

The ONXEO logo is centered within a white circle. The letters 'ON' are in blue, 'X' is a stylized 'X' formed by a pink and green bar, and 'EO' are in blue. The background of the slide features four overlapping diagonal bands in pink, green, yellow, and blue.

ONXEO

Drug-driven HRD: PARP inhibitors & AsiDNA[®] - From bench to bedside and back

Presentation to the ESMO TAT
March 7-9th 2022

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Preclinical Lead

Head of platON platform

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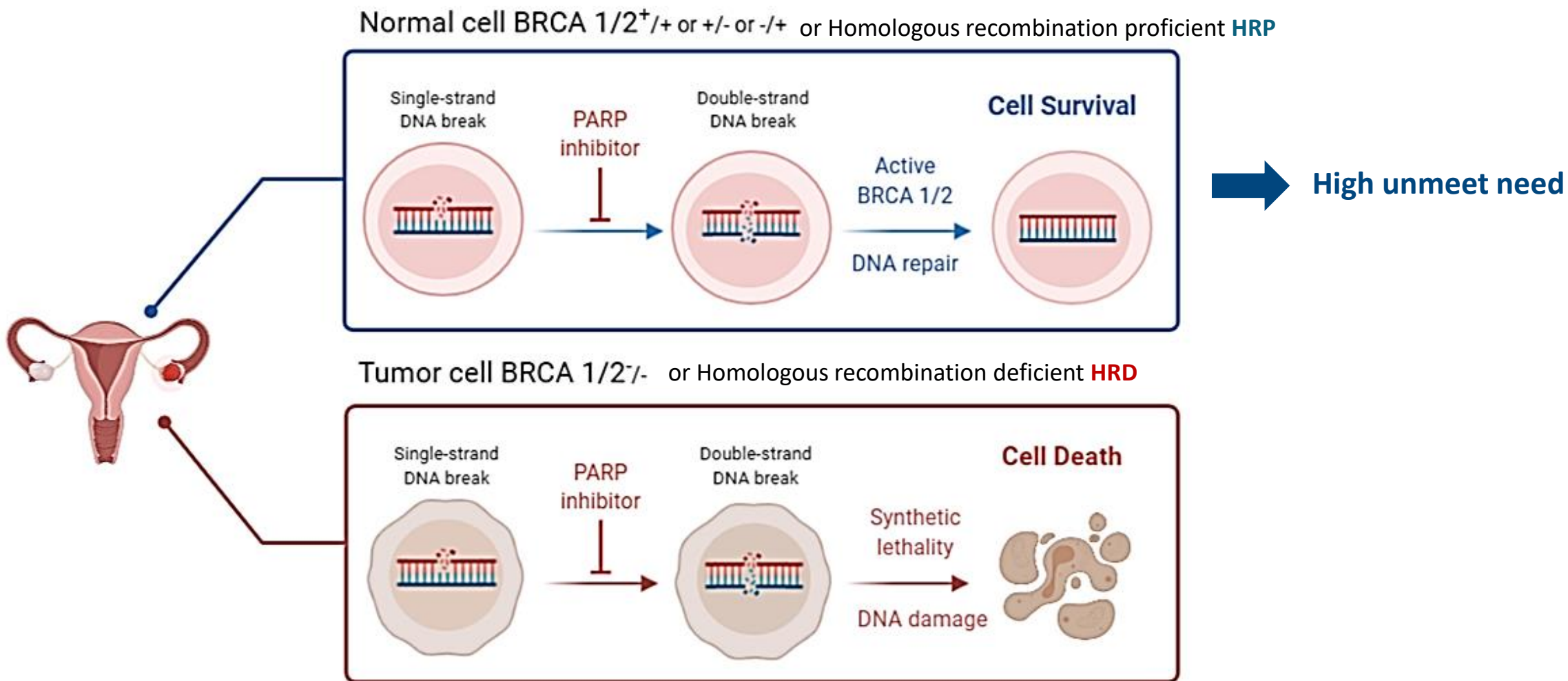
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PARP inhibitors and Homologous Recombination Repair

Treatment of BRCA mutant ovarian cancer

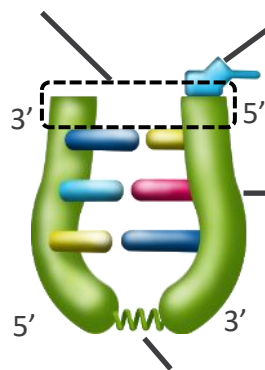




Could AsiDNA[®] save the day here?

