Advancing innovation towards breakthrough cancer therapies

LISTED
EURONEXT | Paris
NASDAQ | Copenhagen

EPA: ONXEO

39th EORTC – PAMM Winter meeting February 2018

ONXEO

ASIDNA™
A FIRST-IN-CLASS COMPOUND TARGETING TUMOR DNA DAMAGE REPAIR PATHWAYS

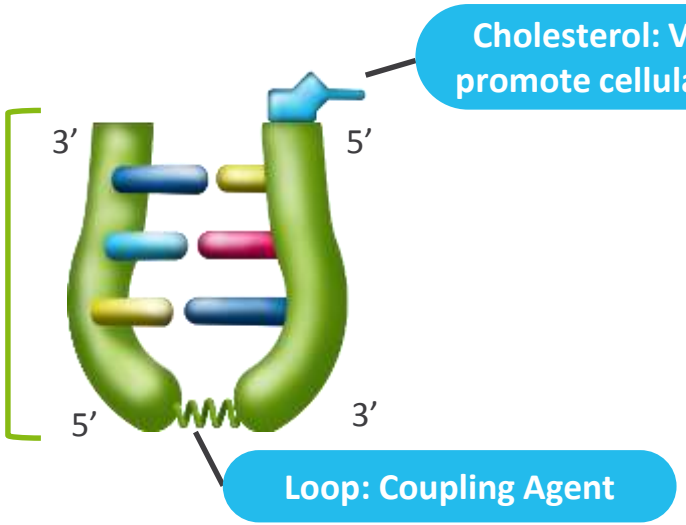
39th EORTC – PAMM Winter meeting February 2018

AsiDNA™: A first-in-class compound in DNA Break Repair inhibition

32 bp DNA duplex with a 5´-Chol-TEG & a non-nucleotidic loop

Active 32 bp DNA duplex

- Binds and activates DNA-PK and PARP signaling enzymes
- Sequence not specific, chosen to be non-homologous
- Genomic DNA length optimize



- Double-stranded 32 bp DNA is tethered with a loop to prevent disassociation[1]
- Phosphorothioate substitutions at the 5' and 3' ends to prevent degradation[1]
- Efficient nuclear uptake of the DNA is mediated via a covalently linked cholesterol molecule[2]

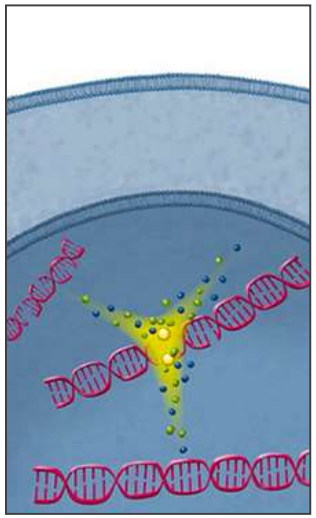
Simple, elegant, unique and safe

[1] Quanz M, et al. PLoS ONE. 2009 4(7), doi: 10.1371/journal.pone.0006298
[2] Berthault N, et al. Cancer Gene Therapy (2011), 1-12, doi: 10.1038/cgt.2011.3

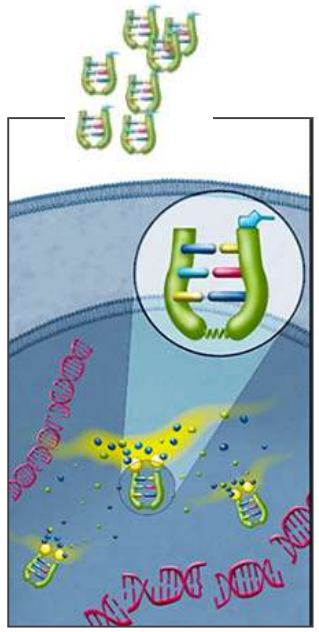
AsiDNA™ - A mechanism of action unlike any other:

DNA break repair inhibition through an agonist mechanism

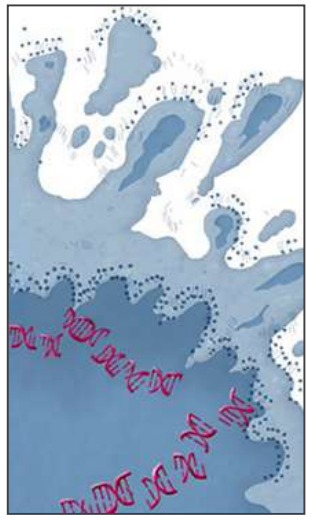
Recruitment of DNA damage signaling and repair proteins to the sites of genomic damage is one of the early events in tumors DNA repair



AsiDNA™ is a double stranded DNA molecule (decoy oligonucleotide) that mimics double stranded DNA breaks to interfere with tumor DNA repair, redirecting repair enzymes away from sites of tumor DNA damage[1,2,3]



Tumoral cells (deficient cell cycle control) keep dividing with damaged DNA leading to DNA fragmentation and loss and then mitotic death.

