, Isabelle Ray-Coquard, Diane M Provencher, Beth Y Karlan, Catherine Lhommé, Gary Richardson, Dolores Gallardo Rincón, Robert L Coleman, Thomas J Herzog, Christian Marth, Arija Brize, Michel Fabbro, Andrés Redondo, Aristotelis Bamias, Marjan Tassoudji, Lynn Navale, Douglas J Warner, Amit M Oza

Summary

Background Angiogenesis is a valid target in the treatment of epithelial ovarian cancer. Trebananib inhibits the binding of angiopoietins 1 and 2 to the Tie2 receptor, and thereby inhibits angiogenesis. We aimed to assess whether the addition of trebananib to single-agent weekly paclitaxel in patients with recurrent epithelial ovarian cancer improved progression-free survival.

Methods For this randomised, double-blind phase 3 study undertaken between Nov 10, 2010, and Nov 19, 2012, we enrolled women with recurrent epithelial ovarian cancer from 32 countries. Patient eligibility criteria included having been treated with three or fewer previous regimens, and a platinum-free interval of less than 12 months. We enrolled patients with a computerised interactive voice response system, and patients were randomly assigned using a permuted block method (block size of four) in a 1:1 ratio to receive weekly intravenous paclitaxel (80 mg/m²) plus either weekly masked intravenous placebo or trebananib (15 mg/kg). Patients were stratified on the basis of platinum-free interval (≥0 and ≤6 months *vs* >6 and ≤12 months), presence or absence of measurable disease, and region (North America, western Europe and Australia, or rest of world). The sponsor, investigators, site staff, and patients were masked to the treatment assignment. The primary endpoint was progression-free survival assessed in the intention-to-treat population. The trial is registered with ClinicalTrials.gov, NCT01204749, and is no longer accruing patients.

Findings 919 patients were enrolled, of whom 461 were randomly assigned to the trebananib group and 458 to the placebo group. Median progression-free survival was significantly longer in the trebananib group than in the placebo group (7·2 months [5·8–7·4] *vs* 5·4 months [95% CI 4·3–5·5], respectively, hazard ratio 0·66, 95% CI 0·57–0·77, p<0·0001). Incidence of grade 3 or higher adverse events was similar between treatment groups (244 [54%] of 452 patients in the placebo group *vs* 258 [56%] of 461 patients in the trebananib group). Trebananib was associated with more adverse event-related treatment discontinuations than was placebo (77 [17%] patients *vs* 27 [6%], respectively) and higher incidences of oedema (294 [64%] patients had any-grade oedema in the trebananib group *vs* 127 [28%] patients in the placebo group). Grade 3 or higher adverse events included ascites (34 [8%] in the placebo group *vs* 52 [11%] in the trebananib group), neutropenia (40 [9%] *vs* 26 [6%]), and abdominal pain (21 [5%] *vs* 22 [5%]). We recorded serious adverse events in 125 (28%) patients in the placebo group and 159 (34%) patients in the trebananib group. There was a difference of 2% or less in class-specific adverse events associated with anti-VEGF therapy (hypertension, proteinuria, wound-healing complications, thrombotic events, gastrointestinal perforations), except bleeding, which was more common in the placebo group than in the trebananib group (75 [17%] *vs* 46 [10%]).

Interpretation Inhibition of angiopoietins 1 and 2 with trebananib provided a clinically meaningful prolongation in progression-free survival. This non-VEGF anti-angiogenesis option for women with recurrent epithelial ovarian cancer should be investigated in other settings and in combination with additional agents. Although oedema was increased, typical anti-VEGF associated adverse events were not prominent.

Funding Amgen.

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See Comment page 776

Creighton University School of Medicine and University of Arizona Cancer Center at St Joseph's Hospital, Phoenix, AZ, USA (B J Monk MD); Fundacion Instituto Valenciano de Oncología, Valencia, Spain (A Poveda MD); University Hospital Leuven, KU Leuven, Leuven, Belgium (I Vergote MD); Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy (F Raspagliesi MD); Saitama Medical University International Medical Center, Hidaka-Shi, Japan (K Fujiwara MD); Samsung Medical Center, Seoul, South Korea (D-S Bae MD); Vall d'Hebron Institute of Oncology, Barcelona, Spain (A Oaknin MD); Université Lyon-I, Centre Léon Bérard, Lyon, France (I Ray-Coquard MD); Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada (D M Provencher MD); Cedars-Sinai Medical Center, Los Angeles, CA, USA (B Y Karlan MD); Gustave Roussy, Villejuif, France (C Lhommé MD); Cabrini Hospital, Malvern, VIC, Australia (G Richardson MD); Instituto Nacional de Cancerologia, Mexico City, Mexico (D Gallardo Rincón MD); University of Texas MD Anderson Cancer Center, Houston, TX, USA (R L Coleman MD); Columbia University Medical Center, New York, NY, USA (T J Herzog MD); Medical University Innsbruck, Innsbruck, Austria (C Marth PhD); Riga Eastern Clinical University Hospital, Riga, Latvia (A Brize MD);

Introduction

Ovarian, fallopian tube, and primary peritoneal cancers, collectively known as epithelial ovarian cancer, are the most lethal gynaecological cancers with more than 150 000 deaths worldwide.[1] Despite high response rates to first-line platinum and taxane-based chemotherapy, the risk of recurrence remains high, and most patients die after relapse.[2] Because most epithelial ovarian cancer is characterised by genomic instability,[3] without identifiable molecular targets, research into improving systemic treatment has recently focused on the tumour microenvironment, with angiogenesis as an important target. Angiogenesis is controlled by growth factors that have key roles in epithelial ovarian cancer, notably VEGF, platelet-derived growth factor, fibroblast growth factor, and the angiopoietin–Tie2 receptor complex. These are central to the complex molecular pathways within the tumour microenvironment and are ideal therapeutic targets.[2]

Regional Cancer Institute Montpellier, Montpellier, France (M Fabbro MD); **University Hospital La Paz, Madrid, Spain** (A Redondo MD); **Alexandra Hospital, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece** (A Bamias PhD); **Amgen, Uxbridge, UK** (M Tassoudji MS); **Amgen, Thousand Oaks, CA, USA** (L Navale MS, D J Warner MD); **and Princess Margaret Cancer Centre, Toronto, ON, Canada** (A M Oza MD)

Correspondence to: Prof Bradley J Monk, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Creighton University School of Medicine at St Joseph's Hospital and Medical Center, University of Arizona Cancer Center, Phoenix, AZ 85013, USA
bradley.monk@chw.edu