AsiDNA[®]

Blunt end mimicking a DNA double-strand break (DSB)



Cholesterol

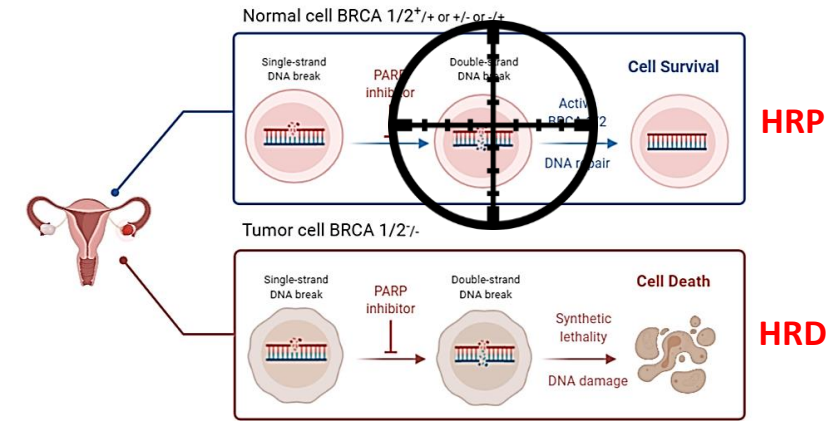
Cellular uptake of the DNA mediated via a covalently linked cholesterol molecule

Active 32 bp DNA duplex

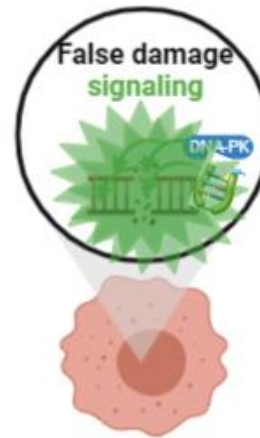
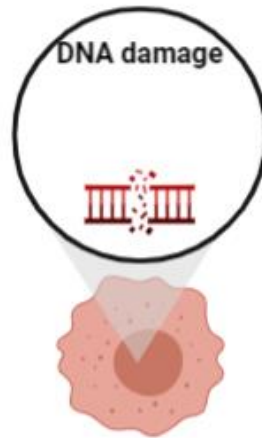
Double-stranded 32 bp DNA is tethered with a loop to prevent dissociation

Loop

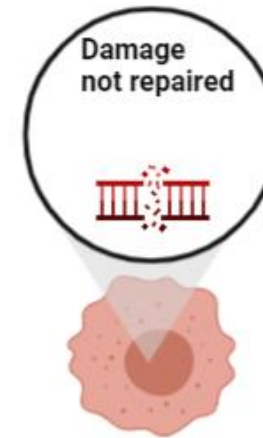
Purposed-built oligonucleotide designed to interfere with repair pathways through a mechanism of capture and hyperactivation of key DDR proteins, notably DNA-PK



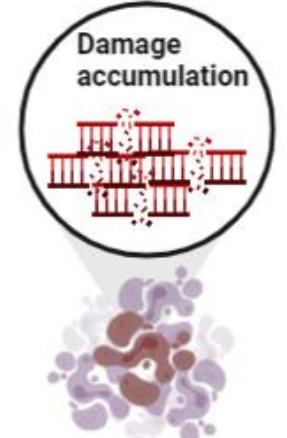
False danger signaling



No efficient danger elimination (due to "firefighter" hijacking and blurring)



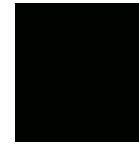
Danger accumulation



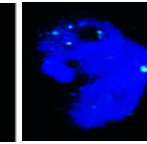
γH2AX



BRCA1

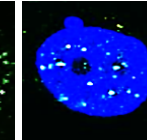
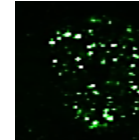
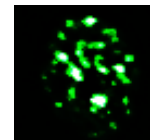


