Long stabilization and disease control with AsiDNA™, a first-in-class DNA Repair Inhibitor in combination with carboplatin with or without paclitaxel in patients with advanced solid tumors: A case report

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Abstract

Chemotherapy and radiotherapy represent the backbone of treatment for many cancers at different stages of the disease. While these treatments have been highly effective, recurrence rate of these cancers remain high, partially due to drug resistance and DNA repair mechanisms. AsiDNA™, a first-in-class oligonucleotide mimicking double-stranded DNA breaks acts as a decoy agonist to DNA damage response in tumour cells. AsiDNA™ was investigated in a phase I dose escalation part of DRIIV-1 study, as single agent (part A of the study) in patients with advanced solid tumors who failed standard anticancer therapy. The drug demonstrated to have a favorable safety and pharmacokinetic profiles, and a robust target engagement was evidenced in tumour biopsies. Part A established the dose of 600 mg as the optimal dose for part B and further clinical development. Currently, AsiDNA™ is investigated in combination with carboplatin with or without paclitaxel (part B of the study) in patients with advanced solid tumors candidate to carboplatin, with the objective to sensitize tumors to carboplatin. A total of 9 patients were treated in part B as of October 18th, 2020; 3 in part B1 with the doublet combination of AsiDNA™ and carboplatin and 6 in parts B2 with the triplet combination of AsiDNA™ with carboplatin and paclitaxel. In this article we discuss 4 case reports of patients with advanced solid tumors treated with AsiDNA™ in combination with either carboplatin or carboplatin plus paclitaxel, for which the treatment with AsiDNA™ resulted in long stabilization. Interestingly, delivered doses of carboplatin were maintained a long time before occurrence of toxicities resulting in dose reduction. AsiDNA™ may play a key role in new combination strategies aiming to treat aggressive and resistant cancers for which the medical needs remain significant.

Keywords: AsiDNA™, DNA Double-Strand Breaks (DSBs), DNA damage response, NSCLC, Carboplatin

Introduction

Despite constant promising medical advances in cancer treatment and patient's care, most of the patients whose disease initially respond to anticancer therapies will develop acquired resistance. Chemotherapy and radiotherapy represent the backbone of treatment for many cancers at different stages of the disease, and their cytotoxicity is at least partly due to unrepaired DNA damage, whereas the ability of cancer cells to recognize DNA damage and initiate repair, is an important mechanism of resistance [1-3]. DNA double-strand breaks (DSBs) are the most severe types of DNA damages that, if left unrepaired, are lethal to the cell [4]. Pharmacologic inhibition of DNA repair has the potential to make cancer cells more vulnerable to the damaging effects of cancer therapies, therefore increasing the response to treatment [5]. Thus, a new concept based on "DNA bait" (DBait) has been recently developed, which uses agonists of enzymes that signal DNA damage in the cell to inhibit DNA repair and trigger a massive false signal, preventing DNA repair enzymes recruitment to sites of DNA damages [6-9].

AsiDNA™ is the lead molecule of this Dbait family. The drug was designed to prevent the repair of DNA damage in tumor cells and thereby to treat cancers. AsiDNA™ consists of a 32 base pair oligonucleotide forming a double helix that mimics double-strand breaks (DSBs) in the tumour cell, sends false alarms (decoy mechanism) then binds, diverts and hyper activates key proteins of the DNA Damage Response (DDR), especially DNA-PK protein complex, and its downstream targets such as histone H2AX. This sustained artificial DNA damage signal (agonist effect) blinds the efficient detection and repair of DSBs and creates a transient drug-driven homologous recombination (HR) and Non-Homologous End -joint (NHEJ) repair deficiencies. The actual tumour DNA breaks are not repaired and accumulate: the cancer cells die when they replicate with damaged DNA. By acting so, AsiDNA™ induces a drug-driven HR deficiency, a pre-requisite genetic alteration in tumours cells to be highly sensitive to several anti-cancer therapies, especially carboplatin and Poly (ADP-Ribose) Polymerase inhibitors (PARPi). NHEJ DSB repair pathway, which is the major DSB repair mechanism when the HR pathway is deficient, is also abrogated by AsiDNA™ (Figure 1), leading to a multi drug driven DSB repair deficiency, and ultimately DNA damage accumulation and cell death. [7,8].

