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Relevant molecular markers and targets

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CURRENT STATUS

Ovarian cancer is a heterogeneous disease that does not appear to have a common driving oncogene, and has a natural propensity to disseminate and spread, making it difficult to diagnose at an early stage. Over two thirds (68%) of women diagnosed with ovarian cancer have distant disease.[1] The moderate prevalence of ovarian cancer in the population is coupled with a poor prognosis. Jemal and colleagues estimate 20,180 new ovarian cancer cases and 15,310 deaths in the United States in 2006.[1] Despite a high clinical response rate to platinum and taxane based chemotherapy [2], the five year survival rate for women with distant disease is only 29%.[1]

Insights into the molecular mechanisms operative in cancer development, progression and metastasis have uncovered a wide array of targets for therapeutic intervention. A plethora of agents are in clinical drug development or in the pipeline. These therapies target tumor cells and/or the tumor microenvironment including stromal cells, endothelial cells, endothelial precursor cells, pericytes, and immune cells. Among these agents are inhibitors of receptor tyrosine kinases (RTK), non-receptor tyrosine kinases, serine/threonine kinases, transferases, proteases as well as other enzymes, processes and pathways. Some are selective inhibitors while others are either dual inhibitors or multiple inhibitors.

In the absence of a common driving oncogene in ovarian cancer, single targeted therapy for ovarian cancer is unlikely to yield significant clinical benefit. Tailored approaches that combine molecular targeting agents with cytotoxic regimens hold great promise when used in primary treatment, during consolidation and maintenance therapy, and in the treatment of persistent or recurrent disease. The most promising treatment strategies are those that not only target individual pathways at multiple places, but also target divergent pathways which later converge to regulate critical events that drive tumorigenesis and enhance the activity of cytotoxic agents.

BACKGROUND AND RATIONALE

Ovarian cancer exhibits extensive cytogenetic and molecular heterogeneity including aneuploidy, chromosomal alterations, mutations and overexpression. These genomic and epigenetic alterations drive tumorigenesis and are often under the control of receptors that are activated by ligands. Following activation, receptors often dimerize and undergo

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conformational changes that transduce signals through the cell that regulate transcription, translation and post-translational modifications. Receptor activation also controls cell proliferation, maturation, migration, invasion, survival and resistance; as well as the production and secretion of growth factors, cytokines and chemokines. These autocrine and paracrine factors affect tumor cells and the tumor microenvironment by regulating angiogenesis, vasculogenesis and anti-tumor immunity.

Inappropriate receptor activation promotes tumorigenesis and can be induced by a number of mechanisms including overexpression of autocrine and paracrine factors. Receptors can also be mutated causing constitutive activation in the absence of ligand binding, or be overexpressed via gene amplification, transcriptional activation or post-transcriptional mechanisms which typically require ligand availability and binding for activation. Cross talk between different receptor superfamilies can activate receptors by a ligand independent mechanism.

In addition, tumorigenesis can be promoted by the amplification, mutation or overexpression of signaling molecules downstream from receptors. Various cell types within the tumor microenvironment can be induced to secrete pro-inflammatory factors that stimulate the vasculature to recruit leukocytes to the tumour. After activation, these tumour-associated leukocytes can release factors that recruit more inflammatory cells and stimulate angiogenesis to sustain tumor growth, promote disease progression, and facilitate tumor metastasis. To achieve long term clinical benefit, effective treatments must target the drivers of tumorigenesis operating in that patient population.

