Minireview: Human Ovarian Cancer: Biology, Current Management, and Paths to Personalizing Therapy

Ignacio Romero and Robert C. Bast, Jr.

Area Clinica Oncologia Ginecologica (I.R.), Instituto Valenciano de Oncologia, 46009 Valencia, Spain; and the Department of Experimental Therapeutics (R.C.B.), University of Texas M.D. Anderson Cancer Center, Houston, Texas 77030

More than 90% of ovarian cancers have been thought to arise from epithelial cells that cover the ovarian surface or, more frequently, line subserosal cysts. Recent studies suggest that histologically similar cancers can arise from the fimbriae of Fallopian tubes and from deposits of endometriosis. Different histotypes are observed that resemble epithelial cells from the normal Fallopian tube (serous), endometrium (endometrioid), cervical glands (mucinous), and vaginal rests (clear cell) and that share expression of relevant *HOX* genes which drive normal gynecological differentiation. Two groups of epithelial ovarian cancers have been distinguished: type I low-grade cancers that present in early stage, grow slowly, and resist conventional chemotherapy but may respond to hormonal manipulation; and type II high-grade cancers that are generally diagnosed in advanced stage and grow aggressively but respond to chemotherapy. Type I cancers have wild-type *p53* and *BRCA1/2*, but have frequent mutations of *Ras* and *Raf* as well as expression of *IGFR* and activation of the phosphatidylinositol-3-kinase (PI3K) pathway. Virtually all type II cancers have mutations of *p53*, and almost half have mutation or dysfunction of *BRCA1/2*, but other mutations are rare, and oncogenesis appears to be driven by amplification of several growth-regulatory genes that activate the Ras/MAPK and PI3K pathways. Cytoreductive surgery and combination chemotherapy with platinum compounds and taxanes have improved 5-yr survival, but less than 40% of all stages can be cured. Novel therapies are being developed that target high-grade serous cancer cells with PI3Kness or BRCAness as well as the tumor vasculature. Both *in silico* and animal models are needed that more closely resemble type I and type II cancers to facilitate the identification of novel targets and to predict response to combinations of new agents. **(*Endocrinology* 153: 1593–1602, 2012)**

Among the gynecological malignancies, ovarian cancer is the leading cause of mortality in developed countries with 225,500 new cases and 140,200 estimated deaths worldwide (1). Despite the global impact of this disease, the lifelong risk of developing ovarian cancer in the United States is one in 70, and the prevalence one in 2500, even in the postmenopausal population that is at greatest risk. Consequently, ovarian cancer is a disease that is neither common nor rare but that has an overall cure rate of less than 40% across all stages. If we are to improve outcomes for women with ovarian cancer, it will be essential to take into account the clinical, cellular, and molecular biology of the disease to move beyond current management and to personalize care.

Biology of Ovarian Cancer

The normal ovary develops from the gonadal ridge near the mesonephros and contains three major cell types: 1) germ cells that are derived from the endoderm and that migrate to the gonadal ridge where they proliferate and differentiate into oocytes, 2) endocrine and interstitial cells that produce estrogen and progesterone, and 3) epithelial cells that are derived from the Mullerian duct and that cover the ovary and line inclusion cysts immediately beneath the ovarian surface. During normal ovulation, oocytes are released from mature follicles and enter the Fallopian tube where fertilization generally occurs. The fimbriae of the Fallopian tube cover the ruptured follicle

ISSN Print 0013-7227 ISSN Online 1945-7170
Printed in U.S.A.

doi: 10.1210/en.2011-2123 Received December 15, 2011. Accepted January 18, 2012.
First Published Online March 13, 2012

Abbreviations: PARP, Poly-ADP-ribose polymerase; PI3K, phosphatidylinositol-3-kinase; VEGF, vascular endothelial growth factor.

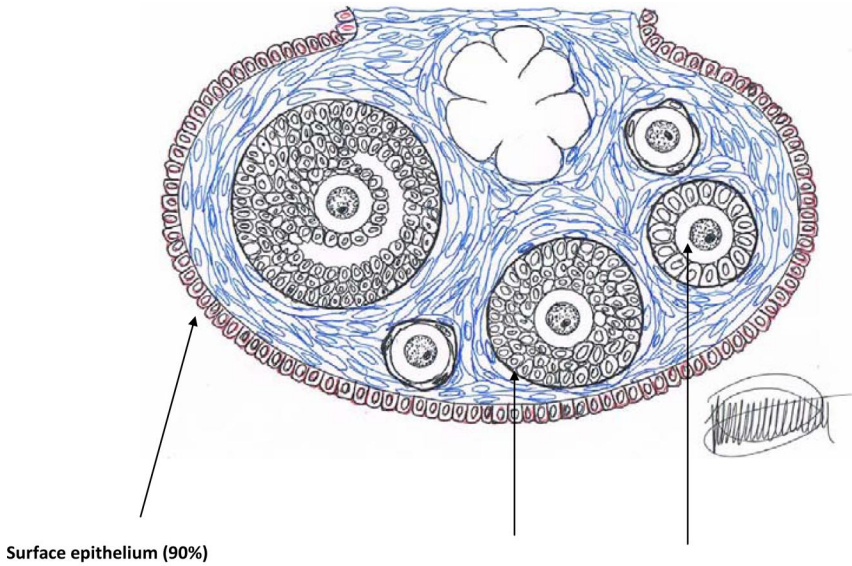

FIG. 1. Different ovarian tumors originate from different cell subtypes. Prevalence of malignant components in parentheses. [Reproduced from V. W. Chen *et al.*: Pathology and classification of ovarian tumors. *Cancer* 97:2631, 2003 (89), with permission. © American Cancer Society.]

and facilitate uptake of oocytes. Both benign and malignant tumors can arise from each of the three ovarian cell types (Fig. 1). Germ cell tumors arise most frequently in the second and third decade and account for 3–5% of ovarian cancers (2). Sex-cord-stromal tumors arise from the ovarian connective tissue, often secrete hormones, and can occur in women of all ages, comprising approximately 7% of all ovarian malignancies. Epithelial ovarian cancers generally develop after age 40 and include approximately 90% of malignant ovarian tumors. In addition to benign and malignant epithelial lesions, borderline tumors of low-malignant potential contain morphologically and molecularly partially transformed epithelial cells that do not invade underlying stroma. Approximately 10% of borderline tumors can recur after resection and prove lethal.

Histological subtypes of epithelial ovarian cancer

Traditionally, ovarian cancers have been thought to develop from flattened nondescript ovarian surface epithelial cells into cancers that resemble epithelium of the Fallopian tube (serous), endometrium (endometrioid), mucin-secreting endocervical glands (mucinous) and glycogen-filled vaginal rests (clear cell) (Fig 2). Ovarian cancer histotypes have been linked to expression of the *HOXA9*, *HOXA10*, and *HOXA11* genes that regulate normal gynecological differentiation (3). In contrast to many other cancers, malignant transformation triggers the program of normal differentiation. Tumor histotype (4) and tumor grade or degree of differentiation (5) affect the stage at diagnosis, rate of growth, prognosis, and responsiveness to chemotherapy.

