Background Hormone receptor (HR)+ breast cancer is a cold tumor that responds poorly to immune checkpoint blockers targeting PD-1, calling for the development of therapeutic strategies that inflame the HR+ tumor microenvironment to restore PD-1 sensitivity. OX425 is a second-generation poly(ADP)-ribose polymerase 1 (PARP1)-targeting decoy oligonucleotide (ODN) that drives PARP1 hyperactivation coupled to exhaustion of the DNA damage response, ultimately killing cancer (but not normal) cells as a function of metabolic breakdown. PARP1-targeting decoy ODNs have been shown to mediate multiple immunostimulatory effects, standing out as promising combinatorial partners for PD-1 blockers in cold tumors.

Methods We harnessed a unique endogenous mouse model that recapitulates key immunobiological features of human HR+HER2 breast cancer, as driven by subcutaneous, slow-release medroxyprogesterone acetate (MPA) pellets combined with 7,12-dimethylbenz[a]anthracene (DMBA) gavage, to investigate the therapeutic efficacy of OX425 delivered intraperitoneally 1X or 2X per week at 100 or 500 mg/mouse, optionally combined with a mouse PD-1 inhibitor (delivered intraperitoneally in 2 doses of 200 mg/mouse 3 days apart from each other). Tumor growth, mouse-adapted RECIST score assessments, progression-free survival, overall survival and other clinically relevant parameters were monitored until ethical endpoint.

Results OX425 at the highest dose (500 mg/mouse 2X per week) was associated with weight loss across treated mice (irrespective of PD-1 blockage) and premature mortality in 10% of the mice, calling for dose reduction to 100 mg/mouse 2X per week. At all other administration schedules, OX425 was well tolerated, effective at controlling tumor growth and extending overall survival in mice bearing MPA/DMBA-driven carcinomas (which are intrinsically resistant to PD-1, similar to HR+ breast cancer in women). Blocking PD-1 increased the therapeutic activity of OX425 when delivered 2X per week at 100 mg/mouse as it inhibited the development of secondary tumors.

Conclusions OX425 at doses < 500 mg/mice 2X per week is well tolerated in mice and mediates single-agent immunotherapeutic activity in models of PD-1-resistant HR+HER2 breast cancer, with a potential for synergy with PD-1. Further investigation of the immunostimulatory and therapeutic properties of OX425 is warranted.

REFERENCES

Ethics Approval This study was approved by Weill Cornell Medicine IACUC.