Ovarian cancer is unique compared with other solid tumours because anti-VEGF therapy alone slows tumour progression, shrinks metastatic lesions, and reduces malignant effusions such as ascites.[4–6] When added to first-line chemotherapy,[7–9] used in maintenance,[10] or added to chemotherapy at recurrence,[11–13] inhibition of the VEGF pathway significantly prolongs progression-free survival (hazard ratio [HR] 0·48–0·84). Angiogenesis is a complex process that includes many pro-angiogenic and anti-angiogenic factors. However, VEGF pathway inhibition has been a major component of several agents approved by the US Food and Drug Administration (FDA; eg, bevacizumab, sorafenib, sunitinib, pazopanib, axitinib, aflibercept, cabozantinib, and regorafenib) to treat various solid tumours including colon, lung, brain, liver, medullary thyroid, soft-tissue carcinoma, gastrointestinal stromal tumours, kidney cancers, and soft-tissue sarcomas. Although clinically active, these drugs are associated with typical side-effects of anti-VEGF treatment, including hypertension, thrombosis, emboli, bleeding, impaired wound healing, proteinuria, bowel perforation, and CNS disorders. In epithelial ovarian cancer, treatment discontinuation because of these adverse events occurs in as many as a third of patients.[10]

Ang1 (angiopoietin-1) and Ang2 (angiopoietin-2) interact with the Tie2 receptor, which is expressed on endothelial cells, to mediate vascular remodelling in a signalling pathway that is distinct from the VEGF axis. Trebananib (formerly known as AMG 386; Amgen, Thousand Oaks, CA, USA) is a peptide-Fc fusion protein (or peptibody) that acts by binding both Ang1 and Ang2, thereby preventing their interaction with the Tie2 receptor.[14] Trebananib has shown antiangiogenesis activity in preclinical models of ovarian cancer,[14] single-agent activity in relapsed epithelial ovarian cancer in a phase 1 study,[15] and prolonged progression-free survival in a randomised phase 2 trial in recurrent epithelial ovarian cancer.[16] Trebananib has a toxicity profile that is distinct from that of VEGF pathway inhibitors; oedema is reported as the most significant toxicity.[17] Here we report the results of Trebananib in Ovarian Cancer-1 (TRINOVA-1), a phase 3 trial investigating the addition of trebananib to single-agent weekly paclitaxel. Weekly paclitaxel was chosen as the chemotherapy backbone for this clinical trial because it is an accepted standard-of-care option, and because both drugs are dosed every week. Moreover, it has been shown that weekly paclitaxel is active even after failure of previous taxane treatment.[18]

Methods

Study design and participants

This randomised, double-blind, placebo-controlled phase 3 trial was done between Nov 10, 2010, and Nov 19, 2012. Women 18 years or older with epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer who had radiographic evidence of disease progression either on or after their last dose of previous chemotherapy were eligible; we used a modified version of Response Evaluation Criteria In Solid Tumors (RECIST) 1·1[19] that allowed patients with non-measurable but evaluable disease (visible tumour) to enter the trial (appendix). Other eligibility criteria included having one previous platinum-based chemotherapeutic regimen for management of primary disease and up to two additional cytotoxic regimens for management of recurrent or persistent disease. Previous anti-angiogenic therapy (eg, bevacizumab) was allowed, but previous maintenance or consolidation treatment with single-agent paclitaxel was not. A performance status score of 0 or 1, normal end-organ function and blood pressure, and life expectancy of 3 months or more were required. Additionally, patients were required to have adequate haematological function (absolute neutrophil count $\geq 1{\cdot}5 \times 10^9$ cells per L; platelet count greater than 100×10^9 and less than or equal to 850×10^9 cells per L; and haemoglobin ≥90 g/L), adequate renal function (creatinine clearance >40 mL/min per 24 h and urinary protein ≤300 mg/L or ≤1+ on dipstick), adequate hepatic function (aspartate aminotransferase and alanine aminotransferase ≤2·5×upper limit of normal [ULN], or ≤5×ULN if liver metastases were present, and total bilirubin ≤1·5×ULN), partial thromboplastin time or activated partial thromboplastin time ≤1·5×ULN (with international normalised ratio ≤1·5); albumin ≥28 g/L; and generally well controlled blood pressure (systolic ≤140 mm Hg; diastolic ≤90 mm Hg; use of antihypertensive drugs was allowed).

We excluded patients with a platinum-free interval greater than 12 months, platinum-refractory patients (recurrence or progression during the first six cycles or less than 6 months after the beginning of the first-line platinum-based chemotherapy), and those with borderline, mucinous, or clear-cell histologies. We also excluded patients if they had history of arterial or venous thromboembolism within the past 12 months; clinically significant bleeding within 12 months; non-healing wound, ulcer, or fracture; CNS metastasis; known active or continuing infection within 14 days (except uncomplicated urinary tract infection); unresolved grade 2 or higher toxicity from previous systemic therapy; peripheral neuropathy grade 1 or higher; history of previous cancer (except adequately treated non-melanomatous skin cancer or lentigo maligna, adequately treated cervical carcinoma, or if treated with curative intent and with no known active disease for ≥3 years before randomisation); positive HIV or hepatitis C test; active hepatitis B infection; history of interstitial lung disease; higher than average risk of bowel perforation; or any other uncontrolled concurrent illness or history of a condition that may interfere with interpretation of the study results. The appendix shows additional details about inclusion and exclusion criteria. The protocol was approved by each centre's independent ethics committee, and all patients provided written informed consent.

See Online for appendix

Randomisation and masking

We randomly assigned patients to receive either placebo or trebananib in a 1:1 ratio, using a permuted block method (block size of four). We enrolled patients with a computerised interactive voice response system. The randomisation sequence was generated at Amgen by a statistician who had no access to study data and was not involved in the analysis. Access to the randomisation sequence was restricted throughout the study. Patients were stratified on the basis of platinum-free interval (≥0 and ≤6 months *vs* >6 and ≤12 months), presence or absence of measurable disease, and region (North America, western Europe and Australia, or rest of world). Platinum-free interval was defined as the time from last dose of the most recent platinum agent until the first date of disease progression. Radiographically documented disease progression, either on or after the last chemotherapy regimen before study entry, was required for study eligibility. Radiographic progression for the purposes of documenting platinum-free interval was not required. Upon enrolling a patient with the interactive voice response system, site staff received a patient identification number that was also used for dose dispensation. Upon a patient's visit to the study site, staff called the interactive voice response system and were informed what masked trebananib or placebo box should be prepared and given. This was a double-blind trial; all site staff, investigators, pharmacists, patients, and study team personnel (including the study statisticians) were masked to the treatment assignments. In view of the level of masking, we did not prespecify or do an assessment of the success of masking.