MOLECULAR TARGETING THERAPIES

RECEPTOR TYROSINE KINASES (RTK)

ErbB Receptor Family—The ErbB family of RTK includes epidermal growth factor receptor (EGFR, ErbB1), Her2 (EGFR2, ErbB2), ErbB3 (Her3) and ErbB4 (Her4) and is activated by such ligands as epidermal growth factor (EGF), heparin-binding EGF (HB-EGF), transforming growth factor α (TGF α), amphiregulin and crypto. Homo- and heterodimerization within the ErbB family of RTK contributes to the diversity of signaling events and biological effects regulated by this class of receptors. ErbB receptors and their ligands drive tumorigenesis by stimulating tumor growth, survival, migration, invasion, angiogenesis, vasculogenesis and drug resistance. A number of small molecule inhibitors and antibodies have been developed to inhibit one or more ErbB receptors.[3,4] Ovarian cancers can express high levels of a number of ErbB ligands including EGF, HB-EGF, TGF α , amphiregulin and crypto [5-7] as well as exhibit amplification of EGFR and Her2 and express EGFR, Her2, ErbB3 and ErbB4 [8-15]. Expression of ErbB ligands and/or receptors in ovarian cancer is associated with poor prognosis.[6,7,9,10]

Gefitinib (Iressa, ZD1839) and erlotinib (Tarceva, OSI-774) are among the small molecule inhibitors of EGFR. Single agent gefitinib was well tolerated but had minimal activity in unscreened patients with recurrent ovarian or primary peritoneal carcinoma (GOG-0170C). [11] Erlotinib, a similar EGFR inhibitor, when used as a monotherapy, exhibited marginal activity and was well tolerated in patients with refractory, recurrent, EGFR-positive epithelial ovarian tumors, who had failed prior taxane and/or platinum-based chemotherapy.[16] Cetuximab (C225), matuzumab (EMD 72000) and ABX-EGF are humanized monoclonal antibodies against the EGFR. The combination of cetuximab and carboplatin is currently undergoing phase II evaluation in patients with recurrent platinum-sensitive ovarian or primary peritoneal cancer (GOG-0146P; BMS # CA225019). Matuzumab is undergoing evaluation as a single agent in an open-label phase II study in women with recurrent EGFR-positive ovarian cancer. Trastuzumab (Herceptin) is a humanized monoclonal antibody against Her2. Single agent trastuzumab exhibited limited activity in patients with measurable persistent or recurrent

ovarian or primary peritoneal cancer overexpressing Her2 (GOG-0160).[17] SUCI02 and CP-724,714 are small molecule inhibitors of Her2. Lapatinab (GW572016) is a small molecule dual EGFR / Her2 inhibitor undergoing phase II evaluation in the treatment of persistent or recurrent ovarian or primary peritoneal carcinoma (GOG-0170G). Canertinib (CI-1033) is an irreversible pan-ErbB inhibitor that showed no activity when evaluated in a phase II, open-label clinical trial in unscreened patients with platinum-refractory or recurrent ovarian cancer. [12]

Activating mutations within the tyrosine kinase domain of EGFR, which have been observed in 3.5% (2/57) of ovarian cancers [11], are associated with dramatic responses to gefitinib [18,19]. This suggests that pre-screening ovarian cancer patients for activating mutations in ErbB receptors may improve the response rate to ErbB inhibitors.[20] In addition, ErbB inhibitors may also have a more effective clinical role in unselected ovarian cancer patients when used in combination with cytotoxic and anti-angiogenic agents. The GOG is initiating a phase III trial in recurrent platinum-sensitive ovarian cancer using erlotinib in combination with bevacuzimab during the maintenance components of one of the treatment arms (GOG-0213).

VEGF and VEGF Receptor Family—Vascular endothelial growth factor receptor (VEGFR, Flt-1) and VEGFR2 (KDR/Flk-1) are members of a family of RTK activated by vascular endothelial growth factor (VEGF). VEGF is the dominant angiogenic factor that not only stimulates endothelial cell growth, migration, survival and vascular permeability, but also regulates the mobilization of endothelial progenitor cells from bone marrow to distant sites of neovascularization, and contributes to drug resistance. A number of agents have been developed to inhibit VEGF, VEGFR and VEGFR2 including monoclonal antibodies, small molecule inhibitors and decoy receptors.[21,22]

