TUMOR AND SPECIMEN COLLECTION

The growing interest in establishing the molecular determinants of outcome and of predictors of therapeutic benefit has led to the frequent incorporation of translational biologic questions in randomized trials. Both exploratory and validation studies may have implications for intellectual property issues relating to correlative biology.

To address these translational questions, collection of tumor and other specimens from each patient enrolled is thus becoming increasingly commonplace. Shipment of specimens across international borders may require permission from a national oversight body or may be forbidden altogether. In some cases, it may be necessary to set up parallel specimen banks and core laboratories in each country or region. If multiple specimen banks and core laboratories are established, however, the trial will need to institute quality assurance procedures to ensure that all specimen banking and analyses are performed using the same techniques.

As correlative science techniques have evolved, so has the need for harmonization of tissue collection, processing, and testing. The NCI has recently published guidelines for tissue acquisition, as has the EORTC.[33] The North American cooperative groups and the Breast International Group have formulated breast cancer–specific guidelines, which they have agreed to incorporate in future studies.[34]

IMAGING FOR STAGING, TREATMENT PLANNING, AND EVALUATION OF RESPONSE

As cancer imaging has grown more sophisticated, the need for quality assurance and quality control of imaging studies has also grown. Therefore, international collaboration in cancer clinical trials often requires the development of guidelines for imaging studies, plans for routine central review of some or all studies, and consideration of a virtual imaging bank in which digitized imaging studies from patients on clinical trials can be collected and reviewed. The NCI, working in collaboration with cooperative groups with expertise in image acquisition, the American College of Radiology Imaging Network, the Quality Assurance Review Center, and the Cancer and Leukemia Group B imaging core laboratory at Ohio State University, developed a virtual imaging evaluation workspace in 2007. The consortium has established an imaging core service and repository with capability of acquiring and storing image objects on a worldwide basis. In addition, the same collaborators plan to develop standard operating procedures for assessment of imaging end points in cancer as well as evaluation of new imaging markers.

RADIATION THERAPY

As a critical modality for cancer treatment, radiation in clinical trials must undergo similar processes for quality assurance and quality control as other modalities of treatment. The NCI supports quality assurance for radiation dosimetry in NCI-sponsored trials through the Radiological Physics Center, quality assurance for radiation delivery methods through the Radiation Therapy Oncology Group and the Quality Assurance Review Center, and, more recently, quality assurance for advanced-technology radiation therapy (eg, three-dimensional conformal radiation therapy, stereotactic radiation therapy, intensity modulation therapy) through the Advanced Technology Consortium.[35-39] These quality assurance activities have been routinely implemented for NCI-sponsored cancer trials in North America, as well as for select academic and pharmaceutical trials in Europe and Japan. Globally, however, quality assurance requirements, such as facility questionnaires, facility credentialing, external reference dosimetry audits, and phantom measurements, vary from group to group, both in content and evaluation criteria. This variation hampers collaboration and makes comparisons and meta-analyses difficult. In addition, both radiotherapy technology and the tools for quality assurance are constantly evolving. Close engagement between clinical trialists and manufacturers is required to integrate new digital formats smoothly and ensure that a common framework for data interpretation can achieve a uniform level of quality.

FINANCIAL AND LOGISTICAL SUPPORT

The ability to conduct cancer clinical trials efficiently requires ongoing support for infrastructure, both centrally and at participating institutions. Building the infrastructure for a specific trial is much less efficient than building and maintaining infrastructure for an ongoing series of trials. The central and institutional costs for cancer treatment trials are summarized in Tables 1 and 2. Support for these costs may come from a variety of sources, including government, industry, charity, and local academic institutional contributions. Government support has varied from country to country and region to region. The NCI began to support the infrastructure for cancer clinical trials in 1956. In 2007 the NCI's budget for the US-based nine clinical trials cooperative groups, which together enroll about 25,000 patients per year to trials, was approximately $145 million. Over the past 10 years, the United Kingdom has formalized and provided centralized funding for standing clinical trials networks throughout the country, initially for oncology, and now for medical research of all types. The United Kingdom provides infrastructure support to all clinical sites participating in approved phase II and III trials and large cohort studies through the National Cancer Research Network. Publicly funded charities such as Cancer Research UK and government agencies, such as the Medical Research Council, provide support for both early- and late-phase

Table 1. Central Costs for Cancer Treatment Trials

Protocol design and development, including support for meetings and conference calls
Preparation of applications to central regulatory authorities and central ethics authorities, as applicable
Collection/monitoring of institutional and investigator regulatory compliance
Verification of patient eligibility and management of treatment assignment
Clinical trial insurance
Patient random assignment
Database development
Data collection and management
Drug supply and distribution
Statistical design and analysis
Tumor, specimen and imaging banking
Quality assurance/quality control
Onsite monitoring and audits of participating sites
Pharmacovigilance

Table 2. Institutional Costs for Cancer Treatment Trials

Ethics review and local competent authority review of proposed trials, open trials, adverse events, amendments
Time of local investigators, research nurses, pharmacists, and data managers
Time and resources for related studies (pathology, imaging) over and above that which is standard of care
Research pharmacy
Quality control efforts

clinical trials through research grants to clinical investigators and trials units.[40,41] The estimated yearly budget for academic cancer clinical trials in the United Kingdom, including support for network infrastructure is about £55 million. The Ireland–Northern Ireland National Cancer Institute Cancer Consortium, with financial support from the Republic of Ireland, the United Kingdom government, and the NCI, established a clinical trials network covering the Republic of Ireland and Northern Ireland.[42] In France, the Ministry of Health and INCa (Institut National du Cancer) have established support for clinical trials through competitive requests for applications as well as support for data management centers, including those of specialized networks. The governments of Japan and Korea have undertaken steps to support infrastructure for and encourage academic clinical trials in cancer. A similar effort is underway in the Middle East. The government of Australia, through Cancer Australia, has recently undertaken support and expansion of existing trials networks, which had previously been funded through a variety of means including fundraising and charitable donations, peer-reviewed grants for individual trials, and infrastructure support for some groups by the New South Wales Cancer Institute. Funds raised by charity (the Canadian Cancer Society) have been used for many years to support the core activity of the NCIC-CTG. Professional medical societies in China, India, Japan, Korea, and other countries have undertaken to start cooperative groups to run clinical trials for cancer patients. Local institutions also have generously contributed their own funds, as well as funds raised through charitable appeals, to help support the infrastructure for clinical trials, such as the costs listed in Tables 1 and 2.