Procedures

Patients received weekly 80 mg/m² intravenous paclitaxel (3 weeks on and 1 week off) and either weekly intravenous placebo or weekly 15 mg/kg intravenous trebananib. Protocol-directed treatment was continued until progression per modified RECIST 1·1,[19] toxic effects, or withdrawal of consent. If patients discontinued one component of their treatment (either paclitaxel, or placebo and trebananib) for reasons other than disease progression or withdrawal of consent, they could continue treatment with the other component of their treatment.

Dose modifications to paclitaxel were based on attributed toxic effects (appendix). Dose modifications to paclitaxel were based on attributed toxic effects and included a reduction in dose of 15 mg/m² per level (appendix). Dose reductions for trebananib or placebo were not permitted, but either was discontinued for grade 3 or higher oedema and withheld for other grade 3 or higher treatment-related toxic effects until it resolved to grade 1 or lower (appendix). Paclitaxel or trebananib and placebo were discontinued if treatment delay because of toxic effects lasted more than 28 days consecutively.

Disease was assessed with CT or MRI of at least the chest, abdomen, and pelvis before cycle 1, every 8±1 week for 2 years from the time of randomisation, and then every 6±1 month thereafter. Imaging was evaluated by the investigator per RECIST 1·1[19] with modifications for radiographic response and radiographic disease progression (ascites and pleural and pericardial effusions were not counted as non-measurable lesions because these are known side-effects of trebananib). Tumour markers (specifically cancer antigen 125 [CA-125]) did not contribute to the assessment of disease response and progression.

We detected binding anti-trebananib antibodies using a Biacore 3000 immunoassay (GE Healthcare Life Sciences, Pittsburgh, PA, USA), and for antibody neutralising activity against trebananib using an electrochemiluminescent receptor-binding assay (appendix). To be deemed positive for neutralising antibodies, a patient had to test positive for binding antibodies that showed neutralising activity at the same timepoint. For patients with neutralising antibodies, attempts were made to assess immunogenicity every 3 months until the antibodies returned to baseline or became negative. Antibody analysis included all patients with a baseline and post-baseline sample.

We assessed patient-reported outcomes with the Functional Assessment of Cancer Therapy–Ovary (FACT-O) questionnaire and the FACT-O ovarian cancer-specific subscale.[20] Health utility states were assessed with the EuroQol EQ-5D and EQ-5D visual analogue scale questionnaires. Questionnaires were completed before study drug (trebananib, placebo, or paclitaxel) infusion and clinical assessments on day 1 of weeks 1, 5, 9, 13, 17, and every 8 weeks thereafter for 2 years; then every 6 months, and at the final safety follow-up visit. Completion rates and summary statistics over time were generated for all instruments.

We monitored toxic effects during the treatment phase and reported them with the Common Terminology Criteria for Adverse Events version 3.0.[21] An independent data monitoring committee external to the sponsor (appendix) did regular safety analyses, and reviewed study adverse events and serious adverse events throughout the treatment phase of the study.

Outcomes

The primary endpoint was progression-free survival, defined as time from randomisation to radiographic disease progression per modified RECIST 1·1,[19] or death from any cause. The key secondary endpoint was overall survival (defined as time from randomisation to death); other secondary endpoints included proportion of patients achieving an objective response as per modified RECIST 1·1, proportion of patients showing a CA-125 response as per Gynecologic Cancer InterGroup (GCIG) criteria,[22] patient-reported outcomes, and incidence of adverse events. The appendix shows additional secondary endpoints specified by the protocol.

Statistical analysis

We calculated a sample size of 900 patients, followed up until at least 510 patients had disease progression or died, would be needed to provide 90% statistical power to detect a 33% reduction in the hazard of progression or death and 85% power to detect a 28% reduction in the hazard of death, while limiting the overall two-sided type I error to 5%. Patients alive and progression-free at the time of this analysis were censored at the last evaluable radiological assessment before the data cutoff date. Events of radiographic progression per modified RECIST 1·1[19] that arose after initiation of subsequent anticancer therapy were not deemed events. Any patients who began new treatment were censored at the last assessable tumour assessment, as were any patients who discontinued treatment for reasons other than disease progression. We assessed progression-free survival and overall survival for the intention-to-treat population, and did log-rank tests, stratified by randomisation factors, on all patients assigned to treatment. We estimated HRs