Rad51



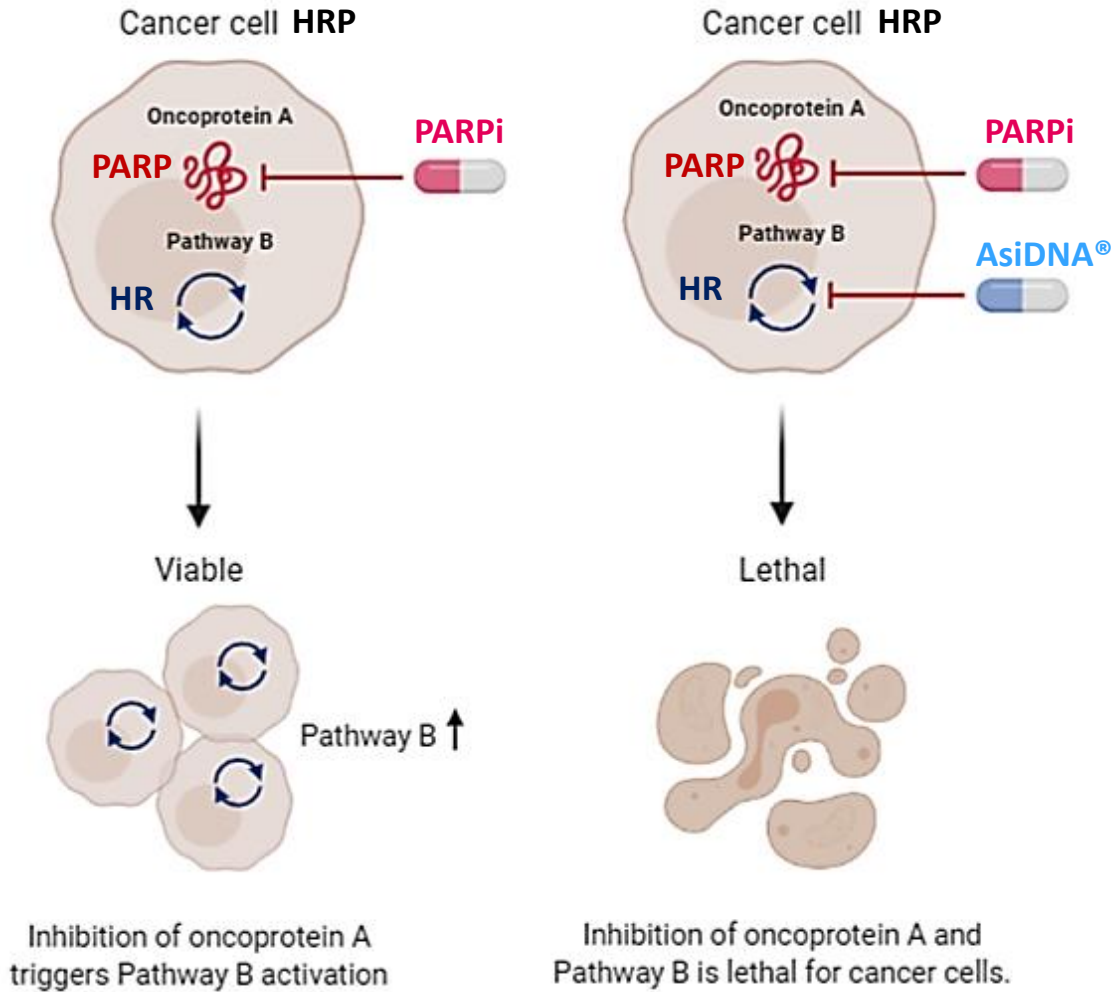
AsiDNA

Without AsiDNA

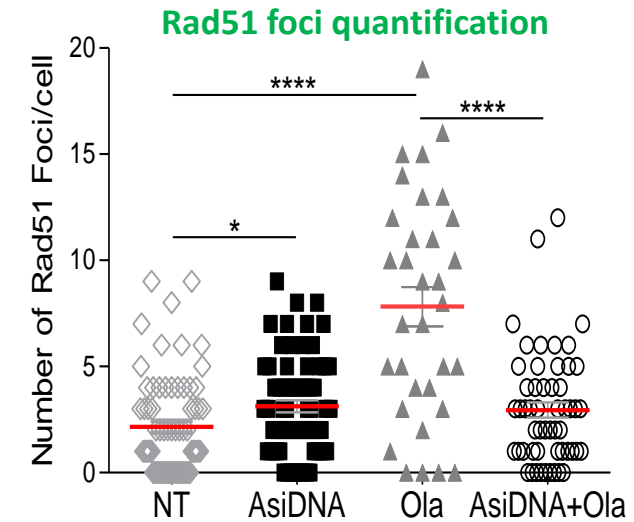
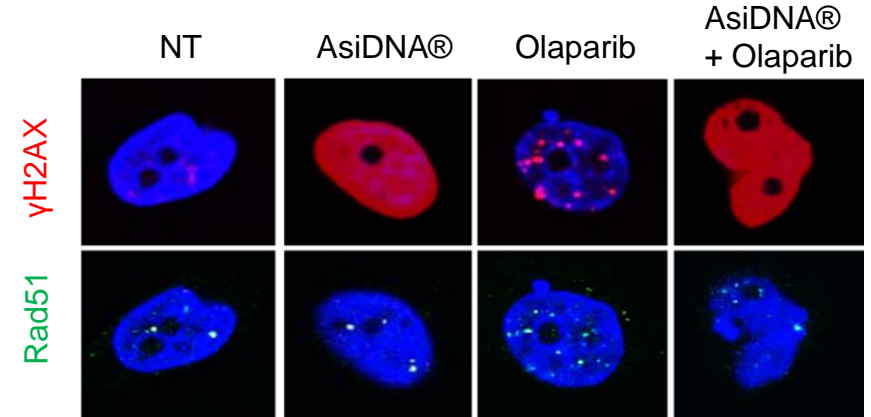




