AsiDNA™ Letter - No. 2

Role of AsiDNA™ in the new combination strategies

IN THIS EDITION

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Medical Director

AsiDNA™ is ideally positioned to play a key role in new combination strategies aiming to treat cancers, for which the medical needs remain significant.

A WORD FROM THE MEDICAL DIRECTOR

Ladies, Gentlemen and Shareholders,

The complexity and diversity of cancers require multiple therapeutic approaches. The combination of several anti-cancer agents has become the norm in oncology, especially to treat the very aggressive or resistant cancers.

Thanks to its original anti-tumor activity and its good tolerance already clinically demonstrated, AsiDNA™ is ideally positioned to play a key role in new combination strategies aiming to treat these cancers, for which the medical needs remain significant.

AsiDNA™ could therefore become a new essential anti-cancer agent in numerous combinations, and this is the objective that we are setting through a reasoned and ambitious clinical development program.

We have already started the DRIIV-1b clinical study that combines AsiDNA™ with two reference chemotherapy treatments and expect to initiate new combination studies within the coming months, notably with a PARP inhibitor.

In this Letter, we are approaching these combinations from the standpoint of two potential indications for AsiDNA™, triple-negative breast cancer and advanced ovarian cancer, two aggressive pathologies with an unfavorable prognosis.

I wish all of you pleasant reading and look forward to the end of summer for new information regarding the progresses in our developments.

WHY COMBINE ANTI-CANCER TREATMENTS?

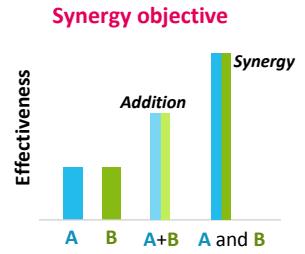
Surgery, radiation, and chemotherapy have been the traditional, treatments for cancer for a long time, used alone, successively or in combination. For example, many solid tumors are treated first by radiation to reduce the tumor, then by surgery to remove as much tumor as possible, and finally, by chemotherapy treatment(s) to eliminate every remaining tumor cell. Similarly, the reference treatment for some cancers such as breast or ovarian cancer is the combination of two chemotherapy treatments, carboplatin and paclitaxel.

Most often, combined therapy increases the chances for recovery or for long-term remission. Indeed, a first treatment can make a tumor more vulnerable to a second one. Or else, the medications act together, each one increasing the strength of the other ones, so that their combined effectiveness is greater than the addition of their individual impacts (synergy). Combining treatments may also enable using lower doses, thus limiting their toxicity or delaying the onset of resistance.

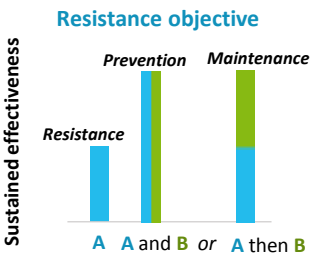
Combined therapy, that is, the utilization of several agents in the treatment of a patient, has become the norm in the treatment of cancer today.

Some new medications today complete the traditional triad, such as "targeted" therapies that aim at genes or at specific proteins in tumor cells, medications that "starve" the tumors or prevent their growth and immunotherapies which uses the immune system against tumors, etc. As with traditional treatments, these new treatments have limitations or are faced with the resistance of tumors.

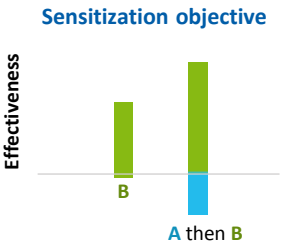
They are thus also evaluated or approved in combination with reference treatments to increase their effectiveness.



