AsiDNA™ Letter - No. 1

The field of DDR and the strategic advantages of AsiDNA™

A WORD FROM THE CEO

Ladies, Gentlemen and Shareholders,

The clinical development of AsiDNA™ is well on its way and we would like to inform you regularly about the progress being made through a Letter dedicated to this first-in-class candidate. In this first issue, we go back to the fundamentals of the DNA Damage Response (DDR) therapeutic approach in oncology, which consists of fighting cancer by preventing it from repairing its DNA, and for which PARP inhibitors are the most advanced representatives.

The mechanism of action of AsiDNA™ is particularly innovative and offers unprecedented biological properties which we recall here, and that are highly sought after in a booming field in terms of scientific, financial and strategic agreements.

In our upcoming issues, we will cover, in detail, the indications and combinations, which we plan to assess very soon in new clinical studies with AsiDNA™.

We hope you enjoy this summertime read and look forward to sharing with you the next AsiDNA™ Letter in a few weeks' time.

Judith Greciet,
Chief Executive Officer

IN THIS FIRST ISSUE

FIGHTING CANCER BY PREVENTING IT FROM REPAIRING ITS DNA

The therapeutic approach targeting the DNA Damage Response (or DDR) is a relatively new field in oncology. Its importance has particularly been hailed by the scientific community by the awarding of the 2015 Nobel Price in Chemistry to three researchers for their studies on the DNA repair mechanisms. Professor Tomas Lindahl, a joint recipient of this Nobel Prize, chairs the Onxeo Scientific Committee. The inhibition of DNA repair mechanisms in tumor cells is today recognized as one of the most promising ways of treating cancer.

It is based on the fact that cancer cells accumulate DNA breaks, either due to their uncontrolled proliferation, or following treatments such as chemo- or radiotherapy. Not being able to replicate with damaged DNA, their survival is highly dependent on the DNA repair mechanisms, which activate proteins detecting, signaling and repairing the breaks. By inhibiting these mechanisms, the cancer cells are deprived of the ability to repair their DNA, which leads to their death, when they try to replicate with a damaged DNA.

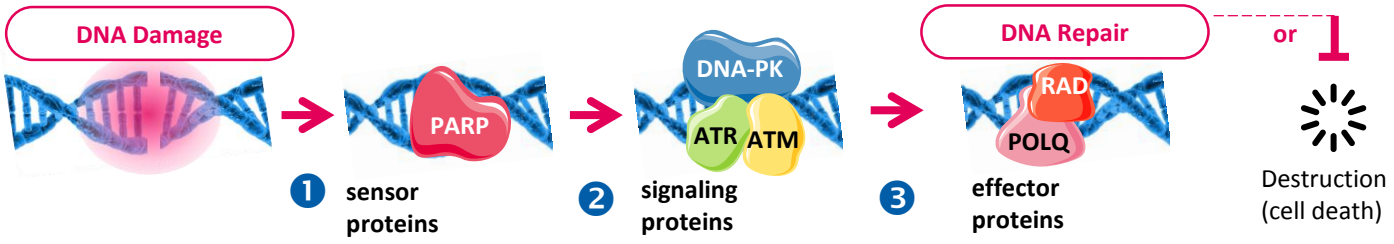
DNA DAMAGE RESPONSE

DNA damage response is a sophisticated cascade of cellular events which can be summarized, in a vey simplified manner*, into three stages:

Detection and identification of the damage with "sensor" proteins such as PARP;

Signaling with "transducer" proteins such as DNA-PK, ATR, etc. whose role is essential in coordinating the most appropriate response, repair of the DNA break or destruction of the cell if the damage is too extensive

Repair with effector proteins such as RAD, POLQ, etc. which will appropriately repair the DNA molecule (resection, replication, insertion, etc.).