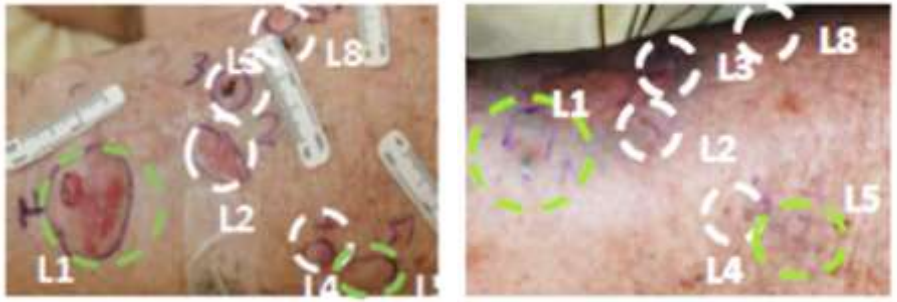


Healthy cells (proficient cell cycle control) stop dividing and reduce transcription then resume division once false signals disappear

[1] Quanz M, et al. Clin Cancer Res 2009 15:1308-1316;
[2] Quanz M, et al. PLoS ONE. 2009 4(7), doi: 10.1371/ journal.pone.0006298;
[3] Jdey W, et al. Oin Can Res. 2016;22:DOI: 10.1158/ 1078-0432.CCR-16-1193

Lesson learn from DRIIM Phase I study
Intratumoral administration for metastatic melanoma + radiotherapy

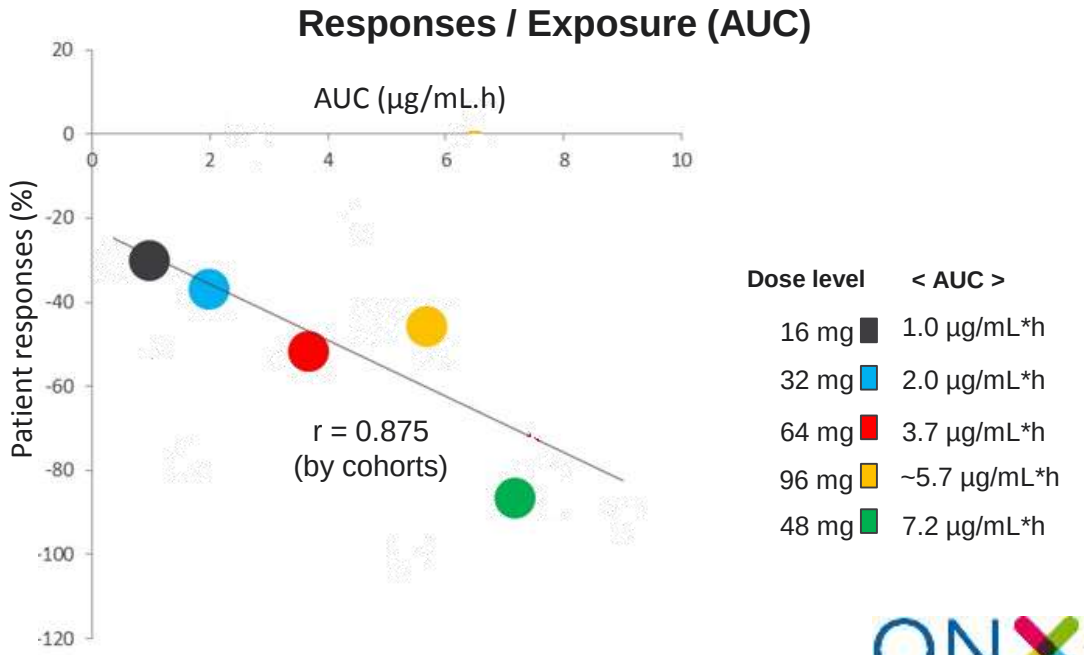
- **Proof of concept established[1]**
  - **Overall response rate = 59%**
  - Complete response = 30%
    (CR from low-dose radiotherapy alone less than 10%[2])
  - Partial response = 29%
  - Durable response (up to 12 months follow up period)



Before treatment | 90 days after treatment

- **Well tolerated compound**
  - Absence of immune response

- **PK/PD properties**
  - **Tumor responses statistically correlated to plasmatic exposure of AsiDNA**