We note that limitation of funding has hindered clinical trial research in many instances. In the United States, for example, the per-patient cost to support research nurses, data managers, and physician time for a hypothetical phase III cancer treatment trial has been estimated at $6,000 (US$) in 2003.[43] NCI funds are only sufficient to underwrite a per-patient payment of $2,000 (US$). Clinical trials groups outside the United States that lack substantive support from charity, industry, or government often must decline participation in promising phase III studies unless separate industry funding is available.

PHARMACEUTICAL INDUSTRY INVOLVEMENT IN INTERNATIONAL TRIALS

Pharmaceutical companies may run international trials on their own, or in conjunction with established clinical trials cooperative groups. Effective collaboration between industry and clinical trials groups has resulted in the successful completion of many important cancer trials. Not surprisingly, however, there may well be tensions between the objectives of the pharmaceutical company, which generally wants to support trials that provide data appropriate for a licensing application, and those of the cooperative group, which wants to evaluate the additive benefit of that new agent to standard treatment. In some cases, the cooperative group may also want to combine or compare agents from two different companies. In addition, in many instances, a trial addressing a question of great importance to oncologists and patients may be of no interest to the pharmaceutical industry. An international consortium of academic breast cancer trialists have recently proposed a model template for successful partnership between academia and industry.[44]

Pharmaceutical support for trials may include the supply and/or distribution of experimental drugs, per-patient payments to participating institutions, and support of central activities, such as investigator education, laboratory assays, statistical analysis, data management, quality control/quality assurance, and audits. The provision of study drug and financing across international boundaries may be complicated due to the variation in licensing arrangements across the globe. Recently, the Chief Executive Officer Roundtable on Cancer, working in partnership with the NCI and academic institutions in the United States, developed a set of common contract clauses designed to shorten the length of time required for legal agreements.[45]

CURRENT REPORT CARD ON GLOBAL COLLABORATION

How should we characterize the current state of global collaboration in cancer treatment trials? Ideally, clinical trials groups for each cancer site should have a regular mechanism for the exchange of ideas about current science and proposed trials. Such a structure would facilitate the design and conduct of complementary trials, avoid unnecessary duplication, and stimulate collaboration on meta-analyses of similar studies. Where appropriate, groups can work together on the design and management of joint global trials.

Regional international networks have been established for decades both in Europe and in North America. For example, leading European oncologists set up the EORTC in 1962. Today, EORTC's top 35 accruing institutions are located in 11 European countries, as well as Turkey and Egypt. Similarly, cancer researchers in Canada and the United States have worked together for many years through such collaborative groups as the National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the Children's Oncology Group. The NCIC-CTG has worked closely with investigators in the United States, Europe, and Australia. Global networks for cancer treatment trials in the developing world have been set up by both the International Network for Cancer Treatment and Research and the International Atomic Energy Agency. In addition, many groups of trialists have established ongoing collaborations to perform meta-analyses based on data from individual patients accrued to clinical trials. A partial list of recent key cancer treatment trials made possible through effective international collaboration is presented in Appendix Table A1 (online only).

Effective interchange between clinical trials groups has most often been accomplished under the umbrella of international intergroup committees. A list of the activities which we would expect from an effective international intergroup is presented in Table 3. One of the best examples of effective intergroup activities is in breast cancer. Globally, the Breast International Group and the International Breast Cancer Study Group bring together 41 member groups from Europe,

Table 3. Expectations for Functional Global Intergroup Committees

Required participation by member groups in at least some intergroup trials
Required participation by groups in intergroup activities
Dues to support intergroup infrastructure and meetings
Attendance at meetings and conference calls
Regular face-to-face meetings, conference calls, and trial-specific workshops
Routine exchange of information about active and planned studies
Joint development of concepts for new trials
Development of joint trials as appropriate and feasible, ideally to include:
Single protocol with country-specific appendices
Common case report forms
Single data base
Development of complementary trials as appropriate and feasible
Routine engagement with industry as an intergroup
Individual-patient date meta-analyses as appropriate

Canada, Latin America, Australia/New Zealand, and Asia, in addition to those from North America. The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization trial (NCT 00490139), sponsored by NCI, the Breast Intergroup, and GlaxoSmithKline is an example of a worldwide trial made possible through international collaboration and industry partnership.[46]

In brain cancer, the EORTC, NCIC-CTG, the Trans-Tasman Radiation Oncology Group (based in Australia and New Zealand), and the United States–based Radiation Therapy Oncology Group and North Central Cancer Treatment Group have developed a joint disease strategy for high-grade gliomas. This work follows up on the joint international temozolamide trial previously mentioned.

In gynecologic cancer, the Gynecologic Cancer Intergroup, formed in 1997, brings together 16 cooperative groups that conduct cancer treatment trials for women with gynecologic cancer. Under the auspices of the Gynecologic Cancer Intergroup, cooperative groups from Australia/New Zealand, Italy, the United Kingdom, and the United States quickly completed accrual of 4,000 women to Gynecologic Oncology group 182/International Collaboration in Ovarian Neoplasia 5, the largest ovarian cancer treatment trial to date.[47]

In addition, there are numerous instances of academic and industry-led trials conducted across the developing and developed worlds. To date, however, global integration of academic cancer treatment trials remains the exception, rather than the norm.

CONCLUSION

The scientific imperative for international collaboration in cancer treatment trials is clear. Our ability to establish international collaborations will result in maximization of our resources and patients, permitting us to complete definitive trials in a timely manner. Regulatory, logistical, and financial hurdles, however, often hamper the conduct of joint trials. The advantages and disadvantages of such international collaboration are listed in Table 4. Ongoing efforts on the part of cancer investigators, cooperative groups, national research institutions, national governments, competent authorities, ethics committees, and pharmaceutical companies are needed to strengthen global collaboration so that we may identify effective treatments for our patients more quickly. In addition, integration of investigators and cooperative groups in China, India, Japan, Korea, Latin America, and other countries in Asia, Africa, the Middle East, and Europe into the existing intergroups and clinical trials networks will make our trials more representative of cancer patients from around the globe and the results from our trials more broadly applicable to those patients.

