Background Defective DNA mismatch repair (dMMR) leads to high levels of microsatellite-instability (MSI-H) and insertions or deletions in coding regions, resulting in the generation of tumor-specific frameshift peptides (FSPs). We selected 209 shared FSPs among subjects with first- or second-line metastatic dMMR/MSI-H colorectal (CRC), gastric, and gastroesophageal junction (GEJ) cancers, to develop an off-the-shelf vaccine for the treatment of dMMR/MSI-H tumors. Selected FSPs were cloned into four proprietary Great Apes Adenoviral (GAd) and four Modified Vaccinia Ankara (MVA) vectors to generate a polyvalent viral vectored vaccine called Nous-209 [Leoni G., et al., Cancer Res. 2020]

Methods This phase 1 first in human (FIH) study (NCT04041310) was designed to evaluate safety and tolerability of two dose levels (one log difference for both GAd and MVA) of Nous-209 genetic polyvalent vaccine in combination with the programmed death receptor-1 (PD-1)-blocking antibody pembrolizumab, to assess immunogenicity of the combination and to detect preliminary evidence of anti-tumor activity. Nous-209 is administered intramuscularly, concomitantly with pembrolizumab (doses and schedule per approved label): one prime (GAd-209-FSP) at the 2nd pembrolizumab infusion and three booster (MVA-209-FSP) injections at subsequent infusions each 3 weeks apart. The study is composed of two sequential cohorts: dose escalation and dose expansion

Results Twelve evaluable subjects with first- or second-line metastatic dMMR/MSI-H cancers were evaluated as of May 28, 2021. Three subjects enrolled in dose level 1 (2 CRC and 1 GEJ cancer) demonstrated durable confirmed partial responses (PRs). In dose level 2 (6 CRC and 3 gastric cancers), 4 subjects had PRs, 2 had stable disease (SD) and 3 had progressive disease (PD). The median follow-up for subjects in dose level 1 is 17.9 months (range 15.3–20 months), and 8 months (range 3.8–12.5 months) for subjects in dose level 2 as of the above cut-off date. No dose limiting toxicities (DLTs) were observed, and the treatment combination was determined to be safe and tolerable. Vaccine immunogenicity was demonstrated by ex-vivo interferon-gamma ELISpot assay in 67% of subjects in dose level 1, and 100% of patients with evaluable samples in dose level 2

Conclusions The combination of the Nous-209 genetic polyvalent cancer vaccine and pembrolizumab has been demonstrated to be safe, immunogenic, and continues to show early signs of clinical efficacy, which may be attributed to the vaccine contribution

REFERENCE