Pattern of spread

Similar to cancers that arise from other sites, epithelial ovarian cancer can spread through lymphatic and blood vessels to nodes and parenchyma of distant organs, including the liver and, because patients are surviving longer with recurrent disease, lung and brain (Fig 3). A distinctive feature of ovarian cancer is the ability to spread through the abdominal cavity, forming nodules on the surface of the parietal and visceral peritoneum including the omentum. Blockage of diaphragmatic lymphatics prevents outflow of proteinaceous fluid from the peritoneal cavity, causing the accumulation of ascites fluid in advanced disease.

Origin of ovarian cancer

Major risk factors for ovarian cancer include advancing age, number of ovulatory cycles, and a positive family history of ovarian, breast, uterine, or colon cancer related to mutations of *BRCA1*, *BRCA2*, mismatch repair genes, or *TP53* in the germ line. Risk is halved by the use of oral contraceptives for as long as 5 yr before menopause, possibly related to reduced ovulation and treatment of transforming cells with progestational agents. If understood in greater depth, oral contraceptives could provide a strategy for prevention. Approximately 15% of ovarian cancers are familial and 85% sporadic. Traditionally, ovarian cancers have been thought to arise from ovarian surface epithelial cells or, more frequently, from similar cells that line cysts immediately beneath the ovarian surface. A morphological and genetic continuum can be demonstrated between normal epithelium, dysplasia and invasive high-grade carcinoma with cortical inclusion cysts of the ovary in both *BRCA* mutation carriers and noncarriers (6). In recent years, it has become apparent that a fraction of ovarian cancers or primary peritoneal carcinomas can also arise from endometriosis, epithelial rests in the normal peritoneum, or the fimbriae of Fallopian tubes. Serous tubal epithelial carcinomas and tubal carcinomas with

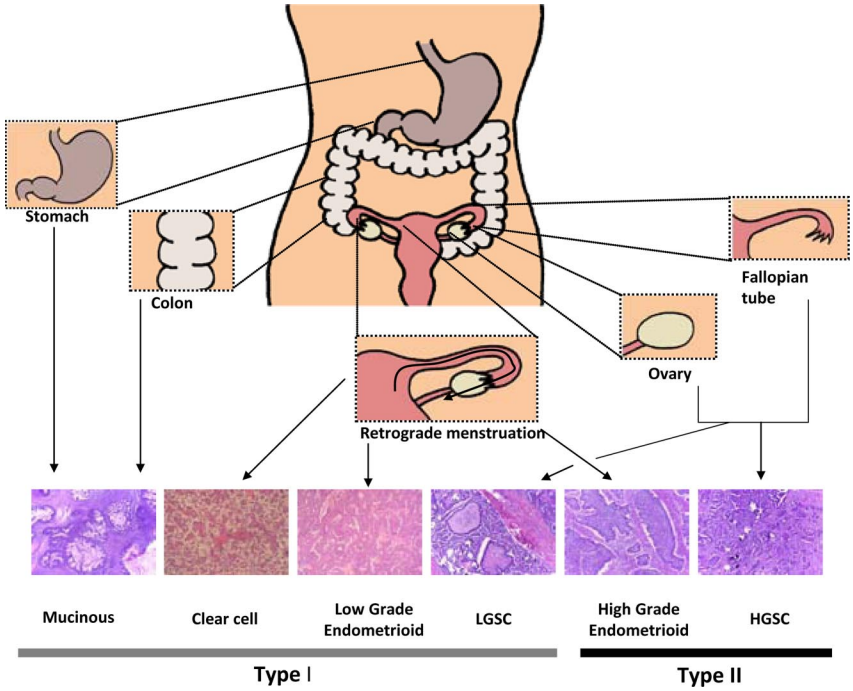

FIG. 2. Origin and histological subtypes associated with type I and type II molecular classification. [Reproduced from S. Vaughan *et al.*: Rethinking ovarian cancer: recommendations for improving outcomes. *Nat Rev Cancer* 11:719, 2011 (14), with permission. © Nature Publishing Group.]

TP53 mutations have been found in up to 80% of prophylactic salpingo-oophorectomy specimens from carriers of mutant *BRCA1* or *BRCA2* genes (7–10) and may account for many of the 20% of sporadic cancers thought to be of primary peritoneal origin. *TP53* mutations have also been found within small cysts in the ovaries, consistent with an early event in carcinogenesis that may permit transforming cells to survive telomeric crisis, leading to multiple amplicons containing genes that promote proliferation, invasion, and metastasis.

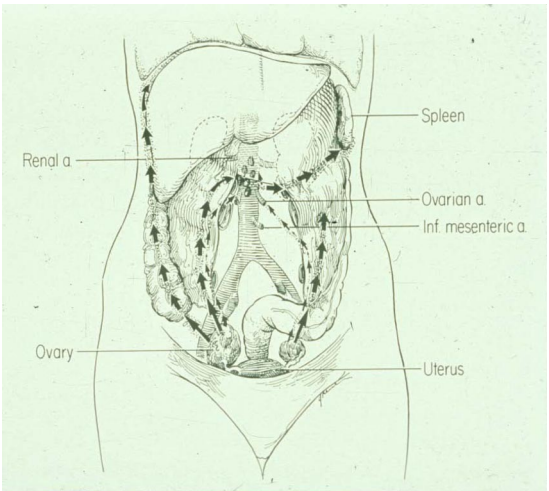

FIG. 3. Pattern of spread of epithelial ovarian cancers. Ovarian cancer cells can spread through lymphatics to nodes at the level of the renal hilum, through blood vessels to the liver, lung, and brain or over the peritoneal surface. [Reproduced from R. C. Knapp *et al.*: Natural history and detection of ovarian cancer. *Gynecology and Obstetrics* (edited by J. W. Sciarra), Harper, Row, Philadelphia, p 1 (90), with permission.]

Type I and type II ovarian cancers

At a clinical, cellular, and molecular level, ovarian cancers fall into two major groups based on histological grade, molecular phenotype, and genotype (Table 1 and Fig. 2) (11–13). Type I cancers are low grade of serous, mucinous, endometrioid, or clear-cell histotype. They are often diagnosed in an early stage (I or II), grow slowly, and resist conventional chemotherapy but may respond to hormonal treatment. The more prevalent type II cancers are high grade of serous, endometrioid, or undifferentiated histotype. These cancers present at late stage (III–IV), grow aggressively, and respond to conventional chemotherapy but less often to hormonal manipulation. The distinction between type I and type II cancers provides an initial step in understanding the heterogeneity of ovarian cancers and applying this new knowledge to personalized care (13, 14).