Table 4. Advantages and Disadvantages of International Collaboration in Cancer Treatment Trials

Advantages	Faster accrual from more sites for patients with common cancers and with all stages of disease
	Faster accrual for patients with uncommon and rare tumors, specific molecular defects, and less common histologic subtypes
	Broader applicability of research results
	Fewer duplicative trials
	More complementary trials
	More rapid dissemination of innovations in cancer treatment
Disadvantages	Differing regulations between countries
	Differing levels of infrastructure support for cancer clinical trials between countries
	Differing processes and schedules for scientific review by funding bodies between countries
	Longer lead time for concept and trial development
	Differing licensing arrangements for specific drugs between countries
	Contractual issues with pharmaceutical companies in different countries
	Drug distribution issues in different countries

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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腫瘍内科，2(3)：220-225，2008

特集 国際共同臨床試験

米国多施設共同研究グループへの参加 1)医師の立場から*

勝俣範之**

Key Words：GOG, international clinical trial, bevacizumab

はじめに

がんの臨床試験が国際化(グローバル化)が進んできている理由として，①新規抗がん剤の開発が爆発的に進んでおり，より早く，より多くの患者を登録することが必要となった，②分子標的治療薬が台頭してくることによって，がん腫の中でもtargetがしぼられることになり，より多くの患者が必要となった，③稀少疾患に対する臨床試験の必要性が増してきた，などがあげられる．近年の国際共同試験の成果としては，一つの国際共同大規模臨床試験によって，全世界的に新たな標準治療が確立されるようになったことは，大きな成果と言えよう．

婦人科がん領域の国際共同試験

婦人科がん領域は，発生頻度が比較的稀であるため，研究者の数が多くないこともあり，国際協調性が以前より取られてきた．欧州ではEORTC(ヨーロッパ中心)(http://www.eortc.be/)，ICON(イギリス中心)のグループで国際共同試験が行われてきた．米国も巻き込んだ組織としては，Gynecologic Cancer Intergroup(GCIG)が1995年に創設され(http://ctep.cancer.gov/resources/gcig/index.html)，国際共同臨床研究を行っている．現在では16か国が参加しており，日本からは，婦人科悪性腫瘍化学療法研究機構〔Japanese Gynecologic Oncology Group：JGOG(http://jgog.gr.jp/)〕が参加しており，現在日本発の国際共同臨床試験である卵巣明細胞がんに対するCDDP＋CPT-11 vs. CBDCA＋Paclitaxelの臨床第III相試験(JGOG3017)が開始されており，すでに韓国が参加を表明，登録を開始，今後も英国，イタリアが参加予定である．

米国多施設共同試験グループ(Gynecologic Oncology Group：GOG)

米国GOGは，米国国立がん研究所(National Cancer Institute：NCI)スポンサーのがん臨床試験グループで米国で唯一の婦人科がんを対象とするグループである．GOGは1970年2月に設立された．研究費はNCIのがん研究費3,200億円(2006年，ちなみに日本のがん研究費の総額は2006年度は61億円)のうち，Cooperative Group Programに年間115億円費やされる．GOGは12のCancer Cooperative Groupの一つであり，年間の研究費は約15億である．これまで行われてきた臨床試験の数は461あり，現在のactive trialは55ある．GOGの組織構造を図1に示す．運営部門のofficeや統計センターなどが設置され，各がん種ごとの委員会が設置されている．Executive committeeとして，Data and Safety Monitoring Board(DSMB)は日本では効果・安全性評価委員会に

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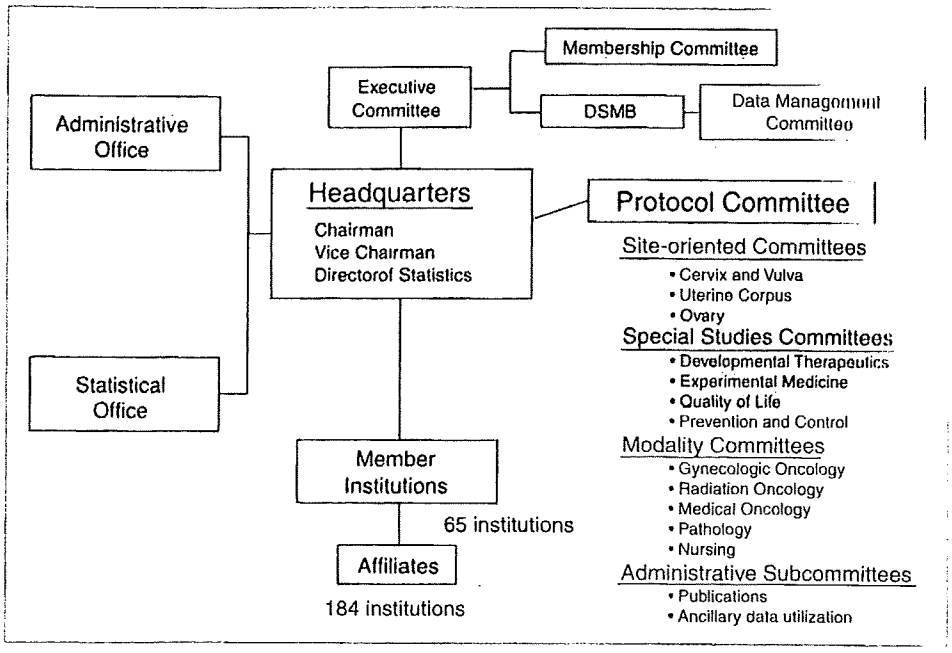

