This year in the United States an estimated 21,650 new cases of ovarian cancer will be diagnosed, with approximately 15,000 women dying of the disease. The most common malignant tumor of the ovary is epithelial ovarian cancer (EOC), accounting for 90% of those cases. Although combination chemotherapy comprises the backbone of therapy for both early-stage and advanced ovarian cancer, only 10% to 30% of patients with stage III or IV disease are alive five years after the diagnosis. This poor survival rate can be attributed to the limitations of existing therapies as well as the ability of ovarian cancer cells to develop resistance to the available agents. The standard of care for patients with early- or advanced-stage disease is a combination of a platinum (cisplatin or carboplatin) and a taxane (paclitaxel or docetaxel) chemotherapy. Recent studies have demonstrated the superiority of intraperitoneal therapy (chemotherapy administered directly into the abdomen in women with less than 1 cm of cancer left in the abdomen following resection) over classic chemotherapy.

Trabectedin (T). Trabectedin is the synthetic version of a compound isolated from the sea squirt, Ecteinascidia turbinata. It is thought to exert its antitumor activity by interacting with the tumor cell DNA. It is approved in Europe and South Korea for the treatment of soft tissue sarcoma under the brand name Yondelis. The results of a large phase III multicenter trial in patients with relapsed epithelial ovarian cancer (EOC) were presented at the European Society for Medical Oncology meeting in 2008. Patients were randomized to either pegylated topotecan and liposomal doxorubicin are alternative agents approved for the treatment of relapsed or refractory ovarian cancer. Over the past decade, an understanding of the pathways involved in carcinogenesis have led to the development of drugs that act on specific targets in the tumor cell. These drugs are being actively tested in ovarian cancer and are in various phases of development. Some of the promising agents in this disease are described in this article.
liposomal doxorubicin (PLD) and T administered every three weeks or to single agent PLD. Six hundred and seventy-two women were enrolled over a period of two years. The addition of T to PLD resulted in a statistically significant increase in progression-free survival (7.3 months vs 5.8 months) and an improved overall response rate (28% vs 19%). The median progression-free survival for platinum-sensitive patients who relapsed 6 months after first-line chemotherapy was 9.2 months for PLD + T vs 7.5 months for PLD alone. This seems to be an active combination in patients with relapsed EOC. Studies are ongoing in breast and prostate cancer.

Bevacizumab. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF), thereby preventing the growth and maintenance of tumor blood vessels. Angiogenesis is thought to play a role in the pathogenesis and growth of ovarian cancer. The vascular endothelial growth factor A receptor (VEGFR-A) is expressed in a majority of ovarian cancer specimens and thus represents an exciting potential therapeutic target. Bevacizumab in combination with cytotoxic chemotherapy is approved for the treatment of colorectal, lung, and, most recently, metastatic breast cancer. Although it was successful in combination with cytotoxic chemotherapy, bevacizumab as a single agent was not effective in the treatment of these cancers. In contrast, two phase II trials of single-agent bevacizumab in relapsed ovarian cancer resulted in response rates of 15.9% and 21%, respectively. The mechanism for this difference is unclear, although it is hypothesized to be due to a greater contribution of VEGF-dependent angiogenesis in relapsed ovarian cancer. The major side effect in one of the studies was gastrointestinal perforation in 11.4% of patients, which is higher than reported in other bevacizumab trials. A phase III trial of bevacizumab or placebo in combination with carboplatin and paclitaxel in newly diagnosed, previously untreated women with stage III or IV ovarian cancer is underway.

Pertuzumab. The human epidermal growth factor family of receptors (HER1/EGFR, HER2, HER 3, and HER4) is widely implicated in tumorogenesis. The HER pathway is involved in the pathogenesis of ovarian cancer. Trastuzumab was tested as a single agent in HER2 over-expressing EOC patients with disappointing results. Pertuzumab is a humanized monoclonal antibody that belongs to a new class of anti-cancer agents known as the HER dimerization inhibitors (HDIs). HDIs block the ability of HER2 to collaborate with other HER receptor family members, leading to downstream growth inhibition and death of the cancer cell. Due to their unique mode of action, this class of anticancer agents has potential activity in tumors that do not over-express HER2. Single-agent pertuzumab was evaluated in heavily pretreated patients with EOC (the median number of prior chemotherapy regimens was five). Tumor biopsies were evaluated for phosphorylation of HER2 (pHER2+) and for HER2 over-expression. Median PFS was 6.6 weeks. PFS improved significantly when pHER2+ patients were compared to those negative for phosphorylation (20.9 weeks vs 5.8 weeks). Phosphorylated HER2 could represent an important predictive marker for this class of agents. Pertuzumab with or without gemcitabine has also been evaluated in a randomized phase II study. The adjusted hazard ratio for PFS was 0.67 in favor of the combination. This may be an active drug for an appropriately selected population of patients with EOC.