AsiDNA™ is currently investigated in a Phase 1 trial (The DRIIV-1 [DNA Repair Inhibitor-administered IntraVenously] study). The study was run in 2 parts: 1) Part A: AsiDNA™ as single agent started in April 2018 and was completed in April 2019. The aim of part A was to determine dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, pharmacokinetics/pharmacodynamics (PK/PD) of AsiDNA™ in patients with advanced solid tumours who failed or were not eligible to standard therapy. AsiDNA™ was administered intravenously daily for three days in the first week then weekly thereafter until disease progression, unacceptable toxicity or patient's refusal to continue, whichever occurred first. A total of 22 patients were enrolled in 5 dose levels: 200, 400, 600, 900, and 1300 mg, using a 3 +3 design. Results were recently published [10] and showed that AsiDNA™ as single agent was well tolerated up to the dose of 1300 mg. The MTD was not reached; two DLTs (Grade 4 and Grade 3 hepatic enzymes increased at 900 and 1300 mg) were reported. Most Treatment Emergent Adverse events (TEAEs) were of mild-to-moderate intensity and most common related ones were asthenia and tinnitus reported in 4 (18.2%) patients, each, followed by AST enzymes increased and hypercholesterolemia in 3 (13.6%) patients each, fatigue, ALT enzymes increased, abdominal

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pain, diarrhea, nausea and anemia in 2 (9.1%) patients each. IV AsiDNA™ PK exhibited a linear dose proportionality in the range of the tested doses. A robust activation of DNA-PK by a significant post-treatment increases of δH2AX and/or pHsp90 was evidenced in tumour biopsies at all dose levels (except DL1:200 mg; no tumour tissue) with highest levels observed at 600 mg (DL3). Also, measurement of tumours cell proliferation by Ki67 expression revealed a decrease or a stabilization in 90% of patients after one cycle of AsiDNA™ treatment. The best overall response was stable disease in 2 patients with metastatic colorectal cancer treated at 600 mg. The dose of 600 mg was identified as the optimal dose for part B of the study and for further development given the favorable safety and PK profiles, and the observed robust target engagement 2) Part B: started in May 2019 and tested AsiDNA™ in patients with advanced solid tumours candidate to carboplatin with the objective to sensitize tumour to carboplatin (increase and/or maintain response to carboplatin). In part B, AsiDNA™ was given at a loading dose on Days (D) 1, 2, 3 then weekly on D8, D15, D22 of a 28 days treatment period during the first cycle followed by a weekly infusion (D1, D8 and D15) of a 21 days treatment cycle in the subsequent cycles in combination with carboplatin area under the curve 5 (AUC 5) on D8 of the first cycle and on D1 of the subsequent cycles (part B1), or with carboplatin used at same dose and schedule as in part B1 in combination with paclitaxel given at the dose of 80 mg/m^2 on D8, D15 and D22 of a 28 day-treatment cycle at cycle 1 and then repeated weekly at D1, D8, D15 of each subsequent cycle (part B2). Part B of the study is still ongoing with a total of 9 patients treated up to October 19th, 2020 (3 patients in part B1 and 6 patients in part B2) (Table 1). Preliminary results (not yet published) show that when AsiDNA™ is combined to carboplatin with or without paclitaxel, the most common reported related TEAEs were diarrhea (in 50% of the patients, all in part B2) and fatigue (33.3% in part B1 and 50% in part B2). There were 4 related (to AsiDNA™ and /or chemotherapy) severe TEAEs reported in 3 (33.3%) patients; 2 patients in part B1 (G3 fatigue, G3 neutropenia and G3 diarrhea) and in one patient (G3 peripheral sensory neuropathy) in part B2. No related TEAEs of grade > 3 were reported during part B1 or part B2 of the study. Of the 9 patients treated in part B, 3 had disease progression as best response (progressed after 2 cycles of treatment), one was non evaluable, and 5 patients showed sign of activity of the doublet or triplet combination (one patient had a partial response and 4 had a stable disease as best response). We propose to describe and discuss 4 of these cases here.