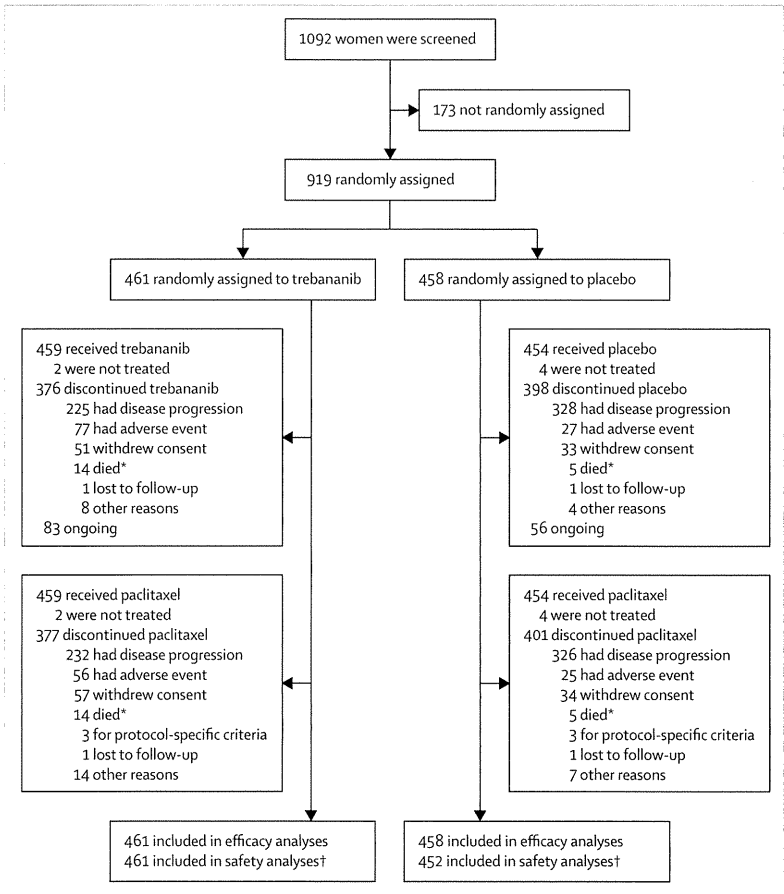

Figure 1: **Trial profile**

*p=0·06 (χ^2 test; 95% CI −0·1 to 4·2) for the difference in number of deaths between groups. Five (1%) patients in the placebo group died; deaths were due to dyspnoea, cardiac arrest, mesenteric occlusion, ileus, and cardiorespiratory arrest. 14 (3%) patients in the trebananib group died; deaths were due to small intestinal obstruction, cardiac arrest, general physical health deterioration, cardiopulmonary failure, hypotension, generalised oedema, metastases to peritoneum, ovarian cancer (three cases), abdominal pain, septic shock, cardiorespiratory arrest, and subileus. The deaths due to general physical health deterioration, metastases to peritoneum, ovarian cancer, cardiorespiratory arrest, and subileus were attributed by the investigator to disease progression. The case of subileus happened 31 days after the last dose of trebananib; per the protocol and statistical analysis plan, we did not regard this as an on-treatment adverse event. However, the study site marked this event as the reason for cessation of trebananib and hence, we recorded this event as an on-treatment death. †In the placebo group, two patients accidentally received trebananib (one dose in one patient; two doses in the other patient). For the safety analysis, those patients were assigned on an as-treated basis (as per statistical analysis plan) to the trebananib group.

	Placebo group (N=458)	Trebananib group (N=461)
Age (years)	59 (50–65)	60 (51–66)
Race		
White	363 (79%)	387 (84%)
Asian	82 (18%)	58 (13%)
Black	7 (2%)	6 (1%)
Other	6 (1%)	10 (2%)
GOG performance status		
0	252 (55%)	259 (56%)
1	205 (45%)	200 (43%)
2	1 (<1%)	2 (<1%)
Primary tumour type		
Ovarian cancer	419 (91%)	423 (92%)
Primary peritoneal carcinoma	24 (5%)	24 (5%)
Fallopian tube cancer	15 (3%)	14 (3%)
Histological type		
Serous	388 (85%)	385 (84%)
Endometrioid	26 (6%)	29 (6%)
Undifferentiated	10 (2%)	15 (3%)
Transitional	2 (<1%)	4 (1%)
Other	32 (7%)	28 (6%)
Histological grade		
Well differentiated	31 (7%)	24 (5%)
Moderately differentiated	84 (18%)	69 (15%)
Poorly differentiated	256 (56%)	274 (59%)
Unknown	87 (19%)	94 (20%)
Previous lines of treatment		
1	172 (38%)	190 (41%)
2	172 (38%)	174 (38%)
3	114 (25%)	94 (20%)
4*	0 (0%)	2 (<1%)
Not available	0 (0%)	1 (<1%)
Platinum-free interval†		
≤6 months	245 (53%)	235 (51%)
>6 and ≤12 months	212 (46%)	223 (48%)
Primary platinum refractory	1 (<1%)	3 (1%)
Previous anti-angiogenic treatment	37 (8%)	35 (8%)
Measurable disease at baseline	433 (95%)	435 (94%)
Region		
North America	91 (20%)	93 (20%)
Western Europe and Australia	189 (41%)	193 (42%)
Rest of the world	178 (39%)	175 (38%)

Data are n (%) or median (IQR). GOG=Gynecologic Oncology Group. *Protocol deviations. †According to most recent platinum-based treatment.

Table 1: **Demographic and baseline characteristics**

with stratified Cox models,[23] assuming proportionality. We assessed non-proportionality by comparing, at the 5% level, the standardised Martingale residuals over time to a normal distribution (comparison result p=0·167).[24] The primary analysis was planned after 510 or more patients had progressed or died. Analysis of overall survival was conditional on seeing a significant difference in progression-free survival between groups; thereafter interim overall survival was planned at the time of 300 deaths or more, and primary survival analysis planned at the time of 600 deaths. All reported p values were two-sided. Analyses of all other efficacy and patient-reported outcomes endpoints are descriptive.

We assessed proportion of patients achieving an objective response for randomly assigned patients who had one or more measurable lesion per RECIST 1·1 at baseline; CA-125 response per GCIG was assessed for randomly assigned patients who had CA-125 concentration twice the ULN or greater at baseline. We calculated the incidence of adverse events for patients who received one or more doses of trebananib or paclitaxel and summarised incidence by actual treatment received.

The patient-reported outcomes analysis included all randomly assigned patients with a patient-reported outcome baseline assessment. For quality-of-life analyses, a pattern-mixture model was used to provide an estimate (and 95% CIs) of whether the change in the FACT-O or FACT-O OCS over time differed between treatment groups, adjusting for the drop-out patterns observed. The pattern-mixture model (with patients grouped into patterns according to their last completed patient-reported outcome assessment) incorporates patient treatment discontinuation. By stratifying data into groups based on the drop-out patterns, pattern-mixture models account for the missing not-at-random patient-reported outcomes data.

Statistical analyses were done with SAS (version 9.2). This trial is registered with ClinicalTrials.gov, number NCT01204749.

Role of the funding source

The funder developed the protocol in collaboration with the study's steering committee chairperson, BJM. The funder collected and collated the data. Employees of the funder and coauthors LN and MT did the statistical analysis. The funder employees and coauthors LN, MT, and DJW contributed to the interpretation of the data. The first draft of the manuscript was written by BJM and funder, employee, and coauthor LN. The funder provided formatting assistance, project management, editing and graphics support during manuscript development. LN, MT, and DJW had access to the raw data; all authors had access to data outputs from the statistical analysis. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

