AsiDNA™, a first-in-class, clinical stage "Decoy Agonist" targeting DNA repair pathways

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Introduction

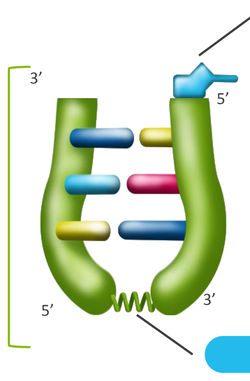
AsiDNA™, is a first-in-class, highly differentiated DNA Damage Response (DDR) inhibitor based on a decoy and agonist mechanism acting upstream of multiple DDR pathways. AsiDNA™ binds and activates (Agonist) DNA-PK and PARP, two key players controlling the initiation of double-strand DNA repair. In tumor cells, AsiDNA™ molecules trigger false DNA break signals (Decoy), which prevents recruitment of DNA-PK and PARP to the site of actual DNA damage and leads to mitotic catastrophe, DNA repair and metabolic exhaustion. Healthy cells, however, are not impacted as they pause cell division until AsiDNA™ is no longer present. This **breakthrough mechanism of action** has already shown its **efficacy, safety and lack of tumor resistance,** in multiple preclinical studies with AsiDNA . A clinical phase I trial **showed target engagement in tumors and excellent safety profile.** A phase 1b cohort expansion study (DRIIV-1b study) is ongoing to evaluate the combination of AsiDNA with chemotherapy and has already shown promising signals of clinical efficacy in intermediate results. Finally preclinical results highlight the therapeutic interest of combining AsiDNA and PARPi to recapitulate drug-driven PARPi resistance abrogation. A Phase1b/2 to confirm AsiDNA-induced abrogation of PARPi-acquired resistance in ovarian cancer (REVOCAN) will start in the next few months.

AsiDNA™ structural design mimicks DNA double strand breaks

A synthetic cholesterol-oligonucleotide conjugate forming an intramolecular hairpin 32-base pair double helix

Active 32 bp DNA duplex

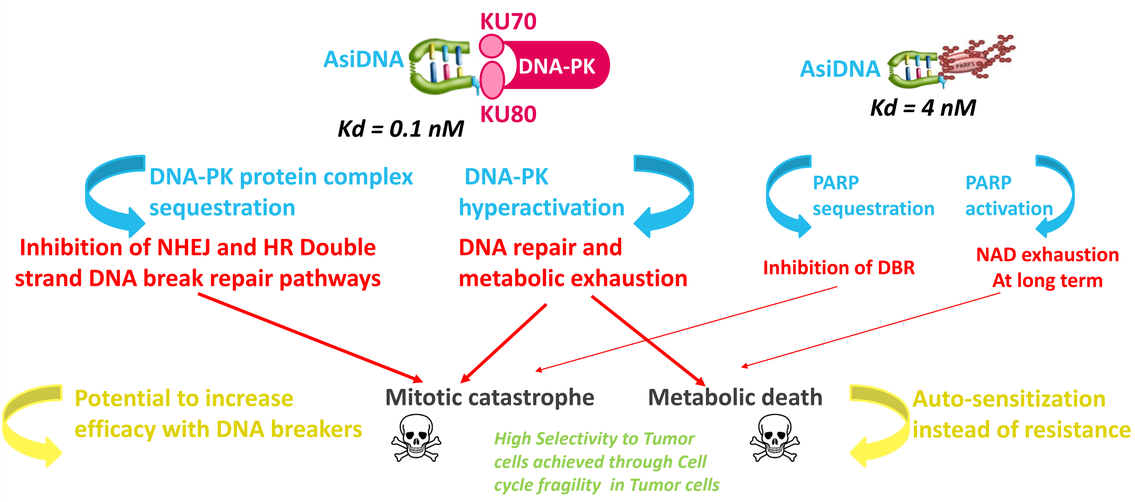
- Double-stranded 32 bp DNA binding & activating DNA-PK and PARP
- 5' and 3' phosphorothioate substitutions to prevent degradation
- Loop to prevent disassociation
- Sequence not specific, non-homologous and not immunogenic (CpG-free)



Cholesterol

- Tumoral and nuclear uptake is mediated via a covalently linked cholesterol molecule
- Molecular weight : 20,931 daltons (free acid)

A unique Decoy Agonist MoA



AsiDNA™ binds with high affinity the two major proteins involved in the initiation of double strand DNA repair: DNA-PK and PARP1, diverts them away from true damages (*decoy mechanism)* and hyperactivates DNA-PK and PARP1 (*agonist effect*).