Molecular alterations in type I ovarian cancers

Among the type I ovarian cancers, low-grade serous carcinomas appear to grow from serous borderline tumors in 60% of cases (15). Often, these cancers exhibit papillary architecture. Low-grade serous cancers tend to have a normal karyotype and wild-type *TP53* and *BRCA1/2* but frequent mutations in the *B-RAF* (2–35%) and *KRAS* genes (19–54%) (16). The IGF receptor is also expressed by the majority of low-grade serous cancers. Like other type I cancers, low-grade serous tumors are resistant but not refractory to standard chemotherapy (17, 18).

Other type I tumors are uncommon and include low-grade mucinous and clear-cell histotypes that respond to conventional platinum-based chemotherapy in only 26% (19) and 15% (20) of cases, respectively. *KRAS* is frequently mutated in mucinous cancers (21) and in associated borderline tumors (22). Clear-cell and low-grade endometrioid carcinomas share a similar gene expression pattern, consistent with a common origin, including two genes associated with chemoresistance, *ANXA4* and *UGT1A1* (23). Inactivating mutations of *ARID1A*, a chromatin-remodeling gene, have been found in 49% of

TABLE 1. Histology, precursors, and distinctive molecular features (13)

Molecular type	Histology	Precursor	Molecular features
I	Low-grade serous carcinoma	Borderline-carcinoma sequence	*KRAS* and *BRAF* mutations
I	Low-grade endometrioid carcinoma	Endometriosis	Mutations *CTNNB1*, *PTEN*, and microsatellite instability
I	Mucinous carcinoma	Cystadenoma-borderline sequence	*KRAS* mutations
I	Clear-cell carcinoma	Endometriosis possibly	*PTEN* mutations and LOH, *PIK3CA* mutations
II	High-grade serous carcinoma	*De novo* from inclusion cysts	*p53* mutations, *BRCA1/2* mutations and *BRCA1* methylation
II	High-grade endometrioid carcinoma	Epithelial inclusion cysts	*p53* mutations, *BRCA1/2* mutations and *BRCA1* methylation
II	Undifferentiated, carcinosarcoma		

LOH, Loss of heterozygosity.

ovarian clear-cell carcinomas and 30% of endometrioid ovarian cancers (24, 25) *PPP2R1A*, the regulatory subunit of a serine-threonine phosphatase required for chromosome segregation, is also mutated in 7% of clear-cell ovarian cancers (24). Low-grade endometrioid cancers exhibit frequent inactivating mutations and epigenetic silencing of *PTEN* and activating mutations of *PIK3CA* that upregulate phosphatidylinositol-3-kinase (PI3K) signaling.

Molecular alterations in type II ovarian cancers

Although low-grade type I cancers appear to be driven by activating mutations on a background of a relatively normal karyotype, high-grade type II cancers are driven by copy number abnormalities and marked genomic instability. The Cancer Genome Atlas Project, which analyzed more than 300 high-grade serous cancers, detected amplification of more than 30 growth-stimulatory genes (26). Amplification and overexpression of genes in the PI3K family occur in more than 40% of type II cancers, conferring PI3Kness, or activation of the PI3K pathway. When ovarian cancers occur in carriers of *BRCA1* or *BRCA2* germline mutations, they are generally type II high-grade tumors. Somatic mutations of *BRCA1* and *BRCA2* can occur, *BRCA1* can be silenced, and upstream mutations can down-regulate BRCA function, producing BRCAness, or homologous DNA repair deficiency in more than 40% of type II ovarian cancers. Mutations of p53 were found in 96% of type II high-grade serous cancers. Judged from their sequence, most of these mutations are inactivating. Other mutations were uncommon, with *NF1*, *RB1*, and *CDK12* mutated in 2–4%. Less than 1% of type II cancers had mutations of *BRAF*, *PI3KCA*, *KRAS*, or *NRAS* found in type I tumors. These genes may, however, be rare but important drivers of high-grade serous cancers. Despite the low prevalence of *Rb* mutations, dysfunction of the Rb pathway has been found in 67% of high-grade serous cancers (26).

Current Clinical Management of Ovarian Cancer

Over the last three decades, 5-yr survival for ovarian cancer patients has increased from 37 to 45%, related to more consistent use of cytoreductive surgery and combination chemotherapy with platinum compounds and taxanes (27). The majority of patients are diagnosed in advanced stage with multiple tumor nodules studding the parietal and visceral peritoneum in the pelvis, omentum, and diaphragm.

Surgery

Ovarian cancer is one of the few malignancies where surgeons will undertake cytoreductive operations, even if all macroscopic tumor cannot be removed. Reducing tumor burden to where no macroscopic tumor is left before chemotherapy is considered optimal cyroreduction (9). Surgery can be performed after neoadjuvant chemotherapy (10) when optimal cytoreduction is not considered feasible at initial diagnosis. Survival increases with the expertise of the surgeon (28), and optimal cytoreductive surgery is an independent prognostic factor (29). The purpose is to achieve both correct FIGO (International Federation of Gynecology and Obstetrics) staging (30) and therapeutic thorough cytoreduction.

In several retrospective series, cytoreductive surgery for recurrent disease has been associated with improved survival when all macroscopic cancer can be removed (31, 32). Two ongoing prospective trials in Europe and the United States are evaluating criteria and outcomes for secondary cytoreduction.

Primary chemotherapy

Six cycles of carboplatin and paclitaxel chemotherapy are considered standard adjuvant treatment for newly diagnosed ovarian cancer after cytoreductive surgery. Car-

boplatin is an alkylating agent that binds covalently to DNA, creating adducts that form intrachain and interchain cross-links. Paclitaxel binds noncovalently to microtubules and increases their stability, interfering with mitotic spindle formation. Both agents induce apoptosis. Chemotherapy has generally been administered iv, but three randomized phase III trials have shown a 20–25% relative risk reduction in mortality after intraperitoneal therapy for patients who have been optimally cytoreduced (33–35). Chemotherapy is generally administered every 3 wk, but weekly dose-dense administration of paclitaxel has produced improved survival in one trial from Japan (36), and a confirmatory trial has not yet been completed.

Empirical addition of three other active drugs including pegylated liposomal doxorubicin, topotecan, and gemcitabine to standard therapy failed to improve upon the progression-free or overall survival observed with paclitaxel and carboplatin alone (37). Two recent trials have added a vascular endothelial growth factor (VEGF)-binding antiangiogenic antibody, bevacizumab, to standard treatment during and for up to 15 months after chemotherapy. Improved progression-free but not overall survival was reported (91, 92).

Chemotherapy for recurrent ovarian cancer

More than 70% of patients with advanced ovarian cancer will experience disease recurrence and become candidates for second-line chemotherapy, within 12 and 18 months. Retreatment with carboplatin and paclitaxel is associated with a 20–50% response when platinum-sensitive disease recurs more than 6 months after primary chemotherapy (Table 2). Although recurrent disease is not curable, combinations of drugs can prolong survival. In platinum-sensitive disease, a combination of carboplatin with paclitaxel (38, 39), gemcitabine (40), or liposomal doxorubicin (41) is superior to single-agent carboplatin (42). Disease that recurs in less than 6 months is considered platinum resistant. In this setting, several drugs produce response rates ranging from 10–30% and increase progression-free survival such as liposomal doxorubicin (43), weekly paclitaxel (44), and topotecan (45). Other drugs have demonstrated activity in phase II clinical studies, including gemcitabine (46), bevacizumab (47, 48), docetaxel (49), and etoposide (50).