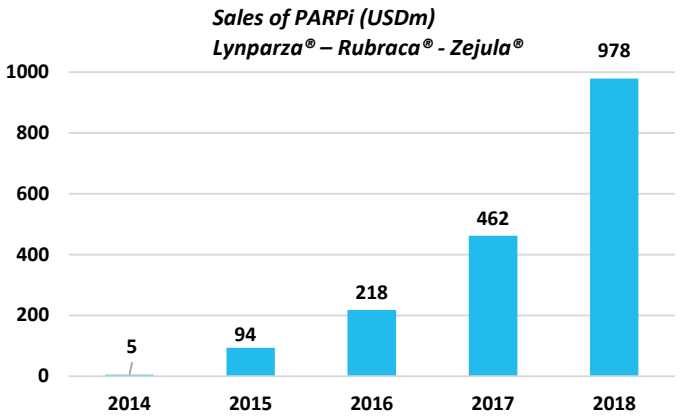


Apart from AsiDNA™ that acts upstream on multiple proteins and pathways, all drugs or candidates developed with this approach are "targeted" therapies which inhibit a particular protein, such as the PARP inhibitors (PARPi), one of the proteins involved in DNA repair.

** In particular, each protein can have several roles*

A FIRST CLINICAL AND COMMERCIAL SUCCESS, THE PARP INHIBITORS (PARPi)

The DNA repair inhibitors' market was initially invested by the PARP inhibitors, one of the DNA damage response proteins, with the approval of the AstraZeneca product olaparib (Lynparza®) in advanced ovarian cancer at the end of 2014.



PARPi approved

Molecule	Trade name 1st approval	Manufacturer	Indication
olaparib	Lynparza® - 12/2014	AstraZeneca	Ovarian, Breast
rucaparib	Rubraca® - 12/2016	Clovis Oncology	Ovarian
niraparib	Zejula® - 03/2017	Tesaro (GSK)	Ovarian
talazoparib	Talzenna® - 10/2018	Pfizer	Breast

PARPi sold in 2018 made revenue of around one billion dollars (1) for the treatment of breast and ovarian cancer. They continue to extend the field of their indications with clinical trials underway in broad indications such as lung or pancreatic cancer.

PARP inhibitors depend on certain genetic mutations, particularly those of the BRCA genes. Despite this limitation, PARPi have shown a real clinical benefit, particularly in ovarian cancer, with, for example for olaparib, a survival rate without progression higher than 60% after 3 years, compared to 27% after chemotherapy (2).

The mechanism of action of AsiDNA™ does not require a particular genetic mutation to operate and enables complementarity to that of PARPi, thereby increasing their efficacy and reversing the resistance to their treatment.

AsiDNA™, A MECHANISM OF ACTION UNLIKE ANY OTHER IN THE FIELD OF DDR

AsiDNA™ lures and sequesters multiple DDR proteins, exhausting the ability of the tumor cell to produce them

AsiDNA™ has a multi-target, decoy agonist mechanism of action, which is unique in the field of DDR

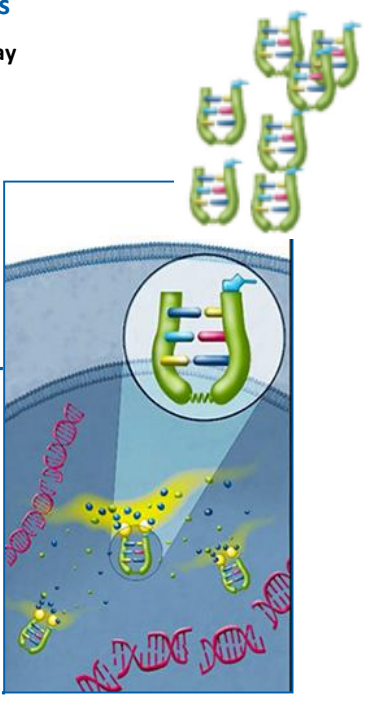
- **Unlike targeted therapies, AsiDNA™ acts on many proteins, particularly PARP and DNA-PK which are involved very early in the damage response, from the detection and signaling stages.**

AsiDNA™ does not cause any resistance and reverses resistance to other treatments

- **AsiDNA™ acts on all repair pathways: the tumor cell cannot use another protein or repair pathway to resist its action, which is the case with targeted therapies.**