AsiDNA® & PARP inhibitors in **HRP** tumors: Drug-driven synthetic lethality



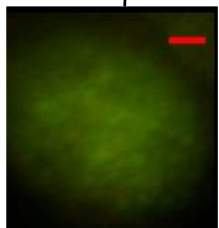
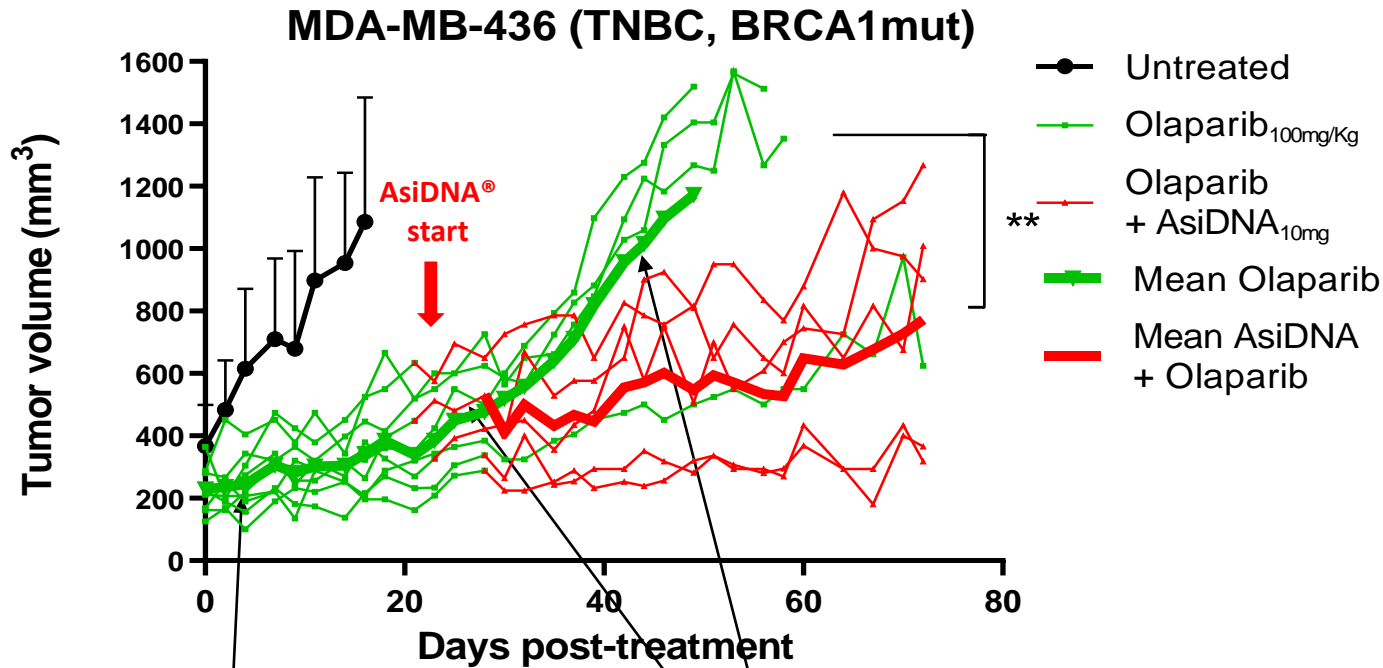
MDA MB 231 - TNBC model - HRP