TABLE 2. Recurrent populations according to interval from last platinum

Term	Definition
Refractory	Progression while receiving last line of platinum-based therapy or within 4 wk of last platinum dose
Platinum resistant	Progression-free interval of less than 6 months
Partially platinum sensitive	Progression-free interval since last platinum of 6–12 months
Platinum sensitive	Progression-free interval since last platinum of 6–12 months

Biomarkers

CA125 (MUC16) is a high-molecular-mass (1 MDa) glycosylated transmembrane mucin that is expressed by 80% of ovarian cancers (51) and is important for adhesion, motility, and invasion of ovarian cancer (52). CA125 is shed from ovarian cancers and circulates in serum where it has provided the first generally useful biomarker for monitoring the response of ovarian cancer to chemotherapy (53). Persistent elevation of CA125 after chemotherapy indicates residual disease with more than 90% accuracy. CA125 has been used routinely to detect recurrence after chemotherapy. A recent trial found that early treatment of recurrent ovarian cancer with chemotherapy based on doubling of CA125 did not prolong survival when compared with treatment 5 months later at the time of clinical or symptomatic relapse (54). Limitations of the trial included inadequate stratification for important prognostic variables, use of suboptimal thresholds for CA125, delays in treatment in one quarter of participants, and suboptimal chemotherapy in two thirds of patients (55). Consequently, only one quarter of patients were treated promptly with combinations of drugs that could improve survival. Given the limitations of chemotherapy for recurrent disease, however, it remains uncertain whether monitoring for recurrence with CA125 improves overall survival, although it does identify patients for secondary cytoreductive surgery and provides time for treatment with multiple conventional and novel drugs.

Additional applications of CA125 include its use in combination with age, ultrasound (56), or other biomarkers (57–59) to identify patients with pelvic masses who would benefit from referral to a specially trained gynecological oncologist for cytoreductive surgery. Although individual values of CA125 are not sufficiently specific for detecting early-stage disease, trials are currently underway to test the value of a rising CA125 to trigger ultrasound that would prompt surgery (60, 61). Preliminary data suggest that this strategy is sufficiently specific that only three exploratory laparotomies will be required to detect an ovarian cancer and that an increased fraction of early-stage disease can be detected.

Enhancing drug sensitivity and overcoming drug resistance

During primary chemotherapy, approximately 70% of ovarian cancers will respond to platinum alone or in com-

bination with paclitaxel (62). In two of three major trials, the addition of paclitaxel to cisplatin or carboplatin increased disease-free and overall survival compared with platinum-based therapy alone (63, 64). Despite an additive increase in overall survival with combination chemotherapy, only 42% of previously untreated patients will respond to paclitaxel, and there is no synergy between platinum compounds and the taxanes. Consequently, more than half of patients receive the toxicity, but not the benefit of taxanes, and there is room for significant improvement. Taxanes induce apoptosis in cancer cells after increasing microtubule stability and delaying or preventing passage through the cell cycle. Recent studies suggest that knockdown of several kinases can enhance paclitaxel sensitivity of ovarian cancer cells (65). In some cases, this relates to enhancing microtubule stability, and in others, it depends upon modifying apoptotic mechanisms or centrosome function (66). Using paclitaxel in combination with specific RNA interference or specific low-molecular-weight kinase inhibitors could lead to a greater fraction of ovarian cancer patients responding to primary therapy.

After treatment with carboplatin and paclitaxel, specifically resistant cancer cells emerge. Knowledge regarding the biology of taxane and platinum resistance is beginning at the preclinical level (67–69), but strategies for reversing drug resistance have not been validated clinically.

Targeted Drugs and Antibodies to Personalize Therapy

Individual targeted agents

Improvement in outcomes might result from therapy that targets the abnormal proteins in each patient's cancer. In the Cancer Genome Atlas Research Program analysis, different fractions of high-grade type II ovarian cancers had amplification of some 22 oncogenes for which specific inhibitory drugs were already available (26). To date, however, individual targeted agents have had only a modest impact on recurrent ovarian cancer in unselected patients. With the exception of bevacizumab, eight targeted drugs, gefitinib, imatinib, sorafenib, temsirolimus, mifepristone, enzastaurine, lapatinib, and vorinostat, have produced objective response rates of less than 10% and have stabilized disease for 6 months in less than 25% of cases in phase II trials. It is clear that we must use multiple agents and seek synthetic lethality if we are to produce deep and long-lasting remissions of recurrent disease and ultimately to improve primary therapy.

BRCAness

One of the best examples of synthetic lethality to reach the clinic to date is provided by the activity of poly-ADP-ribose polymerase (PARP) inhibitors in ovarian cancers that display BRCAness, *i.e.* a deficiency of BRCA1/2 function (70, 71) is associated with a better overall prognosis (72) and response to platinum compounds (73). Although 10–15% of ovarian cancers have germline BRCA1/2 mutations (74–76), up to 47% of type II high-grade serous ovarian cancers have genetic or epigenetic inactivation of *BRCA1/BRCA2* (77). Somatic *BRCA1/2* mutations were present in 19% of unselected ovarian cancer and 23% of high-grade serous cancers (78). Another recent report described *BRCA1/2* mutations or *BRCA1* silencing in 33% of high-grade serous cancers (26).

BRCA1 and BRCA2 mediate homologous recombination, which is one mechanism of DNA repair. Cancers with BRCAness are deficient in homologous repair and cannot repair DNA double strand breaks induced by platinum compounds (79). Inhibition of a second DNA repair pathway, base excision repair, by PARP inhibitors causes synthetic lethality in cancers with BRCAness. PARP inhibitors have produced response rates of more than 40% in ovarian cancers with BRCA1/2 mutations (80).

PI3Kness

Activation of PI3K signaling or PI3Kness can be produced by activating mutations of *PIK3CA*, inactivating mutations of *PTEN*, or amplification of *PIK3CA*, *PIK3CB*, *PIK3R4*, *AKT1*, *AKT2*, or *AKT3* (81). Common copy number gains of *PIK3CA*, *PIK3CB*, and *PIK3R4* in type II high-grade ovarian cancer were associated with decreased survival (82). Currently, mammalian target of rapamycin inhibitors, PI3K and AKT inhibitors are being investigated. In human ovarian cancer cell lines with PTEN deficiency, sensitivity to PARP1 inhibitors and cisplatin, but not to PARP1 inhibitors and paclitaxel, was higher than in the wild type (83). Thus, combinations of drugs that block both PI3K/AKT and PARP should be evaluated in patients with BRCAness and PI3Kness, whereas drugs that block both PI3K/AKT and MAPK kinase should be pursued in patients with abnormalities of the PI3K or Ras/MAPK pathway. The presence of activated pathways is likely to be necessary but not sufficient. Better predictive models will be required in cell cultures, animals, and *in silico*, to identify relevant targets and to choose optimal combinations for individual ovarian cancer patients.