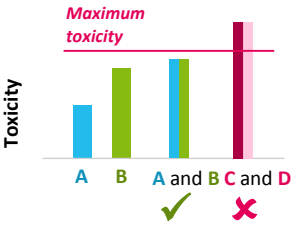
Greater combined effectiveness



Increasing the length of effective treatment



Make the tumor vulnerable to increase the effectiveness



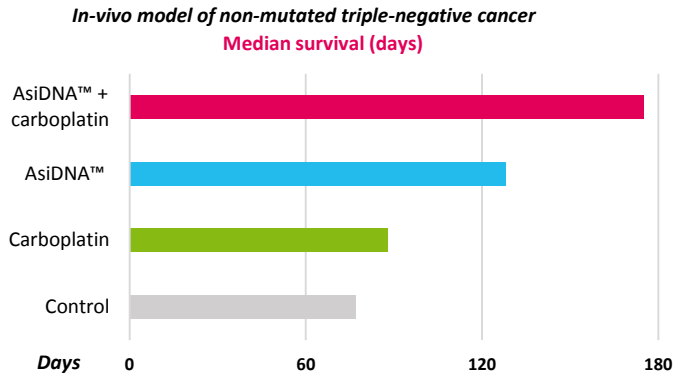
No worsening of the toxicity

AsiDNA™ sensitizes tumor cells, does not trigger resistance and even abrogate the resistance to other treatments, and offers good tolerance. This is an ideal profile to be combined with many other new anti-cancer treatments, as well established ones.

AsiDNA™ has demonstrated its synergy with chemotherapy by increasing the median survival significantly in preclinical studies

AsiDNA™

TRIPLE-NEGATIVE BREAST CANCER AND CHEMOTHERAPIES



For the most common breast cancers, there are some very effective, targeted therapies and many women are cured from their breast cancer today. Yet, 15 to 20% of these patients have a "triple-negative" (TNBC) breast cancer, that is, without any hormonal or protein receptor in the surface of the cancer cells, likely to respond to a targeted therapy. These are very aggressive cancers with a high risk of metastatic recurrence within 3 years of diagnosis. The standard treatment is chemotherapy, with high toxicity risks.

For this cancer with a poor prognosis and difficult to treat, the combination of chemotherapy treatments that cause breaks in the DNA and a compound like AsiDNA™, which prevents the repair of the DNA breaks, is a clinical development pathway supported by the preclinical demonstration of a strong synergy of AsiDNA™ with chemotherapy, including in non-mutated, resistant tumors such as triple-negative breast cancer.

This is why, **DRIIV-1B**, the first AsiDNA™ combination clinical study that began in May 2019 combines it to carboplatin and to paclitaxel in the indications of this chemotherapy, of which TNBC.

First results on the tolerance of the combination and signals of effectiveness are expected at the end of 2019.

A next development phase of AsiDNA™ could be a phase 2 in combination with carboplatin and paclitaxel in triple-negative breast cancer, before ablation surgery of the tumor. The objective would be to increase the complete pathological response rate.

The tolerance profile of AsiDNA™ observed in monotherapy allows us to consider this combination, where a greater effectiveness without worsening of toxicities observed with chemotherapy is being sought. ***Dr. Nuria Kotecki*** *- Institut Jules Bordet - Brussels*

OVARIAN CANCER AND PARPi

Ovarian cancer is the 5th most common cancer among women in developed countries. The majority of the women are diagnosed at the advanced stage (III or IV), where the survival rates are mediocre at 5 years, around 27%[1]. Despite the initial responses raised in chemotherapy based on platinum and surgery, more than 70% of these patients will within 3 years, with few options for effective[2] treatment. In this indication, the PARP (PARPi) inhibitors have brought new hope to patients carrying a BRCA gene mutation and suffering from advanced ovarian cancer. In the Phase 3 SOLO-1 trial, olaparib, used in first-line maintenance of chemotherapy, allowed 60% of the patients to have no disease progression compared to only 27% in the control group. In the absence of the BRCA mutation, the effectiveness of PARPi is much lower and requires combination strategies for which AsiDNA™ provides very significant advantages.

