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Optimising the treatment of the partially platinum-sensitive relapsed ovarian cancer patient

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ABSTRACT

The choice of second-line chemotherapy in patients with recurrent ovarian cancer (ROC) is complex, with several factors to be considered, the most important of which is the length of the platinum-free treatment interval (PFI). Recently ROC patients have been further stratified into platinum sensitive (PS), partially platinum sensitive (PPS) and platinum resistant (PR) subgroups depending on the length of the PFI. Response to second-line therapy, progression-free survival (PFS) and overall survival (OS) are linked to the PFI, all of them improving as the PFI increases. Consequently, there is increasing interest in PFI extension strategies with platinum-free therapeutic options. Such strategies are currently being studied in patients with partially platinum-sensitive disease (PFI 6-12 months), as the treatment of these patients remains clinically challenging. A non-platinum option, trabectedin + pegylated liposomal doxorubicin (PLD) combination, has been evaluated in ROC patients in the pivotal phase III OVA-301 study. The OVA-301 study differed from previous trials in the same setting as it included only patients who were not expected to benefit from or who were ineligible for or who were unwilling to receive re-treatment with platinum-based chemotherapy, including those with PPS and PR disease. Subset analysis of patients with PPS disease in OVA-301 showed that the trabectedin + PLD combination significantly improved PFS compared with PLD alone; median PFS 7.4 versus 5.5 months, p=0.0152. Final survival data from the same subset of patients, showed that trabectedin + PLD also achieved a significant 36% decrease in the risk of death compared with PLD alone (HR=0.64; 95% CI, 0.47–0.88; p=0.0027). Median overall survival (OS) was 22.4 months in the trabectedin + PLD arm versus 16.4 months in the PLD arm. This represents a statistically significant 6-month improvement in median OS in patients treated with trabectedin + PLD compared to those treated with PLD alone.

Stratification of ROC patients according to length of PFI to tailor therapeutic strategies at relapse

The majority (approximately 80%) of patients with ovarian cancer will relapse, with a median progression-free survival (PFS) of 18 months, and require second-line therapy. Further treatment of these patients is complex with several factors to be considered, including the length of the platinum-free interval (PFI) [1].

The stratification of the ROC patient population into different subgroups by PFI (≤4 weeks and <6 months, 6-12 months and >12 months) is important for defining specific therapeutic

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Box 1 – Identifiable subgroups within the ROC patient population [2]

Classifications:

- Platinum sensitive (PS) disease: PFI >12 months
- Partially platinum sensitive (PPS) disease: PFI 6 – 12 months
- Platinum resistant (PR) disease: PFI < 6 months
- (Refractory disease: disease progression while receiving the last line of platinum therapy or within 4 weeks of the last platinum dose)

approaches (Box 1). Clinical studies up until this point have classified relapsing patients as having either platinum-sensitive or platinum-resistant disease.

Rationale for platinum intercalation in PPS patients

Response to second-line therapy and prognosis are linked to the PFI, with both improving as the PFI increases [3,4]. PFI is the most important predictive factor for response to platinum retreatment and the most important prognostic factor for PFS and overall survival (OS) [3,5,6].

As a result, there is increasing interest in PFI extension strategies, including platinum-free therapeutic options. Studies evaluating PFI extension strategies with non-platinum drug regimens have shown pegylated liposomal doxorubicin (PLD) to have equivalent efficacy and less toxicity compared with paclitaxel or topotecan, in patients relapsing after 6 months (PLD vs. topotecan: n=122; HR=1.58; p=0.021); however, until recently, relatively few studies report separate data for the PPS patient population, and the majority of these data are from unplanned retrospective subset analyses [7,8].

The clinical management and optimal treatment of the partially platinum-sensitive subgroup of ROC patients continues to present challenges [4]. Approximately 20% of patients with ROC will relapse within the 6-12 month period. *In vitro* and clinical data suggest that extending the PFI in patients with relapsed PPS ovarian cancer through intercalation of a non-platinum therapy before continuing platinum-based regimens at disease progression could be clinically beneficial [9]. In this clinical setting, the potential benefit of artificially prolonging the PFI has been evaluated in several studies, with data suggesting that extending the PFI may restore platinum sensitivity and lead to clinical responses or stable disease with platinum retreatment, even in heavily pre-treated patients [4,7]. PLD has been included in the National Institute for Health and Care Excellence (NICE) recommendations as a non-platinum treatment option for patients with partially platinum-sensitive disease [10]. A head-to-head randomised study has since proven that the trabectedin + PLD combination is superior to PLD alone. As a result, this guidance is subject to an ongoing NICE appraisal (ROC MTA222/91).

Trabectedin + PLD provides one opportunity for prolonging the platinum-free interval

Trabectedin (Yondelis®), a marine derived anti-neoplastic agent, has been shown to have clinical benefit in patients with ROC. Trabectedin was initially isolated from the tunicate *Ecteinascidia turbinata* and is currently produced synthetically. It was first approved in 2007 within the European Union as monotherapy for the treatment of patients with advanced soft tissue sarcoma (STS). Trabectedin is indicated for the treatment of adult patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents [11].

In patients with relapsed, platinum-sensitive ovarian cancer trabectedin was approved in combination with PLD in 2009. Early phase II trials showed encouraging activity as a single agent in patients with relapsed ovarian cancer, particularly with platinum sensitive disease, and a large,

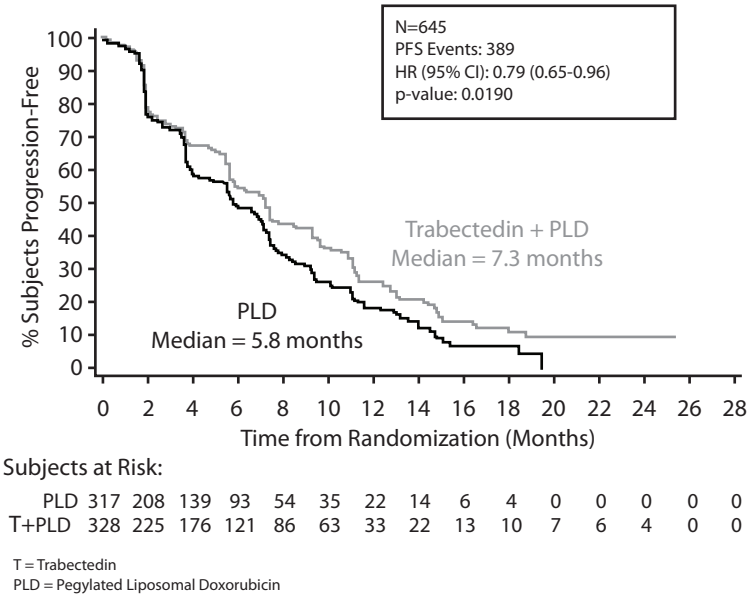

Fig. 1 – OVA-301: PFS final analysis. Final analysis of progression-free survival in OVA-301by independent radiology [12].