Antiangiogenesis

Ovarian cancer metastases cannot grow to greater than 1 mm without blood vessel formation. Endothelial cells

associated with tumor vessels depend upon proangiogenic factors for survival and can proliferate more rapidly than vessels serving normal tissues, providing targets for antiangiogenic therapy (84). Ovarian cancers produce multiple proangiogenic factors including VEGF, IL-8, and basic fibroblast growth factor. Inhibitors of proangiogenic proteins such as VEGF (bevacizumab and aflibercept), angiopoietins (AMG386), PDGF (imatinib and pazopanib), or their receptors VEGF receptor (pazopanib, sorafenib, sunitinib, and BIBF1120) are being tested in the clinic. Bevacizumab, as a single agent or in combination with daily low-dose cyclophosphamide, can produce an objective response rate of 20% in recurrent ovarian cancer and stabilize disease for 6 months in 40%. Given the extraordinary expense of bevacizumab, identifying biomarkers with high negative predictive value is an important unmet need. Putative biomarkers described include circulating endothelial cell precursors, CA125, DII4, VEGF-C, and neuropilin-1 (85). A decrease in perfusion with magnetic resonance imaging has also been evaluated, but predictive tests are not yet sufficiently precise to use routinely (86, 87). Relevant animal models will be crucial to develop multi-agent antivascular therapy and to facilitate identification of relevant predictive biomarkers.

Implications for the Development of Animal Models

Current knowledge regarding the biology and clinical management of ovarian cancer suggests that targeted agents must be used in combination to select the right drugs for the right patient at the right time. Given more than 400 anticancer drugs and antibodies in the current pharmaceutical pipeline, not all combinations can be tested in the clinic. Development of animal models that mimic the biology of human ovarian cancer will be critical for identifying new targets and useful combinations on the path to personalized therapy. The accompanying minireview considers the currently available models for ovarian cancer (88). In judging the relevance of these models, it will be important to consider the ability of primary cancers to metastasize from the ovaries not only through lymphatic and blood vessels but also to the surface of the peritoneal cavity, producing ascites. Animal models should mimic one of the two major types of ovarian cancer: low-grade type I disease driven by mutations of *RAS*, *Raf*, or members of the PI3K pathway on a background of genomic stability, wild-type *TP53* and *BRCA1/2*, and hormonal signaling; or high-grade type II disease driven by amplification and genomic instability with mutant *TP53* and dysfunctional Rb with or without BRCAness or PI3Kness. Models that produce mucinous, endometrioid, or clear-cell histotypes would also be of interest. Because mice and chickens can express CA125, animal models might also be used to identify complementary biomarkers. Whether or not animal models mimic human disease precisely, these ovarian cancers should respond to platinum compounds, taxanes, and inhibitors of Ras/MAPK, proangiogenic factors, PARP, and the PI3K pathway. Whatever the genotype and phenotype of models, validating their predictive power with agents known to be active in the clinic would be important if they are to contribute to translational research.

Acknowledgments

We thank Dr. Sergio Almenar and Dr. Carmen Illueca from the Department of Pathology of the Instituto Valenciano de Oncologia for kindly providing Fig. 1 and the images in Fig. 2, respectively.

Address all correspondence and requests for reprints to: Robert Bast, M.D., M.D. Anderson Cancer Center, Translational Research, Houston, Texas 77030. E-mail: rbast@mdanderson.org.

This work was supported by funds from the M.D. Anderson SPORE in Ovarian Cancer NCI P50 CA83639, the M.D. Anderson CCSG NCI P30 CA16672, 1 R01 CA135354-01, the National Foundation for Cancer research, the Ovarian Cancer Research Fund, and philanthropic support from Golfers Against Cancer, the Tracey Jo Wilson Foundation, the Mossy Foundation, The Zarrow Foundation, and Stuart and Gaye Lynn Zarrow. I.R. was supported by the first Grupo Español de Investigación en Cáncer de Ovario (GEICO)-Jan Vermorken Grant.

Disclosure Summary: R.C.B. receives royalties for the discovery of CA125 from Fujirebio Diagnostics Inc. and serves on scientific advisory boards for Fujurebio Diagnostics Inc., Vermillion, and Illumina.

References

1. **Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D** 2011 Global cancer statistics. CA Cancer J Clin 61:69–90
2. **Smith HO, Berwick M, Verschraegen CF, Wiggins C, Lansing L, Muller CY, Qualls CR** 2006 Incidence and survival rates for female malignant germ cell tumors. Obstet Gynecol 107:1075–1085
3. **Cheng W, Liu J, Yoshida H, Rosen D, Naora H** 2005 Lineage infidelity of epithelial ovarian cancers is controlled by HOX genes that specify regional identity in the reproductive tract. Nat Med 11:531–537
4. **Soslow RA** 2008 Histologic subtypes of ovarian carcinoma: an overview. Int J Gynecol Pathol 27:161–174
5. **Silverberg SG** 2000 Histopathologic grading of ovarian carcinoma: a review and proposal. Int J Gynecol Pathol 19:7–15
6. **Pothuri B, Leitao MM, Levine DA, Viale A, Olshen AB, Arroyo C, Bogomolniy F, Olvera N, Lin O, Soslow RA, Robson ME, Offit K, Barakat RR, Boyd J** 2010 Genetic analysis of the early natural history of epithelial ovarian carcinoma. PLoS One 5:e10358