The more AsiDNA™ is used as a treatment, the more effective it becomes

- **AsiDNA™ is not opposed, but on the contrary encourages, hyper-activates and diverts a natural biological process which is essential for the survival of the tumor cell, and which it cannot stop. Thus, AsiDNA™ is increasingly effective as the tumor cell exhausts its ability to respond to its DNA damage.**



1. AsiDNA™ mimics DNA breaks in the tumor cell, sends false alarms (**decoy mechanism**) then binds and activates key proteins of the DNA Damage Response
2. **This sustained artificial DNA damage signaling (agonist effect) leads to exhaustion of the tumor DNA repair mechanisms**
3. The actual tumor DNA breaks are not repaired and accumulate: the cancer cells die when they replicate with damaged DNA.

(1) Evaluate Pharma - (2) Moore et al. N Engl J Med 2018; 379:2495-2505

UNPRECEDENTED BIOLOGICAL PROPERTIES, SUPPORTED BY A STRONG PRECLINICAL PLAN

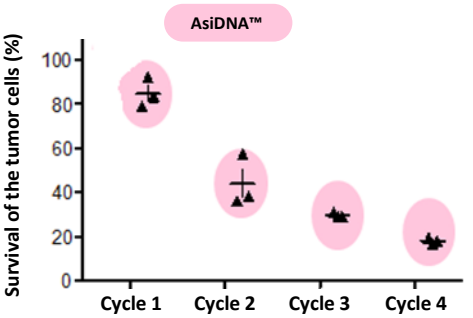
AsiDNA™ does not induce resistance

Unlike targeted therapies that always induce resistance in the longer or shorter term, AsiDNA™ progressively sensitizes the tumor cells to its action which makes it increasingly effective as the treatment is repeated.

As they are exposed to AsiDNA™, fewer and fewer tumor cells survive in this experiment carried out on non-mutated triple negative breast cancer cell lines (low sensitivity to the PARPi).

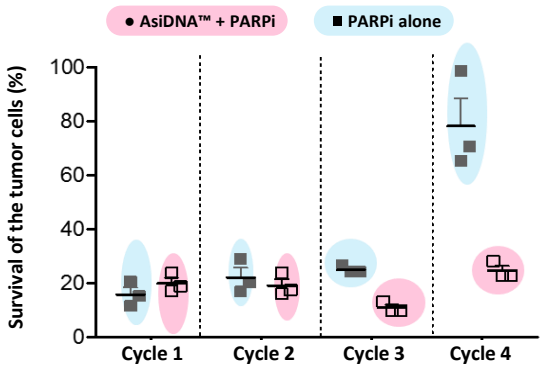
Growing efficacy of AsiDNA™ in a non-mutated triple negative breast cancer model

After 4 cycles, almost all the tumor cells are destroyed.



AsiDNA™ reverses the acquired resistance to other treatments

Example of reversed resistance to a PARPi in a lung cancer model



■ PARPi alone

As of the 4th treatment cycle, the PARPi is no longer effective: the tumor cell has developed an alternate pathway against the effect of the PARPi and becomes resistant.

● AsiDNA™ + PARPi

Co-treated with AsiDNA™, the cells cannot establish alternative pathways and remain sensitive to the treatment even after the 4th exposure.

All targeted therapies are faced with the phenomenon of acquired resistance: the tumor cells set up and use alternative bypass pathways and treatments are then no longer effective.

Not only does AsiDNA™ induce no resistance, but it has shown its ability to stop and even counter the resistance to other targeted treatments, such as the PARPi, when it is combined with them.

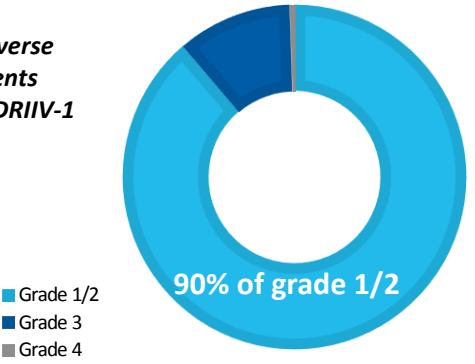
AsiDNA™ has shown an ideal tolerance profile for combinations in two phase I human trials

AsiDNA™ has demonstrated a very favorable tolerance profile in two phase I clinical trials, DRIIM and DRIIV-1. Administered intravenously in DRIIV-1, the maximum tolerated dose was not reached. This good tolerance is particularly important to fully develop the potential of AsiDNA™ in combination, and for targeting greater efficacy without increasing the toxicity. In particular, AsiDNA™ does not present the severe adverse effects of traditional treatments, such as chemotherapy or radiotherapy.