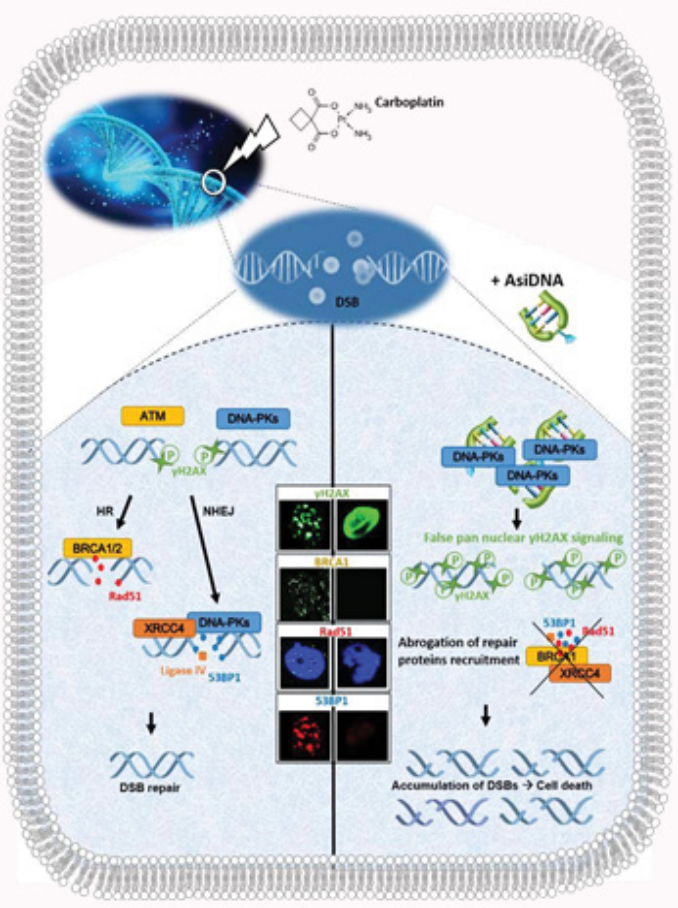
Case Series

Case N°1

A 61-year-old male was initially diagnosed with a stage III squamous non-small cell lung cancer (NSCLC). He received front line chemotherapy with cisplatin and vinorelbine, followed by radiotherapy; he achieved a complete remission and remained in complete remission for 4.5 years. He then presented a loco-regional relapse in the right hilar for which he underwent 6 months of chemotherapy with cisplatin plus vinorelbine with stable disease as best response. Ten months later, a second locoregional relapse was noted and the patient, whose tumours expressed PD-L1 with a ≥ 50% TPS, was started with pembrolizumab for 5 months, then a disease progression was reported in the right hilar and local lymph nodes. The patient was enrolled in the DRIIV-1b study to receive the combination of AsiDNA™ 600 mg with carboplatin AUC 5 as 3d line for advanced disease. The patient had in total 12 cycles of the combination, with no significant toxicity related to AsiDNA™. The dose of carboplatin was reduced to 20% on Cycle 11 due to the occurrence of adverse event (tinnitus grade 1). On D1 of Cycle 12, the patient experienced allergic reaction to carboplatin during the infusion, which lead to permanent interruption of carboplatin. Tumour response was evaluated every 2 cycles and showed disease stabilization after 2 cycles which was maintained up to Cycle 12. A disease progression was noted by CT scan post Cycle 12 and the patient was ultimately removed from the trial. He did not receive any further anticancer therapy and died from his disease.

