Jazz Pharmaceuticals

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Submitted by:
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NCCN Guidelines Panel: Ovarian Cancer

Dear Sir/Madam,

On behalf of Jazz Pharmaceuticals, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Ovarian Cancer to review the enclosed data for ZEPZELCA™ (lurbinectedin) for the treatment of adult patients with platinum-resistant ovarian cancer.

Specific Changes:

We respectfully request your consideration of the following change:

Principles of Systemic Therapy (Page OV-C 8 of 10)

- Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal Cancer - Recurrence Therapy for Platinum-Resistant Disease
    - Add lurbinectedin as a preferred regimen

FDA Approval: The use of lurbinectedin for the treatment of platinum-resistant ovarian cancer is not an FDA-approved indication and is investigational.

ZEPZELCA is an alkylating drug indicated for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy.[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Rationale:

Patients with platinum-resistant ovarian cancer have limited therapeutic options.[2,3] As a result, the therapeutic aim in platinum-resistant ovarian cancer treatment is palliative control, delaying disease progression, and minimizing toxicities from treatments.[3-5] Our recommendation for the proposed change mentioned above is based on the Phase 3 CORAIL study comparing lurbinectedin versus pegylated liposomal doxorubicin (PLD) or topotecan and a Phase 2 study that investigated the activity of lurbinectedin against platinum resistant/refractory ovarian cancer.

Phase 3 CORAIL Study

The Phase 3 CORAIL study was a multicenter, international, randomized trial that evaluated the safety and efficacy of lurbinectedin, an inhibitor of active transcription, compared to PLD or topotecan in patients with platinum resistant ovarian cancer.[6] Patients included in this study received no more than 3 prior chemotherapy lines, Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2, and had platinum-resistant disease (1-6 months after last platinum-based therapy). In total, 420 patients were randomized 1:1 to receive lurbinectedin 3.2 mg/m^2 once every 3 weeks or the control group of either PLD 50 mg/m^2 once every 4 weeks or topotecan 1.5 mg/m^2/day on Day 1–5 once every 3 weeks. The primary endpoint of interest was Independent Review Committee (IRC) assessed progression free survival (PFS).

Selected secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DoR), investigator-assessed PFS, and safety.

The primary endpoint, IRC-assessed PFS, was not met. No significant differences in median PFS, OS, and ORR, were observed between lurbinectedin and PLD or topotecan.[6] Median IRC assessed PFS was 3.5 months in the lurbinectedin group compared to 3.6 months in the control group. The IRC assessed ORR was 14% and 12.2% in the lurbinectedin and control groups, respectively. Interim OS was 11.2 and 11.1 months, respectively.

Grade 3-4 drug-related adverse events (AE) occurred in fewer patients in the lurbinectedin group compared to patients in the control group (48% vs 64%; p=0.0010).[6] Treatment delays and dose reductions were also significantly more common in the control arm (37% of patients vs. 26% of patients with lurbinectedin for delays; 38% of patients vs 17% of patients with lurbinectedin for reductions). The most common Grade 3 and 4 laboratory abnormalities in lurbinectedin arm were anemia (16%), neutropenia (30%), and thrombocytopenia (9%). In the control group, Grade 3 and 4 anemia, neutropenia, and thrombocytopenia occurred in 26%, 39%, and 16%, respectively.

Phase 2 Study of Lurbinectedin Compared to Topotecan

A Phase 2 two-stage study evaluated the use of lurbinectedin in patients with platinum-resistant or platinum-refractory ovarian cancer.[7] Eligible patients had less than 3 prior lines of cytotoxic-containing chemotherapy, ECOG PS ≤2, and platinum-resistant (<6 months after last platinum-based therapy) or platinum-refractory (disease that did not respond during last platinum-based therapy) disease. The primary outcome of interest was ORR.

In the exploratory, single-arm first stage of the trial, 22 patients received lurbinectedin at a fixed flat dose of 7 mg once every 3 weeks.[7] In stage 2 of the study, patients were randomized to the same lurbinectedin regimen from the first stage (n=30) or topotecan 4–2.4 mg/m^2 on Day 1, 8 and 15 every 4 weeks or 1.5–0.75 mg/m^2 on Day 1–5 every 3 weeks (n=29). Seven patients in the first stage and 5 patients in the second stage had confirmed responses from lurbinectedin treatment. The ORR for lurbinectedin (n=52) was 23% (95% CI, 13%-37%), including 1 (2%) complete response and 11 (21%) partial response. Median DoR was 4.6 months (95% CI, 2.5-6.9 months) and was ≥6 months for 23% (95% CI, 0-51%) of those who responded. No responses were observed in the 29 patients treated with topotecan. In stage 2 of the study, median PFS was longer with lurbinectedin compared to topotecan (3.9 months vs 2 months; p=0.0067). In addition, median OS was 9.7 months with lurbinectedin and 8.5 months with topotecan.

The most frequent AE reported for lurbinectedin was myelosuppression, including Grades 3/4 neutropenia (85%) and Grades 3/4 thromboctyopenia (33%).[7] Febrile neutropenia occurred in 11 (21%) patients receiving lurbinectedin and 3 (10%) patients receiving topotecan. The most common non-hematological AEs for lurbinectedin include fatigue (77%), nausea (67%), and vomiting (54%).

We appreciate your consideration of the data we are submitting for ZEPZELCA.

Sincerely,

Francois Di Trapani

References (enclosed):

1. ZEPZELCA (lurbinectedin). Prescribing Information. Jazz Pharmaceuticals, Inc. Palo Alto, CA.
2. Oronsky B, Ray CM, Spira AI, Trepel JB, Carter CA, Cottrill HM. A brief review of the management of platinum-resistant-platinum-refractory ovarian cancer. Med Oncol. 2017;34(6):103.

3. Pujade-Lauraine E, Banerjee S, Pignata S. Management of Platinum-Resistant, Relapsed Epithelial Ovarian Cancer and New Drug Perspectives. J Clin Oncol. 2019;37(27):2437-2448.
4. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial [published correction appears in J Clin Oncol. 2014 Dec 10;32(35):4025]. *J Clin Oncol*. 2014;32(13):1302-1308.
5. Wilson MK, Pujade-Lauraine E, Aoki D, et al. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: recurrent disease. *Ann Oncol*. 2017;28(4):727-732.
6. Gaillard S, Oaknin A, Ray-Coquard IL, et al. Phase III trial of lurbinectedin versus PLD or topotecan in platinum-resistant ovarian cancer patients: results of the CORAIL trial. Oral Presentation at the European Society of Medical Oncology 2018 Congress; October 19 – 23, 2018; Munich, Germany.
7. Poveda A, del Campo JM, Ray-Coquard I, et al. Phase II randomized study of PM01183 versus topotecan in patients with platinum-resistant/refractory advanced ovarian cancer. *Ann Oncol*. 2017;28(6):1280-1287.