10.1002/ijc.27680. [Epub ahead of print]

4. Hanley SJ, Yoshioka E, Ito Y, Konno R, Hayashi Y, Kishi R, Sakuragi N. Acceptance of and attitudes towards human papillomavirus vaccination in Japanese mothers of adolescent girls. Vaccine. 2012 Aug 24;30(39):5740-7.

5. Dong P, Karaayvaz M, Jia N, Kaneuchi M, Hamada J, Watari H, Sudo S, Ju J, Sakuragi N. Mutant p53 gain-of-function induces epithelial-mesenchymal transition through modulation of the miR-130b-ZEB1 axis. Oncogene. 2012 Jul 30. doi: 10.1038/onc.2012.334.

6. Todo Y, Suzuki Y, Azuma M, Hatanaka Y, Konno Y, Watari H, Kato H, Matsuno Y, Yamashiro K, Sakuragi N. Ultrastaging of para-aortic lymph nodes in stage IIIC1 endometrial cancer: A preliminary report. Gynecol Oncol. 2012 Aug 30.

7. Sakuragi N. Emerging concept of tailored lymphadenectomy in endometrial cancer. J Gynecol Oncol. 2012 Oct;23(4):210-2. doi: 10.3802/jgo.2012.23.4.210. Epub 2012 Sep 19.

8. Todo Y, Sakuragi N. Randomized controlled trial versus comparative cohort study in verifying the therapeutic role of lymphadenectomy in endometrial cancer. Int J Clin Oncol. 2012 Dec 1. [Epub ahead of print]

9. Todo Y, Sakuragi N. Systematic lymphadenectomy in endometrial cancer. J Obstet Gynaecol Res. 2012 Dec 21. doi: 10.1111/j.1447-0756.2012.02062.x. [Epub ahead of print]

10. Kang S, Todo Y, Odagiri T, Mitamura T, Watari H, Kim JW, Nam JH, Sakuragi N. A low-risk group for lymph node metastasis is accurately identified by Korean gynecologic oncology group criteria in two Japanese cohorts with endometrial cancer. Gynecol Oncol. 2013 Jan 13. doi:pii: S0090-8258(13)00015-2. 10.1016/j.ygyno.2013.01.005. [Epub ahead of print]

11. Kobayashi N, Abedini M, Sakuragi N, Tsang BK. PRIMA-1 increases cisplatin sensitivity in chemoresistant ovarian cancer cells with p53 mutation: a requirement for Akt down-regulation. J Ovarian Res. 2013 Jan 26;6(1):7. [Epub ahead of print]

（分担研究者：青木大輔）

1. Tamada Y, Takeuchi H, Suzuki N, Aoki D, Irimura T: Cell surface expression of hyaluronan on human ovarian cancer cells inversely correlates with their adhesion to peritoneal mesothelial cells. Tumour Biol, 33: 1215-1222, 2012.

2. Tanaka K, Takada H, Isonishi S, Aoki D, Mikami M, Kiguchi K, Iwamori M: Possible involvement of glycolipids in anticancer drug resistance of human ovarian serous carcinoma-derived cells. J Biochem, 152: 587-594, 2012.

3. Toyama A, Suzuki A, Shimada T, Aoki C, Aoki Y, Umino Y, Nakamura Y, Aoki D, Sato TA: Proteomic characterization of ovarian cancers identifying annexin-A4, phosphoserine aminotransferase, cellular retinoic acid-binding protein 2, and serpin B5 as histology-specific biomarkers. Cancer Sci, 103: 747-755, 2012.

4. Akahane T, Hirasawa A, Tsuda H, Kataoka F, Nishimura S, Tanaka H, Tominaga E, Nomura H, Chiyoda T, Iguchi Y, Yamagami W, Susumu N, Aoki D: The origin of stroma surrounding epithelial ovarian cancer cells. Int J Gynecol Pathol, 32: 26-30, 2013.

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学会発表その他

1. Eriko Aotani. International Clinical Trials Management in Rare Cancer. International Workshop on Clinical Trial for Rare Diseases. St. Marianna University School of Medicine. April 10, 2012.
2. 藤原恵一、青谷恵利子、竹内正弘、落合和徳.【シンポジウム

講演】新薬グローバル開発試験の枠組み：JGOG. 第50回日本癌治療学会学術集会:シンポジウム27 グローバルスタディの現状と未来. 2012年10月26日. 横浜市.

3. 青谷恵利子【講演】先進医療Bとして実施する臨床試験. 平成24年度第2回JCOGリンパ腫グループ合同班会議. 2013年1月19日. 東京.

4. 青谷恵利子【シンポジウム講演】日本主導型グローバル臨床研究体制整備事業の計画について. 第2回臨床研究・治験活性化協議会. 2013年2月4日. 神奈川県相模原市.