Angiogenesis plays a critical role in ovarian cancer progression and prognosis.[23-28] Ovarian cancers not only express a number of angiogenic markers including VEGF, VEGFR, VEGFR2 [23-29], but the level of many of these markers is associated with poor survival.[25,28,30] Bevacuzimab (Avastin), a recombinant humanized monoclonal antibody against VEGF, is under active clinical development for the treatment of primary as well as persistent or recurrent ovarian cancer. A single case report study described how single-agent bevacizumab induced an objective durable response in a patient with recurrent and refractory serous carcinoma of the ovary after failing the eleventh line cytotoxic therapy.[31] In a phase II trial, bevacuzimab was evaluated as a single agent in the second or third line treatment of patients with persistent or recurrent ovarian or primary peritoneal cancer (GOG-0170D).[32] This VEGF inhibitor was well-tolerated and efficacious with 13/62 (21.0%) clinical responses and 25/62 (40.3%) patients who survived progression-free for at least 6 months. The California Cancer Consortium evaluated bevacuzimab in combination with low-dose metronomic oral cyclophosphamide and observed a 28% clinical response in a study of 29 patients with recurrent ovarian or primary peritoneal cancer.[33] A 10 patient case control study demonstrated that bevacizumab and weekly taxane was well tolerated and induced a short but significant improvement in cancer-related symptoms in women with advanced, recurrent, refractory epithelial ovarian cancer.[34] The GOG is currently evaluating the combination of carboplatin and paclitaxel with either placebo or bevacuzimab followed by placebo or extended bevacuzimab to prolong progression-free survival and overall survival in previously untreated patients with stage III-suboptimal or all stage IV ovarian or peritoneal primary cancers (GOG-0218).

The other types of anti-angiogenic agents under development include decoy receptors, small molecule inhibitors and anti-angiogenic mimetics. VEGF-Trap (AVE-0005), a decoy receptor for VEGF, was evaluated in a phase I trial in patients with refractory solid tumors or non-

Hodgkin's lymphoma.[35] One patient in this study had carboplatin-, taxane-, and gemcitabine-resistant advanced ovarian cancer and achieved a RECIST-defined partial response, a 67% reduction in serum CA125 levels, radiographic resolution of abdominal ascites and subjective improvement of performance status after receiving four cycles of VEGF Trap.[35] Several phase II trials, including one to be conducted by the GOG in the 170 series, are being initiated to evaluate VEGF-Trap in patients with platinum-resistant or platinum-sensitive persistent or recurrent ovarian or primary peritoneal carcinoma. There are also small molecule inhibitors of VEGFR under development including vatalanib (PTK787; ZK 222584), CP-547,632, CGP79787, AZD2171, and YM-359445. ABT-510 is a small peptide thrombospondin-1 mimetic under development to inhibit angiogenesis.

c-Kit and PDGFR—c-Kit (stem cell factor receptor), platelet derived growth factor receptor (PDGFR)- α and PDGFR- β are RTK that stimulate tumor cell growth, angiogenesis and vasculogenesis. Imatinib mesylate (STI571; Gleevec) is small molecule inhibitor of c-Kit, PDGFR- α , PDGFR- β and the fusion protein BCR-ABL.[36,37] AMN107, BMS-353,825 and ON012380 have been developed as novel ABL inhibitors for imatinib mesylate resistant cancers.[36,37] Researchers have demonstrated that c-Kit and PDGFR as well as their respective ligands are expressed in ovarian cancer.[38,39] In addition, patients with PDGFR- α positive ovarian cancers demonstrated an overall shorter survival compared with patients whose tumors were PDGFR- α negative.[39]

An open-label single institution phase II trial was performed in patients with recurrent platinum- and taxane-resistant ovarian or primary peritoneal cancer, and demonstrated that imatinib mesylate was well tolerated but did not produce clinical responses.[40] The GOG conducted a phase II trial of imatinib in the second or third line treatment of patients with persistent or recurrent ovarian or primary peritoneal carcinoma (GOG-0170E). Results using in vivo model systems suggest that imatinib mesylate should be combined with cytotoxic agents or with anti-angiogenic therapies.[41,42]

