Translational relevance of the combined treatment PARP inhibitors and AsiDNA in homologous recombination proficient tumors

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PARP inhibitors (PARPi) have shown significant benefits in cancer patients with deficient homologous recombination repair (HRD; induced by *BRCA* mutations for example). However, they show no or very limited efficacy in tumors with active or proficient homologous recombination repair (HRP). In the current study, we propose a novel therapeutic strategy, based on drug combination to achieve synthetic lethality independently of the tumor genetics.

AsiDNA^{TM} is a double-strand DNA molecule that mimics endogenous DNA breaks to interfere with the DNA damage (DD) response. This decoy agonist molecule induces a false DD signaling through DNA-PK over-activation, and thus hijacks several DNA repair proteins from sites of real DD. We analyzed the effects of AsiDNA treatment on double strand break repair activities through homologous recombination and assessed the efficacy of the combination with PARPi (Olaparib and Talazoparib) in HRP tumor models.

The AsiDNA-induced false damage signaling abrogated the HR repair through a “bluring” effect which limited the efficient recruitment of HR proteins (BRCA1, RAD51) to sites of PARPi-induced double-strand DNA breaks. The combined treatment induced a drug-driven synthetic lethality which was specific to tumor cells and is not observed in non-tumor cells predicting a good safety of the association. The AsiDNA-induced functional HRD was confirmed in different tumor models (breast, ovarian and prostate cancer cells) and is driven for at least one to two weeks after AsiDNA treatment, paving the way for a more appropriate patient-friendly treatment schedule. This concept was also validated in patient biopsies from DRIIV-1a clinical trial, where AsiDNA-treated tumors for three weeks showed clear tendency to switch from HRP to HRD. In addition to primary HRP tumors intrinsically resistant to

PARPi, AsiDNA also sensitized *de novo* HRP tumors, that evolved from HRD to HRP under PARPi treatment pressure, through the restoration of the HR pathway.

These results point to the therapeutic opportunity of combining AsiDNA and PARPi in HRP tumors to overcome intrinsic or acquired resistance in clinical situation.