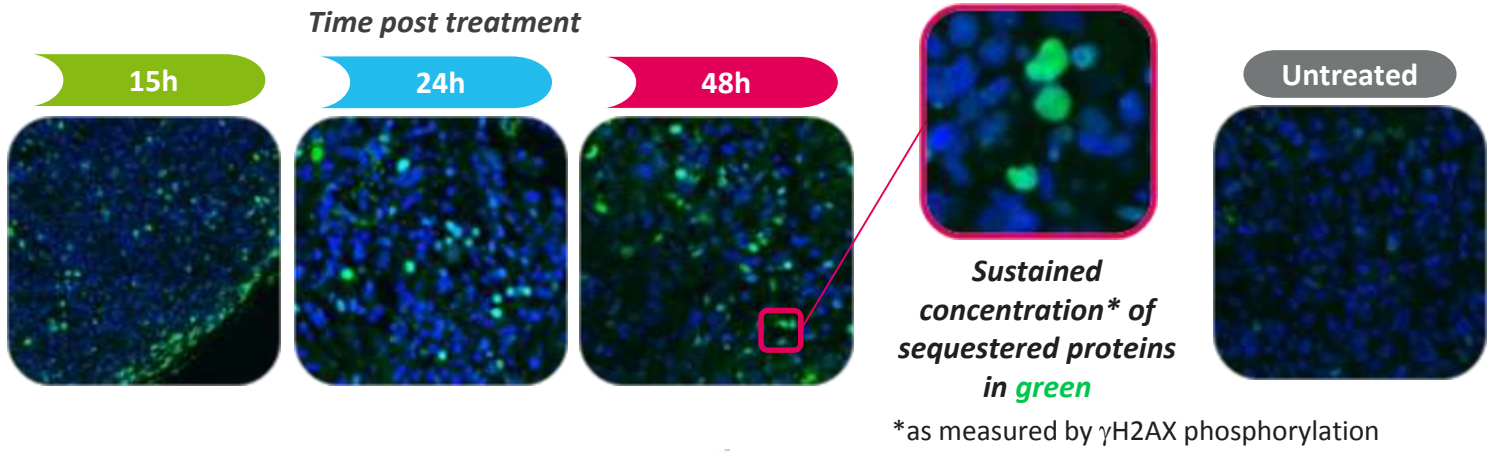


1. Le Tourneau et al. Br J Cancer. 2016 May 24;114(11):1199-205 ; 2. Olivier et al., Cancer 2007; Konefal et al., Radiology 1987

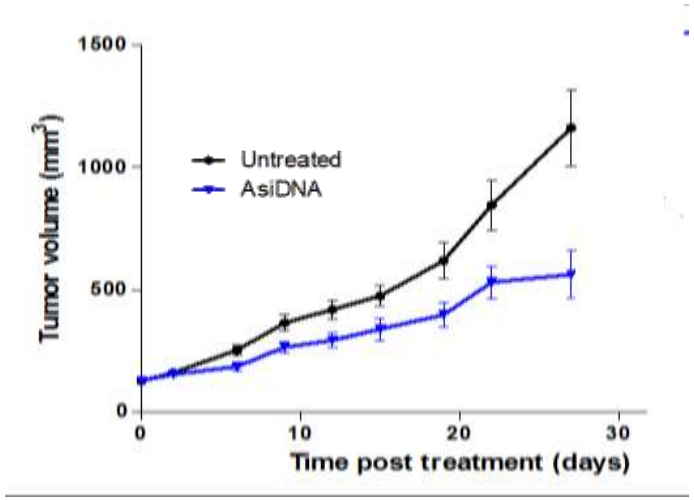
AsiDNA™ therapeutic efficacy demonstrated after IV injection in a murine model of Triple Negative Breast Cancer

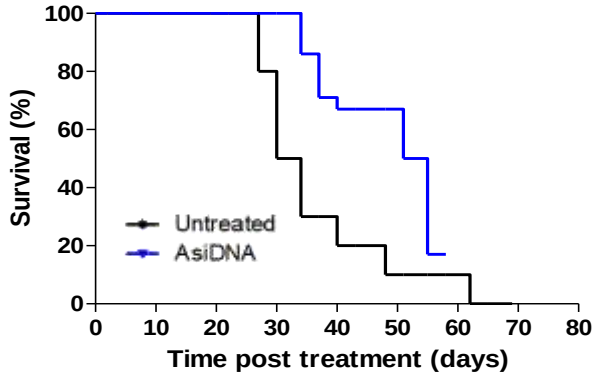
- **AsiDNA™ sequesters and sustainably hyperactivates the key DNA repair proteins DNA-PK thus preventing effective DNA repair in tumors**

