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February 04, 2020

Kristina Gregory
3025 Chemical Road
Plymouth Meeting, PA 19462
USA

Dear Ms. Gregory,

Please consider the following information.

Response(s):

- YONDELIS - NCCN Communication - February 2020

I look forward to working with you as you consider the enclosed information. The information provided is not intended as an endorsement of any usage not contained in the Prescribing Information. For complete information, please refer to the full Prescribing Information, including the following sections: INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS.

If you require further information, please feel free to contact me via the Janssen Medical Information Center at 1-800-JANSSEN (1-800-526-7736).

Sincerely,

Cynthia Toso

Cynthia Toso, PharmD

Associate Director
Medical Information

Inquiry #:01629081

Enclosure(s)/Electronic Link(s):

- YONDELIS® (trabectedin) Prescribing Information at https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-32e706f2-400f-4587-bcb4-6bc2b502f3bb
- Monk BJ et al. Gynecologic Oncology 2020
- YONDELIS Prescribing Information

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YONDELIS® (trabectedin)
NCCN Compendium Communication – February 2020

February 4, 2020

Name: Cynthia Toso, PharmD
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Date of request: February 4, 2020
NCCN Guidelines® Panel: Ovarian Cancer

Dear NCCN,

On behalf of Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® Ovarian Cancer Panel review the enclosed efficacy and safety outcomes from a prespecified subgroup analysis based on germline *BRCA*1/2 mutation status and platinum-free interval (PFI) of 6-12 months from OVC-3006, a phase 3, randomized, open-label trial comparing trabectedin (T) plus pegylated liposomal doxorubicin (PLD) versus PLD alone for the treatment of advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer.[1] Included as supporting material are two exploratory analyses based on OVA-301, a phase 3 randomized open-label trial comparing T+PLD versus PLD alone in relapsed ovarian cancer (ROC) examining partially platinum-sensitive (PFI 6-12 months) and germline *BRCA1* subpopulations.[2-4]

As per our prior communication dated February 7, 2018, due to an interim analysis exceeding the futility threshold for overall survival (OS) and higher observed rates of adverse events among patients treated with T+PLD, the OVC-3006 study was discontinued in December 2017 based on the recommendation of an independent data monitoring committee (IDMC). However, prespecified subgroup analyses demonstrated significantly improved outcomes in patients with germline *BRCA*1/2 mutation and/or partially platinum-sensitive disease, as included within this submission.[1]

Specific Change: We request an update to the Guidelines to include trabectedin (1) in combination with pegylated liposomal doxorubicin as an acceptable therapy for recurrent epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer in partially platinum-sensitive patients (PFI 6-12 months) who have progressed after first-line platinum-based chemotherapy and are not candidates for subsequent platinum-based therapy; and (2) in patients with *BRCA*1/2 mutations who have failed two prior lines of platinum-based chemotherapy (OV-C 6 of 9, Version 3.2019).

FDA Clearance: YONDELIS® (trabectedin) is approved for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.[5]

The data presented in this communication for recurrent ovarian cancer are considered off-label and non-registrational data.

Rationale: The efficacy of T+ PLD was previously demonstrated in a randomized phase 3 study (OVA301) where an improvement in median progression-free survival (PFS) was observed in comparison to PLD alone in patients with ROC who had progressed after first-line platinum-based chemotherapy (hazard ratio [HR]=0.79; 95% confidence interval [CI]: 0.65-0.96; *P*=.0190).[2] In an exploratory analysis, patients with partially platinum-sensitive disease (PFI for 6-12 months) showed improved OS with T+PLD versus PLD alone (median OS: 22.4 vs 16.4 months, HR=0.64; 95% CI: 0.47-0.86; *P*=0.0027).[6] In patients with germline *BRCA1* mutations, T+PLD demonstrated improved PFS and OS compared to PLD alone (median PFS: 13.5 vs 5.5 months, *P*=0.0002; median OS: 23.8 vs 12.5 months, *P*=0.0086).[4]

Given the demonstrated efficacy from the OVA-301 study,[2] a randomized multicenter, global phase 3 registration study, OVC-3006, was carried out to evaluate the efficacy and safety of T+PLD therapy in the third-line setting in patients with advanced-relapsed ovarian cancer who had previously responded to platinum-based therapies in the first- and second-line settings. The primary endpoint was OS and secondary endpoints included investigator-assessed PFS and objective response rates (ORR).[1] From the OVA-301 sub-analyses[3, 4] and trabectedin's mechanism of action which supports synergism with damaged DNA repair processes,[7, 8] patients were stratified by (1) time from last dose of first-line platinum therapy to disease progression, (2) *BRCA1/2* germline mutational status, (3) prior PLD therapy, and (4) ECOG grade 0 or 1 at the time of randomization.[1]

By the time of study discontinuation, 576 patients had been randomized (T+PLD, n=289; PLD, n=287). Median OS was 23.82 months with T+PLD vs 22.21 months with PLD (HR=0.92; 95% CI:0.73-1.18; *P*=0.524). Median PFS was 7.52 vs 7.26 months (HR=0.93, 95% CI:0.76-1.15; *P*=0.517) for T+PLD vs PLD alone. The ORR was 46% vs 35.9% (OR:1.52, 95% CI:1.07-2.16; *P*=0.014) for T+PLD vs PLD alone.[1]