図1　Organizational Structure of GOG

相当する委員会である．Membership committeeでは，施設の認定を行う委員会である．参加メンバー施設はfull memberとprovisional memberと分けられるが，full memberとは正規の認定された施設であり，provisional memberとは見習い段階の施設，言うなれば二群施設というわけである．現在のGOGメンバー施設(full member)は65施設，メンバー施設に付随した関連施設(affiliate institute)は184施設であり，計249施設が参加している．Full membershipを維持するためには，①最低登録症例数の確保(関連施設を合わせた合計の年間150ポイントが必要，1症例登録ごとにポイントが加算される．Phase II studyで3ポイント，phase III studyで6ポイントであり，150ポイント維持には，phase III studyで25症例の登録が年間必要．メンバー施設，関連施設ともに年間3例以上の登録が必須)，②施設データのqualityとして，登録症例の90%以上が適格例であること，case report form(CRF)の85%以上が遅滞なく提出されていること，CRFの90%以上が常に完全に記載されていること，施設訪問監査を3年に1度受けなければならないこと，その際に85%以上の正確性が確保されていること，③年2回のbusiness meetingに参加すること，が義務づけられており，full membershipを維持するためにはかなり厳しい規準となっている．それゆえ，GOGのfull membershipを獲得することは，施設のqualityの高いことが保証されることにもなる．GOGは2001年より，国際共同プロジェクトを開始し，2001年には英国，豪州・ニュージーランドが参加，2002年に日本が，2003年に北欧グループが，2005年に参加，provisional memberとなっている．GOGが行った国際共同試験としては，進行卵巣がんに対する初回化学療法のランダム化比較試験(GOG182)があり[1]，この試験は4,312名の患者が，わずか3年間という速さで登録されており，英国，豪州・ニュージーランドが参加している．

米国GOGへの参加

わが国でもJGOGやJapan Clinical Oncology Group(JCOG)が婦人科がんの臨床試験を行ってきたが，国際共同試験を行おうという機運がしだいに高まり，2001年，米国GOGより国際メンバーとして参加の打診を受け，当時川崎医大(埼玉医科大学国際医療センター)婦人科の藤原恵

表1　GOG-Japan登録状況

Phase	Diagnostic	III	III	III	II	II	I	Total
GOG Study ID	171	174	175	209	187	232B	9917	
2003年	29	1	−	−	0	−	−	30
2004年	35	1	0	−	2	−	1	39
2005年	28	1	15	0	0	−	1	45
2006年		3	14	5	0	0	0	22
2007年				24	0	2	3	29+
								165+

参加施設：鹿児島市立病院，国立がんセンター，北海道大学，慶應義塾大学，九州がんセンター，呉医療センター，慈恵会医科大学，四国がんセンター，岩手医科大学，近畿大学，東北大学，埼玉医科大学，鳥取大学，神戸医療センター，広島大学

先生を中心にして米国への申請手続きの準備を開始した．参加各施設は，10施設を選定し，GOG Japanとして組織した．GOG JapanはJGOGの付属委員会として組織された．米国の臨床試験に参加するためには，米高規制当局への諸手続きをまずは行わなければならなかった．すなわち，各参加施設の倫理審査委員会(IRB)を米国規制当局(Office for Human Research Protections：OHRP)へ登録，Federalwide Assurance(FWA)取得(施設登録)，各参加施設医師NCI investigator numberの取得，investigatorの被験者保護に関する教育記録の提出〔米国NIHが規定する一定の倫理教育プログラムを受講・承認されなければならない．OHRPホームページから受講可能である(http://ohrp-ed.od.nih.gov/CBTs/Assurance/login.asp)〕・conflict of interest宣誓書の提出を行った．また，米国GOGへ，がん診療専門医の配置確認証明書，施設長および各科長の承諾書，年間症例数およびがん患者登録に関する調査書などの提出を行い，米国2002年1月にprovisional memberとして承認された．また，GOGの臨床試験へ登録するに際し，プロトコールの日本語版作成，同意説明文書の日本語訳作成を行い，施設IRBに提出，2003年3月より症例登録を開始した．2004年8月米国GOGよる監査(監査員2名)を受け入れ，日本の代表2施設(鹿児島市立病院，川崎医科大学)がGOG臨床試験の実施状況を監査され，IRB(年1回のプロトコールの更新)，informed consentのレビュー，薬剤の管理状況，治療状況の詳細，評価判定の確認，毒性の判定，などが，米国NCIが規定する監査事項に従って行われたが，acceptableと判定され，米国NCIにも報告された．2003年には25症例，2004年には36例，2005年には54例を登録し，full memberに必要となる年間150ポイントを獲得し，2005年にfull memberに昇格．2007年12月現在，日本からは15施設(国立がんセンター中央病院，九州がんセンター，四国がんセンター，東北大学，神戸医療センター，鹿児島市立病院，慶応大学，慈恵医科大学，近畿大学，鳥取大学，北海道大学，呉医療センター，岩手医科大学，埼玉医科大学，広島大学)が参加し，2007年12月現在まで日本から，165例を登録している(表1)．

米国GOG参加の問題点と課題

現在，日本から米国へ登録している臨床試験は，表2に示す4つのみである．Full membershipを維持していくためにも，多くの臨床試験に参加することが必要であるが，GOGで行われている臨床試験の多くは，日本での未承認薬，または適応外薬剤が使用されている．国際共同試験を円滑に効率に進めていくためにも，未承認/適応外薬剤の問題は一刻も早く解決することが必要である．未承認薬剤に関しては，後述する医師主導治験を推進させることが望ましい．適応外薬剤の問題に関しては，こうした国際共同試験のようなレベルの高い臨床試験を行う場合には，保険適応を認めるなどの仕組みを作っていくことも必要となろう．また，今後も国際共同試験を行っていくに際して，海外の研究者たちと対等にdiscussionできる若手研究者の育成も大切である．JGOGでは，若手研究者育成のため

表2

- GOG9917 : A dose-escalating phase I study with an expanded cohort to assess the feasibility of intraperitoneal carboplatin and intravenous paclitaxel in patients with previously untreated epithelial ovarian, primary peritoneal, or fallopian tube carcinoma
- GOG232B : A phase II evaluation of paclitaxel (taxol NSC #673089) and carboplatin (paraplatin NSC #241240) in the treatment of advanced, persistent or recurrent uterine carcinosarcoma
- GOG187 : Phase II study of paclitaxel for ovarian stromal tumors as first-line or second -line therapy
- GOG209 : Randomized Phase III trial of doxorubicin/cispratin /paclitaxel and G-CSF versus carboplatin/ paclitaxel in patients with stage III & IV or recurrent endometrial cancer

に，臨床試験の立案・作成のための教育セミナーなどを2007年から開始している．また，臨床試験のインフラストラクチャーであるデータマネージメント，データ解析を行っていくためのデータセンターの設立，セントラルデータマネージャーの人員育成と確保も言うまでもなく重要課題である．