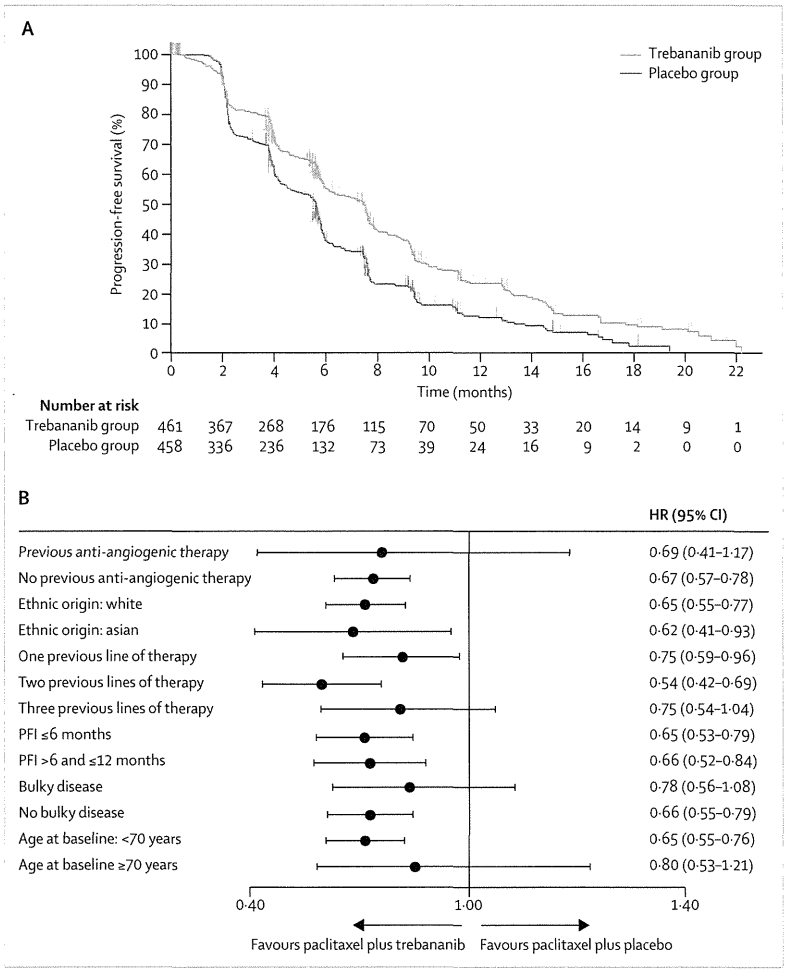

Figure 2: **Progression-free survival**
(A) Kaplan-Meier curves for progression-free survival. (B) A forest plot of progression-free survival for prespecified covariates. PFI=platinum-free interval.

	Placebo group (N=433)	Trebananib group (N=435)
Objective response rate (%; 95% CI)*	29·8 (25·5–34·3)	38·4 (33·8–43·1)
Complete response	20 (5%)	17 (4%)
Partial response	109 (25%)	150 (35%)
Stable disease	170 (39%)	159 (35%)
Progressive disease	113 (26%)	64 (15%)
Unevaluable†	2 (<1%)	5 (1%)
Not done‡	19 (4%)	40 (9%)

Data are n (%) unless otherwise stated. RECIST=Response Evaluation Criteria In Solid Tumors. *p=0·0071. †Patients for whom imaging was not done at the scheduled assessment of response. ‡Patients with a response assessment of complete response, partial response, or stable disease before the scheduled first assessment of response without an additional assessment of response.

Table 2: **Best response per RECIST**

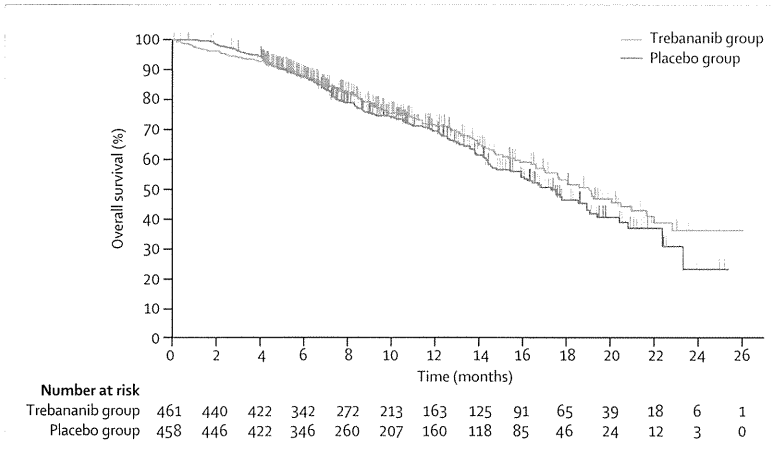

Figure 3: Overall survival

Results

Between Nov 10, 2010, and Nov 19, 2012, 919 patients from 179 sites in 32 countries were randomly assigned to treatment groups (figure 1). 458 patients were randomly assigned to placebo, and 461 to trebananib. The data cutoff date was March 19, 2013. In the randomised treatment groups, 362 patients (39%) had received one previous regimen, 346 (38%) had received two, and 208 (23%) had received three (table 1). Most deaths in the study were attributed to disease progression (appendix). The median number of trebananib and placebo cycles given was 5·0 (IQR 3–8) in the placebo group and 5·0 (3–8) in the trebananib group, and the median relative dose intensity for paclitaxel exceeded 92% in both groups (appendix).

919 patients were evaluated for progression-free survival. After a median follow-up of 10·1 months (IQR 6·4–15·2), 326 (71%) of 458 patients in the placebo group and 239 (52%) of 461 patients in the trebananib group had disease progression; 35 (8%) and 71 (15%), respectively, had died. Median progression-free survival was significantly longer in the trebananib group compared with the placebo group (5·4 months [95% CI 4·3–5·5] *vs* 7·2 months [5·8–7·4], respectively, HR 0·66, 95% CI 0·57–0·77, p<0.0001; figure 2).

The treatment effect was consistent across most prespecified groups (figure 2). In a subgroup analysis, trebananib seemed to prolong progression-free survival after previous anti-angiogenesis treatment, including bevacizumab, although this result was not significant, perhaps due to the small number of patients in this subgroup (59 events in 72 patients). The treatment effect did not seem to be affected by the number of previous regimens or by platinum-free interval. 34 patients (13 in the placebo group and 21 in the trebananib group) were censored for progression-free survival in the protocol-specified analysis because they received new anticancer treatment before documentation of radiographic disease progression. One of those patients (in the placebo group) had documented radiographic progression after initiation of new anticancer treatment (ie, 33 of 34 patients would have been censored irrespective of this aspect of the progression-free survival definition).

Objective responses were significantly more common with trebananib than with placebo (30% [129 of 433 patients with ≥1 measurable lesion per RECIST version 1·1 at baseline] in the placebo group *vs* 38% [167 of 435 patients] in the trebananib group; table 2) as were CA-125 responses (49% [180 of 371 patients with CA-125 ≥2×ULN at baseline] *vs* 56% [206 of 365 patients]; p=0·03).

The interim overall survival analysis did not show any significant difference between groups (17·3 months [95% CI 15·4–19·1] in the placebo group *vs* 19·0 months [17·0–21·7] in the trebananib group, HR 0·86, 95% CI 0·69–1·08, p=0·19; figure 3).