- Demonstrated therapeutic efficacy of AsiDNA™ alone administered intravenously



*as measured by γH2AX phosphorylation





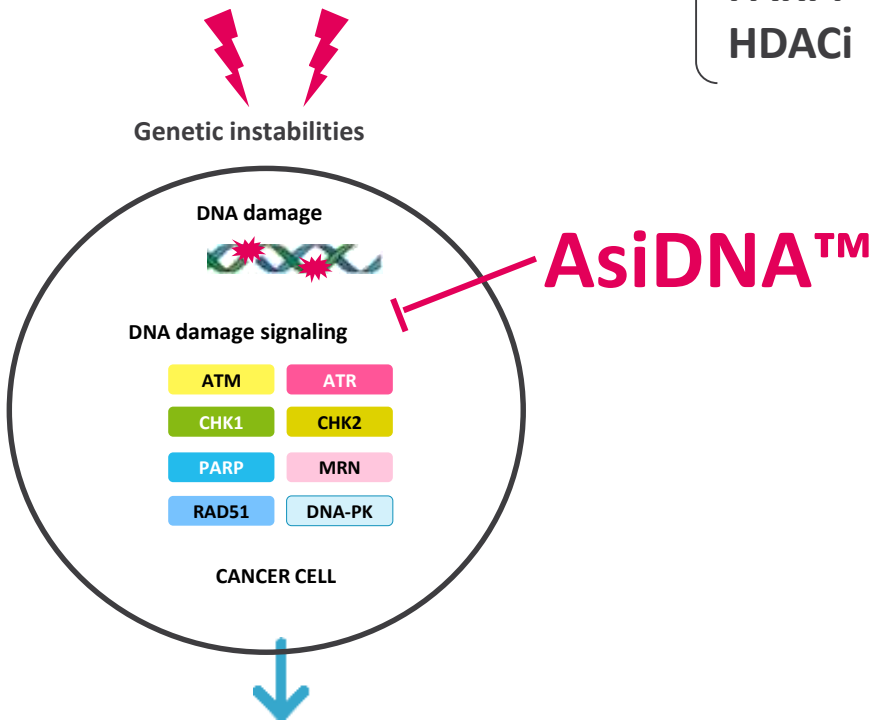
AsiDNA systemic application : Clear path towards Phase 1 clinical trial

1	In vitro activity and comparison with competitors	Done
2	In vitro genotoxicity and in vivo safety profile	Done
3	Pharmacokinetic/Biodistribution and metabolism	Done
4	Patents filing	Done
5	PK/PD establishment and in vivo POC	Done

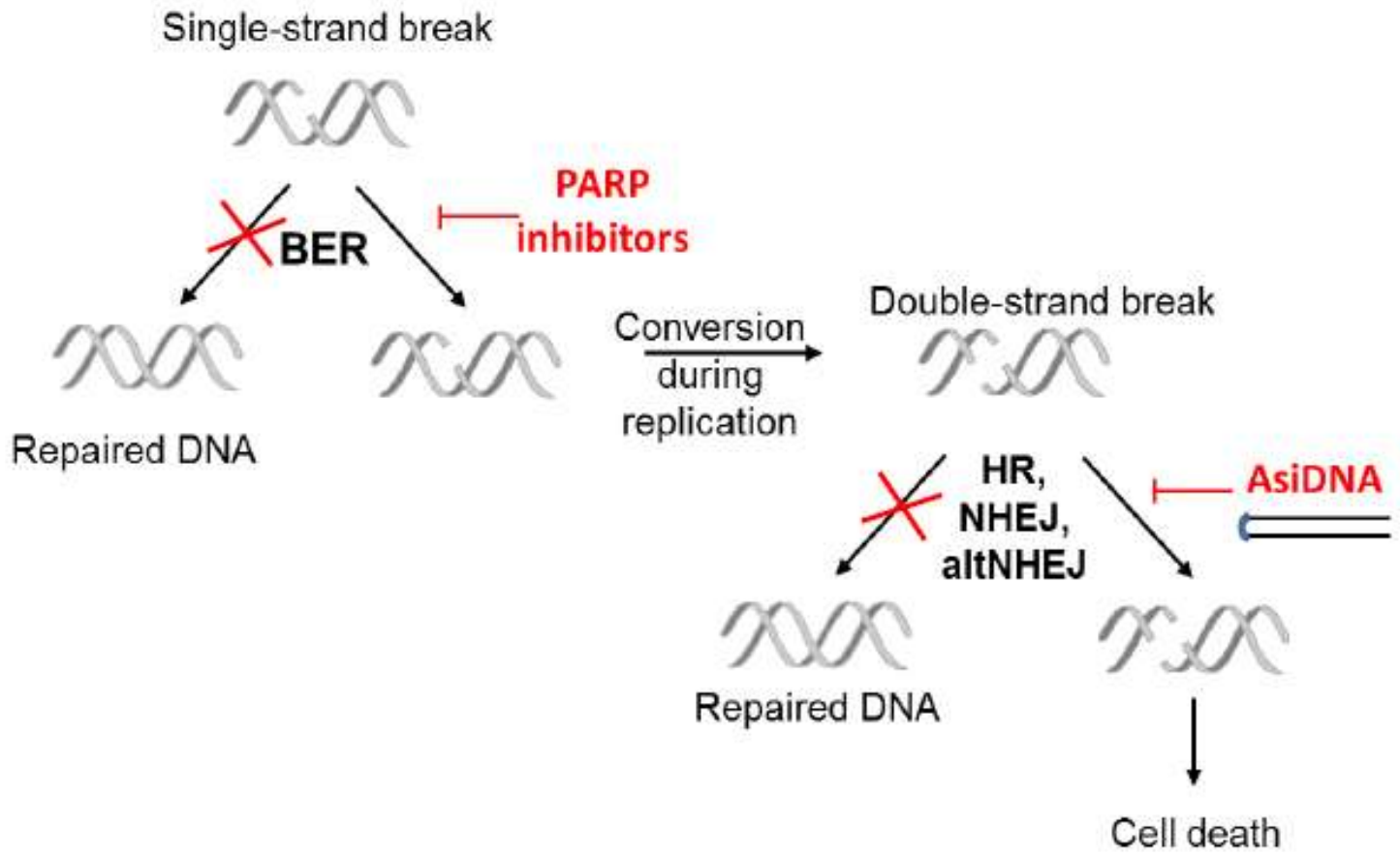
AsiDNA a potent enhancer of DNA double strands damaging agents anti-tumoral activities