5. 青谷恵利子【セミナー講演】日本主導型グローバル臨床研究拠点での実際. 日本病院薬剤師会主催　第15回CRC養成フォローアップ研修会. 2013年3月1日. 東京.

6. 青谷恵利子【講演】臨床研究の倫理とは何か. 埼玉医科大学卒後教育セミナー. 2013年3月13日.

原著

1. 青谷恵利子、秦友美、川上温子、坪井沙絵、沼上奈美、牛谷真由美、宮田かおる、野中美和、竹内正弘、武林亨、藤原恵一. 高度医療評価制度下で実施する臨床試験の支援に関する研究－がん領域における多施設共同試験の課題. Jpn Pharmacol Ther (薬理と治療, 日本臨床試験研究会雑誌), 2012年3月25日: 40 suppl 1 : S67-S79.

総説/報告書

1. 青谷恵利子. HAM/TSP国際共同試験の体制整備に関する研究. 厚生労働科学研究費補助金（難治性疾患克服研究事業）(H23-難治-一般-126） HTLV-1 関連脊髄症（HAM）の新規医薬品開発に関する研究　研究代表者　山野嘉久 分担研究報告書. 2012年4月.

2. Øyvind Melien, Eriko Aotani, Cleola Anderiesz, et al. Report from subgroup Education, Training, Infrastructure and Patient Involvement under OECD GSF working group to facilitate international cooperation in non-commercial clinical trials. Jpn Pharmacol Ther 2012; 40 suppl 2 [Journal of Japan Society of Clinical Trials and Research] : S137-182.

3. 青谷恵利子、竹内正弘、藤原恵一、落合和徳. 婦人科がんの臨床試験. 遥か EPS Magazine, vol. 8, 33-38, 2013年1月20日.

4. 青谷恵利子. 臨床試験を運営するために必要な組織 15. 中央事務局. 医学のあゆみ、244(13): 2013年3月30日 In Press.

5. Melien O, Siegfried N, Steinhausen K, Aotani E, Cazap E, Chan A, Ghersi D, Kvalheim G, Makanga M, Ren J, Stuart G, Vaz F,

Sgard F. Health in Action: Stronger infrastructure, better training and more involved patients will facilitate the conduct of non-commercial, multinational clinical trials. PLOS Med, 2013. In Press.

（分担研究者：万代昌紀）
論文業績

Yamamura S, Matsumura N, Mandai M, Huang Z, Oura T, Baba T, Hamanishi J, Yamaguchi K, Kang HS, Okamoto T, Abiko K, Mori S, Murphy SK, Konishi I.
The activated transforming growth factor-beta signaling pathway in peritoneal metastases is a potential therapeutic target in ovarian cancer.
Int J Cancer. 2012 Jan 1;130(1):20-8.

Yamanoi K, Mandai M, Suzuki A, Matsumura N, Baba T, Yoshioka Y, Kosaka K, Konishi I.
Synchronous primary corpus and ovarian cancer: High incidence of endometriosis and thrombosis
Oncol Lett. 2012 Sep;4(3):375-380.

Ueda Y, Mandai M, Matsumura N, Baba T, Suzuki A, Yoshioka Y, Kosaka K, Konishi I.
Adenoid cystic carcinoma of Skene's glands: a rare origin in the female genital tract and the characteristic clinical course.
Int J Gynecol Pathol. 2012 Nov;31(6):596-600.

Mandai M, Matsumura N, Kosaka K, Yasumoto K, Baba T, Yoshioka Y, Suzuki A, Konishi I.
Laparoscopic tubo-ovarian transposition prior to chemoradiation for uterine cervical cancer
Int J Case Rep Imag. 2012 3(6):42-45.

Yasumoto K, Suzuki A, Matsumura N, Baba T, Oiwa Y, Miyamoto S, Matsuura M, Obama K, Kido A, Umeoka S, Minamiguchi S, Mikami Y, Yoshioka Y, Kosaka K, Mandai M, Konishi I.
Cancer risk and management in a womanwith Peutz-Jeghers syndrome.
Int Canc Conf J. 2012 1:1-14.

Baba T, Su S, Umeoka S, Abiko K, Nakamoto Y, Mandai M, Matsumura N, Konishi I.
Advanced extragonadal yolk sac tumor serially followed up with (18) F-fluorodexyglucose-positoron emission tomography and

computerized tomography and serum alpha-fetoprotein.
J Obstet Gynaecol Res. 2012 Mar;38(3):605-9.

Mandai M, Suzuki A, Matsumura N, Baba T, Yamaguchi K, Hamanishi J, Yoshioka Y, Kosaka K, Konishi I
Clinical management of ovarian endometriotic cyst (chocolate cyst)-diagnosis, medical treatment and minimal invasive surgery.
Curr Obstet Gynecol Rep. 2012 1:16-24.

