PTU-109

ERADICATION OF METASTATIC GASTRIC CA OF THE ANTRUM RESISTANT TO TRASTUZUMAB AND CETUXIMAB FOLLOWING IMMUNOCHEMOGENE TREATMENT WITH SV-IV, A STEALTH NANOPARTICLE FORMULATION COMPOSED OF CLAMP PNA AGAINST MRNA OF SGCA1/B1, DOCETAXEL, AND MUC1 CHIMERIC MAB

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Introduction The unmet medical need for metastatic gastric Ca of the antrum is very high because of potent chemoresistance. We aim to circumvent these resistant factors.

Methods We obtained surgically tumour cells from patients with stage IV gastric Ca overexpressing MUC1, sGC heterodimer a1b1, and bcl-2. We synthesised 6 mer homopyrimidine triplex ((PNA)₂/RNA) hybridised to the 5' end (Leader), and 10 mer purine/pyrimidine duplex (PNA/RNA) hybridised to the 3'-end (Trailer) of the AUG start codon region on the mRNA of sGCa1/b1. ClampPNA anti-sGCa1/b1 was incorporated in the polar phase, and docetaxel was entrapped in the lipid phase,

which was surrounded by the stealth polymer layer, and biological recognition layer with linked chimeric MAbs against MUC1 of a nanoparticle formulation (SV-IV), with which we treated xenograft animal models developed from gastric Ca cells obtained from the stage IV patients.

Results Post-treatment, we observed that downregulated MUC1 blocked binding of TKIs, such as cetuximab and trastuzumab, by inhibiting direct steric hindrance onto HER2 and EGFR via the MUC1 cytoplasmic tail. MUC1 phosphorylation was inhibited, blocking Ras/Raf/(Mek)Erk1/2/MAPK, PI3K/AKT, VEGF and MMP-2. The clamp PNA hybridised to the leader, and trailer region of the AUG start codon region on mRNA sGC forming Watson-crick double helices, which inhibited sGCα1/b1 and nitric oxide inducing p53-indept apoptosis or type I PCD. Inhibition of B-Raf, downregulated VEGFR-1-2-3, PDGFR-β, FIR-3, FGFR-1 and upregulated p21CIP1, p16INK4a, and p27KIP1. Downregulation of ERK1/2 blocked angiogenesis and lymphangiogenesis. RIN, TSC2, PTEN were upregulated, and PI3K/AKT/mTOR pathway was blocked. Inhibition of eIF4E led to strong autocrine/paracrine downregulation, inducing apoptosis. Docetaxel phosphorylated bcl-2 releasing beclin-1, which with upregulated BIM induced caspase-indept type II PCD or autophagy.

Conclusion Administration of immunochemogene formulation SV-IV eradicated metastatic gastric Ca of the antrum after circumvention of chemoresistance.

Competing interests None.

Keywords gastric Ca, clampPNA, antiMUC1, trastuzumab, cetuximab, nanomedicine, PCD.