CLINICAL RESPONSE AND PHARMACODYNAMIC ASSESSMENT OF INVAC-1, A DNA PLASMID ENCODING AN INACTIVE FORM OF HUMAN TELOMERASE REVERSE TRANSCRIPTASE (hTERT), ON IMMUNE RESPONSES, IMMUNE TOLERABILITY, TUMOR BURDEN AND CIRCULATING TUMOR DNA (ctDNA) IN PATIENTS (PTS) WITH ADVANCED SOLID TUMORS

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BACKGROUND

INVAC-1 is an optimized DNA vaccine encoding an inactive form of human telomerase reverse transcriptase (hTERT), an "universal" tumor antigen expressed in more than 85% of human cancers with little or no expression in normal somatic cells (1,2). Telomerase activation is associated with maintenance of telomere length and accounts for the unlimited proliferative capacity of cancer cells.

In preclinical models, INVAC-1 vaccination triggered strong and long-lasting hTERT-specific CD8+ as well as CD4+ T-cell responses and also promoted antitumor effect (3,4). **Preliminary results of this first clinical study with INVAC-1 vaccine as a single agent in solid tumors were presented at ASCO 2017 (Teixeira L. et al., abst. 3087). Here, we report updated toxicity and efficacy results, as well as pharmacodynamics data.**

METHODS

STUDY DESIGN

A First-in-Human, Phase I, open label classical 3+3 design, multiple dose study of single agent INVAC-1 in pts with relapsed or refractory solid tumors (NCT02301754).

STUDY TREATMENT

- Doses of INVAC-1 tested: 100 (3 pts), 400 (3 pts), 800 µg (3 pts), extension 800 µg (11 pts)
- Route: Intradermal injection/Electroporation using Cliniporator®2.
- Cycles of INVAC-**1 lasting 28 days**. Follow up: up to one year from first dose of INVAC-1.

STUDY POPULATION

•**Twenty adult pts** with histological diagnosis of advanced/metastatic solid tumors relapsed or refractory to standard treatment and with a life-expectancy > 4 months and Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 were included.
•Patients had to have an adequate bone marrow, renal, liver and cardiac function.
•Written informed consent was obtained from each patient.

SAFETY ANALYSES

- **The primary endpoint of the study was the occurrence of Dose-Limiting Toxicities** (DLTs).
- Full safety evaluation was also included (Treatment-Emergent Adverse Events (TEAE), Routine laboratory abnormalities, Cytokine release, Circulating auto-antibodies).

EFFICACY AND PHARMACODYNAMICS ANALYSES

- Elispot interferon (IFN)-γ to assess hTERT-specific CD4 and CD8 T-cells: positive response was defined as: (i) at least 10 spot forming cells per 100,000 blood lymphocytes, and (ii) a 2-fold or greater increase above background levels.
- Tumor response, RECIST CRITERIA V1.1
- Progression free survival and overall survival.
- Evaluation of circulating tumor DNA (ctDNA).

HISTOLOGICAL DIAGNOSES

Infiltrating ductal carcinoma (C1, EC, EC, EC, EC), of which 3 had triple negative breast cancer, Colorectal adenocarcinoma (C1, C2, C3), Mesothelioma (C1, EC), Adenocarcinoma of the prostate (C3, EC), Endometrial adenocarcinoma (C3, EC), Peritoneal carcinoma of ovarian origin (EC), Pancreatic adenocarcinoma (EC), Clear cell renal cell carcinoma with a sarcomatoid component (EC), Adenocarcinoma with unknown primitive tumor (C2), Epidermoid carcinoma of the male urethra (C2), Large-cell neuroendocrine carcinoma (EC).

PATIENTS EXPOSURE

The protocol was scheduled for an administration of 3 cycles, with a possible extension of treatment duration up to 9 cycles if clinical benefit. All 20 pts received at least two injections and were evaluable for DLT as follows:

Cycles:	2	3	4	5	6	7	8	9
Cohort 1: 100 µg (n = 3)			1					2
Cohort 2: 400 µg (n = 3)	1	1	1					
Cohort 3: 800 µg (n = 3)		1	1			1		
Extension cohort: 800 µg (n = 11)	5	2	1	1	1	1		

Number of cycles > 3

RESULTS

PATIENT CHARACTERISTICS

Characteristic	n=20
Age (years)	
Median (range)	59 (31–74)
Sex, n	
Male	11
Female	9
ECOG	
0	13
1	7
Number of prior therapies for metastatic disease	
1	3
2	3
3	4
≥4	10

DOSE-LIMITING TOXICITIES

No DLTs were reported. No death occurred within 28 days after the last dose of study treatment. 13 pts (65%) died from disease progression after these 28 days during follow-up. No deaths were considered as related to study treatment.

SERIOUS TEAE

- 5 serious TEAE most of them considered as **not related** to study treatment (except one: lymph node abscess).
- 3/5 serious TEAE (acute kidney injury, B cell lymphoma and lymph node abscess) resulted in premature discontinuation of the study treatment.