Belinostat. Histone deacetylase inhibitors (HDACi) modulate the expression of genes by affecting histone acetylation, thereby regulating chromatin structure and transcription. Vorinostat (brand name Zolinza) is an HDACi approved for the treatment of cutaneous T-cell lymphomas. In preclinical models, belinostat exhibited synergism when combined with carboplatin and paclitaxel. A phase II multicenter trial presented at ASCO in 2008 combined belinostat with carboplatin and paclitaxel in patients with relapsed ovarian cancer. The overall response was 31%, with stable disease documented in 46% of patients.

A majority of the new agents are being tested in patients with the epithelial subtype of ovarian cancer. Belinostat as a single agent was also evaluated in
Cediranib (AZD 2171). Cediranib is a novel oral tyrosine kinase inhibitor. It binds to and inhibits three classes of vascular endothelial growth factor receptors (VEGF-1, 2, and 3), thereby blocking angiogenesis and tumor cell growth. It is also a potent inhibitor of platelet-derived growth factor receptor (PDGFR) and c-kit. Two phase II trials evaluating the role of cediranib in recurrent ovarian cancer have demonstrated efficacy in this patient population.\(^{10,11}\) Toxicities were similar to other tyrosine kinase inhibitors, with fatigue, diarrhea, and hypertension accounting for the majority of those side effects.

Pazopanib. Pazopanib is a potent multikinase inhibitor that blocks tumor growth and inhibits angiogenesis. It is active in renal cell cancer and in early trials of lung cancer. Its efficacy in relapsed ovarian cancer was evaluated in a 35-patient phase II trial.\(^{12}\) The primary end-point was a decrease in blood levels of CA-125, which was used as a marker for response to chemotherapy. Thirty-one percent of patients had a greater than 50% decrease in their levels of CA-125. The median duration of response was close to four months. A phase III study is being planned.

AZD 2281. Lifetime risk estimates of ovarian cancer for women with alterations in the BRCA1 or BRCA2 genes range from 16% to 60%. Patients with these mutations have a defect in their DNA repair mechanism. Poly-ADP ribose polymerase (PARP) is an enzyme involved in the repair of DNA single-strand breaks. A phase I study of the PARP inhibitor AZD 2281 in BRCA-deficient ovarian cancer patients resulted in responses and disease stability.\(^{13}\) There are currently at least five PARP inhibitors in clinical development. This selective targeting of the DNA repair mechanism by PARP inhibitors in tumors with deficiencies in DNA repair genes represents a novel approach to ovarian cancer and other malignancies deficient in BRCA1 and 2.

Afiblercept. Malignant ascites is a significant source of morbidity in patients with EOC. Afiblercept (VEGF Trap) is a potent angiogenesis inhibitor fusion protein. It binds all forms of Vascular Endothelial Growth Factor-A (VEGF-A) and Placental Growth Factor (PLGF). In a pilot study, afiblercept was administered in patients with advanced EOC and symptomatic ascites requiring frequent paracenteses.\(^{14}\) The primary end-point was the repeat paracentesis response rate. Afiblercept was active in prolonging the time to repeat paracentesis. A randomized placebo trial is currently ongoing.

The past decade has seen significant progress in the management of ovarian cancer. New agents have been approved and different routes of drug delivery have proven to be effective (intraperitoneal chemotherapy). However, a lot still needs to be accomplished, especially in the management of platinum refractory and relapsed disease. Recent understanding of molecular and genetic changes impacting tumor growth has led to the development of drugs directed towards specific molecular targets. In the coming years, agents discussed in this article may improve survival and the quality of life in women with ovarian cancer.