Suzuki A, Kariya M, Matsumura N, Baba T, Yagi H, Mandai M, Konishi I, Fujii S
Expression of p53 and p21WAF-1, apoptosis, and proliferation of smoth muscle cells in normal myometrium during the menstrual cycle.
Med Mol Morphol. 2012 Dec;45(4):214-21.

Taki M, Baba T, Mandai M, Suzuki A, Mikami Y, Matsumura N, Konishi I
A case of solitary fibrous tumor arising slowly in vulva over 10 years – case report and review.
J Obstet Gynaecol Res. 2012 May;38(5):884-8.

野溝万吏、馬場長、鈴木彩子、山西恵、山口綾香、角井和代、松村謙臣、吉岡弓子、近藤英治、佐藤幸保、濱西潤三、小阪謙三、万代昌紀、小西郁生
子宮びまん性平滑筋腫症を認めた姉妹例
産婦人科の進歩　65：40-45、2012

万代昌紀、山口建、松村謙臣、岡本尊子、天野泰彰、馬場長、小西郁生
卵巣明細胞腺癌における特異的遺伝子発現と分子標的治療への展開
産科と婦人科　79：1279-1284、2012

万代昌紀、小阪謙三、松村謙臣、馬場長、鈴木彩子、吉岡弓子、小西郁生
初期子宮体癌症例に対する腹腔鏡下骨盤リンパ節郭清術の導入
産婦人科の進歩　64：361-363、2012

万代昌紀、松村謙臣、馬場長、鈴木彩子、小西郁生
卵管癌の臨床診断と治療
日本臨床　70：増刊号 4　664-669、2012

万代昌紀、濵西潤三、安彦郁、吉岡弓子、小西郁生
卵巣癌の転移機構－免疫学的機序
日本臨床　70：増刊号 4　507-511、2012

松村謙臣、万代昌紀、馬場長、小西郁生
卵巣癌の転移機構－播種性転移の分子機構

日本臨床　70：増刊号 4　498-501、2012

万代昌紀、鈴木彩子、松村謙臣、馬場長、小西郁生
子宮筋腫の発生メカニズムの最新知見は？
産科と婦人科　79：267-273、2012

万代昌紀、濵西潤三、安彦郁、松村謙臣、馬場長、小阪謙三、吉岡弓子、小西郁生
卵巣癌の播種・進展と免疫環境との関連分子を標的とした治療法の開発
産婦人科の実際、61：201-205、2012

II. プロトコル

プロトコル文書

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PROTOCOL GOG-0213

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL (OR GEMCITABINE) ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #113912) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #113912) **(12/19/2011) (10/01/12)**

NCI Version 08/09/12

Includes Revisions #1-10

POINTS:

PER CAPITA –14

MEMBERSHIP –6 and 6 additional if surgical candidate is randomized

TRANSLATIONAL RESEARCH PER CAPITA – Award up to 6.5 points based on specimen submissions.
Distribution:

- Archival fixed and embedded primary or metastatic tumor (block or 16 unstained slides)-1 point,
- Frozen recurrent tumor-1 point
- Fixed recurrent tumor in a jar of formalin or embedded in a paraffin block-1 point
- Frozen normal tissue-0.5 point
- Fixed normal tissue in a jar of formalin or embedded in a paraffin block-0.5 point
- Frozen pre-op serum-0.5 point
- Frozen pre-op plasma-0.5 point
- Whole blood-0.5 point (for all patients not just patients randomized to surgery)**(06/22/09)**

TRANSLATIONAL RESEARCH MEMBERSHIP - Bonus membership point will be awarded for **submission of satisfactory** fixed primary tumor, frozen recurrent tumor, fixed recurrent tumor, frozen serum and frozen plasma.