DNA damaging agents/epigenetic drugs

- Radiotherapy
- DNA targeting chemotherapies
- **PARPi**
- **HDACi**



AsiDNA leads to cancer cell death in combination with PARPis

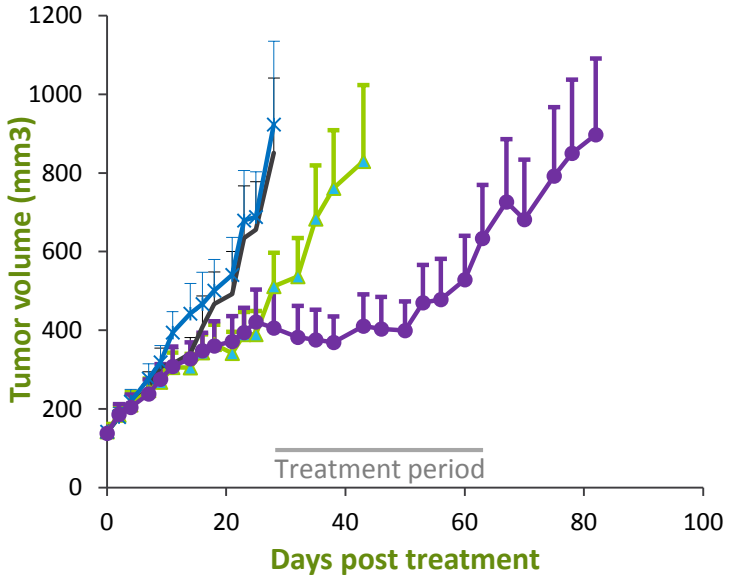


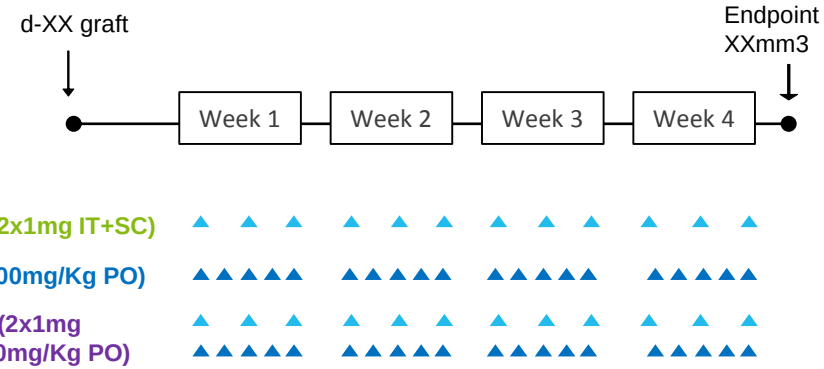
Tumor cells cannot escape to combine treatment

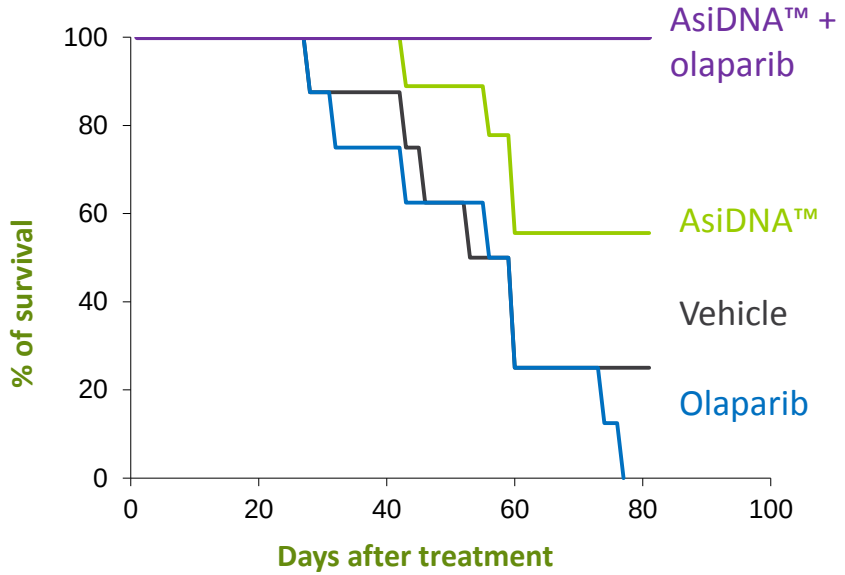
Synergistic effect of AsiDNA™ + olaparib combined treatment on TNBC HR proficient tumor xenograft model in mice