Dual or Multiple Receptor Tyrosine Kinases—Lapatinab (GW572016) is an example of small molecule dual EGFR / Her2 inhibitor. Canertinib (CI-1033) is an example of an irreversible pan-ErbB inhibitor. ZD6474 and AEE788 are examples of dual tyrosine kinase inhibitors of EGFR and VEGFR signaling. ABT-869 is a potent dual inhibitor of VEGFR and PDGFR. Sorafenib (BAY 43-9006) is a small molecule inhibitor of VEGFR, PDGFR and Raf. Sunitinib maleate (sutent; SU11248), AG-013736 and BAY 57-9352 are inhibitors of VEGFR, PDGFR and c-Kit. SU11657 is a multi-targeted tyrosine kinase inhibitor of PDGFR, VEGFR and Fms-like tyrosine kinase 3 (FLT3). JNJ-17029259 is a potent inhibitor of VEGFR, PDGFR and FGFR. CHIR-258 is an inhibitor of VEGFR, PDGFR, c-Kit, CSFR, FLT3 and FGFR. Benzoylstaurosporine (PKC412) inhibits Akt signaling, fibroblast growth factor receptor 3 (FGFR3), FLT3 and Akt signaling. ZK304709 inhibits VEGFR, PDGFR and cyclin-dependent kinase (CDK) 1 and 2. AMG 507 is a potent, oral small molecule multi-kinase inhibitor of VEGFR, c-Kit and PDGFR that is under development for evaluation by the GOG in a phase II trial for the second or third line treatment of persistent or recurrent ovarian or primary peritoneal cancer (the 170 series).

NON-RECEPTOR TYROSINE KINASES

Src Family—Src represents a family of cytoplasmic tyrosine kinases, activated by a number of RTK, G-protein coupled receptors and integrins, and are involved in different aspects of tumorigenesis including tumor growth, survival and metastasis.[43] Src is expressed and activated in a number of advanced stage ovarian cancers. Ovarian cancer cell lines have been used to demonstrate that Src promotes survival and drug resistance [44] while inhibition of Src reduces VEGF expression and interferes with microvessel vascularization.[45] Dasatinib

(BMS-354825) is an example of a small molecular inhibitor of the Src family of kinases with activity in imatinib resistant CML. PD173956, PD173958, PD180970 and AP23846 are other Src inhibitors under development.

JAK / STAT Pathway—A number of cytokine receptors and RTK activate members of the janus-activated kinase (JAK) family of tyrosine kinases which subsequently activate members of the signal transducer and activator of transcription (STAT) family. The JAK / STAT pathway has been shown to regulate various processes that drive tumorigenesis including proliferation, survival, angiogenesis and anti-tumor immunity.[46] Increased expression and phosphorylation of STAT3, a downstream target of JAK2, are frequent events in advanced stage ovarian cancers.[47] Phosphorylation of STAT3 and STAT5 have also been shown to be elevated in tumor cells and endothelial cells in ovarian cancers compared with benign and normal ovarian tissue.[48] Together these findings suggest that the JAK / STAT pathway may be an appropriate target for the treatment of ovarian cancer, especially when used in combination with anti-angiogenic therapies and cytotoxic agents. Cucurbitacin B, E and I (JSI-124) are selective inhibitors of the JAK2 / STAT3 pathway, whereas cucurbitacin Q selectively inhibits the activation of STAT3 and cucurbitacin A inhibits Jak2.

SERINE / THREONINE KINASES

PI3K / AKT / mTOR Pathway—The phosphoinositide 3-kinase (PI3K) / AKT (protein kinase B; PKB) / mammalian target of rapamycin (mTOR) pathway is activated by RTK, cytokine receptors and integrins. This pathway regulates many cellular processes that are important for the formation and progression of cancer including cell cycle progression, apoptosis, transcription, translation, metabolism and angiogenesis, and is a relevant target for cancer treatment [49-51]. PI3K has been shown to mediate ovarian cancer angiogenesis and vascular permeability.[52] AKT2 is activated, overexpressed or amplified in ovarian cancer specimens [53-55]. AKT activation in ovarian cancer is associated with phosphorylation of mTOR.[56] In addition, studies in chemosensitive and resistant ovarian cancer cells have shown that the PI3K / AKT pathway regulates cisplatin resistance.[57-58]

