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Immunogenicity and clinical activity of Tipapkinogen sovacivec (TG4001), an HPV-16 cancer vaccine: a randomized phase 2 study in recurrent or metastatic (R/M) anogenital cancers

Background: Human papillomavirus 16 (HPV-16) infection is associated with several cancer types with limited treatment options in the locally R/M settings. Furthermore, immune checkpoint inhibitors have limited activity against advanced HPV-cancers. TG4001 is a viral vector vaccine targeting HPV E6 and E7 antigens. We have previously shown in a single-arm, dose finding phase 1 study that TG4001 combined with PD-L1 blockade using avelumab was safe and associated with a response rate of 22%. Herein we report preliminary data on immunogenicity and clinical activity of TG4001 in a randomized phase 2 study comparing TG4001 plus avelumab versus avelumab alone.

Methods: Eligibility criteria: R/M HPV16+ anogenital cancer including cervical, vulvar, vaginal, penile, and anal cancers; immunotherapy naïve and with no more than one prior line of chemotherapy. HPV-16 positivity was required and centrally determined using a PCR based assay. Patients were randomly assigned 1:1 to receive either TG4001 plus avelumab (Vaccine arm) or avelumab alone. Randomization was stratified by tumor type (cervical, anal, genital). TG4001 was administered *s.c* at $5 \cdot 10^7$ pfu, Q1w for 5 weeks, then Q2w until month 6 followed by Q12w until progressive disease and avelumab *i.v at* 800 mg Q2w until progressive disease. PBMC were collected at baseline, day 43 and day 85 to assess T-cell responses against E6 and E7 antigens using ex-vivo IFNg ELISPOT and immunophenotyping of circulating T cells. Vaccine immune response (IR) was defined as onset of a new T-cell response against either antigen or amplification of a pre-existing response under treatment. Tumor response was assessed using RECIST 1.1.

Results: 59 pts had been randomized by the time of data cut-off. IR was assessed in 24 pts in the vaccine arm and 16 pts in the avelumab arm. T cells against E6 or E7 antigens at baseline were rare with only 4 pts having a low intensity ELISPOT readout against either target prior to initiation of treatment. 11/24 pts in the vaccine arm had an IR, while none of the patients in the avelumab arm had an IR. Occurrence of IR was detected at day 43 and tended to gain in intensity at D85. In the vaccine arm, IR was associated with tumor response with 3 clinical responders among 11 pts with positive IR versus 1 response observed among the 13 patients without IR. Conversely, only 2 progressive disease pts among 11 positive IR compared favorably to the 6/13 vaccine arm pts with no IR. Remarkably, a complete clinical response was observed in a vaccine treated pt exhibiting the strongest E6 and E7 IR.

Conclusions: TG4001 can induce a de novo immune response against HPV-16 antigens E6 and E7 in advanced HPV-16 cancers. The data suggest that these IRs are associated with anti-tumor response and that TG4001 vaccination in combination with ICI has the potential to drive clinical benefit in R/M anogenital cancers.