Abstract #51

Title: A phase I/II study of chemo-immunotherapy with durvalumab (durva) and pegylated liposomal doxorubicin (PLD) in platinum-resistant recurrent ovarian cancer (PROC): Genomic sequencing and updated efficacy results

Objective: The objectives of this study, where durvalumab (durva, an anti-PD-L1 antibody) is added to pegylated liposomal doxorubin (PLD), standard therapy for platinum-resistant ovarian cancer (PROC), are to evaluate the efficacy and safety of the combination and to identify genomic characteristics associated with response and progression-free survival (PFS).

Method: This is a phase I/II, multicenter, single-arm, open-label study (NCT02431559). PLD is reported to have a 6-month PFS (PFS6) of 25%. The null hypothesis of PFS6 ≤ 25% was tested against the alternative hypothesis at 0.05 level using 90% 2-sided CI; the primary endpoint, PFS6, was reported at ESMO 2018. Exom sequencing was done on PBMCs and tumor samples at baseline. Updated efficacy and DNA sequencing results are provided.

Results: In phase II, 40 patients (median age 65 years [32–83] years) each received at least 1 dose of the study drug (PLD 40 mg/m^2 + durva 1,500 mg every 4 weeks IV). PFS6 by RECIST1.1 was 47.7% (per protocol *n* = 36, 90% CI 33.1–60.9) and 42.9% (ITT *n* = 40, 90% CI 27–57.8). Response rate (ORR) was 22.5% (90% CI 10.8–38.5, 4 CR, 5 PR); median PFS was 5.5 (0.3 to 28.8+) months; and median overall survival was 17.6 (1.7 to 32.5+) months. Treatment-related adverse events ≥ grade 3 in ≥2 patients were palmar-plantar erythrodysesthesia syndrome/rash (27.5%), stomatitis (10%), lymph count decrease (10%), lipase increase (5%), and anemia (5%). Exom sequencing data are available for 28 of 40 patients. No patient had *BRCA1*/*BRCA2* mutation; 3 patients had hypermutated non-MSI phenotypes. Analysis of copy numbers found multiple potential mechanisms for resistance to the PLD + durva combo. Deletions of LRP1B were previously shown to drive resistance to PLD. We also found that PFS (*P* = 0.0016) for patients on PLD + durva negatively correlated with LRP1B deletions. Patients with MYC amplifications had a lower response (*P* = 0.0005) and shorter PFS (*P* = 0.006, HR = 2.889) on the PLD + durva combination. In the TCGA ovarian cancer dataset, MYC amplification is linked to overexpression of IDO1, CXCL17, CXCL11, suggesting a unique immune suppressive microenvironment driven by MYC amplifications. Additional analyses including *BRCA* mutation are ongoing and will be presented.

Conclusion: The PLD + durva combination has a tolerable safety profile and promising efficacy. The study met its primary endpoint with improvement in PFS6. We confirm the negative impact of LRP1B deletions on PLD-based therapies. MYC amplification may be central in driving resistance to the combination and has not been previously linked to PLD efficacy.

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