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

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Background

- AsiDNA™ is a first-in-class oligonucleotide that mimics double-stranded DNA breaks and acts as a decoy to disrupt the DNA damage response at the "real" sites of DNA damage.
- AsiDNA™ activates the DNA-PK and PARP enzymes that induce the phosphorylation of H2AX and proteins parylation, respectively.
- As a result, repair enzymes are no longer recruited to the damage sites, ultimately leading to tumor cell death.
- Importantly, healthy cells, which display proficient cell cycle control, halt their cell division until AsiDNA™ is depleted.
- AsiDNA™ intratumoral and peritumoral injection in combination with radiotherapy is safe in patients with skin metastasis of melanoma and provides antitumor activity (DRIIM study).[1]
- We present the results of a the first-in-human phase 1 trial evaluating the IV administration of AsiDNA™ in patients with advanced solid tumors.

Objectives

Primary Objective

To determine the dose-limiting-toxicities (DLTs) and maximum tolerated dose (MTD) of AsiDNA™ IV.

Key secondary objectives

1) Safety Profile of AsiDNA™
2) Pharmacokinetics (PK)
3) Preliminary efficacy data

Exploratory objective

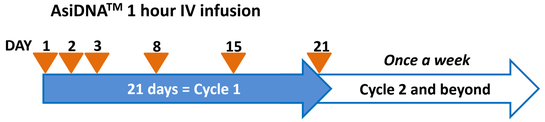
Pharmacodynamics (PD) : γH2AX, HSP90

Patient and Methods

Study design

1) Phase 1, Open label, non-randomized, multi-center, cohorts of 3-6 evaluable patients received escalating dose of AsiDNA™.
2) Six dose levels: 200 (n=3), 400 (n=4), 600 (n=3), 900 (n=6), 1300 (n=6) and 1800 mg (n=0).
3) Dosing is planned to continue until disease progression, unacceptable toxicity or patient's decision.

Administration scheme



All patients received a loading dose of AsiDNA™ for 3 consecutive days (1 hour IV infusion), followed by once a week infusion in a 21 days cycle. In each subsequent cycle, AsiDNA™ was given weekly.

Key Eligibility criteria

1) Patients with histologically or cytologically documented advanced/metastatic primary or recurrent solid tumors who failed or are not eligible to standard therapy.
2) ECOG performance status 0 or 1.
3) Adequate organ and hematopoietic function.
4) Mandatory sequential tumor biopsies.

Results

22 evaluable patients with pretreated metastatic cancer were enrolled in the 5 dose levels (153 infusions).

Patients characteristics

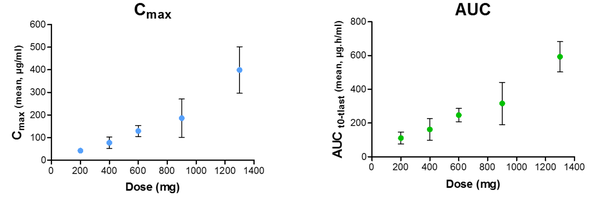
Male / Female, n (%)	9 (40.9%) / 13 (59.1%)
Median age, year (range)	60.5 (38-78)
ECOG 0 / ECOG 1, n (%)	14 (63.6%) / 8 (36.4%)
Tumor types: - Colorectal - Breast - Uterus - Pancreas - Others: ovary, liver, testicle, stomach, oesophagus, vater ampula - Sarcoma: - thigh, - uterus, - stomach	 6 3 2 2 6 1 1 1
Median number of metastatic sites	2 (0–5)
Prior lines of chemotherapy: 1 2 ≥ 3	 1 (4.5%) 2 (9.1%) 19 (86.4%)

Safety (n=22 treated patients)

1) No DLT, no SAE at DL1, DL2 and DL3
2) 1 DLT at DL4:
- G4 hepatic enzyme increase
3) 1 DLT at DL5:
- G3 hepatic enzyme increase
4) Other related severe AEs:
- G3 orthostatic hypotension at D28 (DL4)
- G3 hypophosphataemia at D42 (DL4)

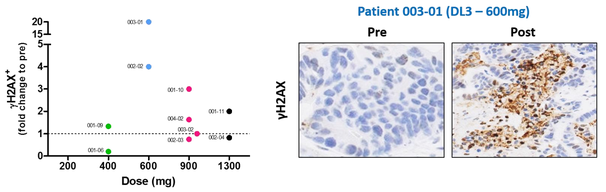
Pharmacokinetics

AsiDNA™ Cmax and AUC are increased proportionally and consistently with dosing.



Pharmacodynamics

AsiDNA™ optimal biological activity was observed at 600mg based on H2AX phosphorylation (γH2AX).



Antitumor activity

AsiDNA™ best overall response was disease stabilization in 2 pts with colorectal cancer at DL 600.

Conclusions

AsiDNA™ IV was safe. The MTD was not reached.
Proof of mechanism was demonstrated with the increase of γH2AX.
DL 600 was identified as the optimal biological dose for further development given the favorable safety and PK profiles, and robust target engagement.

Reference

1. Le Tourneau C et al. First-in-human phase I study of the DNA-repair inhibitor DT01 in combination with radiotherapy in patients with skin metastases from melanoma. British Journal of Cancer (2016), 114:1199-1205.

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