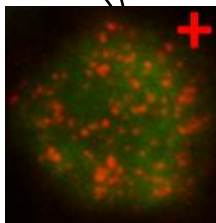


AsiDNA[®] reverses acquired resistance to olaparib *in vivo*

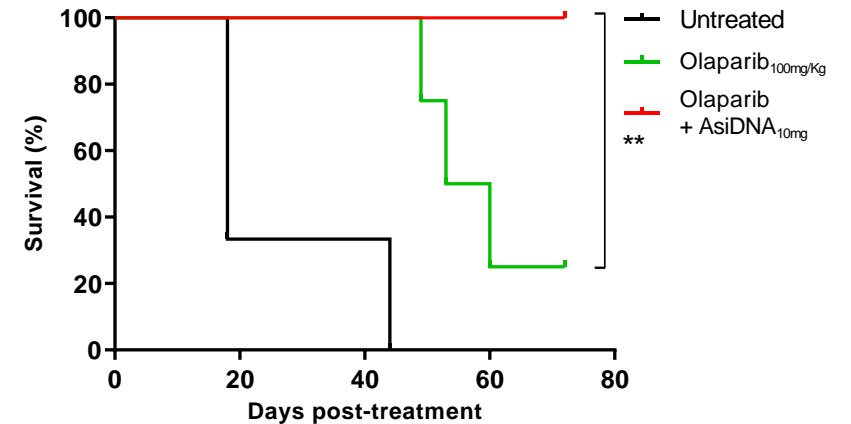
MDA-MB-436 cell-derived xenografts



RAD51- (HRD)



RAD51+ (HRP)

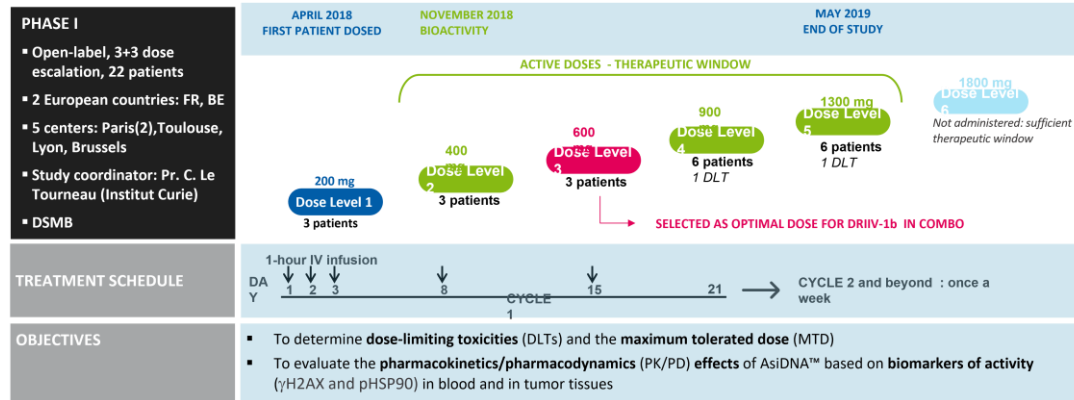


AsiDNA[®] treatment, started at early relapse, reverses HR pathway restoration-induced acquired resistance to olaparib