国際共同医師主導治験の開始

進行卵巣がんの治療成績は依然として不良であり，さらなる治療成績向上が望まれている．現在開発中の新しい薬剤の中で，血管新生阻害剤であるBevacizumabは卵巣がんにもっとも期待がされている．Bevacizumabは，大腸がん，非小細胞性肺がんについては米国など，世界各国で承認されているが，卵巣がんについては患者数が少なく経営的な判断から企業主導の臨床試験は世界いずれにおいても実施されておらず，承認のある国はない現状である．しかし，既治療の治療抵抗性卵巣がんに対してBevacizmab単剤投与でも高い奏効率が得られていることから，その臨床導入は世界中から求められている．これまで再発・難治性卵巣がんに対して行われたBevacizumab単剤投与の第II相試験は米国から2つ報告[2][3]があり，奏効率18%(11/62名)，16%(7/44名)と，Bevacizumab単剤による奏効率は固形がんの中でもっとも高かった．卵巣がんに対するBevacizumab投与のランダム化第III相比較試験として，2005年9月26日より米国GOGにより患者登録が開始されている(図2)．しかし，予定症例集積期間3年である目標症例数2,000例にもかかわらず，2006年12月の時点で221例の登録しか進んでおらず，試験参加がNCIより求められた．日本からも，企業治験で行うことを当初企業に打診したが，企業としては日本でBevacizumabの卵巣がんに対する治験を行う予定がまったくないということであった．今後，GOG218またヨーロッパでも計画されている卵巣がんに対するBevacizumabのランダム化比較試験によって，Bevacizumabの有用性が証明された場合，試験が終了してから改めて企業治験を開始した場合，他の薬剤と同様5～10年の日本での承認の遅れが予想されるため，医師主導治験として手続きを行い，GOG218へ参加することとした．

2007年から準備を開始，NCI-CTEPとの治験薬輸入に関する協議，厚生労働省担当部署と治験薬搬送手続きについての協議，米国GOGミーティングに参加し，米国の研究者と国際共同臨床試験をどうやって進めていくかについて協議を行った．また，医師主導治験開始に際して，治験審査委員会に提出する書類作成として，GOG218プロトコール(英文)の和訳，説明同意文書(対訳版，意訳版)，標準業務手順書(医師主導治験取り扱い規定，治験審査委員会，自ら治験を実施する者，モニタリング，監査，被験者補償，治験薬取扱い，安全性情報取扱い，治験調整医師，効果・安全性評価委員会，治験薬概要書の作成，治験実施計画書の作成，説明同意文書の作成)を行った．その後，企業からの治験薬概要書の作成，企業への監査業務の委託契約，効果安全性評価委員会の設置・依頼，各施設での米国臨床試験に参加するための届け出書・責任医師，治験分担医師のNCI investigator numberの取得，施設倫理審査委員会・倫理審査委員

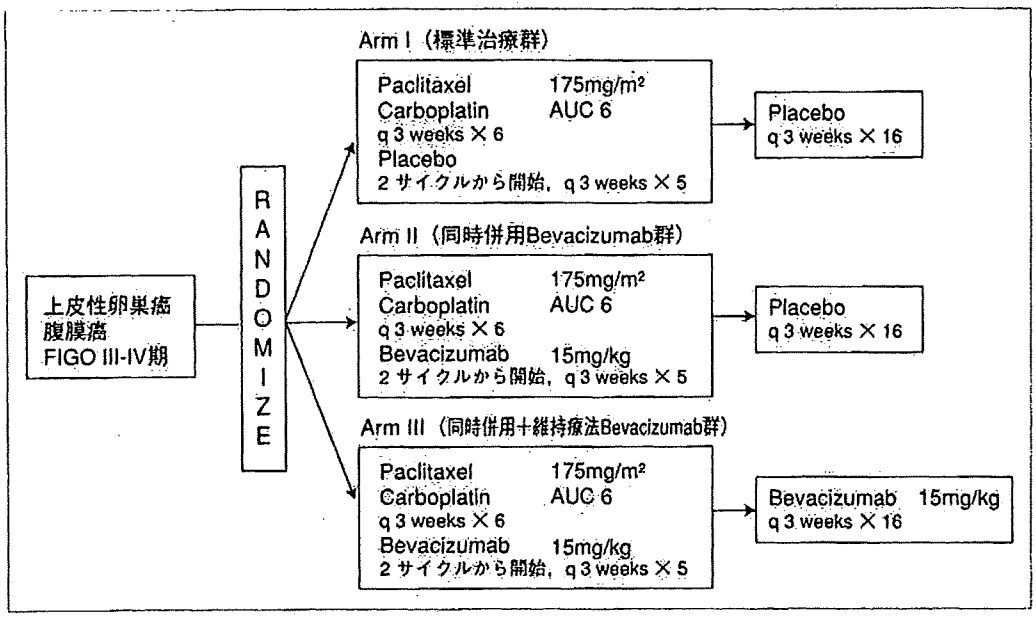

図2　GOG218試験デザイン
AUC：area under the curve

表3　医師主導治験―米国との比較

	米国	日本
治験届け	NCI	自ら治験を実施する者(医師)
治験薬搬送業務，SOP作成	NCI	外部委託(北里研究所)
有害事象報告業務，SOP作成	NCI-FDA-GOG	自ら治験を実施する者(医師) 外部委託(北里研究所)
プロトコール作成	NCI-FDA-GOG	自ら治験を実施する者(医師)
監査業務	NCI-GOG	企業に委託
モニタリング	GOGデータセンター	外部委託(北里研究所)
データマネージメント	GOGデータセンター	外部委託(北里研究所)
統計解析	GOGデータセンター	外部委託(北里研究所)
患者登録，治験実施	GOG参加施設	自ら治験を実施する者(医師)
臨床試験数	55 (GOG)	4 (JGOG＋本研究)
医師主導治験数	14 (GOG) 140 (NCI全体)	1 (婦人科がん) 5 (日本全体)