Case N°2

A 72-year-old female with an initial stage II metaplastic triple negative breast cancer (TNBC) without germline mutation. She was initially treated with neo-adjuvant fluorouracil-epirubicin and cyclophosphamide (FEC) regimen, followed by surgical resection (lumpectomy with axillary lymph nodes dissection) and radiotherapy. Eleven months later, she was diagnosed with a relapse in the same breast, the patient underwent a mastectomy. One month later, she was found with a lung metastasis and received 4 cycles of chemotherapy with docetaxel; she achieved a complete response on the lung, but a new lesion in the liver was noted. The patient stopped treatment and did not receive any treatment (wait and watch attitude) for 6 months, until new lesions were noted in



Note: Tumor cells treated with a DNA damaging agent, such as Carboplatin, will accumulate DNA Double-strand breaks (DSB), which will be managed especially by homologous recombination (HR) or Non-Homologous End-joining (NHEJ) DSB repair pathways. Indeed, DSB are "tagged" through the phosphorylation of histone H2AX (γH2AX – focalized green signal) in the vicinity of the DSB, a signal which will initiate a cascade of damage signaling, detection and repair, involving different repair proteins like 53BP1, which is recruited to sites of DSB (focalized red signal). This well-orchestrated repair machinery fixes the DSB leading to tumor cell survival. When combined to Carboplatin, AsiDNA molecules are recognized by DNA-PK as a DSB (the decoy agonist mechanism). This trigger a hyperactivation of DNA-PK and its down-stream targets such as histone H2AX. Thus, a false pan-nuclear γH2AX signaling is induced (diffuse green signal), and DNA repair proteins like 53BP1, BRCA1 or RAD51 are no more recruited to sites of genomic DSB, leading to a drug-driven HR and NHEJ deficiencies. Carboplatin-induced DSB are not repaired and accumulate in the nucleus, leading to tumor cell death.

Figure 1. AsiDNA, a decoy agonist driver of DSB repair deficiency and sensitizer to DNA damaging agents.

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Table 1. Summary of patient's characteristics treated in DRIIV-1b study.

AsiDNA IV 600 mg	Sex/ Age	Tumor type and TNM stage at initial diagnosis	Metastatic site at start of AsiDNA	Prior lines of anticancer therapy and best response	N° of cycles received/ duration	Best response
Combo A+C	F/54	Stage III Gastric	Abdominal wall/ mesentery	Surgery Primary tumor (Stomach, Pancreas, Gall bladder) Adjuvant: Folfox (Oxaliplatin, 5-Fluorouracil, Folinic Acid) + 5-FU L1: Paclitaxel, Ramucirumab B, best response unknown, PD 4 mo L2: Folfiril (Irinotecan, 5-Fluorouracil, Folinic Acid), Best response unknown, PD 5 mo.	2 (1.5 mo)	PD
Combo A+C (Case N°1)	**M/61**	**Stage III NSCLC**	**Right hilar pulmonary/ Mediastinal lymph nodes**	**CDDP-Vinorelbine then RDT for stage III initial diagnosis, CR 4.5 y** **1st locoregional relapse: CDDP+ Vinorelbine, SD 6 mo** **2nd locoregional relapse: Pembrolizumab, SD 5 mo**	**12 (8,5 mo)**	**SD**
Combo A+C (Case N°2)	**F/72**	**Stage II TNBC**	**Lung/liver**	**Neoadjuvant Fluorouracil-Epirubicin-Cyclophosphamide / surgical resection/RDT** **1st local relapse in breast removed by surgery** **L1: Docetaxel, CR on lung, new lesion on liver** **L2: Antibody-drug conjugate (investigational drug), SD** **L3: Capecitabine, CR on liver new lesion on lung** **L4: Eribulin, PD** **L5: Doxorubicin, SD, 4.5 mo**	**7 (5.5)**	**SD**
Combo A+C+P (Case N°3)	**M/50**	**Stage IV NSCLC**	**Lung and buttock nodule**	**L1: Pembrolizumab/palliative RDT to brain, SD 7 mo**	**14 (10 mo)**	**PR at cycle 4 SD at cycle 10**
Combo A+C+P (Case N°4)	**F/62**	**Stage IV NSCLC**	**Bone/lung**	**L1: CDDP+pemetrexed/palliative RDT to bone** **L2: Nivolumab/ palliative RDT to bone, SD, 11 mo** **L3: Docetaxel 1 inj, toxicity**	**4 (3 mo)**	**PR at cycle 4**
Combo A+C+P	M/58	Stage III NSCLC	Renal/ lung// mediastinum	L1: CDDP, Pemetrexed L2: Tecentricq, PD 7 mo L3: Docetaxel, Vargaref	4 (3 mo)	SD
Combo A+C+P	M/58	Stage IV NSCLC	Brain/ mediastinal lymph nodes/ adrenal gland	L1: CDDP-pemetrexed +RDT/navelbine +CDDP, 4 mo L2: Nivolumab, PD 16 mo L3: Taxotere + canakinumab	2 (1.5 mo)	PD
Combo A+C+P	M/62	Stage IV Prostate	Breast / axillary	L1: Decapeptil, Casodex, PD L2: Docetaxel, Toxicity 5 mo L3: Xtandi, PD 22 mo L4: Cabazitaxel, PD 6 mo L5: Abiraterone, PD 4mo L6: SIRP ALPHA inhibitor, PD 8 mo	2 (1.5 mo)	PD
Combo A+C+P	F/64	Stage III NSCLC	Lung/adrenal gland/ mediastinum/ brain	Palliative RDT Lung 2018 and brain 2019 Surgery Metastases Lymph Nodes 2018-2019 Neo Adj: Cisplatine, Navelbine L1: Docetaxel, PD 1 mo L2: Atezolizumab, PD 2 mo	<1 (3 d)	NA