7. **Lee Y, Miron A, Drapkin R, Nucci MR, Medeiros F, Saleemuddin A, Garber J, Birch C, Mou H, Gordon RW, Cramer DW, McKeon FD, Crum CP** 2007 A candidate precursor to serous carcinoma that originates in the distal fallopian tube. J Pathol 211:26–35
8. **Piek JM, van Diest PJ, Zweemer RP, Jansen JW, Poort-Keesom RJ, Menko FH, Gille JJ, Jongsma AP, Pals G, Kenemans P, Verheijen RH** 2001 Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer. J Pathol 195:451–456
9. **Stuart GC, Kitchener H, Bacon M, duBois A, Friedlander M, Ledermann J, Marth C, Thigpen T, Trimble E** 2011 Gynecologic Cancer InterGroup (GCIG) consensus statement on clinical trials in ovarian cancer: report from the Fourth Ovarian Cancer Consensus Conference. Int J Gynecol Cancer 21:750–755
10. **Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, Verheijen RH, van der Burg ME, Lacave AJ, Panici PB, Kenter GG, Casado A, Mendiola C, Coens C, Verleye L, Stuart GC, Pecorelli S, Reed NS** 2010 Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 363:943–953
11. **Landen Jr CN, Birrer MJ, Sood AK** 2008 Early events in the pathogenesis of epithelial ovarian cancer. J Clin Oncol 26:995–1005
12. **Shih IeM, Kurman RJ** 2004 Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol 164:1511–1518
13. **Bast Jr RC, Hennessy B, Mills GB** 2009 The biology of ovarian cancer: new opportunities for translation. Nat Rev Cancer 9:415–428
14. **Vaughan S, Coward JI, Bast Jr RC, Berchuck A, Berek JS, Brenton JD, Coukos G, Crum CC, Drapkin R, Etemadmoghadam D, Friedlander M, Gabra H, Kaye SB, Lord CJ, Lengyel E, Levine DA, McNeish IA, Menon U, Mills GB, Nephew KP, Oza AM, Sood AK, Stronach EA, Walczak H, Bowtell DD, Balkwill FR** 2011 Rethinking ovarian cancer: recommendations for improving outcomes. Nat Rev Cancer 11:719–725
15. **Malpica A, Deavers MT, Lu K, Bodurka DC, Atkinson EN, Gershenson DM, Silva EG** 2004 Grading ovarian serous carcinoma using a two-tier system. Am J Surg Pathol 28:496–504
16. **Hsu CY, Bristow R, Cha MS, Wang BG, Ho CL, Kurman RJ, Wang TL, Shih IeM** 2004 Characterization of active mitogen-activated protein kinase in ovarian serous carcinomas. Clin Cancer Res 10: 6432–6436
17. **Schmeler KM, Sun CC, Bodurka DC, Deavers MT, Malpica A, Coleman RL, Ramirez PT, Gershenson DM** 2008 Neoadjuvant chemotherapy for low-grade serous carcinoma of the ovary or peritoneum. Gynecol Oncol 108:510–514
18. **Gershenson DM, Sun CC, Bodurka D, Coleman RL, Lu KH, Sood AK, Deavers M, Malpica AL, Kavanagh JJ** 2009 Recurrent low-grade serous ovarian carcinoma is relatively chemoresistant. Gynecol Oncol 114:48–52
19. **Hess V, A'Hern R, Nasiri N, King DM, Blake PR, Barton DP, Shepherd JH, Ind T, Bridges J, Harrington K, Kaye SB, Gore ME** 2004 Mucinous epithelial ovarian cancer: a separate entity requiring specific treatment. J Clin Oncol 22:1040–1044
20. **Itamochi H, Kigawa J, Sugiyama T, Kikuchi Y, Suzuki M, Terakawa N** 2002 Low proliferation activity may be associated with chemoresistance in clear cell carcinoma of the ovary. Obstet Gynecol 100: 281–287
21. **Pieretti M, Hopenhayn-Rich C, Khattar NH, Cao Y, Huang B, Tucker TC** 2002 Heterogeneity of ovarian cancer: relationships among histological group, stage of disease, tumor markers, patient characteristics, and survival. Cancer Invest 20:11–23
22. **Garrett AP, Lee KR, Colitti CR, Muto MG, Berkowitz RS, Mok SC** 2001 k-ras mutation may be an early event in mucinous ovarian tumorigenesis. Int J Gynecol Pathol 20:244–251
23. **Zorn KK, Bonome T, Gangi L, Chandramouli GV, Awtrey CS, Gardner GJ, Barrett JC, Boyd J, Birrer MJ** 2005 Gene expression profiles of serous, endometrioid, and clear cell subtypes of ovarian and endometrial cancer. Clin Cancer Res 11:6422–6430
24. **Jones S, Wang TL, Shih IeM, Mao TL, Nakayama K, Roden R, Glas R, Slamon D, Diaz Jr LA, Vogelstein B, Kinzler KW, Velculescu VE, Papadopoulos N** 2010 Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma. Science 330:228–231
25. **Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, Senz J, McConechy MK, Anglesio MS, Kalloger SE, Yang W, Heravi-Moussavi A, Giuliany R, Chow C, Fee J, Zayed A, Prentice L, Melnyk N, Turashvili G, Delaney AD, Madore J, Yip S, McPherson AW, Ha G, Bell L, *et al.*** 2010 ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med 363:1532–1543
26. **Cancer Genome Atlas Research Network** 2011 Integrated genomic analyses of ovarian carcinoma. Nature 474:609–615
27. **Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ** 2009 Cancer Statistics 2009. CA Cancer J Clin 59:225–249
28. **Giede KC, Kieser K, Dodge J, Rosen B** 2005 Who should operate on patients with ovarian cancer? An evidence-based review. Gynecol Oncol 99:447–461
29. **Colombo N, Pecorelli S** 2003 What have we learned from ICON1 and ACTION? Int J Gynecol Cancer 13(Suppl 2):140–143
30. **Odicino F, Pecorelli S, Zigliani L, Creasman WT** 2008 History of the FIGO cancer staging system. Int J Gynaecol Obstet 101:205–210
31. **Harter P, Hahmann M, Lueck HJ, Poelcher M, Wimberger P, Ortmann O, Canzler U, Richter B, Wagner U, Hasenburg A, Burges A, Loibl S, Meier W, Huober J, Fink D, Schroeder W, Muenstedt K, Schmalfeldt B, Emons G, du Bois A** 2009 Surgery for recurrent ovarian cancer: role of peritoneal carcinomatosis: exploratory analysis of the DESKTOP I Trial about risk factors, surgical implications, and prognostic value of peritoneal carcinomatosis. Ann Surg Oncol 16:1324–1330
32. **Chi DS, McCaughty K, Diaz JP, Huh J, Schwabenbauer S, Hummer AJ, Venkatraman ES, Aghajanian C, Sonoda Y, Abu-Rustum NR, Barakat RR** 2006 Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. Cancer 106:1933–1939
33. **Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, Wadler S, Sickel J** 2001 Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 19:1001–1007
34. **Alberts DS, Liu PY, Hannigan EV, O'Toole R, Williams SD, Young JA, Franklin EW, Clarke-Pearson DL, Malviya VK, DuBeshter B** 1996 Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 335:1950–1955
35. **Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, Copeland LJ, Walker JL, Burger RA; Gyncologic Oncology Group** 2006 Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 354:34–43
36. **Katsumata N, Yasuda M, Takahashi F, Isonishi S, Jobo T, Aoki D, Tsuda H, Sugiyama T, Kodama S, Kimura E, Ochiai K, Noda K** 2009 Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 374:1331–1338
37. **Bookman MA, Brady MF, McGuire WP, Harper PG, Alberts DS, Friedlander M, Colombo N, Fowler JM, Argenta PA, De Geest K, Mutch DG, Burger RA, Swart AM, Trimble EL, Accario-Winslow C, Roth LM** 2009 Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. J Clin Oncol 27:1419–1425
38. **González-Martín AJ, Calvo E, Bover I, Rubio MJ, Arcusa A, Casado A, Ojeda B, Balañá C, Martínez E, Herrero A, Pardo B, Adrover E, Rifá J, Godes MJ, Moyano A, Cervantes A** 2005 Randomized phase

II trial of carboplatin versus paclitaxel and carboplatin in platinum-sensitive recurrent advanced ovarian carcinoma: a GEICO (Grupo Espanol de Investigacion en Cancer de Ovario) study. Ann Oncol 16:749–755

