genitourinary tumours, non-prostate

**Aim:** Cabazitaxel (Cab) is a novel tubulin-binding taxane active in preclinical models against docetaxel-sensitive and resistant tumors. Cab is approved for the treatment of metastatic castration resistant prostate cancer (mCRPC) after docetaxel failure; however, its activity against other cancers remains unexplored. SOGUG 2011-04 is a phase II clinical trial designed to explore the efficacy of Cab in advanced genitourinary TCC after progression to a platinum-based regime. As part of this trial, a pharmacogenetic study to identify single-nucleotide polymorphisms (SNPs) predictive of Cab toxicity and response was conducted.

**Methods:** DNA was extracted from blood samples from 45 patients in this trial. Nine key SNPs in genes involved in the pharmacokinetic and pharmacodynamic pathways of Cab (CYP3A4 rs35599367; CYP3A5 rs776746; CYP2C8 rs11572080 and rs1113129; ABCB1 rs1045642, rs1128503 and rs2032582; TUBB1 rs6070697 and rs463312) were genotyped using standard techniques. Logistic regression was used to study toxicity and response, and Cox regression to analyze progression free survival (PFS) and overall survival (OS), using an additive genetic model. Preliminary results are presented.

**Results:** CYP3A5 rs776746 (splicing defect) protected against gastrointestinal (GI) toxicity (OR = 0.06, 95%CI = 0.007-0.63, P = 0.018) and was associated with reduced PFS (HR = 4.4, 95%CI = 1.6-11.7, P = 0.0032). Adjusting for patient prognosis, according to Bellmunt’s classification, did not change the results. Furthermore ABCB1 rs1045642, rs1128503 and rs2032582 were associated with the total number of Grade 3-4 toxicity events (P values of 0.009, 0.041, and 0.043, respectively, multivariable analysis). TUBB1 Q43P missense polymorphism was associated with reduced OS (P = 0.0023) although only three patients carried this variant.

**Conclusions:** Polymorphisms in CYP3A5 may define a subset of patients with decreased Cab activity resulting in less GI adverse events and shorter PFS. Additionally, variation in ABCB1 may be associated with the severity of Cab toxicity. These results need to be validated in larger and independent series but suggest potential markers for Cab treatment optimization. *This study has been supported by an unrestricted educational grant of Sanofi-Aventis to the Spanish GU Oncology Group (SOGUG)*

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