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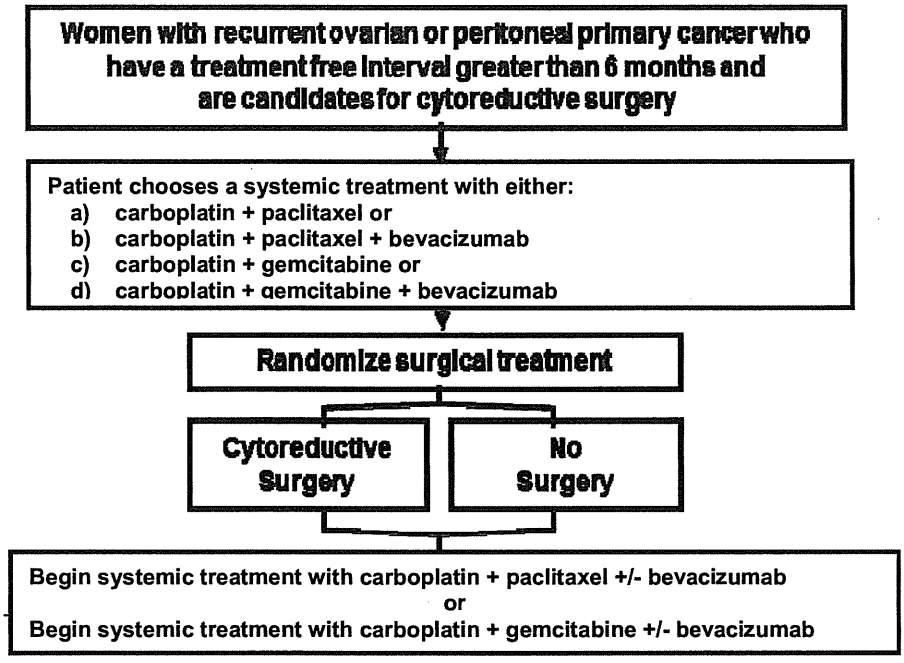
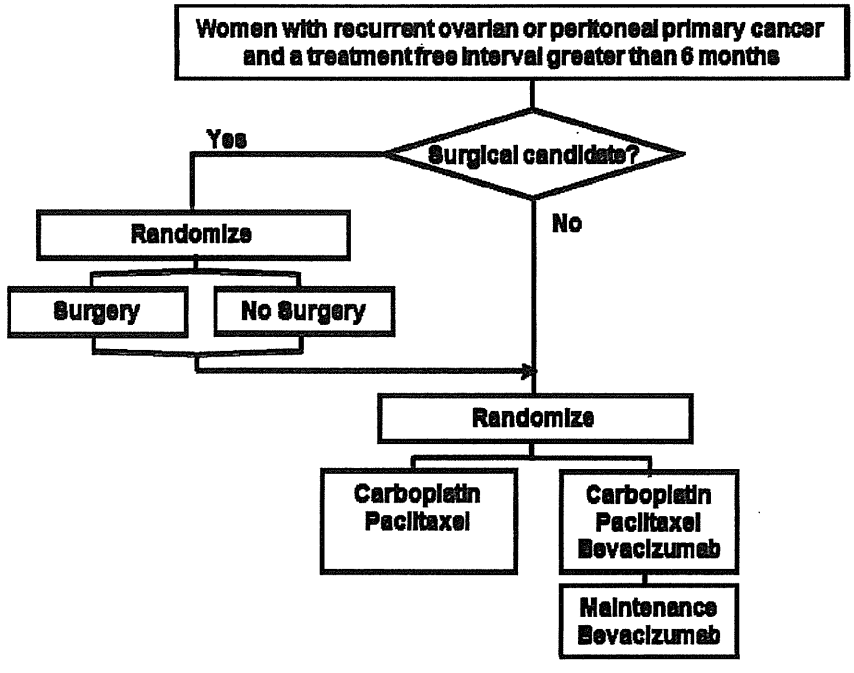
OPEN TO PATIENT ENTRY DECEMBER 06, 2007
REVISED AUGUST 4, 2008
REVISED JUNE 22, 2009
REVISED MARCH 15, 2010
REVISED AUGUST 23, 2010, REVISED JANUARY 3, 2011 REVISED AUGUST 29, 2011 REVISED SEPTEMBER 26, 2011, REVISED DECEMBER 19, 2011, REVISED OCTOBER 1, 2012

SCHEMA beginning 8/29/2011(08/29/11) (12/19/11) (10/01/12)



The following schema was in effect between 12/6/2007 to 8/28/2011. Once the accrual goal for evaluating the chemotherapy regimens was attained, that randomization was eliminated and only the surgical randomization remains (see the schema above). **(08/29/11)(12/19/11)**

SCHEMA **(06/22/09)**



Please see Section 7.32 and Appendix III (Specimen Procedures) for details regarding the specimen requirements and laboratory testing for this protocol. Archival tumor, tissue specimens from secondary cytoreductive surgery and two tubes of blood (to make serum and plasma) will only be required from women randomized to surgery and who consent to allow their specimens to submitted and used for this research study. A new specimen requirement was added to this protocol. The collection of whole blood will apply to all of the patients who provide consent regardless of randomization and treatment including those already enrolled on GOG-0213. Women already enrolled on GOG-0213 will need to be re-consented for this collection. If the patient does not give permission, select "No" in the online Specimen Consent Application for the question "Did your patient give permission for her blood to be collected for submission and use for this research study" and enter "patient refusal" as the reason the specimen was not collected/submitted in item 5 on the SP Form for WB01.

Post surgical randomization treatment options now include either paclitaxel or gemcitabine in combination with carboplatin. Either chemotherapy doublet may be administered with bevacizumab at the discretion of the investigator. If chosen, bevacizumab maintenance is given until disease progression or unacceptable toxicity. **(10/01/12)**

TABLE OF CONTENTS (08/04/08) (06/22/09)

1.0 OBJECTIVES

1.1 Specific Hypotheses: **(08/04/08)**

Two principle hypotheses will be directly addressed in this randomized, phase III clinical trial in recurrent platinum-sensitive ovarian, peritoneal primary or Fallopian tube cancer patients.