Currently, a number of the inhibitors of PI3K, AKT, and mTOR are fairly toxic limiting their clinical utility, but others are under development with potential to be less toxic. LY294002, wortmannin and ZSTK474 are PI3K inhibitors, while 9-methoxy-2-methylellipticinium acetate (termed API-59-OME) is a small molecule inhibitor of AKT. N-benzoylstauropine (PKC412) inhibits AKT signaling, FGFR3 and FLT3 which sensitizes cancer cells to drug and radiation induced DNA damage. KP372-1 inhibits PDK-1, AKT, and FLT3. Rapamycin and the rapamycin analogs including temsirolimus (CCI-779), RAD001, and AP23573 are mTOR inhibitors. The GOG submitted a letter of intent to the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) to conduct a phase II evaluation of temsirolimus in the 170 series which includes patients with persistent or recurrent ovarian or primary peritoneal carcinoma having received one to two prior chemotherapy regimens.

Ras / Raf / MEK / MAPK Pathway—The Ras / Raf / mitogen-activated protein kinase/ extracellular signal-regulated kinase (MEK) / mitogen activated protein kinase (MAPK) pathway is activated by RTKs, cytokine receptors and integrins, and has been shown to drive tumorigenesis by stimulating tumor growth, production of matrix degrading metalloproteinases (MMP) and drug resistance. Moreover this pathway has been shown to be mutated or activated via autocrine and paracrine loops in a number of cancers including ovarian cancer. Activating mutations have been documented in invasive ovarian cancers in Ras [59, 60] and b-Raf [61]. In addition, c-Raf and b-Raf are expressed in ovarian cancers, and high c-Raf expression is associated with poor prognosis, while increased expression of b-Raf is associated with improved survival,[62,63]

CGP 69846A (ISIS 5132), a DNA 20-mer oligonucleotide against Raf-1 mRNA, was well tolerated but did not exhibit any responses as a single agent in a phase II trial in recurrent epithelial ovarian cancer [64], but may have a more effective clinical role when used in combination with cytotoxic agents. BAY 43-9006, originally identified as an oral Raf inhibitor, was later shown to also inhibit VEGFR-2, VEGFR-3, PDGFR β , FLT-3, c-KIT and P38 α . This agent has shown clinical activity in a phase I trial when given in combination with gemcitabine. The GOG is currently conducting a phase II evaluation of BAY43-9006 in the second or third line treatment of women with recurrent or persistent ovarian cancer and primary peritoneal carcinonoma (GOG-0170F). MEK, a dual specificity kinase, is a key player in this pathway as it is downstream from both Ras and Raf and activates ERK1/2 through phosphorylation of key tyrosine and threonine residues. UO126, PD98059, PD184352 (CI-1040) are inhibitors of MEK and ERK1/2. SB203580 is an inhibitor of p38 MAPK.

PKC Family—Protein kinase C (PKC) is a family of serine-threonine kinases, that transduces signals from membrane receptors to the nucleus, stimulates apoptosis or survival in an isoform-specific manner, activates ion fluxes, promotes proliferation and metastasis, signals tumor-induced angiogenesis, and is a target for the treatment of cancers.[65] A number of PKC isoforms are expressed, amplified or overexpressed in ovarian cancer.[66,67] Aprinocarsen is a 20-base antisense oligonucleotide inhibitor of PKC alpha that did not exhibit significant clinical activity when evaluated as a single agent in a phase II trial in patients with platinum-sensitive or platinum-resistant ovarian cancer.[68] Bryostatin-1, phospholipid analogues, CGP41251 and UCN-01 are examples of other PKC inhibitors that have been evaluated for antitumor activity in cancer patients. Enzastaurin is an example of a potent and selective inhibitor of PKC β in clinical development. The GOG is currently developing a phase II trial to evaluate Enzastaurin in the 170 series for the treatment of recurrent or persistent ovarian cancer and primary peritoneal carcinonoma having received one to two prior chemotherapy regimens.