39. **Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB, Wheeler S, Swart AM, Qian W, Torri V, Floriani I, Jayson G, Lamont A, Tropé C** 2003 Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 361:2099–2106
40. **Pfisterer J, Plante M, Vergote I, du Bois A, Hirte H, Lacave AJ, Wagner U, Stähle A, Stuart G, Kimmig R, Olbricht S, Le T, Emerich J, Kuhn W, Bentley J, Jackisch C, Lück HJ, Rochon J, Zimmermann AH, Eisenhauer E** 2006 Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 24:4699–4707
41. **Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, Gebski V, Heywood M, Vasey PA, Volgger B, Vergote I, Pignata S, Ferrero A, Sehouli J, Lortholary A, Kristensen G, Jackisch C, Joly F, Brown C, Le Fur N, du Bois A** 2010 Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol 28:3323–3329
42. **Bast Jr RC, Markman M** 2010 A new standard combination for recurrent ovarian cancer? Nat Rev Clin Oncol 7:559–560
43. **Gordon AN, Tonda M, Sun S, Rackoff W; Doxil Study 30–49 Investigators** 2004 Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. Gynecol Oncol 95:1–8
44. **Gynecologic Oncology Group; Markman M, Blessing J, Rubin SC, Connor J, Hanjani P, Waggoner S** 2006 Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol Oncol 101:436–440
45. **ten Bokkel Huinink W, Gore M, Carmichael J, Gordon A, Malfetano J, Hudson I, Broom C, Scarabelli C, Davidson N, Spanczynski M, Bolis G, Malmström H, Coleman R, Fields SC, Heron JF** 1997 Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol 15:2183–2193
46. **Friedlander M, Millward MJ, Bell D, Bugat R, Harnett P, Moreno JA, Campbell L, Varette C, Ripoche V, Kayitalire L** 1998 A phase II study of gemcitabine in platinum pre-treated patients with advanced epithelial ovarian cancer. Ann Oncol 9:1343–1345
47. **Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI** 2007 Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol 25:5165–5171
48. **Cannistra SA, Matulonis UA, Penson RT, Hambleton J, Dupont J, Mackey H, Douglas J, Burger RA, Armstrong D, Wenham R, McGuire W** 2007 Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 25:5180–5186
49. **Berkenblit A, Seiden MV, Matulonis UA, Penson RT, Krasner CN, Roche M, Mezzetti L, Atkinson T, Cannistra SA** 2004 A phase II trial of weekly docetaxel in patients with platinum-resistant epithelial ovarian, primary peritoneal serous cancer, or fallopian tube cancer. Gynecol Oncol 95:624–631
50. **Rose PG, Blessing JA, Mayer AR, Homesley HD** 1998 Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 16:405–410
51. **Yin BW, Lloyd KO** 2001 Molecular cloning of the CA125 ovarian cancer antigen: identification as a new mucin, MUC16. J Biol Chem 276:27371–27375
52. **Bast Jr RC, Spriggs DR** 2011 More than a biomarker: CA125 may contribute to ovarian cancer pathogenesis. Gynecol Oncol 121: 429–430
53. **Bast Jr RC, Klug TL, St John E, Jenison E, Niloff JM, Lazarus H, Berkowitz RS, Leavitt T, Griffiths CT, Parker L, Zurawski Jr VR, Knapp RC** 1983 A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med 309:883–887
54. **Rustin GJ, van der Burg ME, Griffin CL, Guthrie D, Lamont A, Jayson GC, Kristensen G, Mediola C, Coens C, Qian W, Parmar MK, Swart AM** 2010 Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet 376:1155–1163
55. **Bast Jr RC** 2010 Commentary: CA125 and the detection of recurrent ovarian cancer: A reasonably accurate biomarker for a difficult disease. Cancer 116:2850–2853
56. **Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG** 1990 A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol 97:922–929
57. **Ueland FR, Desimone CP, Seamon LG, Miller RA, Goodrich S, Podzielinski I, Sokoll L, Smith A, van Nagell Jr JR, Zhang Z** 2011 Effectiveness of a multivariate index assay in the preoperative assessment of ovarian tumors. Obstet Gynecol 117:1289–1297
58. **Moore RG, Jabre-Raughley M, Brown AK, Robison KM, Miller MC, Allard WJ, Kurman RJ, Bast RC, Skates SJ** 2010 Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. Am J Obstet Gynecol 203:228.e1–6
59. **Moore RG, Miller MC, Disilvestro P, Landrum LM, Gajewski W, Ball JJ, Skates SJ** 2011 Evaluation of the diagnostic accuracy of the risk of ovarian malignancy algorithm in women with a pelvic mass. Obstet Gynecol 118:280–288
60. **Menon U, Gentry-Maharaj A, Hallett R, Ryan A, Burnell M, Sharma A, Lewis S, Davies S, Philpott S, Lopes A, Godfrey K, Oram D, Herod J, Williamson K, Seif MW, Scott I, Mould T, Woolas R, Murdoch J, Dobbs S, Amso NN, Leeson S, Cruickshank D, McGuire A, Campbell S, Fallowfield L, Singh N, Dawnay A, Skates SJ, Parmar M, Jacobs I** 2009 Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Lancet Oncol 10:327–340
61. **Lu KH, Skates S, Bevers TB, Newland W, Moore RG, Leeds L, Harris S, Adeyinka OW, Fritsche HA, Bast RC** 2010 A prospective U.S. ovarian cancer screening study using the risk of ovarian cancer algorithm (ROCA). J Clin Oncol 28:15s (Abstract 5003)
62. **Muggia FM, Braly PS, Brady MF, Sutton G, Niemann TH, Lentz SL, Alvarez RD, Kucera PR, Small JM** 2000 Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. J Clin Oncol 18:106–115
63. **McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, Clarke-Pearson DL, Davidson M** 1996 Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 334:1–6
64. **Piccart MJ, Bertelsen K, Stuart G, Cassidy J, Mangioni C, Simonsen E, James K, Kaye S, Vergote I, Blom R, Grimshaw R, Atkinson R, Swenerton K, Trope C, Nardi M, Kaern J, Tumolo S, Timmers P, Roy JA, Lhoas F, Lidvall B, Bacon M, Birt A, Andersen J, Zee B, Paul J, Pecorelli S, Baron B, McGuire W** 2003 Long-term follow-up confirms a survival advantage of the paclitaxel-cisplatin regimen over the cyclophosphamide-cisplatin combination in advanced ovarian cancer. Int J Gynecol Cancer 13:144–148
65. **Ahmed AA, Wang X, Lu Z, Goldsmith J, Le XF, Grandjean G, Bartholomeusz G, Broom B, Bast Jr RC** 2011 Modulating micro-