SOP：Standard Operating Procedures, 標準業務手順書

患者相談担当窓口・CRC・安全性業務担当者の倫理セミナーの受講)，効果安全性評価委員会の業務委託契約，などの作業を9月までに終了，9～10月の期間で，各施設にて，プロトコールの治験審査委員会への提出・承認を得た．2007年11月6日，独立行政法人医薬品医療機器総合機構へ治験届提出．現在，参加施設システム監査および各施設Kick-off meetingを開始している．今後は，2007年度12月初旬までに，NCIからの治験薬の搬送テストを実施し，安全に搬送可能であることを確認，各施設のシステム監査・Kick-off meeting終了，2008年3月31日現在までに4例の登録が進んでいる．

国際共同医師主導治験の問題点と課題

GOG218試験は進行性卵巣癌の初回化学療法におけるBevacizumabの併用療法および維持療法としての有用性を評価するランダム化比較試験と

して計画したものであり，良い結果が得られれば，日米での公的臨床試験に基づく卵巣がん効能に対する同時期の承認申請・取得が得られることになる．その結果，卵巣がんに対する治療成績向上への国際貢献に結びつくことになり，また海外とのdrug-lag解消の糸口となる可能性があり，今後，国際共同臨床試験(治験)を推進させるための基盤整備の充実にも貢献できることとなるが，現段階での問題点と今後の課題は多くある．

わが国では2003年の薬事法改正により医師主導治験が可能となったが，煩雑な事務手続き，巨額な費用がかかることが問題となっている．米国の医師主導治験はInvestigational New Drug (IND)と呼ばれる新薬の承認を得るための臨床試験を，Cooperative Groupの場合はNCIが行っている(表3)．今回のGOG218試験に関しても，NCIが企業(Genentech社)から薬剤の提供を受け，治験届け，治験薬の管理，標準業務手順書(SOP)作成などの事務作業はすべてNCIが行っている．プロトコール作成もNCI-FDAが関与しており，研究者のみで立案されているわけではなく，peer reviewがかかるシステムになっている．また，有害事象報告はすべてweb上で行われるようになっており，重篤有害事象(SAE)報告に際しては，施設からのSAE報告は，同時にGOG, NCI, FDAに報告されるシステムになっており，タイムラグが生じないようになっている．データマネージメントは，NCIが認定したデータセンターにて管理される．GOGのactive trial数が55あり，そのうち，医師主導治験は14あり，医師主導治験の割合が大きいことがわかる．一方，日本の医師主導治験は，自ら治験を実施する者が，治験届け，プロトコール作成，有害事象報告など，すべて医師自ら行わなければならず，医師個人にかかる負担が大きい．治験届けは，多施設共同試験を行う場合，施設代表者連名で届けるため，すべての施設のIRB承認を待ってから，治験届けを出さなければいけなくなるため，治験の開始が遅れてしまう．データマネージメントやモニタリング，監査などは，外部委託に頼ることが多くなるので，コスト高となる．わが国でも国際共同医師主導治験をより活性化させるためには，米国Cooperative Groupの良いシステムを積極的に取り入れることによって，こうした問題点を早急に解決することが望まれる．

文　献

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*　　*　　*

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PROTOCOL GOG-0218

A PHASE III TRIAL OF CARBOPLATIN AND PACLITAXEL PLUS PLACEBO VERSUS CARBOPLATIN AND PACLITAXEL PLUS CONCURRENT BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY PLACEBO, VERSUS CARBOPLATIN AND PACLITAXEL PLUS CONCURRENT AND EXTENDED BEVACIZUMAB, IN WOMEN WITH NEWLY DIAGNOSED, PREVIOUSLY UNTREATED, STAGE III OR IV, EPITHELIAL OVARIAN, PRIMARY PERITONEAL OR FALLOPIAN TUBE CANCER

NCI-SUPPLIED AGENT(S):
BEVACIZUMAB/ PLACEBO (NSC #704865, IND #7921) **(06/26/06) (08/06/07)(10/14/08)**

NCI Version Date: 05/18/09
Includes: Revisions 1-6

POINTS:
PER CAPITA –30
MEMBERSHIP - 6

TRANSLATIONAL RESEARCH PER CAPITA–Award based on specimen submissions. Distribution: Frozen tumor-3 points, tumor block-2 points (2nd choice tumor sections and scroll-1 point), frozen serum-0.5 point, frozen plasma-0.5 point **(06/26/06)**, and whole blood-0.5 point. **(03/16/09)**
TRANSLATIONAL RESEARCH MEMBERSHIP - Bonus membership point will be awarded for submission of satisfactory frozen tumor, tumor block, frozen serum and frozen plasma. **(06/26/06)**

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OPEN TO PATIENT ENTRY SEPTEMBER 26, 2005 REVISED JANUARY 16, 2006 REVISED JUNE 26, 2006 REVISED AUGUST 6, 2007 REVISED OCTOBER 14, 2008 REVISED MARCH 16, 2009. REVISED JUNE 1, 2009

This study is supported by the NCI Cancer Trials Support Unit (CTSU). **(08/06/07) (10/14//08)**

Institutions not aligned with GOG 0218 will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix. **See instructions in Appendix VIII for New Institutions prior to enrollment of first patient**

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the GOG. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to GOG unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by GOG via GOG's web based system. Please send query responses and delinquent data to GOG as directed and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the GOG Statistical and Data center.

Patient enrollments from institutions that are not aligned with GOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to CTSU Data Operations unless otherwise specified in the CTSU logistical appendix. CTSU will use the GOG-0218 number as required for reporting to GOG and NCI and when registering patients through the GOG Registrar. CTSU participants and institutions will be instructed to use the GOG-0218 study number on all data forms.

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION (08/06/07)(10/14/08)

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 8:00 AM – 8:00 PM Eastern Time, Monday Friday (excluding holidays) [For CTSU patient enrollments that must be completed within approximately one hour or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]	GOG Statistical and Data Center at Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263 **Call GOG User support 716-845-7767 to obtain user name and password to submit electronic data** Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.