A: AsiDNA, C: Carboplatin, CDDP: Cisplatin, P: Paclitaxel, mo: Months, SD: Stable Disease, TNBC: Triple Negative Breast Cancer, L: Line of Anticancer Therapy for Metastatic Disease, PD: Progressive Disease, y: year, NSCLC: Non-Small Cell Lung Cancer, CR: Complete Response, PR: Partial Response, RDT: Radiotherapy, NA: Not Applicable.
In bold: Case reports described in this manuscript.

lung, as an increase of the liver lesion. The patient was therefore treated with an antibody-drug conjugate (ADC) that targets cancer cells expressing transmembrane glycoprotein NMB (GPNMB) (experimental drug) with a SD achieved as best response. The treatment was stopped due to toxicity and one month later disease progression was observed. She was subsequently treated with capecitabine for 8 months. Best response under capecitabine, was complete response on liver metastases, but new lesions appeared in lung. The patient was subsequently treated, with eribulin as 4th line for metastatic disease, with progression on lung and liver, then with doxorubicin with a stable disease as best response for 4.5 months; she progressed after 6.5 months of start of doxorubicin on lung and liver. The patient was then enrolled in the DRIIV-1b study to receive the combination of AsiDNA™ and carboplatin as 6th line of treatment for metastatic disease. She presented still pulmonary and liver metastases. She received 7 cycles of the doublet combination. During the treatment, she experienced a worsening of pre-existing grade 1 fatigue to grade 2, and then grade 3 post C4 D1, assessed as definitely related to chemotherapy and AsiDNA™. The carboplatin dose was reduced to AUC 4 on C5D1 and C6D1. On C6D1, the