1.11 Surgical secondary cytoreduction prior to adjuvant chemotherapy increases the duration of overall survival in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.12 The addition of bevacizumab to second-line paclitaxel and carboplatin and maintenance phases of treatment increases the duration of overall survival relative to second-line chemotherapy alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary, or Fallopian tube cancer.

1.2 Primary Objectives:

1.21 To determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy increases the duration of overall survival in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.22 To determine if the addition of bevacizumab to the second-line and maintenance phases of treatment increases the duration of overall survival relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.3 Secondary objectives: **(08/04/08)**

1.31 To determine if the addition of bevacizumab to the second-line and maintenance phase of treatment increases the duration of progression-free survival relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.32 To prospectively determine the incidence of carboplatin and paclitaxel hypersensitivity in these patients undergoing retreatment with both agents as first recurrence therapy.

1.33 To determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy increases quality of life (QOL) in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer, as measured by the FACT-O trial outcome index and Rand SF-36 physical functioning scale.

1.34 To determine if the addition of bevacizumab to the second-line and maintenance phases of treatment increases QOL relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian, peritoneal primary or Fallopian tube cancer.

1.4 Translational Research Hypotheses **(08/04/08)**

The following translational research hypotheses will be tested in the tissue and serum specimens submitted from GOG-0213 patients undergoing secondary surgical cytoreduction.

1.41 Molecular and biochemical profiles can be identified that are associated with time to first disease recurrence or death.

1.42 Molecular determinants can be identified within patients with platinum-sensitive recurrent ovarian, peritoneal primary or Fallopian tube carcinoma which predicts for sensitivity/resistance to combination chemotherapy with or without bevacizumab followed with or without maintenance bevacizumab therapy.

1.5 Translational Research Objectives **(08/04/08)**

The following translational research objectives will be evaluated in the tissue and serum specimens submitted from GOG-0213 patients undergoing secondary surgical cytoreduction.

1.51 To define molecular and biochemical profiles associated with the duration of progression-free survival in platinum-sensitive recurrent ovarian, peritoneal primary or Fallopian tube carcinoma treated with combination chemotherapy with or without bevacizumab followed with or without maintenance bevacizumab therapy in the presence or absence of secondary surgical cytoreduction.

1.52 To identify molecular determinants that predict sensitivity or resistance to carboplatin and paclitaxel with or without bevacizumab followed with or without maintenance bevacizumab therapy.

1.53 To bank DNA from whole blood for research and evaluate the association between single nucleotide polymorphisms (SNPs) and measures of clinical outcome including overall survival, progression-free survival and adverse events. **(06/22/09)**

2.0 BACKGROUND AND RATIONALE

2.1 Rationale for Selected Approach and Trial Design

Ovarian cancer remains the most lethal primary gynecologic malignancy in the United States. This year over 16,000 women will die from their disease. The principle reason for this outcome is disease recurrence and the emergence of drug resistance. Patients with recurrent disease frequently undergo multiple cycles of multiple drug regimens. Those fortunate to achieve a response to chemotherapy are however, rarely cured and find that their remission cycles are short-lived. Even if a complete response is re-achieved it is usually of a shorter duration than the first disease-free interval. Those not achieving a response to recurrence therapy live less than 2 years. While effective therapy following disease recurrence is a major unmet need, few interventions have successfully altered the natural history of recurrence. We propose to address two important interventions, surgery and combination chemotherapy with biologics, neither previously studied in a prospective randomized design, in order to determine their impact on survival.

2.2 Rationale for Surgery

The capacity of cytoreductive surgery to improve survival for patients with advanced, newly diagnosed epithelial ovarian cancer is generally accepted.[1] However, the role of tumor-reductive surgery for patients with recurrent disease continues to evolve.[2] Several series have demonstrated the importance of tumor reductive surgery prior to the initiation of second-line chemotherapy.[1,3,4] Preliminary results indicate a maximal survival benefit for patients rendered visibly disease-free prior to second-line therapy.[1,4,5] The frequency of reported optimal operative outcomes has ranged from 37% to 83% in small series, using various criteria for "optimal cytoreduction".[6] The relative importance that differences in study cohorts, attitude, technical capability and experience have in accounting for variation of operative outcomes is unknown. In a recent series, the largest yet published, approximately 80% of the patients had complete cytoreduction.[5] Clinical criteria such as the median age, median disease-free interval, amount of prior chemotherapy, performance status, size of intra-abdominal disease, and locations of disease suggests patients in that series to have disease at least as advanced as other reports.[1,3,4,7] That investigation prospectively demonstrated that secondary cytoreductive surgery, followed by salvage chemotherapy, allows survival that is significantly improved. The 34.4 month overall median survival from the time of secondary operation and the 35.9 month overall median survival from the time of recurrence in the most recent series exceed what is typically reported in the salvage chemotherapy literature. Another noteworthy observation from this study was that the median survival after diagnosis of recurrence for patients who did not have salvage chemotherapy before secondary operation (48.4 months) dramatically exceeded the overall median survival for those who were pretreated (24.9 months). Furthermore, an estimated 40% of the patients operated on before administration of salvage therapy survived more than five years after recurrence compared to only 15% in the pretreated group. Of note, patients whose disease responded to a recent repeat course of platinum containing agents, and patients treated with non-platinum containing agents before secondary operation, both had poor survival, that did not remotely approach the overall group who had secondary cytoreductive operations prior to salvage chemotherapy. Perhaps pretreatment with salvage chemotherapy induces drug resistance. Regardless,