IMMUNOLOGICAL SAFETY

- **Plasma inflammatory cytokines:**
  - **No significant modification of IL-1-$_8$, IL-17, IL-8 , IFN-γ, IL-6 observed at D2, D8 or End of Treatment.**
  - TNF-α increases significantly at EOT compared to other timepoints (p<0,02).
- **Circulating auto-antibodies**:
  - No significant modification of ANA positivity has been observed, whatever the study group.
- **Potential clinical sign of auto-immunity:**
  - 5 pts had expected clinical potential TEAE (erythema, visual brightness, skin rash, arthralgia and hyperthyroidism). All were considered as unrelated to INVAC-1.
  - 4 pts (20.0%) experienced 12 mild hyperglycemia. All events resolved spontaneously within few days. They were not considered as related to INVAC-1.

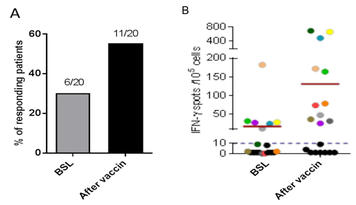
ctDNA

- **14/20 pts have interpretable results.** The most frequent mutations were **TP53, KRAS and PIK3CA.**
- A ct DNA decrease was observed in 5 cases, a stable ct DNA level was observed in 5 cases and an increase of ct DNA level was observed in 4 cases.
  - There were some trends suggesting a ctDNA stabilization or decrease concomitantly with stabilization of the disease during the treatment cycles, but **no clear correlation**.

LYMPHOCYTE PHENOTYPING

- Low levels of total lymphocytes and subtype populations (CD3, CD4, CD8, CD19 and NK) were observed at inclusion (pre-dose) of the pts. **No significant change of cell counts or modification of lymphocyte phenotypes were observed** during the treatment and follow up periods.

EFFICACY & PHARMACODYNAMICS EVALUATION



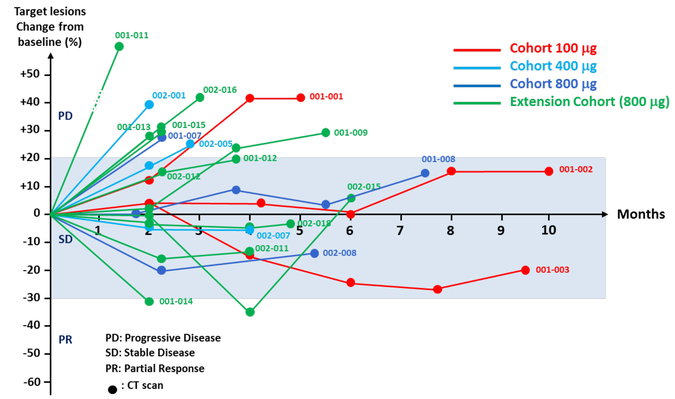
Anti-hTERT CD4 T cell response of 20 pts in all cohorts (100, 400 and 800 µg INVAC-1).

A. Frequency of responding pts

B. Magnitude of anti-hTERT CD4 T cell response (red line represents mean of IFN-γ). BSL: Baseline

- **30% of pts (6/20) presented a spontaneous CD4 Th1 T cell response against hTERT** before vaccination treatment supporting previous data (5,6).
- **After vaccination with INVAC-1, the number of pts showing an anti-hTERT CD4 T cell response increased to 55%** (11 pts out of 20) leading to the assumption that INVAC-1 triggered de novo anti-hTERT CD4 immune response in 25% of pts (A).
- The majority of pts mounted the anti-hTERT T cell response following the 2nd or 3rd vaccination. In most of the pts who had a pre-existing anti-hTERT immunity, INVAC-1 vaccination increased the magnitude of the anti-hTERT CD4 immune response suggesting that **INVAC-1 is also capable of boosting a pre-existing natural immune response** (B).
- Among the 16 pts evaluated for the **CD8 T cell response, only 3 pts exhibited a robust specific CD8 T cell response** against matched HLA-restricted hTERT peptides.

SUMMARY OF OVERALL RESPONSE ir-RECIST



Best overall response: 60.0% (n=12) of pts had stable disease (3, 2 and 7 pts at the 100 µg, 400 µg and 800 µg dose levels, respectively).

Progression free survival: The Kaplan-Meier estimated **median PFS was 3.6 months** (95% CI: [1.8-4.9]).

Overall survival:

- The first patient was treated with INVAC-1 in November 2014. As of 24 Nov. 2017 the estimated **median overall survival** was**12.4 months** (95% CI: [6.5-16.3]) with estimated **1 year survival rate of 53% %** (SE: 1.4).

CONCLUSIONS

- Intra-dermal INVAC-1 administration was safe, well tolerated and strongly immunogenic at the doses and schedule tested. **No DLT was observed** and no MTD was achieved.
- Early anti-tumor activity has been observed. Although no response has been confirmed on the long term, **the disease was stabilized for 60**% of the pts and **the median OS was higher than one year.**
- **INVAC-1 also appeared to be capable to stimulate both CD4 and CD8 T cells against hTERT.**
- **The recommended dose of INVAC-1** vaccine for phase II studies is **a monthly intra-dermal injection of 800 µg.** This study is still ongoing with a further set of 6 pts in whom an alternative intra-dermal injection device (Tropis®, a needle-free injection system) is being evaluated instead of Electroporation.
- The results obtained encourage a future evaluation of INVAC-1 is solid tumors, as well as in hematologic malignancies, either as monotherapy or in combination with various immunotherapeutic drugs. A phase II study in Chronic Lymphocytic Leukemia (CLL) pts is being initiated.

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