- **AsiDNA™ blocks double stand DNA repair pathways in tumor cells**
- **AsiDNA™'s unique MoA results in selective activity in tumor cell**

MoA enables AsiDNA™ to deliver Resistance & Synergies key benefits

No acquired resistance to AsiDNA™

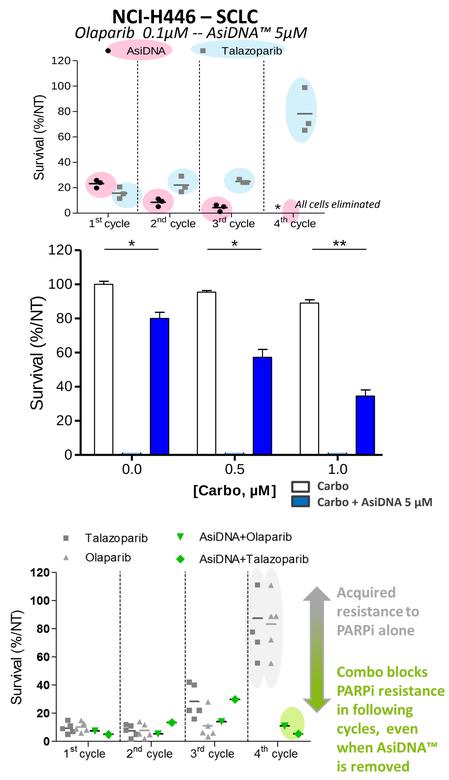
Repeated treatment by AsiDNA™ leads to AsiDNA™ sensitization and does not generate resistance, in contrast to PARP inhibitors

Profound synergy with DNA breakers

AsiDNA™ displays synergistic anti-tumoral activities with DNA breakers such as radiation therapy, chemotherapies and PARP inhibitors (regardless of HR status)

AsiDNA™ prevents resistance to PARPi

AsiDNA™, at sublethal doses, abrogates acquired resistance to PARP inhibitors by inhibiting Homologous Recombination (HR) reactivation

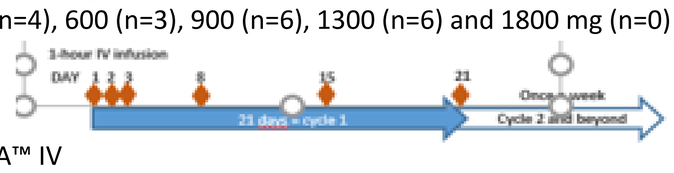


DRIIV-1 Phase 1 study of AsiDNA™ via IV route demonstrated excellent safety and target engagement in tumors

Study design

1) Phase 1, open label, non-randomized, multicenter, cohorts of 3(+3) evaluable patients (with advanced solid tumors) received escalating dose of AsiDNA™
2) 6 dose levels (DL): 200 (n=3), 400 (n=4), 600 (n=3), 900 (n=6), 1300 (n=6) and 1800 mg (n=0)

Administration scheme



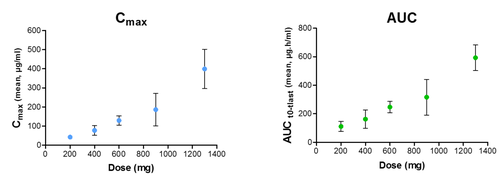
Primary objective

To determine DLTs and MTD of AsiDNA™ IV

Key secondary objectives

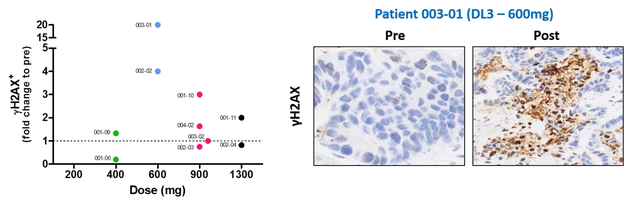
(1) Safety profile; (2) pharmacokinetics (PK) and pharmacodynamics (PD); (3) Prelim. efficacy data

Pharmacokinetics



Cmax and AUC increase proportionally with dosing

Pharmacodynamics



Optimal bioactivity at 600mg based on γH2AX

Preliminary efficacy

Best overall response: disease stabilization in 2 patients (9%) with colorectal cancer at DL 600

Conclusions

- **Maximum tolerated dose (MTD) not reached, favorable safety profile confirmed**
- **Biological activity evidenced by the increase of γH2AX**
- **600 mg identified as the optimal biological dose for further development given favorable safety & PK profiles, robust target engagement and disease stabilization in 2 CRC patients**

DRIIV-1b study preliminary results (at Sept 18, 2019)

MAY 2019	Q3 2019	FROM Q1 20	H1 2020
FIRST PATIENT DOSED	INTERMEDIATE RESULTS PART 1 START OF PART 2	PRELIMINARY EFFICACY OUTCOMES	END OF STUDY