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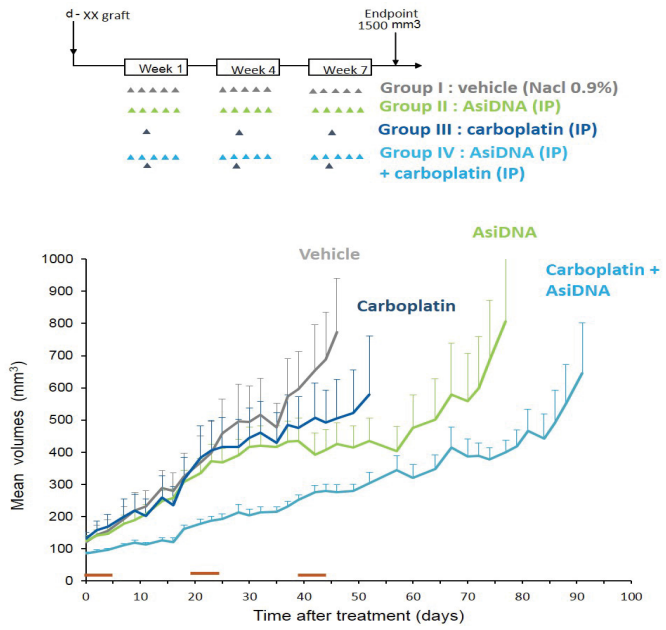

Note: Growth of tumors mock-treated (grey; n=6), treated with carboplatin alone (dark blue; n=8) or carboplatin + AsiDNA (light blue; n=10) was measured during more than three months after treatments start. Data are represented as mean +/- SEM.

Figure 2. Efficacy of the combined treatment Carboplatin + AsiDNA in MDA-MB-231 cell-derived xenografts.

patient experienced allergic reaction grade 1 to carboplatin and neutropenia grade 2 increased to grade 3 which led to delay of C7D1. The dose of carboplatin was further reduced to AUC 3 at C7D1, the patient experienced new episode of allergic reaction of grade 2 to carboplatin on C7D1, despite dose reduction, which lead to patient's withdrawn from the study. The patient achieved a stable disease post C2 which was maintained for 3 months (post C6). Two months later, the patient progressed and received vinorelbine as 7th line, then immunotherapy (experimental drug) as 8th line treatment. The patient died from disease progression.

Case N°3

A 50- year-old male was diagnosed initially with stage IV EGFR Wide-type (WT), ALK/ROS negative NSCLC. He presented lung and cerebral metastases at diagnosis. As the tumor was expressing PD-L1 (TPS 50%), the patient received upfront pembrolizumab (anti-PD-L1) monotherapy, and palliative radiotherapy to the brain. Best response under pembrolizumab was stable disease, which lasted for 7 months. Ten months after the start of pembrolizumab, he progressed on lung and soft tissue (metastatic buttock nodule) and was enrolled in the DRIIV-1b study to receive the triplet combination of AsiDNA™ plus carboplatin and weekly paclitaxel as 2nd line for metastatic disease. He received 14 cycles of AsiDNA™ in combination with carboplatin AUC5 and paclitaxel. The treatment with the triple combination was initially well tolerated and the patient did not experience any significant toxicities related to AsiDNA™ or chemotherapy during the first 6 cycles of the triplet combination. On C7D1, administration of AsiDNA™ and chemotherapy was delayed by one week, and chemotherapy was skipped on C7D15 due to hematological toxicity (grade 2 thrombocytopenia). The dose of paclitaxel was reduced to 80% for all subsequent cycles. On C8D1, carboplatin dose was reduced to AUC 4 due to thrombocytopenia grade 1. After 12 cycles of the combination, best response was stable disease on lung with a new non target lesion in the buttock. The decision was made by the physician that the patient could continue treatment with the combination. The patient received 2 additional cycles; he experienced a grade 1 allergic reaction to carboplatin on C13D1 and a grade 2 allergic reaction to carboplatin on C14D1, which resulted in permanent discontinuation of carboplatin. Tumor evaluation post C14 showed a partial response on lung and soft tissue, but a progression on brain, he was then discontinued from study treatment.