Serious treatment-related adverse events (AEs) occurred in 41.3% of patients in the T+PLD group versus 20.6% in the PLD monotherapy group. Drug-related grade 3/4 AEs and AEs of special interest (ALT/AST increase and febrile neutropenia) occurred more frequently with T+PLD compared to PLD monotherapy. The incidence of grade 3-4 neutropenia was higher in the T+PLD group (43.4%) versus PLD monotherapy (20.9%).[1]

For patients pre-stratified by having *BRCA1/2* mutations, the median OS was 34.2 months with T+PLD versus 20.9 months with PLD alone (HR=0.54; 95% CI:0.33-0.90; *P*=0.016). Correspondingly, the median PFS was 10.1 months for T+PLD versus 7.6 months with PLD (HR=0.72; 95% CI:0.48-1.08; *P*=0.039).[1] This is aligned with a recent Phase 3 study in similar patients with *BRCA*-mutated ROC.[9]

For patients pre-stratified by having a PFI of 6-12 months, the median OS was 24.8 months for T+PLD versus 17.4 months with PLD (HR=0.69; 95% CI: 0.48-1.01; *P*=0.056) while a 28.5% reduction in the risk of disease progression or death was observed (HR=0.71; 95% CI: 0.52–0.99; *P*=0.039). Correspondingly, patients with both a *BRCA1*/2 mutation and a PFI of 6-12 months, a 52.8% reduction in risk of disease progression or death was observed in the T+PLD group compared with patients on PLD monotherapy (HR=0.47; 95% CI: 0.25-0.87; *P*=0.014). Lastly, patients with both a *BRCA1*/2 mutation and PFI of 6-12 months had a 62.6% reduction in the risk of death with T+PLD compared with PLD alone (HR=0.37; 95% CI: 0.17-0.82; P=0.011). For patients stratified by prior PLD therapies, T+PLD versus PLD alone did not appear to impact OS, PFS or ORR.[1]

The following article is submitted in support of this proposed change:

- Monk BJ, Herzog TJ, Wang G, et al. A phase 3 randomized, open-label, multicenter trial for safety and efficacy of combined trabectedin and pegylated liposomal doxorubicin therapy for recurrent ovarian cancer [published online ahead of print January 13, 2020]. *Gynecol Oncol*. doi:10.1016/j.ygyno.2019.12.043

Sincerely,

Cindy Toso, PharmD
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Janssen Scientific Affairs, LLC

REFERENCES

1. Monk BJ, Herzog TJ, Wang G, et al. A phase 3 randomized, open-label, multicenter trail for safety and efficacy of combined trabectedin and pegylated liposomal doxorubicin therapy for recurrent ovarian cancer [published online ahead of print January 13, 2020]. *Gynecol Oncol*. doi:10.1016/j.ygyno.2019.12.043.
2. Monk BJ, Herzog TJ, Kaye SB, et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. *J Clin Oncol*. 2010;28(19):3107-3114.
3. Poveda A, Vergote I, Tjulandin S, et al. Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer: outcomes in the partially platinum-sensitive (platinum-free interval 6-12 months) subpopulation of OVA-301 phase III randomized trial. *Ann Oncol*. 2011;22(1):39-48.
4. Monk BJ, Ghatage P, Parekh T, et al. Effect of BRCA1 and XPG mutations on treatment response to trabectedin and pegylated liposomal doxorubicin in patients with advanced ovarian cancer: exploratory analysis of the phase 3 OVA-301 study. *Ann Oncol*. 2015;26(5):914-915.
5. YONDELIS (trabectedin) [Prescribing Information]. Horsham, PA: Janssen Products, LP; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-32e706f2-400f-4587-bcb4-6bc2b502f3bb.
6. Monk BJ, Herzog TJ, Kaye SB, et al. Trabectedin plus pegylated liposomal doxorubicin (PLD) versus PLD in recurrent ovarian cancer: overall survival analysis. *Eur J Cancer*. 2012;48(15):2361-2368.
7. Takahashi N, Li WW, Banerjee D, et al. Sequence-dependent enhancement of cytotoxicity produced by ecteinascidin 743 (ET-743) with doxorubicin or paclitaxel in soft tissue sarcoma cells. *Clin Cancer Res*. 2001;7(10):3251-3257.
8. Meco D, Colombo T, Ubezio P, et al. Effective combination of ET-743 and doxorubicin in sarcoma: preclinical studies. *Cancer Chemother Pharmacol*. 2003;52:131-138.
9. Penson RT, Valencia RV, Cibula D, et al. Olaparib monotherapy versus chemotherapy for germline BRCA-mutated platinum-sensitive relapsed ovarian cancer patients: phase III SOLO3 trial. Oral Presentation presented at: 2019 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31 - June 4, 2019; Chicago, IL.