limiting the role of surgery to palliation of symptoms for patients who failed multiple salvage regimens and the strategy of treating with salvage chemotherapy before an attempt at secondary cytoreductive surgery may greatly diminish the chances for subsequent survival. Confirmation of this observation within the context of a multi-center randomized trial may dramatically improve the survival potential for women with recurrent epithelial ovarian cancer.

2.3 Rationale for Combination Chemotherapy **(10/01/12)**

Most patients medically suitable to undergo therapy at the time of recurrence will be offered chemotherapy. To date, a limited number of agents (i.e. etoposide, liposomal doxorubicin, topotecan, etc) have been formally approved for administration in this setting. In addition, several other agents have been studied and are documented to have clinical activity. Joining these novel agents are the taxanes and platinates commonly used as standard therapy in the front-line setting. In light of this expansion of potentially active chemotherapeutics, physicians are administering more agents, longer to more patients. Nonetheless, the degree to which this practice is benefiting patients in terms of survival is unclear.

An additional challenge lies in how to determine when to recommend which agents or combinations to patients with recurrent disease. A common determinant for many clinicians lies in reference to the patient's time in remission following front-line therapy. Those disease-free for more than six months are commonly considered to be potentially sensitive to retreatment with platinum. Response characteristics with single agent platinum in this setting produce results similar to patients treated with novel agents. Patients with longer disease-free interval are commonly treated with combination platinum and taxane therapy similar to the regimens received as primary therapy. The degree to which this philosophy of care has affected survival is unknown but data from the limited number of randomized trials would suggest the following:

- Non-platinum novel agents such as topotecan, gemcitabine, liposomal doxorubicin, and paclitaxel have similar response and survival characteristics as compared to platinum in randomized phase III trials.
- No difference in response has been observed in these novel agents among platinum sensitive or resistant patients. However, treatment with liposomal doxorubicin demonstrated a survival benefit in comparison to topotecan in the absence of a response benefit among patients with platinum-sensitive disease.[8] The reasons for this are not clear but may relate to either intrinsic drug activity or to trial design (limited availability to liposomal doxorubicin in topotecan failures).
- Platinum, and platinum combinations have favorable response characteristics in platinum-sensitive patients.[9, 10] Platinum and taxane combination therapy appears to be at least as effective as single agent platinum and data from one large phase III trial would suggest clinical superiority.[11] Although the randomized population in that trial was dissimilar to those commonly treated in the US, a second randomized phase II clinical trial in a more selective population essentially confirmed the observed benefit.[12] Further, a randomized clinical trial of gemcitabine and carboplatin demonstrated superiority in progression-free survival over carboplatin alone in platinum-sensitive patients.[13] Although a survival benefit was not demonstrated, the trial was underpowered to address this endpoint.

- Recently, gemcitabine, carboplatin and bevacizumab was compared to gemcitabine and carboplatin demonstrating further enhancement in progression-free survival (12.4 mos vs 8.4 mos, HR 0.48, 95% CI:0.39-0.61), response rate (79% vs 57%, p<0.0001) and duration of response (10.4 mos vs 7.4 mos, 95% CI: 0.41-0.70). Although immature at the time of reporting, there was no overall survival benefit with nearly 50% of events recorded.[73]

  From these observations, it would appear the greatest activity and potential for survival enhancement lies in combination, platinum-based chemotherapy among those deemed potentially platinum (and taxane) sensitive. As demonstrated above, a survival benefit is also suspected in this cohort for surgery. A randomized trial is needed to evaluate the addition of surgery to combination therapy to determine their impact on survival.