Case N°4

A 62-year-old female was diagnosed initially with a stage IV EGFR WT/ALK /ROS1 negative, PD-L1 unknown non-squamous NSCLC with lung and bone involvement. She received 6 cycles of cisplatin and pemetrexed and palliative radiotherapy on bone lesions. Best response was stable disease after this 1st line chemotherapy for metastatic disease. Eleven months later, a progression on lung was noted on pulmonary CT-scan. She was then treated by nivolumab (anti PD-1) and palliative radiotherapy to the bone, with a stable disease for 11 months on lung. Nivolumab was discontinued and the patient remained on stable disease for 15 months without any further therapy for the metastatic disease except local palliative radiotherapy to the bone, then she was diagnosed with a progressive disease on lung and bone and was consequently treated with docetaxel as 3rd line therapy, which was stopped after the first dose due to an allergic reaction and typhlitis. The patient was subsequently enrolled in the DRIIV-1b study to receive the triple combination of AsiDNA™ plus carboplatin plus weekly paclitaxel as 4th line treatment. At the start of the treatment, the patient was progressing on lung and bone (pelvic girdle metastases). She received 4 cycles of AsiDNA™ and carboplatin and paclitaxel. During the treatment, the patient experienced at C1D8 an event of pulmonary embolism that was considered as serious but not related to AsiDNA™ and 2 episodes of diarrhoea; one episode of grade 2 on C1D13, possibly related to chemotherapy, which resolved after 18 days, without any action taken on study drugs, another episode of grade 3 on C4D3, possibly related to AsiDNA™ and chemotherapy, which resulted in drugs interruption; the event resolved after 6 days. Neutropenia grade 2 related to chemotherapy was observed on C2D1 (chemotherapy was delayed for one week). The patient also reported fatigue grade 2 on C3D1 and on C4D1 related to treatment. Carboplatin dose was reduced to AUC 4 on C3D8 and chemotherapy was cancelled on day 15 because of palliative radiotherapy to a bone lesion. The patient received in total 4 cycles of the triplet combination, she achieved a stable disease post C2, then a partial response post C4. After cycle 4, the patient decided, not to continue treatment. She did not receive any further systemic anticancer therapy for 7 months until a progression on bone was noted.

Discussion

The use of inhibitors of DNA damage signaling and/or repair pathways appears to provide an interesting opportunity for targeting genetic differences between tumor and normal cells [11]. DNA repair inhibitors, particularly small-molecule inhibitors, hold great promise for damaging tumor cells. Their specificity can be honed to target a single step or single protein of a DNA repair pathway. Achieving that goal moves us closer to truly personalized medicine. By its unique mechanism of action, AsiDNA™ represents a new opportunity to overcome intrinsic resistance of the tumor cell to chemotherapeutic agents that act by damaging cellular DNA.

This article illustrates 4 case reports of patients treated with the novel combination of AsiDNA™ plus carboplatin at an advanced stage of their metastatic disease. In this setting of advanced and difficult to treat tumours, the doublet (or triplet) combination of AsiDNA™ with carboplatin (with or without paclitaxel) yielded long stabilization of the disease with increased duration of treatment, compared to the previous treatment lines received by these patients. The duration of the disease stabilization under the doublet or triplet combination of AsiDNA™ plus carboplatin and paclitaxel ranged between 5.5 to 10 months. Case report 2 with TNBC without germline mutation was treated with the combination of AsiDNA™ and carboplatin as 6th line of treatment for metastatic disease and achieved longer duration of disease stabilisation when compared to the response obtained with prior lines of anticancer therapies received. However, this patient has not been exposed to prior cisplatin-based therapy.

Three of the 4 described case reports harboured a NSCLC disease, 2 of them had received prior cisplatin-based chemotherapy: one in the neoadjuvant setting and one for metastatic disease, and