FACT-O and FACT-O OCS questionnaires were completed by most patients (FACT-O, 411 [90%] of 458 patients in the placebo group and 391 [85%] of 461 patients in the trebananib group; FACT-O OCS, 415 [91%] and 400 [87%]). With a pattern-mixture model, mean change in the FACT-O and FACT-O OCS over time were −2·44 (95% CI −4·57 to −0·31) for FACT-O early drop-out (last visit at or before 25 weeks), −1·65 (−5·32 to 2·02) for FACT-O late drop-out (last visit after 25 weeks), −0·68 (−1·36 to 0·00) for FACT-O OCS early drop-out, and 0·17 (−0·99 to 1·33) for FACT-O OCS late drop-out. The data suggest that trebananib treatment did not result in an overall change in patient-reported outcomes scores compared with placebo; detailed data will be reported separately.

We assessed health utility states with the EQ-5D and EQ-5D visual analogue scales; completion rates for the EQ-5D remained higher than 85% (range 85–100%) for the first 57 weeks of treatment in both treatment groups. The median difference in the EQ-5D summary score from baseline between the placebo and the trebananib group was 0 (IQR −0·50 to 0·11) versus 0 (−0·11 to 0·08) at week 17, 0 (−0·11 to 0·12) versus 0 (−0·16 to 0·11) at week 25, and 0 (−0·29 to 0·15) versus 0 (−0·11 to 0·15) at week 57.

The appendix shows the overall incidence of any grade 3 or higher adverse event. Of patients included in the safety analysis population, 244 of 452 (54%) patients in the placebo group and 258 of 461 (56%) patients in the trebananib group had a grade 3 or higher adverse event, and 125 (28%) and 159 (34%), respectively, had a serious adverse event. Three patients in the placebo group and four in the trebananib group had treatment-related fatal adverse events. Trebananib was associated with more adverse event-related treatment discontinuations than was with placebo (77 [17%] patients *vs* 27 [6%], respectively) and higher incidences of oedema (294 [64%] patients had any-grade oedema in the trebananib group *vs* 127 [28%] patients in the placebo group; table 3), including generalised oedema (with one grade 5 event), localised oedema, and lymphoedema (2% [seven patients] *vs* 6% [29 patients]). Pleural effusion, ascites, weight increased, and blurred vision were also increased in the trebananib group

	Placebo group (N=452)				Trebananib group (N=461)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Patients reporting treatment-emergent adverse events	190 (42%)	192 (42%)	34 (8%)	18 (4%)	188 (41%)	205 (44%)	28 (6%)	25 (5%)
Localised oedema*	112 (25%)	4 (1%)	0 (0%)	0 (0%)	240 (52%)	24 (5%)	0 (0%)	0 (0%)
Nausea	165 (37%)	6 (1%)	0 (0%)	0 (0%)	179 (39%)	7 (2%)	1 (<1)	0 (0%)
Alopecia	161 (36%)	2 (<1%)	0 (0%)	0 (0%)	154 (33%)	0 (0%)	0 (0%)	0 (0%)
Fatigue	120 (27%)	17 (4%)	0 (0%)	0 (0%)	112 (24%)	15 (3%)	0 (0%)	0 (0%)
Diarrhoea	109 (24%)	13 (3%)	0 (0%)	0 (0%)	125 (27%)	11 (2%)	0 (0%)	0 (0%)
Abdominal pain	110 (24%)	20 (4%)	1 (<1%)	0 (0%)	110 (24%)	19 (4%)	2 (<1%)	1 (<1)
Asthenia	104 (23%)	15 (3%)	0 (0%)	0 (0%)	116 (25%)	13 (3%)	0 (0%)	0 (0%)
Constipation	124 (27%)	4 (1%)	0 (0%)	0 (0%)	102 (22%)	2 (<1%)	1 (<1%)	0 (0%)
Neutropenia*	85 (19%)	30 (7%)	10 (2%)	0 (0%)	73 (16%)	22 (5%)	4 (1%)	0 (0%)
Vomiting	89 (20%)	12 (3%)	0 (0%)	0 (0%)	108 (23%)	14 (3%)	0 (0%)	0 (0%)
Peripheral neuropathy	63 (14%)	8 (2%)	0 (0%)	0 (0%)	84 (18%)	13 (3%)	0 (0%)	0 (0%)
Anaemia*	74 (16%)	19 (4%)	0 (0%)	0 (0%)	42 (9%)	5 (1%)	0 (0%)	0 (0%)
Ascites*	19 (4%)	34 (8%)	0 (0%)	0 (0%)	40 (9%)	52 (11%)	0 (0%)	0 (0%)
Decreased appetite	73 (16%)	5 (1%)	0 (0%)	0 (0%)	77 (17%)	5 (1%)	0 (0%)	0 (0%)
Headache	71 (16%)	4 (1%)	0 (0%)	0 (0%)	60 (13%)	3 (1%)	0 (0%)	0 (0%)
Dyspnoea	46 (10%)	4 (1%)	1 (<1%)	1 (<1%)	62 (13%)	9 (2%)	1 (<1)	0 (0%)
Cough	58 (13%)	2 (<1%)	0 (0%)	0 (0%)	65 (14%)	1 (<1%)	0 (0%)	0 (0%)
Back pain	58 (13%)	2 (<1%)	1 (<1%)	0 (0%)	52 (11%)	2 (<1%)	0 (0%)	0 (0%)
Pyrexia	55 (12%)	2 (<1%)	0 (0%)	0 (0%)	39 (8%)	1 (<1%)	0 (0%)	0 (0%)
Pleural effusion*	9 (2%)	8 (2%)	0 (0%)	0 (0%)	49 (11%)	13 (3%)	0 (0%)	0 (0%)
Dizziness	44 (10%)	3 (1%)	0 (0%)	0 (0%)	53 (11%)	1 (<1%)	0 (0%)	0 (0%)
Dysgeusia	54 (12%)	0 (0%)	0 (0%)	0 (0%)	37 (8%)	0 (0%)	0 (0%)	0 (0%)
Nasopharyngitis*	28 (6%)	0 (0%)	0 (0%)	0 (0%)	56 (12%)	0 (0%)	0 (0%)	0 (0%)
Pain in extremity	39 (9%)	1 (<1%)	0 (0%)	0 (0%)	48 (10%)	1 (<1%)	0 (0%)	0 (0%)
Abdominal distension	33 (7%)	3 (1%)	0 (0%)	0 (0%)	46 (10%)	4 (1%)	1 (<1%)	0 (0%)
Hypokalaemia	25 (6%)	7 (2%)	3 (1%)	0 (0%)	30 (7%)	18 (4%)	3 (1%)	0 (0%)
Insomnia	48 (11%)	0 (0%)	0 (0%)	0 (0%)	39 (8%)	0 (0%)	0 (0%)	0 (0%)
Upper abdominal pain	31 (7%)	2 (<1%)	0 (0%)	0 (0%)	53 (11%)	0 (0%)	0 (0%)	0 (0%)
Rash	49 (11%)	0 (0%)	0 (0%)	0 (0%)	29 (6%)	0 (0%)	0 (0%)	0 (0%)
Generalised oedema*	12 (3%)	0 (0%)	0 (0%)	0 (0%)	38 (8%)	12 (3%)	0 (0%)	1 (<1)
Myalgia	44 (10%)	0 (0%)	0 (0%)	0 (0%)	44 (10%)	1 (<1%)	0 (0%)	0 (0%)
Arthralgia	40 (9%)	2 (<1%)	0 (0%)	0 (0%)	47 (10%)	0 (0%)	0 (0%)	0 (0%)
Paraesthesia	42 (9%)	0 (0%)	0 (0%)	0 (0%)	45 (10%)	1 (<1%)	0 (0%)	0 (0%)

