Aim: In the collaborative Euro-EWING99 study (EE99), Ewing sarcoma patients (EW pts) received vincristine ifosfamide doxorubicin etoposide induction (VIDE); maintenance treatment was stratified by initial staging and histological response. We conducted a genome-wide association study (GWAS) to identify Single Nucleotide Polymorphisms (SNPs) which may influence efficacy outcomes.

Methods: 289/807 French pts registered in EE99 before 2010 were genotyped for 598,821 SNPs. Association of each SNP with poor histological response to VIDE (>10% viable cells) was assessed by logistic regression adjusted for age, gender and the first two eigenvectors to correct for population stratification. Three genetic models were tested: additive, dominant and recessive. Multivariate Cox models were used to test for association with progression-free and overall survival (PFS, OS). To account for multiple comparisons, we set the p-value threshold for significant associations at $5 \times 10^{-7}$.

Results: After quality control, 277 pts (median age 14.7y [0.5; 48.4]; 96/277 metastatic; median follow-up 6.9y) and 561,924 SNPs are included in the analysis. 146/194 pts operated after VIDE induction were good responders. We detected no genome-wide significant association with histological response. The lowest p-value was obtained for SNP rs2247119 (OR=4.5 [95%CI 2.4; 8.3] p=2.10$^{-6}$, additive model) located in the PHF11 gene (transcription factor). An association between PHF11 down-regulation through hypermethylation in EW samples and poor prognosis has been described (Alholle 2013). Two SNPs were associated with PFS: rs4653137 (chr 1, KIAA0319L gene, HR=3.9 [2.3; 6.6] p=3.10$^{-7}$) and rs9489215 (chr 6, DCBLD1 gene, HR=2.3 [1.6; 3.2] p=1.10$^{-7}$). DBCLD1 has been found associated with poor prognosis in small cell lung cancer (Han 2014). These 2 SNPs were not significantly associated with OS (p=1.10$^{-5}$ and 2.10$^{-5}$), unlike SNP rs3781854 (chr 11, ELP4 gene, HR=2.5 [1.8; 3.6] p=6.10$^{-7}$).

Conclusions: The GWAS study showed weak signals of association with treatment efficacy in EW. Further studies are needed to validate these associations, and explore the mechanisms and clinical utility of these variants.

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