Xenograft mice - HR proficient Breast Cancer model

- **AsiDNA™** (IT + SC, n=9)
- **olaparib** (PO, n=8)
- **AsiDNA™ + Olaparib** (n=9)
- **NT** (n=8)



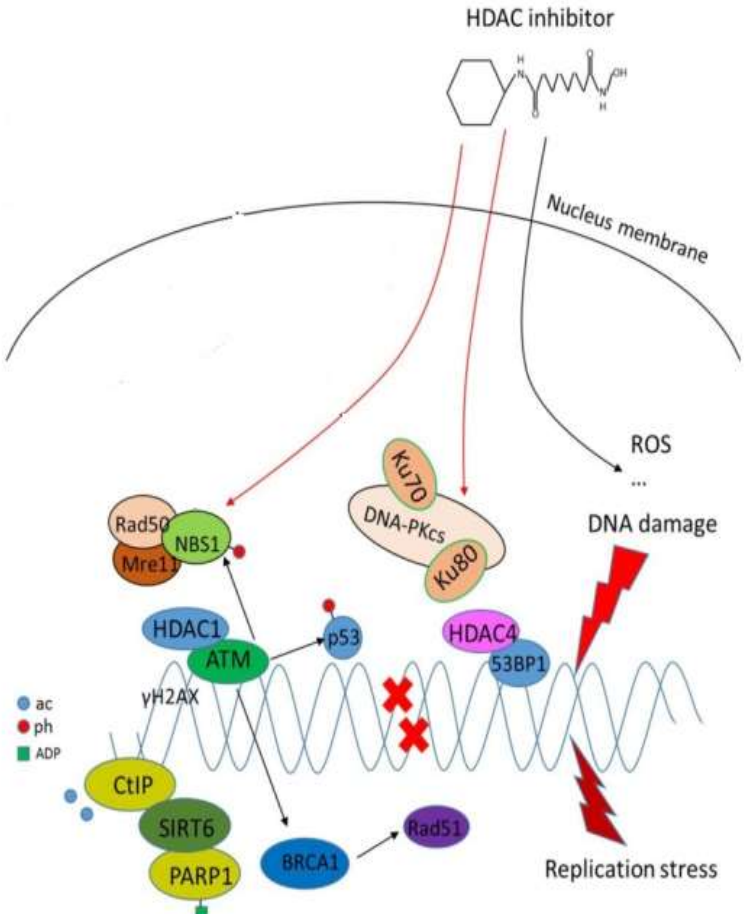




Source: AACR 2017 "AsiDNA™ induce tumor sensitivity to PARP inhibitors in homologous recombination proficient breast cancer", Wael Jdey et al.

HDACs are involved in almost every aspect of DNA repair

- Detection of, and signalling from, DNA lesions to the removal or reversal of the damage.
- Expression, activation and degradation of key factors involved in DNA damage signalling,



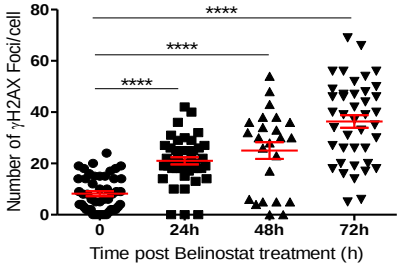
Adapted from Li Z, Zhu WG - Int. J. Biol. Sci. (2014)

AsiDNA™ and HDACi, a 2-way synergistic mechanism

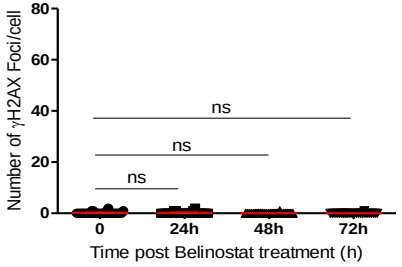
- **Belinostat induces a strong increase of DNA breaks and genetic instability on tumor cells, but not on healthy cells**