*Adverse events with a >5% difference between treatment groups.

Table 3: **Adverse events in ≥10% of patients in either treatment group**

compared with placebo (appendix). Grade 3 oedema led to protocol-mandated treatment discontinuation in three (1%) patients in the placebo group and in 37 (8%) in the trebananib group; two other patients in the trebananib group discontinued because of grade 1 and grade 2 oedema (not protocol-mandated discontinuations). Adverse events of any grade arising more frequently in the trebananib group were localised oedema, pleural effusion, generalised oedema, ascites, weight increased, nasopharyngitis, peripheral neuropathy, lymphoedema, upper abdominal pain, increased lachrymation, dry skin, hyponatraemia, paryonychia, and skin fissures (figure 4). Adverse events of interest were hypertension (16 [4%] patients of 452 in the placebo group *vs* 28 [6%] of 461 patients in the trebananib group), bleeding (75 [17%] *vs* 46 [10%]), pulmonary embolism (nine [2%] *vs* five [1%]), arterial thrombotic events (three [1%] *vs* three [1%]), proteinuria (13 [3%] *vs* 15 [3%]), impaired wound healing (two [<1%] *vs* two [<1%]), gastrointestinal perforations (one [<1%] *vs* seven [2%]), and venous thromboembolic events (17 [4%] *vs* 29 [6%]).

Of 391 assessable patients in the trebananib group, 38 (10%) developed non-neutralising anti-trebananib binding antibodies; of those, 12 were only transiently positive, with negative samples at follow-up for patients with neutralising antibodies. 22 of assessed patients in the trebananib group had pre-existing antibodies, and one patient with pre-existing antibodies had neutralising antibodies. In the placebo group, 39 (9%) of 442 assessable

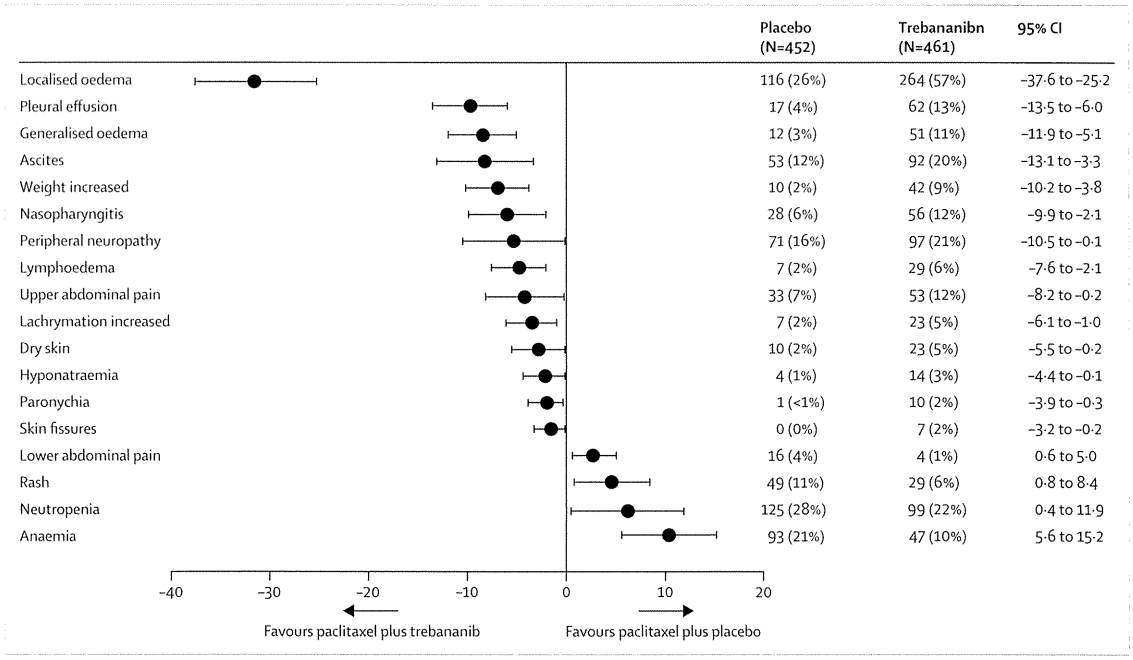

Figure 4: **Treatment-emergent adverse events and 95% confidence intervals of their difference between treatment groups**

patients tested positive for anti-trebananib antibodies after dosing (one patient had transient neutralising antibodies). Assessment of adverse events in patients who developed anti-trebananib antibodies did not suggest any specific adverse event associated with the development of these antibodies.

Discussion

When added to weekly paclitaxel in the treatment of recurrent epithelial ovarian cancer, trebananib significantly increased progression-free survival compared with placebo (panel). The value of progression-free survival in the assessment of the clinical benefit of new drugs in the setting of epithelial ovarian cancer has been controversial, but there seems to be consensus that overall survival, and other clinically relevant endpoints such as proportion of patients achieving an objective response, adverse events, and disease-related symptoms including patient-reported outcomes, should be collectively included an assessment of efficacy.[25] Indeed, the present study verifies the clinical activity of trebananib; we reported that proportion of patients achieving an objective response is significantly increased with treatment and there is no reduction in patient-reported outcomes. Moreover, overall survival, a key secondary study endpoint, does not currently show a difference between groups but will add crucial data to the assessment of the progression-free survival results once the final analysis is available.