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all benefited from immunotherapy, either in early stage (case report N°1) or for metastatic disease (case reports N°3 and n°4). One patient (case report N°4) treated with the triple combination of AsiDNA™ plus carboplatin and paclitaxel achieved a partial response when prior line with platinum-based chemotherapy best response was only stable disease. The 2 others achieved long stable disease of 8.5 and 10 months with the doublet or triplet combination of AsiDNA™. These observed preliminary results are encouraging in a context where the reported median progression-free survival of the combination of immunotherapy plus cisplatin-based chemotherapy in 1st line metastatic disease ranged between 7 and 13 months [12-14]. The rationale behind combining AsiDNA™ with carboplatin (with or without paclitaxel), a potent DNA-breaker, is based on the synergistic effect showed in non-clinical studies [15]. The potential of AsiDNA™ to sensitize tumours to carboplatin has been investigated and validated in a preclinical model of breast cancer, showing a significant synergy between the two drugs (Figure 2). In this study [15], mice xenografted with the TNBC model (MDA-MB231) received once daily intraperitoneal administration of AsiDNA™ at 5 mg (Q1D on Day 1 to 5) for 3 sessions with two weeks of rest between each session, 1 administration of carboplatin at 50 mg/kg every 21 days (Day 2, 23, 44) and combination of AsiDNA™ and carboplatin (injected 4 hrs after the second injection of AsiDNA™). The antitumor activity was evaluated by measuring the tumor volume during and after treatment. AsiDNA™ showed a significant standalone efficacy with a median survival of 128 days compared to vehicle-treated control group in which the median survival was 77 days. Carboplatin alone showed a slight effect with a median survival of 88 days. AsiDNA™ and carboplatin combined treatment showed a better tumor growth control compared to standalone treatments, with a median survival of 175 days.

Furthermore, *in-vitro* and *in-vivo* studies, showed that sensitivity of tumour cells to AsiDNA™ increases after long term treatment and does not generate acquired resistance [16]. AsiDNA™ does not oppose, but on the contrary encourages, hyper-activates and hijacks a natural biological process so essential for its survival that the tumour cell cannot stop it. Thus, AsiDNA™ is increasingly effective as the tumour cell exhausts its ability to respond to DNA damage [9]. This unprecedented property might be related to DDR genes down-regulation after AsiDNA™ repeated treatments strongly suggesting a DNA repair exhaustion, which may explain long stabilization in our reported cases after repeated treatment with AsiDNA™ [16]. The more AsiDNA™ is used as a treatment, the more effective it becomes [16]. In preclinical studies, AsiDNA™ had a broad antitumoral activity in various genetically instable tumor models (uveal and cutaneous melanoma, glioblastoma, colorectal cancer, breast cancer, liver cancer, lung cancer, cervix cancer and head and neck cancer) [17]. The preclinical data also suggest that AsiDNA™ could have a similar ability to prevent and abrogate resistance to multiple anti-cancer agents. Because AsiDNA™ affects all components of DNA repair machinery, it should be harder for cancerous cells to develop resistance to the compound. Finally, AsiDNA™ mechanism of action is significantly differentiated in the field of DNA damage response as it does not inhibit specific enzymes (such as PARPi) but targets several DNA repair processes, acting upstream of multiple DDR pathways as an agonist through a decoy mechanism.

In clinic, in DRIIV-1a study part, the drug has already shown to be well tolerated up to the tested dose of 1300 mg when administered intravenously, as single agent, in the 22 patients with solid tumours treated in the range of the tested doses with advanced solid tumours [10]. In DRIIV 1b study part, preliminary safety data from the first 9 patients treated including the 4 case reports described in this paper show that AsiDNA™ at the dose of 600 mg in combination with carboplatin with or without paclitaxel does not increase the toxicity of carboplatin. Moreover, delivered doses of carboplatin were maintained a long time before occurrence of toxicities resulting in dose reduction.

Conclusion

These case reports suggest a potential benefit of AsiDNA™ to standard chemotherapy such as carboplatin; AsiDNA™ displayed long disease control in pre-treated patients with advanced solid tumours. More robust efficacy data are warranted to better characterize responders to the doublet or triplet combination with AsiDNA™. A formal phase II randomized study is planned with AsiDNA™ in combination with carboplatin in patients with advanced NSCLC to start in 2021, to assess the efficacy and safety of the combination versus standard of care in this indication.

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Competing Interests

NK is the Principal investigator of the study and declared to have no CI

CJ is sub-investigator of the study and declared to have no CI

FH is study nurse and declared to have no CI

JJC is sub-investigator of the study and declared to have no CI

BC is sub-investigator of the study and declared to have no CI

OdB: is employee Onxeo.

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