DRIIV-1 also validated the tumor activity of AsiDNA™ in humans – the proof of its mechanism of action in the tumor cell when administered intravenously.

AsiDNA™ has an ideal tolerance profile to be combined with many other anti-cancer treatments, without increasing their toxicity.

Adverse events in DRIIV-1



AsiDNA™ has a new and unique mechanism of action with the potential to bypass cancer cells resistance to treatment while sparing healthy cells.
Professor Tomas Lindahl *– joint recipient of the 2015 Nobel Prize in Chemistry*

These unique properties of AsiDNA™ are major differentiation points in respect of other products in the field of DDR and which open up numerous possibilities for clinical development, particularly in combination.

A BOOMING FIELD, WITH MANY STRUCTURING AGREEMENTS

There are tens of clinical trials underway in the field of DDR, either for new molecules inhibiting one of the repair proteins (CHK1, ATR, ATM, etc.) or for treatment combinations, particularly to overcome the phenomenon of acquired resistance.

Apart from four PARP inhibitors that have been approved, most of the other molecules are at an early development stage, in pre-clinical or in phase I/II, just like AsiDNA™.

The field of DDR is of interest to many renowned players and is part of a strong partnership, M&A and licensing activity, due to the potential combinations it offers with other types of therapies such as immuno-oncology.

AstraZeneca and Merck KGaA are very committed to DDR, with respectively 6 and 4 products in their portfolio targeting this field.

ACQUISITIONS

of Tesaro (niraparib) by GSK (12/18)
of Medivation by Pfizer (08/16)
of KuDOS by AstraZeneca (12/05) …

STRATEGIC PARTNERSHIP

between AstraZeneca and Merck & Co, particularly to explore the combinations between PARP inhibitors and immunotherapies, etc.

CLINICAL COLLABORATIONS

between Roche/Genentech and Tesaro
between Clovis Oncology and BMS …

LICENSES

from Vertex programs in DDR to Merck KGaA
from Repare Therapeutics to Ono Pharmaceuticals
from Tesaro to Takeda and Janssen
from Biomarin to Medivation …

The acquisition of AsiDNA™ in 2016 has clearly positioned Onxeo in a booming therapeutic area that is generating a strong partnership activity in the widest sense. The development activities carried out since then have highlighted the unique potential of this product, and the next clinical milestones will be key in further reinforcing the value of this asset.

OVERVIEW OF UPCOMING ISSUES OF THE AsiDNA™ LETTER …

- **A word from the CMO: foreword of Olivier de Beaumont, Chief Medical Officer of Onxeo**
- **A closer look at the potential indications of AsiDNA™**
- **Why combinations are the norm in oncology**
- **Interviews of renowned oncologists**
- **…**

We wish you a lovely summer and look forward to sharing the next issue with you.

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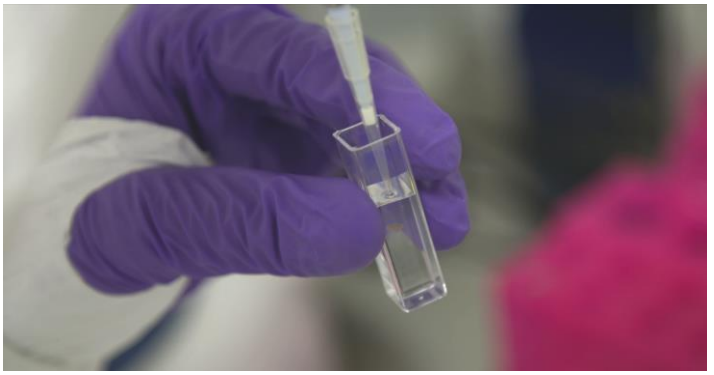

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