Although some have argued that patient-reported outcomes are the most important metric in the assessment of new chemotherapeutic options in solid tumours with low proportions of patients achieving objective responses and short overall survival, patient-reported outcomes are especially problematic because almost all studies of epithelial ovarian cancer enrol patients with small-volume disease who are consequently asymptomatic. In fact, most recent agents approved in epithelial ovarian cancer by the FDA (gemcitabine in combination with carboplatin)[26] or by the European Medicines Agency (trabectedin plus pegylated liposomal doxorubicin[27] and bevacizumab plus various chemotherapies[8,9,12]) were approved on the basis of progression-free survival alone because patient-reported outcomes did not effectively capture disease-related symptoms, and showing an increase in overall survival given long survival after disease progression is difficult.[25,28] Alternatively, results from the AURELIA study recently showed that treatment with bevacizumab, when added to chemotherapy, was associated with an increase in the number of patients who achieved at least 15% improvement in patient-reported outcomes by weeks 8 and 9, compared with those who received chemotherapy alone.[11] Although women with advanced or recurrent epithelial ovarian cancer respond to many available therapeutic agents, almost all die from their disease, which makes the discovery of new active compounds important. Assessment of potential biomarkers of response to trebananib is in progress. In preliminary analyses, baseline levels of Ang1, Ang2, and the soluble form of their receptor Tie2 did not show a consistent predictive or prognostic association with progression-free survival (unpublished data).

Trebananib is distinct from other anti-angiogenesis agents with respect to its mechanism of action and toxicity

profile. Prevention of Ang1 and Ang2 from binding to the Tie2 receptor with trebananib does not seem to be associated with the typical adverse events found with anti-VEGF treatment.[29] Compared with the AURELIA trial of bevacizumab plus single-agent chemotherapy in platinum-resistant recurrent epithelial ovarian cancer,[11] the efficacy results in comparable patients in TRINOVA-1 seemed similar, although cross-trial comparisons are difficult. For example, AURELIA enrolled women with platinum-free interval of less than 6 months and up to two previous regimens, whereas TRINOVA-1 enrolled those with platinum-free interval of less than 12 months and up to three previous chemotherapeutic interventions. Because the reintroduction of carboplatin in the setting of a platinum-free interval between 6 and 12 months is controversial, especially when the volume of disease is small and asymptomatic,[30] TRINOVA-1 allowed such patients to enter the trial at the discretion of the treating physician. AURELIA did not contain a placebo in the control group, and only a third of patients received weekly paclitaxel as in TRINOVA-1. Together, these are the only two randomised clinical trials to show a significant improvement in progression-free survival in patients who are platinum-resistant, which represents a high unmet medical need. Many other clinical trials have studied platinum-sensitive recurrent ovarian cancer. Most notably, the OCEANS study[12] added bevacizumab to carboplatin plus gemcitabine. The HR for the 6–12 months platinum-free interval group was 0·36 (95% CI 0·25–0·53). However, this triplet was much more marrow-suppressive than the doublet studied in TRINOVA-1.

The major toxic effect associated with trebananib treatment was oedema (including ascites and pleural effusions), which is in line with previous results from various phase 2 studies.[16,31,32] Factors underlying the occurrence of oedema associated with trebananib treatment, or its natural history, are unknown. Not all oedema seems to be caused by trebananib because some patients receiving placebo also developed oedema (26% of patients in the placebo group had localised oedema in the present study, compared with 57% in the trebananib group).[16,31] In TRINOVA-1, oedema events were generally mild in severity and rarely led to study drug discontinuation, and at least some cases of oedema seemed to be reversible. Because the FACT-O and FACT-O OCS instruments did not include questions specific to oedema or lymphoedema (although there were questions on abdominal discomfort and bloating) analysis assessing the association of health-related quality of life with oedema or lymphoedema was not done. However, because even mild oedema can cause a burden for patients with cancer, early management is likely to be important. In the present study and other studies of trebananib across various tumour types, the management of oedema followed individual institutional standards, which might have included compression garments, manual drainage, or diuretics.[17] Finally, the weekly schedule of trebananib might be inconvenient for patients, although not when given with drugs such as paclitaxel that are commonly given on a weekly schedule.

Panel: Research in context

Systematic review

To identify publications focused on treatment options for patients with epithelial ovarian cancer, we searched the National Library of Medicine, PubMed, and abstracts presented at recent international clinical oncology meetings. Search terms included "ovarian", "recurrent", and "paclitaxel", without date or language limits. Careful review and qualitative assessment of identified articles and abstracts suggested that outcomes in this setting were poor, and that there was a large unmet need in patients with recurrent epithelial ovarian cancer.

Interpretation

In the Trebananib in Ovarian Cancer-1 (TRINOVA-1) study, trebananib plus weekly paclitaxel significantly extended progression-free survival compared with placebo plus paclitaxel in women with recurrent epithelial ovarian cancer. Although oedema (a typical angiopoi etin inhibitor side-effect) was increased, other typical anti-VEGF-associated adverse events such as hypertension were not prominent. The results from the TRINOVA-1 study are clinically significant because they validate both a new target and a new therapeutic agent in the setting of epithelial ovarian cancer. Trebananib plus paclitaxel might provide a non-VEGF anti-angiogenesis treatment option to women with recurrent epithelial ovarian cancer, if approved by regulatory agencies.

The use of non-platinum chemotherapy might be a valuable treatment option for patients with partially platinum-sensitive disease. Response to platinum-containing recurrence therapy varies among this patient subgroup. Additionally, some patients might not be eligible to receive a platinum doublet as recurrence treatment for various reasons (eg, hypersensitivity). Additionally, because response to a subsequent round of treatment with a platinum-containing agent improves with increasing time between treatments with platinum agents, there is thought to be some benefit to introducing a non-platinum agent before rechallenge with platinum, thus limiting the tumour's ability to acquire drug resistance.[33]

Two other phase 3 studies have added trebananib to pegylated liposomal doxorubicin (TRINOVA-2; NCT01281254), another standard agent in recurrent epithelial ovarian cancer, and to first-line carboplatin and paclitaxel (TRINOVA-3; NCT01493505). TRINOVA-2 enrolment was modified after the manufacturer's notice of a pegylated liposomal doxorubicin shortage in certain regions (ie, the USA and Australia). This supply shortage, in addition to a previous global pegylated liposomal doxorubicin supply disruption, undermined the integrity of the study and led to the decision to permanently close enrolment. The TRINOVA-3 study was resized from 2000 to 1000 patients because a smaller sample size than initially planned could adequately assess progression-free survival, the study's primary endpoint; the outcome of this study will provide further data on the efficacy of trebananib in this patient population.

In summary, trebananib significantly improved progression-free survival when added to paclitaxel,