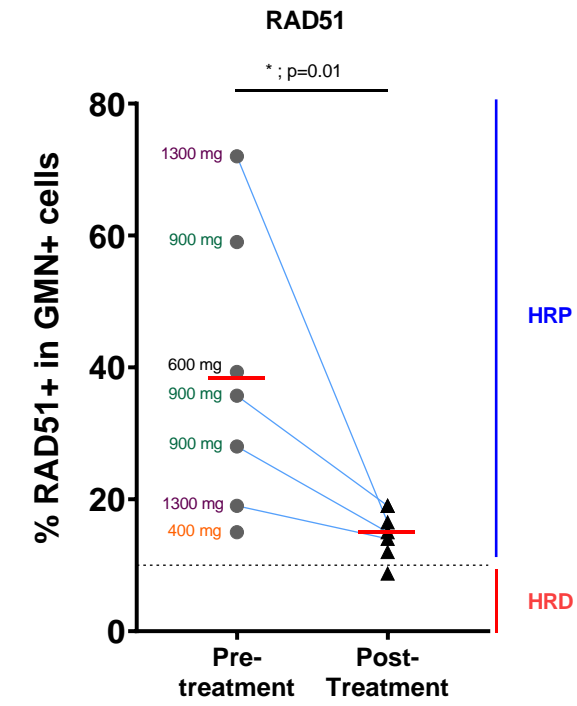
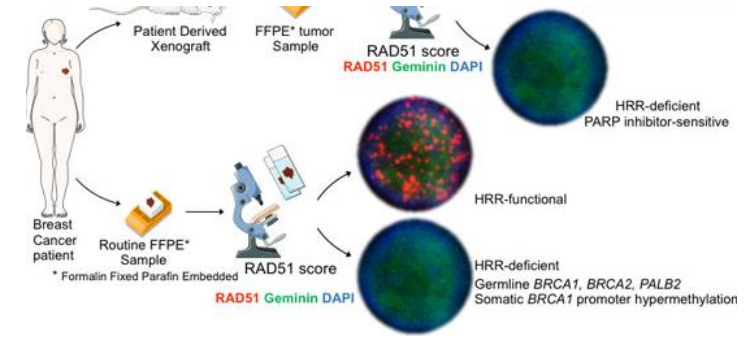
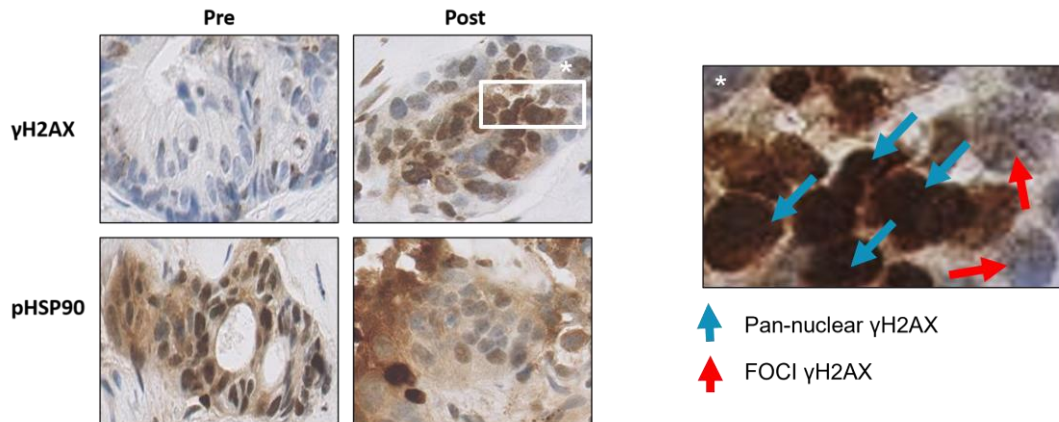


The AsiDNA[®]-driven Homologous recombination deficiency HRD: Clinical PoC

DRIIV-1 study: AsiDNA[®] I.V. administration as monotherapy in advanced/metastatic Solid Tumors



Patient 002-02 (DL3 – 600mg)



One cycle of treatment with AsiDNA[®] (Day 22) showed clear tendency to push tumors into a HRD status ⁷