(1) OMS, 2008; (2) Siegel et al, 2012; Hanker et al, 2012

Simplified diagram of the reference treatment in ovarian cancer

1. **Chemotherapy as 1st line treatment**
   - *If response* →
2. **PARPi as 1st line maintenance**
   yet inevitable resistance in the more or less long-term
   - *If maintenance > 6 months without relapse* →
3. **Chemotherapy as 2nd line treatment** after relapse
   - *If response* →
4. **PARPi as 2nd line maintenance, etc.**

A 1st combination clinical study could be initiated at the end of 2019, to validate the abrogation of resistance to the PARPi by AsiDNA™

AsiDNA™ would be particularly well-suited to a combination with a PARPi. The effect of AsiDNA™ is not limited by the presence of a BRCA gene mutation and its agonist (activating) effect on the repair proteins has shown a synergy of effectiveness with PARPi and especially, the abrogation of the acquired resistance to PARPi, *a unique property.*

Example* of the phase 1b/2 design combining AsiDNA™ to a PARPi in 1st line of maintenance in advanced ovarian cancer

4. **PARPi in 2nd line of maintenance**
   - *From 6 months* →
   - **Monitoring of the CA-125 resistance biomarker**
     - *Elevation of CA-125* → *Introduction of AsiDNA™*
5. **PARPi + AsiDNA™**
   - *Monitoring of CA-125*

*The elevation of **CA-125** marks the inevitable appearance of a relapse, and is validated as a reliable sign of the appearance of resistance to PARPi.*

Objectives

- **Good tolerance of the combination**
- **Stop or break the resistance**
- **Prolong the treatment by PARPi and its effect on the survival without progression**

** Illustrative example only. The effective kick-off of such a study and its final approved design would be the subject of a press release*

THE POINT OF VIEW OF THE ONCOLOGIST: 3 QUESTIONS TO DR. JEAN-PIERRE BIZZARI

What do you think of the potential of AsiDNA™ in oncology?

Dr. Bizzari: I joined the Board of Directors of Onxeo at the beginning of 2016, when the company purchased DNA Therapeutics and its product - AsiDNA™, in part because I consider the potential of this product and its underlying technology, platON™, with lots of enthusiasm. Immunotherapy has revolutionized the world of oncology for the past 5 years. The entire pharmaceutical industry has since been dedicating resources in this area, not without reason, but in turn neglecting innovation in any other field. The approach that consists of acting on the repair mechanisms of tumor DNA has already shown important clinical benefits with the success of PARPi. Within this approach, AsiDNA™ presents a particularly interesting and unique mechanism of action. It represents one of the rare, radically innovative projects in development today. Now that its systematic activity has been demonstrated in the DRIIV study, it is possible to consider its combination with a large number of traditional chemotherapy treatments or targeted therapies like the PARP inhibitors.

Why did you choose you to demonstrate first the potential of AsiDNA™ in combination with other treatments?

Dr. Bizzari: Molecules such as AsiDNA™ that act on DNA repair pathways have no cytotoxic action, they do not directly destroy tumor cells but lead indirectly to their death by inhibiting or by preventing mechanisms necessary for their survival. These products have therefore a very strong added-value in the modern strategies of combined therapies against advanced or aggressive cancers and those naturally resistant to cytotoxic drugs. For this type of difficult indications, clinicians like regulators are in search of innovative combinations to improve the therapeutic effectiveness of current therapies and it is in this context that AsiDNA™ can most quickly show proof of its value. Certainly, monotherapy remains an objective, and bio-markers of genetic sensitivity with AsiDNA™ currently being validated to allow this utilization in the future, for patients who are responding best to its action. But the priority remains combination strategies that offer quicker development conditions and better market access opportunities to AsiDNA™.

Why evaluate first the combination with chemotherapy ?

Dr. Bizzari: Chemotherapy treatments remain the foundation of the anti-cancer therapeutic arsenal, with established and well-controlled treatment modalities. At the advanced stages of cancer, 40 to 50% of the patients will receive one or several chemotherapies during their treatment. But chemotherapy treatments can be ineffective or partially effective, particularly in the presence of an innate or acquired resistance by the tumors. From a purely operational standpoint, evaluating first the combination of AsiDNA™ with chemotherapy presented the advantage of having rapid access to a broad patient population, in indications of advanced or aggressive cancers for which the needs of therapeutic solutions remain very significant. In addition, AsiDNA™ has shown in preclinical studies a very strong synergy with reference platinum-based chemotherapy treatments such as carboplatin, a cytotoxic drug that breaks the DNA. AsiDNA™ disturbs and exhausts the DNA repair capabilities of the tumor cell. It is therefore particularly well adapted to a combination with these chemotherapy treatments.