DNA breaks

γH2AX quantification



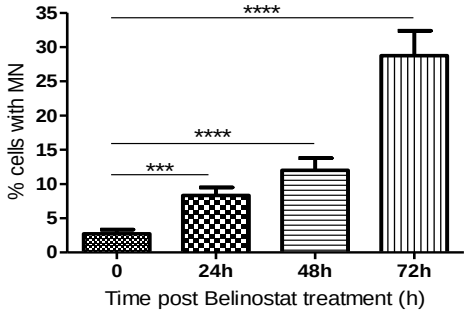
Tumor cell line
MDA-MB-231



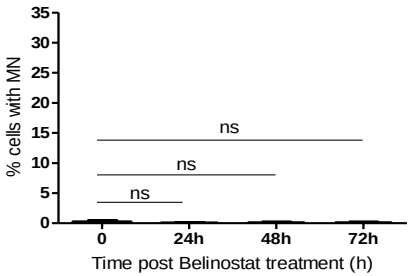
Healthy cell line
MCF-10A

Genetic instability

Micronucleus quantification



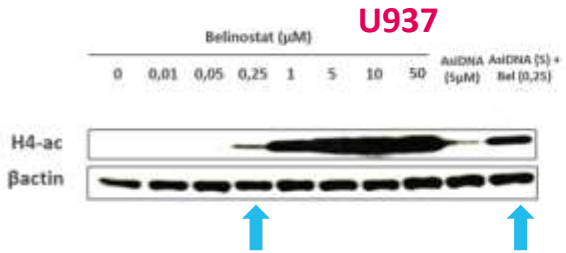
Tumor cell line
MDA-MB-231



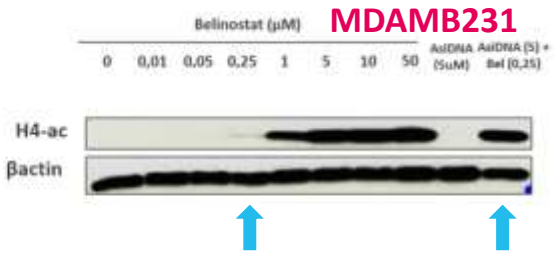
Healthy cell line
MCF-10A

- **AsiDNA™ increases belinostat-induced histone 4 acetylation in both tumor cell lines**

U937



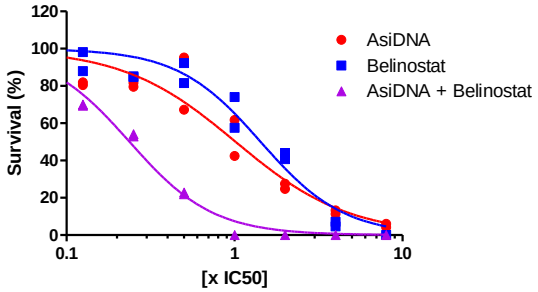
MDAMB231



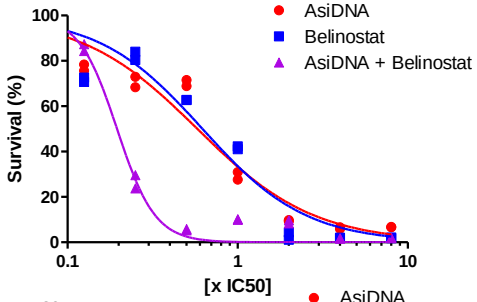
HDAC inhibitors demonstrate strong synergy in combination with DNA break repair inhibitor AsiDNA™

- **Synergistic effect of belinostat combined with AsiDNA™ : Increased cell lethality in different tumor cell lines (MDAMB 231 and U937), no lethality observed in healthy cells (MCF-10A)**