For patient eligibility or treatment-related questions contact the Study Chair of the Coordinating group. For questions unrelated to patient eligibility, treatment or data submission contact the CTSU Help Desk by phone or email:

All other questions (including forms-specific questions) should be communicated by phone or e-mail to:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Public Web site is located at: www.ctsu.org

The CTSU Registered Member Web site is located at http://members.ctsu.org

CTSU logistical information is located in Appendix VIII.. (08/06/07)

SCHEMA **(08/06/07) (10/14/08)**

ELIGIBILITY
•Epithelial ovarian, peritoneal primary or fallopian tube cancer
•FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV **(06/26/06)**

Randomization (cycle = 21 days):

Arm I (standard chemotherapy)

Phase A Chemotherapy * day 1 every 21 days x 6 cycles
Placebo (for bevacizumab) ** day 1 every 21 days beginning with cycle 2 x 5 cycles

↓

Re-registration

↓

Phase B Placebo (for bevacizumab) ** day 1 every 21 days cycles 7 through 22 **(06/26/06)**

Arm II (concurrent bevacizumab)

Phase A Chemotherapy * day 1 every 21 days x 6 cycles
bevacizumab ** day 1 every 21 days beginning with cycle 2 x 5 cycles

↓

Re-registration

↓

Phase B Placebo (for bevacizumab) ** day 1 every 21 days cycles 7 through 22 **(06/26/06)**

Arm III (extended bevacizumab)

Phase A Chemotherapy * day 1 every 21 days x 6 cycles
bevacizumab ** day 1 every 21 days beginning with cycle 2 x 5 cycles

↓

Re-registration

↓

Phase B bevacizumab ** day 1 every 21 days cycles 7 through 22 **(06/26/06)**

*Paclitaxel 175mg/m^2 IV over 3 hours followed by Carboplatin AUC 6 IV over 30 minutes day 1 of cycles 1 through 6 only (Note: docetaxel 75mg/m^2 IV over 1 hour may be substituted for paclitaxel [see sections 2.65, 5.322, and 6.51].)

**bevacizumab / Placebo 15mg/kg IV day 1 of each cycle beginning with cycle 2

OUTCOME MEASURES **(10/14/08) (03/16/09)**

•Primary Endpoint:
-Progression-free survival (PFS)
•Secondary Endpoints:
-Overall Survival (OS)
-Response Rate (RR)
-Toxicity
-Quality of Life
-Translational Research - Please see Section 7.2 as well as Appendix VI (Specimen Procedures) and Appendix VII (Laboratory Procedures) for details regarding the specimen requirements and laboratory testing for this protocol. The banking of whole blood for future research will apply to all of the patients who provide consent regardless of randomization and treatment including those already enrolled on GOG-0218.

Patients treated on this trial will not be eligible for therapy on clinical trials evaluating consolidation or maintenance therapy while on or off study.

TABLE OF CONTENTS **(1-16-06)**

1.0 OBJECTIVES **(10/14/08)**

This is a phase III randomized study to evaluate new treatment programs for patients with International Federation of Gynecologic Oncology (FIGO, Appendix I) stages III and IV, epithelial ovarian, peritoneal primary or fallopian tube cancer. **(06/26/06) (08/06/07)**

1.1 Primary Objectives

1.11 To determine if the addition of 5 concurrent cycles of bevacizumab to 6 cycles of standard therapy (carboplatin and paclitaxel) [Arm II] increases the duration of progression-free survival (PFS) when compared to 6 cycles of standard therapy alone [Arm I] in women with newly diagnosed stage III (with any gross residual disease) and stage IV, epithelial ovarian, peritoneal primary or fallopian tube cancer. **(06/26/06) (08/06/07)**

1.12 To determine if the addition of 5 concurrent cycles of bevacizumab **(06/26/06)** plus extended bevacizumab for 16 cycles beyond the **(06/26/06)** 6 cycles of standard therapy (carboplatin and paclitaxel) [Arm III] increases progression-free survival when compared to 6 cycles of standard therapy [Arm I] in women with newly diagnosed stage III (with any gross residual disease) and stage IV, epithelial ovarian, peritoneal primary or fallopian tube cancer. **(06/26/06) (08/06/07)**

1.2 Secondary Objectives (10/14/08)

1.21 In the event that both Arm II and Arm III regimens are superior to the Arm I regimen with respect to progression-free survival, to determine whether the Arm III regimen prolongs progression-free survival when compared to the Arm II regimen.

1.22 To determine whether the Arm II or Arm III regimen increases the duration of overall survival when compared with the Arm I regimen.

1.23 To compare each of the experimental regimens to the Arm I regimen with respect to the incidence of severe toxicities or serious adverse events.

1.24 To determine the impact on Quality of Life (QOL, as measured by the **FACT-O TOI**) following treatment with the above regimens.

1.3 Translational Research Objectives

1.31 To assess the relationship between angiogenic markers and clinical outcome including tumor response, progression-free survival and overall survival in patients randomized to standard cytotoxic chemotherapy (paclitaxel and carboplatin) without bevacizumab, with concurrent bevacizumab or with extended bevacizumab.

1.32 To assess the predictive value of a set of genes whose expression correlates with survival of patients with stage III (with any gross residual disease) and stage IV, epithelial ovarian, peritoneal primary or fallopian tube cancer. **(06/26/06) (08/06/07)(10/14/08)**

1.33 To bank whole blood for research. **(03/16/09)**

1.34 To determine if genetic variations in genes associated with essential hypertension including WNK lysine deficient protein kinase 1 (WNK1), G protein-coupled receptor kinase 4 (GRK4) and kallikrein B (KLKB1) predict which patients are likely to develop bevacizumab-induced hypertension. **(03/16/09)**

2.0 BACKGROUND AND RATIONALE

2.1 Standard Management of Advanced Ovarian and Peritoneal primary Carcinoma

After initial surgical diagnosis, staging and cytoreduction, the standard primary systemic chemotherapy for women with advanced epithelial ovarian, and peritoneal primary cancer consists of chemotherapy with a platinum and taxane combination,[1,2] usually carboplatin[3-6] and paclitaxel. While significant advances have been made in patient management, this disease still carries the highest fatality to case ratio for all gynecologic malignancies diagnosed in the United States. It is estimated that in 2004, 25,580 new cases will have been diagnosed and 16,090 women will have died of the disease.[7] Over the past two decades, there have been only modest improvements in overall 5-year survival, and while 5-year survival has increased steadily from 30% to 50% overall, it has improved by only 5%, from 20% to only 25% for women with advanced-stage tumors. Clearly improvements are needed in primary therapeutic strategies.