Aurora Kinase Family—The Aurora family of serine/threonine kinases regulates chromosome segregation and cytokinesis during mitosis, plays a role in tumorigenesis and progression in a wide range of human tumours, including ovarian cancer, and is a target for cancer treatment.[69] Elevated expression of Aurora A has been detected in over 50% of ovarian cancers [70]. MK-0457 (L-001281814 and VX-680) is a small molecule inhibitor of the Aurora kinases that will be undergoing phase I testing in combination with docetaxel in patients with recurrent ovarian, fallopian tube and primary peritoneal cancer. Aurora kinase inhibitors are thought to exhibit limited toxicity in resting cells due to the low or undetectable expression and activity of Aurora protein in non-cycling cells. An open-label, non-randomized two part phase I trial is currently underway in patients with recurrent ovarian, fallopian tube and primary peritoneal cancer.

ADDITIONAL TARGETS

Transferases—Tipifarnib (R115777; Zarnestra), Lonafarnib (SCH66336), BMS-214662 and L778123 are examples of farnesyl transferase inhibitors (FTI) that inhibit the process of farnesylation by inhibiting the farnesyl protein transferase that modifies several proteins post-translationally including Ras.[71] Phase II and III trials of tipifarnib as monotherapy have been disappointing and combination trials of tipifarnib with cytotoxic, hormonal or biological therapies are ongoing.

Telomerase is an enzyme that transfers telomeric repeats in tandem at the 3'hydroxyl end of telomeres and contributes to cancer development by maintaining telomere length allowing cancer cells to continue to divide and by enhancing cell proliferation, regulating death-receptor signal transduction and playing a role in drug resistance. A number of strategies are under

development for inhibiting the RNA component of telomerase, the catalytic subunit of telomerase, telomerase activity or accessory proteins.[72]

Proteases—Degradation of the extracellular matrix by MMPs is essential for tumor invasion, metastasis, angiogenesis, vasculogenesis and anti-tumor immunity. Marimastat (BB-2516) and BAY 129566 are examples of MMP inhibitors in clinical development in ovarian cancer. There are also peptidomimetic, nonpeptidic and natural MMP inhibitors in preclinical or clinical development.[73] MMPs are expressed by the epithelial and stromal components of ovarian cancers, and high expression of MMPs is associated with shorter disease-specific survival. [74]

The ubiquitin-proteasome pathway plays an essential role in protein degradation and in regulating cell cycle progression and metastasis. The 26S proteasome is an ATP-dependent multicatalytic protease. The tumor suppressor p53, the cell cycle inhibitors p21 and p27, and the protein IKB which inhibits the nuclear factor-KB (NF-KB) are regulated by proteasome-dependent proteolysis. Bortezomib (PS-341, Velcade) is an example of a potent and reversible inhibitor of the 26S proteasome. The GOG evaluated bortezomib at two doses in a phase II trial for treatment of persistent or recurrent platinum-sensitive ovarian or primary peritoneal cancer (GOG-0146N).

The urokinase plasminogen activator (uPA) system consists of the serine protease uPA, the glycolipid-anchored receptor, uPAR, and the 2 serpin plasminogen activator inhibitors (PAI-1 and PAI-2). The uPA system promotes cancer invasion and metastasis by remodeling the extracellular matrix, enhancing cell proliferation and migration, and modulating cell adhesion. [76] WX-UK1 and WX-671 are inhibitors of the uPA system in clinical development. A6, a peptide derived from human uPA, is currently undergoing evaluation in a phase II trial in ovarian cancer.