2.31 Docetaxel

Taxanes are a class of anticancer agents that exert cytotoxic effects by their unique inhibition of microtubular assembly by stabilizing tubulin polymer bundles.14, 15 Both paclitaxel and docetaxel belong to the taxane family and have demonstrated activity in tumors that are refractory to conventional chemotherapy regimens. Paclitaxel is a diterpene plant product derived from the bark of the Western yew (Taxus brevifolia), while docetaxel is a semisynthetic derivative of 10-deacetylbaccatin III, a compound extracted from the needles of the European yew (Taxus baccata). While the relative efficacy of paclitaxel and docetaxel has not been compared clinically, docetaxel has increased activity in vitro, as well as clinical activity in paclitaxel resistant tumors.

In Vitro Activity.
The cytotoxicity of docetaxel in comparison with paclitaxel was evaluated in several murine and human long-term cell culture lines. Docetaxel was found to be generally more cytotoxic (1.3-12-fold), a result that could be explained by its higher achievable intracellular concentration, its higher affinity for microtubules, and its slower cellular efflux.[14-21] Furthermore, docetaxel affects centromere organization resulting in abortive mitosis.[22] These cellular events may account for the greater cytotoxicity of docetaxel compared to that seen with paclitaxel. In terms of cross-resistance with other antitumor agents, there was cross-resistance to docetaxel in multidrug-resistant sublines such as P388/DOX_3, CEM/VLB 1000 and Chinese hamster ovary AUXB1 line.[23] However, no cross-resistance to docetaxel was observed in CHO cells expressing a low level of vincristine-resistance but P-glycoprotein positive.[23] This means that cross-resistance to docetaxel was not definitively observed in sublines expressing the MDR phenotype.[24] These findings were in agreement with cell line studies showing that docetaxel was active in paclitaxel-resistant cells.[16] In addition, there was a lack of cross-resistance to cisplatin in certain cell lines.[17,22]

Efficacy in Murine Tumor Models
In a murine tumor model with B16 melanoma, docetaxel demonstrated clear superiority to paclitaxel, having a 2.7 times greater log cell kill than paclitaxel.[25] Docetaxel at a dose of 100 mg/ m^2 has demonstrated significant

activity with response rates of 23-40% as second-line therapy in platinum resistant ovarian carcinoma.[26-28] More recently, its activity in paclitaxel-resistant tumors has been studied. The use of docetaxel at a dose of 100 mg/ m^2 every 21 days in paclitaxel-resistant breast cancer has demonstrated a 17.5% response rate in 41 evaluable patients.[29] Additionally, the use of docetaxel at this same dose in paclitaxel-resistant ovarian cancer has recently demonstrated a 37.5% response rate in 8 evaluable patients.[30] The in vitro, in vivo and clinical data make docetaxel an excellent agent to evaluate after primary platinum and paclitaxel therapy. Hematologic toxicity is the dose-limiting toxicity, with neutropenic fever occurring in 8- 48% of patients.[26-28] Hematologic toxicity is considerably more severe with poorer hepatic function.[31] A comparative study of patients with or without liver dysfunction treated with docetaxel at a dose of 100 mg/ m^2 was recently reported. Patients with impaired liver function defined as an SGOT or SGPT > 1.5 x upper limit of normal or alkaline phosphatase > 2.5 x upper limit of normal, had a higher rate of neutropenic fever 23.8% vs 12.9% (p=0.06) and toxic death 11.9% vs 1.7%, (p=0.001). For that reason strict criteria for hepatic function are required for this study.

Efficacy in Humans

Several phase II and one randomized phase III trial have been conducted evaluating clinical efficacy of docetaxel in primary and recurrent ovarian cancer. Rose et al., reporting on behalf of the GOG, demonstrated a 22.4% overall response rate (5% CR and 17% PR) in 60 patients with platinum and taxane resistant recurrent disease (defined as progression on or within 6 months of completion of primary therapy). Docetaxel for this trial was administered at 100 mg/ m^2. Grade IV hematologic toxicity was observed in 75% of patients at this dose.[32] Similarly, Verschraegen et al., reported a 23% response rate and a median PFS of 3.5 months among 30 assessable patients in a slightly less resistant population. Grade IV granulocytopenia occurred in 72% of protocol patients and like the Rose trial was a reflection of higher docetaxel dosing (100 mg/ m^2).[30] Markman, evaluated docetaxel (75 mg/ m^2) in 30 taxane-resistant ovarian cancer patients. In this study, taxane-resistance was defined as progression on or within 3 months of paclitaxel therapy. Patients with longer intervals from paclitaxel were to be retreated with that agent – and progressed – prior to docetaxel. In this trial, 3 patients (10%) had an objective response. Hematologic toxicity was reduced (30%, Grade IV), likely a reflection of reduced dosing.[33]

Based on objective clinical activity in these resistant patient cohorts, a randomized clinical trial comparing taxane and platinum combination therapy in front line ovarian cancer treatment was conducted and recently reported. Vasey and colleagues reported similar PFS (15.0 vs 14.8 months, HR: 0.97 (0.83-1.13) and OS rate at 24 months (64.2% vs. 68.9%, HR: 1.13 (0.92-1.39) for the docetaxel/carboplatin combination compared with the industry standard paclitaxel/carboplatin. In this 1077 patient trial toxicity was significantly different with more hematological toxicity seen in the docetaxel combination (Grade III/IV granulocytopenia 94% vs. 84%, $P < 0.001$) but more severe and longer lasting sensory-motor neurotoxicity for paclitaxel/carboplatin (11% vs. 30, $P < 0.001$).[34] These trials establish clinical efficacy and safety for docetaxel and suggest possible non-cross resistance with paclitaxel. Given the lack of a

clear dose response for this agent we propose to utilize 75 mg/ m^2 to initiate the trial.

