Trabectedin May Prolong Ovarian Cancer Survival

BY JANE SALADOF MACNEIL
Senior Editor

Stockholm — Trabectedin, a synthetic version of a compound derived from sea squirts, significantly delayed progression of recurrent ovarian cancer in a large, randomized phase III trial presented at the European Society for Medical Oncology Congress.

When combined with pegylated liposomal doxorubicin (Doxil/Caelyx), the novel drug brought progression-free survival to 7.3 months vs. 5.8 months for a control group treated with pegylated liposomal doxorubicin alone (hazard ratio, 0.79; P = .0190), reported the principal investigator, Dr. Bradley J. Monk of the University of California Irvine Medical Center.

Overall survival results, a secondary end point, were not yet mature, but also suggested the possibility of an advantage with trabectedin (Yondelis). With more than half of 672 women in the trial still alive, overall survival had reached 20.5 months in those given the combination and 19.4 months in the arm that received single-agent care (HR, 0.85; P = .1506).

More patients responded to treatment in the combination arm as well (28% vs. 19%).

Trabectedin is currently approved for treatment of advanced soft-tissue sarcoma in Europe and South Korea. Initially isolated from the marine animal Ecteinascida turbinata, it binds selectively with the minor groove of DNA, and drives cells to apoptosis by interfering with DNA repair and transcription factors.

Two drug companies, PharmaMar, S.A. in Spain and Johnson & Johnson Pharmaceutical Research and Development in the United States, cosponsored the Ova-301 trial. PharmaMar has announced plans to seek European approval for trabectedin in ovarian cancer, and Johnson & Johnson is expected to seek an indication in the United States, according to Dr. Monk, who disclosed receiving honoraria from Johnson & Johnson.

Noting that numerous other agents are under study for ovarian cancer, he extolled trabectedin as the first to succeed in a phase III study. “The list is short in late-stage development, and many of those late trials are negative,” he said in an interview. “To have a study which is actually positive for its primary end point, and to bring a new drug to cancer patients, is a big deal. And that is why we are so excited.”

Investigators at 124 hospitals in 21 countries completed patient enrollment in the trial on May 29, 2007. Participants had to have measurable epithelial ovarian, epithelial fallopian tube, or primary peritoneal cancer that had progressed after six full cycles of therapy or 6 months after front-line therapy. Only patients with one previous platinum-based front-line therapy were included; women given anthracyclines were excluded as were those who progressed during platinum-based front-line therapy. Maintenance or consolidation therapy was allowed.

The study randomized 335 women to 50 mg/m² of pegylated liposomal doxorubicin by 90-minute infusion every 4 weeks and 337 women to the combination regimen: a 90-minute infusion of 30 mg/m² of pegylated liposomal doxorubicin followed by 1.1 mg/m² of trabectedin over 3 hours every 3 weeks. Of these, 330 and 333, respectively, were treated. Premedication with dexamethasone was required in the combination arm of the trial.

The population had a median age of 57 years; more than two-thirds had papillary/serous histology, of which 65% was platinum sensitive based on a platinum-free interval of more than 6 months from first-line therapy. Dr. Monk reported that trabectedin appeared to be more active in women with platinum-sensitive disease, compared with patients who were platinum resistant. More platinum-sensitive patients responded to the combination than to the single agent (37.5% vs. 22.6%; P = .0042), he said. Response rates in platinum-resistant patients were lower and similar (13.4% and 12.2%, respectively).

Progression-free survival in those who did not have a recurrence for at least 6 months after their initial treatment was longer with the combination than with single-agent care (HR 0.73; P = .0170). This same measure was just 4 months and 3.7 months, respectively, in platinum-resistant patients.

Progression-free survival was based on review by an independent radiologist who used RECIST (Response Evaluation Criteria in Solid Tumors). An analysis of grade 3/4 toxicity in treated patients showed less hand and foot syndrome and mucositis/stomatitis but more vomiting, nausea, and febrile neutropenia (8% vs. less than 3%) in the combination arm. More patients had severe neutropenia (52% vs. 36%) and elevated liver enzymes, but Dr. Monk said the latter were transient and mostly resolved without the need for dose reductions. Cardiac disorders were described as uncommon in both arms.

All told, 11% of patients discontinued treatment because of treatment-related adverse events. In all patients, the median number of completed cycles was five.

Discussant Dr. Cristiana Sessa of the National Cancer Institute in Milan, Italy, said preclinical data show trabectedin has a different mechanism of action from previous drugs and antitumor activity in xenografts. It has not shown significant activity in resistant ovarian disease, she said, but may have “a therapeutic index better than standard therapies in partially platinum-sensitive disease.”

Its role in ovarian cancer will be determined by other studies, she suggested. These include trials comparing pegylated liposomal doxorubicin and trabectedin with paclitaxel and carboplatin, and comparing single-agent pegylated liposomal doxorubicin with single-agent trabectedin.

Exenatide/ Metformin Combo Benefits Women With PCOS

BY MIRIAM E. TUCKER
Senior Writer

Rome — Treatment of polycystic ovary syndrome with exenatide plus metformin was more effective than either medication alone in improving menstrual cycle frequency and in ameliorating hormonal and gynecologic complications, according to a study of 60 patients.

The study findings were presented at the annual meeting of the European Association for the Study of Diabetes by Dr. Ted Okerson of Amylin Pharmaceuticals Inc. on behalf of the scheduled presenter, Dr. Rajat Bhushan of the Metabolic Center of Louisiana Research Foundation, Baton Rouge, who was unable to attend the meeting because of a hurricane. Dr. Karen Elkind-Hirsch of the same institution was unable to attend on behalf of the scheduled presenter, Dr. Bradley J. Monk of the University of California Irvine Medical Center.

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