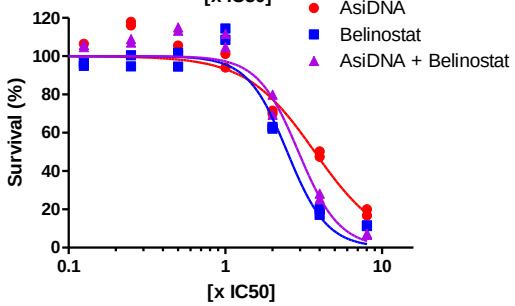
MDAMB 231

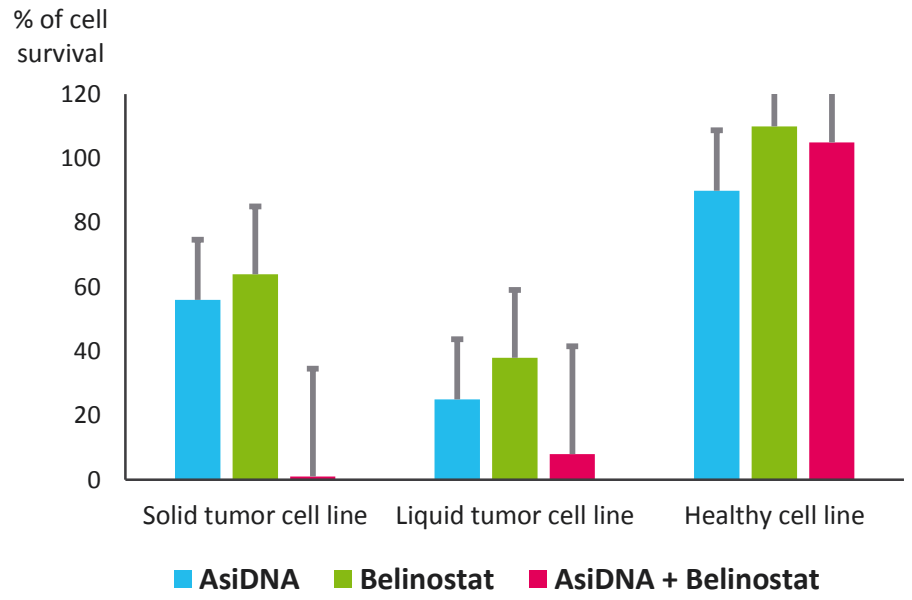


U937



MCF-10





Same results obtained with **vorinostat, entinostat and romidepsin**

AsiDNA™ Development Strategy

Proprietary technology
(Method of Use)
patent until 2024

Drug product and related compounds
protected until
2031

- **Confirm AsiDNA™ activity via systemic administration (IV)** — *H1 2018*
  - Ongoing in vivo preclinical study in several tumors/combo (PARPi, HDACi…)
- **First-in-man Phase I AsiDNA™ IV in advanced malignancies** — *CTA Filed Q4 2017 First patient March 2018*
  - Confirm proof of mechanism in man, determine optimal clinical dose
  - Translational clinical outcomes, relationship between exposure, activity & safety
- **Clinical development program extension in solid / liquid tumors** — *CTA filing in 2018 First data for end 2018 / early 2019*
  - Phase I/II AsiDNA™ IV in combination with DNA damaging agents (PARPi, HDACi…)
  - AsiDNA™ IV alone for genetically unstable tumors

Leading-edge R&D Pipeline in DNA-targeting

	Programs	INDICATION	PRECLINICAL	PHASE I	PHASE II	PHASE III	UPCOMING MILESTONES
Platform	**platON™** Proprietary chemistry platform of decoy oligonucleotides	GENERATION OF NEW DNA-TARGETING COMPOUNDS					▪ Next compound H1 2018
DNA Break repair Inhibition	**AsiDNA™ IV**[1]	**Solid tumors**					▪ Phase I filing Q4 17 ▪ Proof-of-Mechanism (PoM) in man end 2018
	AsiDNA™ + PARPi	**Solid tumors**					▪ Ready to initiate Proof-of-Concept (PoC) in man in 2018
	AsiDNA™ + chemo/radio	**Solid tumors**					▪ IT[1] PoC confirmed (DRIIM phase I study) ▪ Ongoing for IV
	AsiDNA™ + belinostat /HDACi	**Solid tumors**					▪ Ready to initiate PoC in man in 2018
Epigenetics	**Oral belinostat**	**Liquid & solid tumors**					▪ Ready for clinical phase I 2018
	Beleodaq®[2] **+ CHOP**[3]	**PTCL**[4] **1st line**					▪ Phase III required by the FDA from SPPI[5] as MA holder in 2nd line
BD	**Livatag®**	**Hepatocellular carcinoma**					▪ Looking for a partner to explore other options (HBV, 1st line, combo…)

[1] IT: intratumoral – IV: intravenous
[2] Beleodaq®: commercial brand name of belinostat (IV form) in the US in r/r PTCL
[3] CHOP: Cyclophosphamide, Vincristine, Doxorubicine, Prednisone

[4] PTCL : Peripheral T-cell lymphoma – a rare form of blood cancer
[5] SPPI : Spectrum Pharmaceuticals, Onxeo's partner and Market Authorization holder in the US for the use of Beleodaq in the treatment of PTCL in 2nd line

platON™: a broad potential beyond AsiDNA™

Properties of AsiDNA™

- Unique mechanism of action (decoy role & agonist effect): blocks multiple repair pathways without inducing resistance mechanisms
- Enhancer of the antitumoral properties of DNA damaging agents

Objectives for platON™ future products

- Target the regulation of tumor DNA functions through a decoy mechanism
- Generate decoy oligonucleotides able to induce cancer cell death and trigger immune response within the tumor without any effect on healthy cells
- platON™ upcoming products having a clinical positioning differentiated from AsiDNA™

Onxeo: Advancing innovation towards breakthrough cancer therapies

A clear value-creation strategy : drive innovative programs to best inflexion points and generate deals

A robust translational expertise to drive optimal compounds' development

R&D programs based on 2 of the most promising mechanisms of action, with multiple development paths and wide potential of applications

A proven capacity to generate transactions and enrich the pipeline

CONTACTS

Judith Greciet – CEO
Nicolas Fellmann – CFO
Tel: +33 1 45 58 76 00
contact@onxeo.com

Françoise Bono – CSO
f.bono@onxeo.com

COMPANY INFORMATION

www.onxeo.com