BIO **Jean-Pierre Bizzari**

A medical doctor specialized in oncology, Jean-Pierre Bizzari was notably the Executive Vice-President and Manager of Clinical Development in oncology of Celgene up to 2015. He has been the Director of Onxeo since 2016 and member of the scientific council of the INC (National Cancer Institute) and the EORTC (European Organisation for Research and Treatment of Cancer).

AsiDNA™ represents one of the rare, radically innovative projects in development today.

UTILIZING FULLY THE POTENTIAL OF AsiDNA ™ IN COMBINATION

Multiple combination options* in indications with unmet medical needs

AsiDNA™

+ **Chemotherapy** — *Indication: breast*
Objective: synergy
DRIIV-1b study in progress

+ **PARP inhibitor** — *Indication: ovary*
Objective: abrogation/ reversal of resistance

+ **Radiotherapy** — *Indication: sarcoma, glioblastoma, etc.*
Objective: sensitization, synergy

+ ... *Preclinical validation of other combinations in progress*

Combining AsiDNA™ with other anti-cancer agents offers a significant and fast potential for value creation in the short and mid-term.

That is why Onxeo is considering an extensive clinical program to study AsiDNA™ in combination, which began with the DRIIV-1b proof of concept study (AsiDNA™ and chemotherapy), and which is going to continue in 2019 and 2020, as industrial or academic partnership agreements progress.

Proof of concept of the combination of AsiDNA™ with a PARPi is a priority since their complementary action mechanisms enable the abrogation of acquired resistance to PARPi, an unprecedented class effect. This effect can be quickly highlighted thanks to a resistance biomarker, that allows considering a brief study with rapid results, in ovarian cancer for example.

Similarly, in the wake of DRIIV1-b, a phase 2 evaluating the combination of AsiDNA™ with pre-surgery chemotherapy can be carried out within the framework of brief, well-established protocols for very virulent cancers, such as metastatic breast cancer. The evaluation of the benefit of the combination of AsiDNA™ in this setting could be quick, on the basis of the residual size of tumors post-excision.

The program of clinical studies plan of AsiDNA ™ in combination aims to obtain short-term, material and measurable results. It will target defined indications, with significant unmet medical needs and in priority, indications for which an orphan drug designation and an accelerated access to the market are possible.

** Combinations and indications only for example and illustrative purposes. The effective developments will be the subject of press releases.*

KEY SHORT-TERM DEVELOPMENT MILESTONES

S1 2019

- ✓ *1st patient included in the phase 1b (DRIIV-1b) study of AsiDNA™ in combination with chemotherapy (carboplatin + paclitaxel).*

S2 2019

- ✓ *Final DRIIV-1 data (tolerance, PK / PD, bio-markers, etc.)*
- **In-vivo pre-clinical proof of concept of a new combination**
- **Preliminary results of DRIIV-1b**
- **Presentation of the DRIIV-1 results at the EORTC conference (Boston, United States)**
- **Filing a phase 1b/2 application in combination with a PARPi**
- **Filing a clinical trial application (IND) in the United States**

S1 2020

- **Initiation of a 1b/2 study in combination with other agents**
- **Final DRIIV-1b results**
- **Initiation of a phase 2 in combination with chemotherapy**
- **Preliminary results of combination studies**

AND NUMEROUS MEETINGS AFTER THE SUMMER!

- **Continuously: new AsiDNA ™ Letters to illustrate our developments**
- **Investir Day on October 3, in Paris, France**
- **MidCap Event on October 14-15, in Paris, France**
- **Galien MedStart'Up Event on October 23-24, in Boston, US**
- **Presentation of the DRIIV-1 results at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics on October 26-30, in Boston, US**
- **Direct Dirigeants Event on November 6, in Paris, France**

We wish you a lovely summer and look forward to discussing more news in September

Management Team

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