2.4 Rationale for Angiogenesis Targeted Therapy

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 and normal endothelial cells into the local microenvironment. There is accumulating evidence that angiogenesis plays a central role in ovarian cancer disease progression and prognosis.[35-38] A strong relationship exists between the expression of angiogenesis biomarkers and the behavior of epithelial ovarian cancer, suggesting pharmacological inhibitors of angiogenesis could arrest tumor progression.[39, 40] Neutralizing anti-VEGF monoclonal antibodies have demonstrated therapeutic activity in a variety of pre-clinical solid tumor models.[41] 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.[42] A recent phase II trial of single agent bevacizumab for patients with recurrent, platinum/taxane refractory epithelial ovarian and peritoneal primary cancer has been reported in the GOG (GOG-0170D). Sixty-two women were enrolled in the phase II trial, and objective responses were observed in 17.7%.[43] Response duration was 10.3 months. This was an extremely unusual observation for a compound presumed to be at best cytostatic when administered as a single agent. Further exploration in combination with chemotherapy is warranted in ovarian cancer patients given the survival benefits observed for bevacizumab-combinations in other solid tumors such as breast, renal, lung and colon cancers.

2.5 Rationale for Combination Cytotoxic and Biologic 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 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. 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 in this patient population has been conducted by ECOG; the final analysis of this study is pending.

More importantly, a recently reported phase III trial, AVF2107, of over 800 previously untreated patients with metastatic colorectal cancer randomized to receive either bevacizumab for one year plus the Saltz chemotherapy regimen (5-FU/Leucovorin/CPT-11, IFL) or the Saltz regimen plus placebo for one year met its primary endpoint of improving overall survival. The magnitude of benefit observed far exceeded what the study was designed to demonstrate. The trial also met the secondary

endpoints of progression-free survival, response rate, and duration of response (see following table).

	IFL/Bevacizumab (n = 403)	**IFL/Placebo (n = 412)**	**Hazard Ratio (p-value)**
Response Rate	44.9%	34.7%	(0.0029)
Median TTP	10.6 mos	6.2 mos	(0.00001)
Median Survival	20.3 mos	15.6 mos	0.65 (0.00003)

Bleeding, thrombosis, asymptomatic proteinuria and hypertension were identified in phase II studies as possible safety events, but only Grade 3 hypertension and arterial thrombosis events were clearly increased in this phase III study.

Preliminary results from a more recent, large, randomized phase III trial for patients with advanced colorectal cancer who had previously received treatment show that those who received bevacizumab in combination with an oxaliplatin regimen known as FOLFOX4 (oxaliplatin, 5-fluorouracil and leucovorin) had a significantly prolonged survival over patients who received FOLFOX4 alone. The Data Monitoring Committee overseeing the trial, known as E3200, recommended that the results of a recent interim analysis be made public because the study had met its primary endpoint of demonstrating improved overall survival, which was 17% longer in the bevacizumab arm. Specifically, the median overall survival in the bevacizumab plus FOLFOX4 arm was 12.5 months compared to 10.7 months for patients treated with FOLFOX4 alone. There was a 26 percent reduction in the risk of death (hazard ratio of 0.74) for patients in this study who received bevacizumab plus FOLFOX4 compared to those who received FOLFOX4 alone. Treatment toxicities observed in this study were consistent with those adverse effects observed in other clinical trials in which bevacizumab was combined with chemotherapy. These included hypertension and bleeding as more predominant in the bevacizumab arm.

Multiple phase I-III trials, such as those cited above, have demonstrated the safety and tolerability of bevacizumab with traditional schedules and dosing of carboplatin and paclitaxel.

2.6 Gastrointestinal Perforation/Fistula

GI perforations/fistulas were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase III trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. In various phase II series of bevacizumab in recurrent ovarian cancer the rate of GI perforation has ranged from 0-14%. No phase III randomized trials of bevacizumab alone or in combination with chemotherapy have been conduct heretofore. Review of cases reported to CTEP in an open-label phase II ovarian cancer trial of bevacizumab did not specifically isolate risk factors for this complication; however, most patients were heavily pretreated and had abdominal tumor burden (CTEP IND Action Letter, October 4, 2005). GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, or co-morbid GI