2.2 New Therapeutic Strategies to Improve Outcomes

GOG-0182-ICON5 was a 5-arm randomized clinical trial comparing standard therapy (carboplatin and paclitaxel) with four investigational arms incorporating gemcitabine, topotecan and liposomal doxorubicin, either in combination or in sequence with paclitaxel and carboplatin. Major ovarian cancer clinical trials groups throughout the world participated in this study, including the MRC ICON investigators in the United Kingdom, European Institute of Oncology in Italy, and the Australia-New Zealand GOG Consortium. This international collaboration provided a unique opportunity to accrue large numbers of patients in a timely manner which facilitated the simultaneous evaluation of multiple agents in a prospective randomized trial. With international participation, accrual exceeded 1,200 patients per year, and the trial reached its targeted accrual goal within four years of activation.

While the results of GOG-0182-ICON5 will help establish optimum chemotherapy for previously untreated patients with advanced ovarian and peritoneal primary cancer, the next generation of clinical trials will explore the impact of molecular targeted therapies in conjunction with chemotherapy. In particular, growth factor signal transduction inhibitors and anti-angiogenic agents as single agents and in combination with cytotoxic drugs are currently undergoing phase I and II trials in women with these tumors. Many of these agents have been shown to have cytostatic effects and have shown synergy with chemotherapy in experimental models of human cancer. In addition, since it is postulated that such biologic agents may also have a role in maintenance therapy, the

general approach in phase III trials will be the evaluation of the impact on outcome of active biologic agents in combination with standard cytotoxic therapy plus or minus extended single agent administration, compared with standard cytotoxic therapy alone, in patients with advanced disease.

2.3 Rationale for Angiogenesis -Targeted Therapeutics

Angiogenesis is one of the cardinal processes leading to invasion and metastasis of solid tumors. The angiogenic-signaling pathway may be triggered by the release of angiogenic promoters such as vascular endothelial growth factor (VEGF) from tumor cells into the local microenvironment. There is accumulating evidence that angiogenesis plays a central role in ovarian cancer disease progression and prognosis.[8-13] Given that a direct relationship has been demonstrated between the expression of biomarkers of angiogenesis and the behavior of epithelial ovarian cancer, it would seem implicit that pharmacological inhibitors of angiogenesis could arrest tumor progression.[14-17] Neutralizing anti-VEGF monoclonal antibodies have demonstrated therapeutic activity in a variety of pre-clinical solid tumor models.[18,19]

2.4 Role of Bevacizumab, an Anti-VEGF Monoclonal Antibody, in Epithelial Ovarian and Peritoneal primary Cancer Therapy (10/14/08)

Bevacizumab is a recombinant humanized version of a murine anti-human VEGF monoclonal antibody, named rhuMAb VEGF. Bevacizumab has been advanced into clinical development for use as a single agent to induce tumor growth inhibition in patients with solid tumors and for use in combination with cytotoxic chemotherapy to delay the time to disease progression in patients with metastatic solid tumors.[20]

The results of two single agent trials of bevacizumab for patients with recurrent epithelial ovarian and peritoneal primary cancer have been published.[21,22] GOG (GOG-0170-D) utilized two co-primary efficacy endpoints: clinical response by NCI RECIST criteria and proportion surviving progression-free for at least 6 months. 62 participants received bevacizumab at 15 mg/kg every 21 days until clinical or radiographic evidence of disease progression or development of unacceptable toxicity. The primary disease characteristics were typical of patients with recurrent ovarian cancer, and approximately 43% of patients were considered primarily platinum resistant. A 21% response rate was observed, and 40% were progression-free for at least 6 months, with a median PFS 4.7 months, compared with 1.8 months for a historical control based on previous negative phase II trials of cytotoxic agents in populations with similar clinical characteristics. Genentech AVF 2949 examined patients with a higher risk profile in terms of the potential for disease progression and adverse events, allowing only patients considered either primarily or

secondarily platinum resistant and having received 2 or 3 previous cytotoxic regimens. These differences in eligibility ultimately translated into a higher level of platinum resistance, a greater number of prior regimens and a slightly worse performance status profile in the AVF population. Forty four patients were treated at the same dose and schedule for bevacizumab as used in GOG 170-D. Seven (16%) responses were documented, and 12 (27%) were progression-free for at least 6 months.

The observed spectrum and degree of toxicity between these trials was not unexpected, for example with respect to arterial thrombotic and reno-vascular events. However, unlike GOG 170-D, in which no gastrointestinal perforations or fistulae were observed, 5 such events occurred in 44 patients enrolled to AVF 2949; these events led to early termination of AVF 2949 and an IND Action Letter in 2005. It is possible that the higher risk profile of AVF participants and imaging evidence of intestinal wall thickening as a precursor may account for this observation, but this is still speculative - some of these events occurred after discontinuing bevacizumab for disease progression, the natural history of gastrointestinal perforation and fistula in patients with advanced recurrent ovarian cancer is not well documented, and one cannot account for statistical variation without a controlled trial. That being said, Han et al. recently reviewed published data from phase II trials and historical cohort studies of open-label use of bevacizumab as a single agent and in combination with cytotoxic drugs. This review revealed an overall incidence rate of 5.2% in 308 patients, about double the rate seen in other solid tumor populations. While not all of these gastrointestinal perforations and fistulae have required open surgical management and most patients have recovered, prospective pre-clinical and clinical work is needed to identify mechanisms and risk factors. This is one of the goals for GOG-0218.

2.5 Experience with Combination Bevacizumab - Cytotoxic Therapy

Evidence from pre-clinical studies and recent phase II and III clinical trials in other solid tumors has demonstrated enhanced anti-tumor activity of traditional cytotoxic regimens, when combined with bevacizumab. For example, Devore and colleagues reported on a three-arm phase II randomized trial of carboplatin/paclitaxel at with or without bevacizumab (7.5 mg/kg or 15 mg/kg dose levels) every 21 days until disease progression, in 99 patients with stages IIIB and IV non-small cell lung cancer.[23] Response rates were 21.9 percent (7/32 patients) in the low dose and 42.9 percent (14/35 patients) in the high dose bevacizumab combination arms, compared to a response rate of 31.3 percent (10/32 patients) in the chemotherapy alone arm. A phase II/III trial