HDAC Family—Histone deacetylase (HDAC) is a family of enzymes that alters transcription by deacetylating nucleosome histones leading to tight coiling of chromatin and silencing of the transcription of various genes. This family of enzymes appears to play a role in tumor initiation and progression by the deacetylating histones and non-histone proteins including specific cell cycle regulatory proteins. Vorinostat (suberoylanilide hydroxamic acid [SAHA]) and LBH589 are examples of HDAC inhibitors in clinical development that exhibit anti-tumor activity in vivo by inhibiting migration, invasion, metastasis, angiogenesis and vasculogenesis. [77] Vorinostat is currently being evaluated in a phase II trial as a single agent in the treatment of persistent or recurrent epithelial ovarian or primary peritoneal carcinoma having received one to two prior chemotherapy regimens (GOG-0170H).

Other Processes and Pathways—There are also additional processes and pathways being targeted for cancer treatment including heat shock protein 90 (HSP90) inhibited by 17-allylamino-demethoxy geldanamycin (17-AAG) [78], poly(ADP-ribose) polymerase (PARP) inhibited by ABT-888, INO-1001 and AG140699 [79], and cyclin-dependent kinase pathways inhibited by flavopiridol, seliciclib (CYC202, cyclacel), BMS-387032 and PD 0332991.[80]. Integrins, cyclooxygenase-2, p53, hypoxia inducible factor, and the RTK EphA2 as well as transforming growth factor β and hedgehog signaling pathways are also being developed as targets for cancer treatment.

FUTURE CHALLENGES AND DIRECTIONS

Given the array of targeted therapeutics and combinations that need to be evaluated, our clinical trial programs need to proactively address the challenges of running concurrent trials with more than one primary end point and embedded translational research. In order to extend treatment

duration and induce more sustained clinical benefits with more acceptable toxicities, an increasing number of agents including molecular targeting therapies and cytotoxic drugs will need to be evaluated at biologically effective rather than maximally tolerated doses. These efforts will require creativity in trial designs, merging of resources and an adaptive infrastructure that can support and prioritize timely development and conduct of clinical protocols as well as the publication and dissemination of results. To be successful, we not only need cooperation and coordination between CTEP, GOG, the Ovarian Specialized Programs of Research Excellence (SPOREs), Cancer Centers, hospital, clinics, industry and the Food and Drug Administration (FDA), but more aggressive outreach to patients and their advocates. Each of these will be essential to accrue the maximal number of patients to these trials as rapidly as possible and to advance the treatment options and prognosis of patients diagnosed with ovarian cancer.

More sensitive and specific screening tests will be needed for the diagnosis of ovarian cancer at an early stage. Relevant biomarkers will be needed during each stage of drug development to evaluate drug activity, define biologically effective doses, and predict prognosis, response, resistance and toxicities. Validated biomarkers, expression profiles, pharmacogenomic profiles and proteomic profiles will be needed to stratify study populations and implement tailored therapies based on the biochemical and molecular characteristics of the patients' cancer. Surrogate markers and end points that substitute for clinical end points like progression-free survival and overall survival will be needed to facilitate the drug development process. Additional clinically-relevant *in vitro* and *in vivo* models of ovarian cancer will be needed to not provide the rationale for selecting the most promising agents and combinations for clinical testing, but also to optimize scheduling, evaluate novel deliveries and develop strategies for evading drug resistance. Screening tests will be needed to detect innate as well as acquired forms of resistance to the molecular targeting therapies and the conventional cytotoxic drugs to eliminate or at least limit exposing patients to inactive agents.

Clearly translational research has become an ever present part of clinical trials in ovarian cancer. As we look to the future, we will need to continue to raise the bar on the quality of the the translational research incorporated into these trials. This will be accomplished using validated laboratory and statistical methods as well as testing only the high quality specimens prepared by trained and equipped staff using validated standardized operating procedures (SOPs). In addition, the translational research objectives must not only identify, but also validate diagnostic, predictive and prognostic biomarkers and profiles for ovarian cancer. Specimens are crucial to satisfy these objectives. We will continue to have debates regarding the issues, policies and procedures that surround the collection and use of specimens for research, and will need input from patient advocates to make the best ethical, scientific and financial decisions for future clinical trials.

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