Part 1
3 pts
AsiDNA™ 600 mg + carboplatin

- 3 multi-treated patients whose metastatic tumors were progressing at inclusion
- Stable disease (no tumor progression) in 2/3 pts, with treatment duration > previous lines
- Satisfactory tolerance of the combination

Part 2
6 pts
ongoing
AsiDNA™ 600 mg + carboplatin + paclitaxel

- Carboplatin + paclitaxel is a standard chemotherapy protocol for many cancers
- Preliminary efficacy results expected from Q1 20
- Full data set by end H1 2020

Positive intermediate results from Part 1 of the study
Part 2 started with first results expected by early 2020

REVOCAN: Tolerance and abrogation of acquired resistance to PARPi

REVersion of resistance in Ovarian Cancer with AsiDNA™ and Niraparib (Platinum-Sensitive Relapsed Ovarian Cancer)

Up to 26 patients in 2nd line maintenance, treated with niraparib (PARPi) for at least 6 months

CA125 biomarker elevation, which is predictive of short-term tumor progression

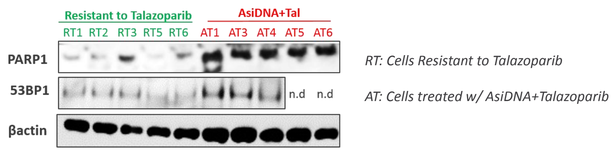
Addition of **AsiDNA™** to niraparib and follow-up: decrease in CA 125 (short term, indicative of the abrogation of resistance) and progression-free survival / overall survival (medium/ long term)

Inclusion of the first patients in H1 2020, first results end 2020

Mechanisms underlying PARPi resistance abrogation

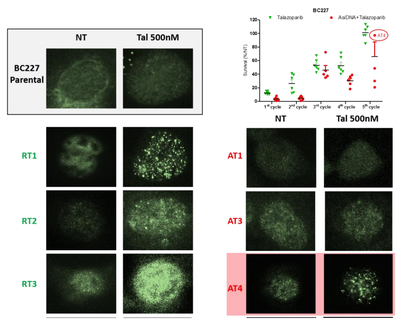
Analysis of proteins implicated in PARPi resistance

PARP1 protein decrease (target decrease) and 53BP1 loss (alternative pathway activation) are associated with resistance to PARPi.



→ **Decrease in PARP1 and 53BP1 expression in resistant cells compared to double-treated sensitive cells.**

HR pathway status in resistant cells vs sensitive double-treated cells



→ **HR pathway reactivation in Talazoparib resistant cells. Except AT4 (resistant), no HR pathway reactivation in double-treated cells.**

Conclusions

- **AsiDNA™ is the first of an entirely new class of anticancer therapeutics**
  - Unique decoy mechanism with an agonist effect
  - Excellent safety and bioactivity demonstrated in man through successful DRIIV-1 study
- **AsiDNA™ is now tested in combination with carboplatin with or without paclitaxel in patients with advanced solid tumors (DRIIV-1b study)**
  - Promising signals of clinical efficacy in intermediate results (**AsiDNA + carboplatin**): 2 out of 3 treated showed ongoing **stable disease (RECIST)**, i.e. for up to 5 months (as of Sept 18, 2019)
- **AsiDNA™ offers great potential in combination with PARP inhibitors**
  - Combining PARPi with AsiDNA™ has the potential to broaden beyond HRD tumors, increase and prolong PARPi activity in patients
  - Phase 1b/2 Study AsiDNA™ in association to PARP inhibitor with Objective
  - **to confirm abrogation of PARP inhibitor resistance**

Related publications:
C. Le Tourneau, et al. (2019) AACR-EORTC Conference, Phase I dose escalation study evaluating the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of AsiDNA, a first-in-class DNA Repair Inhibitor, administered intravenously (IV) in patients with advanced solid tumors
C. Le Tourneau, et al. (2016) Br J Cancer. May 3. doi: 10.1038/bjc.2016.120. First-in-human phase I study of the DNA repair inhibitor DT01 in combination with radiotherapy in patients with skin metastases from melanoma.
M. Quanz, et al. (2009) PloS ONE 4(7) e6398. Hyperactivation of DNA-PK by Double-Strand Break Mimicking Molecules Disorganizes DNA Damage Response.
Jdey W, Thierry S, Russo C, Devun F, Al Abo M, Noguiez-Hellin P, et al. Drug-Driven Synthetic Lethality: Bypassing Tumor Cell Genetics with a Combination of AsiDNA and PARP Inhibitors. Clin Cancer Res. 2017 Feb 15;23(4):1001–11.
Jdey W, Thierry S, Popova T, Stern M-H, Dutreix M. Micronuclei frequency in tumors is a predictive biomarker for genetic instability and sensitivity to the DNA repair inhibitor AsiDNA. Cancer Res. 2017 Jun 6;canres.2693.2016.