tubule stability enhances the cytotoxic response of cancer cells to paclitaxel. Cancer Res 71:5806–5817
66. **Ahmed AA, Lu Z, Jennings NB, Etemadmoghadam D, Capalbo L, Jacamo RO, Barbosa-Morais N, Le XF, Australian Ovarian Cancer Study Group, Vivas-Mejia P, Lopez-Berestein G, Grandjean G, Bartholomeusz G, Liao W, Andreeff M, Bowtell D, Glover DM, Sood AK, Bast Jr RC** 2010 SIK2 is a centrosome kinase required for bipolar spindle formation that provides a potential target for therapy in ovarian cancer. Cancer Cell 18:109–121
67. **Selvakumaran M, Pisarcik DA, Bao R, Yeung AT, Hamilton TC** 2003 Enhanced cisplatin cytotoxicity by disturbing the nucleotide excision repair pathway in ovarian cancer cell lines. Cancer Res 63:1311–1316
68. **Reed E, Yu JJ, Davies A, Gannon J, Armentrout SL** 2003 Clear cell tumors have higher mRNA levels of ERCC1 and XPB than other histological types of epithelial ovarian cancer. Clin Cancer Res 9:5299–5305
69. **Agarwal R, Kaye SB** 2003 Ovarian cancer: strategies for overcoming resistance to chemotherapy. Nat Rev Cancer 3:502–516
70. **Turner N, Tutt A, Ashworth A** 2004 Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 4:814–819
71. **Bast Jr RC, Mills GB** 2010 Personalizing therapy for ovarian cancer: BRCAness and beyond. J Clin Oncol 28:3545–3548
72. **Chetrit A, Hirsh-Yechezkel G, Ben-David Y, Lubin F, Friedman E, Sadetzki S** 2008 Effect of BRCA1/2 mutations on long-term survival of patients with invasive ovarian cancer: the national Israeli study of ovarian cancer. J Clin Oncol 26:20–25
73. **Tan DS, Rothermundt C, Thomas K, Bancroft E, Eeles R, Shanley S, Ardern-Jones A, Norman A, Kaye SB, Gore ME** 2008 "BRCAness" syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. J Clin Oncol 26:5530–5536
74. **Malander S, Rambech E, Kristoffersson U, Halvarsson B, Ridderheim M, Borg A, Nilbert M** 2006 The contribution of the hereditary nonpolyposis colorectal cancer syndrome to the development of ovarian cancer. Gynecol Oncol 101:238–243
75. **Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Fan I, Tang J, Li S, Zhang S, Shaw PA, Narod SA** 2006 Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst 98:1694–1706
76. **Pal T, Permuth-Wey J, Betts JA, Krischer JP, Fiorica J, Arango H, LaPolla J, Hoffman M, Martino MA, Wakeley K, Wilbanks G, Nicosia S, Cantor A, Sutphen R** 2005 BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer 104:2807–2816
77. **Press JZ, De Luca A, Boyd N, Young S, Troussard A, Ridge Y, Kaurah P, Kalloger SE, Blood KA, Smith M, Spellman PT, Wang Y, Miller DM, Horsman D, Faham M, Gilks CB, Gray J, Huntsman DG** 2008 Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities. BMC Cancer 8:17
78. **Hennessy BT, Timms KM, Carey MS, Gutin A, Meyer LA, Flake DD 2nd, Abkevich V, Potter J, Pruss D, Glenn P, Li Y, Li J, Gonzalez-Angulo AM, McCune KS, Markman M, Broaddus RR, Lanchbury JS, Lu KH, Mills GB** 2010 Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. J Clin Oncol 28:3570–3576
79. **Bhattacharyya A, Ear US, Koller BH, Weichselbaum RR, Bishop DK** 2000 The breast cancer susceptibility gene BRCA1 is required for subnuclear assembly of Rad51 and survival following treatment with the DNA cross-linking agent cisplatin. J Biol Chem 275:23899–239903
80. **Audeh MW, Carmichael J, Penson RT, Friedlander M, Powell B, Bell-McGuinn KM, Scott C, Weitzel JN, Oaknin A, Loman N, Lu K, Schmutzler RK, Matulonis U, Wickens M, Tutt A** 2010 Oral poly-(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet 376:245–251
81. **Bast Jr RC, Mills GB** 2012 Dissecting "PI3Kness": the complexity of personalized therapy for ovarian cancer. Cancer Discovery 2:16
82. **Huang J, Zhang L, Greshock J, Colligon TA, Wang Y, Ward R, Katsaros D, Lassus H, Butzow R, Godwin AK, Testa JR, Nathanson KL, Gimotty PA, Coukos G, Weber BL, Degenhardt Y** 2011 Frequent genetic abnormalities of the PI3K/AKT pathway in primary ovarian cancer predict patient outcome. Genes Chromosomes Cancer 50:606–618
83. **Mendes-Pereira AM, Martin SA, Brough R, McCarthy A, Taylor JR, Kim JS, Waldman T, Lord CJ, Ashworth A** 2009 Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors. EMBO Mol Med 1:315–322
84. **Folkman J** 1995 Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med 1:27–31
85. **Jubb AM, Harris AL** 2010 Biomarkers to predict the clinical efficacy of bevacizumab in cancer. Lancet Oncol 11:1172–1183
86. **Mehta S, Hughes NP, Buffa FM, Li SP, Adams RF, Adwani A, Taylor NJ, Levitt NC, Padhani AR, Makris A, Harris AL** 2011 Assessing early therapeutic response to bevacizumab in primary breast cancer using magnetic resonance imaging and gene expression profiles. J Natl Cancer Inst Monogr 2011:71–74
87. **Hirashima Y, Yamada Y, Tateishi U, Kato K, Miyake M, Horita Y, Akiyoshi K, Takashima A, Okita N, Takahari D** 21 July 2011 Pharmacokinetic parameters from 3-Tesla DCE-MRI as surrogate biomarkers of antitumor effects of bevacizumab plus FOLFIRI in colorectal cancer with liver metastasis. Int J Cancer 10.1002/ijc.26282
88. **Richards JS** 2012 Animal models and mechanisms of ovarian cancer development. Endocrinology 153:1585–1592
89. **Chen VW, Ruiz B, Killeen JL, Coté TR, Wu XC, Correa CN** 2003. Pathology and classification of ovarian tumors. Cancer 97:2631–2642
90. **Knapp RC, Berkowitz RS, Leavitt Jr T, Bast Jr RC** 1988 Natural history and detection of ovarian cancer. In: Sciarra JW, ed. Gynecology and obstetrics. Philadelphia: Harper, Row; 1–16
91. **Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Kurzeder C, du Bois A, Sehouli J, Kimmig R, Stähle A, Collinson F, Essapen S, Gourley C, Lortholary A, Selle F, Mirza MR, Leminen A, Plante M, Stark D, Qian W, Parmar MK, Oza AM; ICON7 Investigators** 2011 A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med:365(26):2484-96; 2012 Erratum in: N Engl J Med:366(3):284
92. **Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, Mannel RS, Homesley HD, Fowler J, Greer BE, Boente M, Birrer MJ, Liang SX; Gynecologic Oncology Group** 2011 Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med:365(26):2473-83