Final results of First-in-Human Phase I Study of INVAC-1, an Optimized Human Telomerase (hTERT) DNA Vaccine in Patients with Advanced Solid Tumors

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BACKGROUND

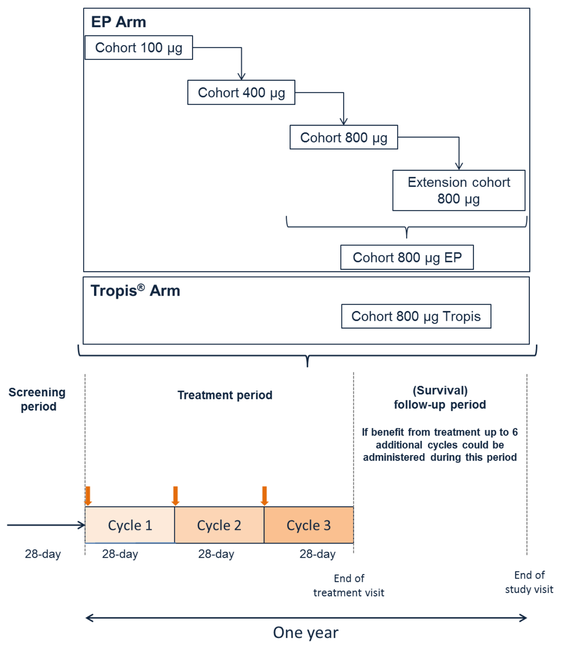
INVAC-1 is an optimized **DNA vaccine** encoding an inactive form of **human telomerase reverse transcriptase (hTERT)** a prototype of shared tumor antigen expressed in more than 85% of human cancers. Telomerase activation is associated with maintenance of telomere length and accounts for the unlimited proliferative capacity of cancer cells.

Primary PD, safety pharmacology and toxicology studies, including biodistribution and local tolerance, showed that INVAC-1 was enzymatically inactive, immunogenically safe and well-tolerated. In preclinical studies, INVAC-1 vaccination triggered strong and **long-lasting hTERT-specific CD8+** as well as **CD4+ Th1 T-cell responses**. INVAC-1 was also able to **slow tumor growth** and **increased survival rate by 50% in tumor-bearing mice** (SarcT2r model) (Thalmensi *et al.*, 2016, OncoImmunology).

Here, we report clinical and pharmacodynamics results of the **first-in-human phase I study** with **INVAC-1** vaccine administered **ID** (either with electroporation or by Needle-free Injection System Tropis®) as a **single agent** in multiple solid tumors.

Needle-free core injector system and single use, sterile, disposable needle-free syringe of 0.1 mL

METHODS



INVAC-1 intra-dermal + electroporation or INVAC-1 intra-dermal using Tropis® Needle Free Injection System on day 1 of each cycle followed by a 28-day observation period

Study design

- First in Human, Phase I, open label classical 3+3 design, multiple dose study of single agent INVAC-1 in patients with relapsed or refractory solid tumors presenting progressive disease (**NCT02301754**)
- Administration ID followed by electroporation (EP) (n=20 patients) or NFIS Tropis® (n=6 patients)
- At least 3 sequential cycles (could be prolonged up to 6 additional cycles)

Study population

- 26 patients aged >18 years 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 skin status and adequate bone marrow, renal, liver and cardiac function.
- Female patients not enrolled if they were pregnant or of child-bearing potential.
- Written informed consent was obtained from each patient.

Safety

- Primary endpoint: Dose Limiting Toxicities
- Secondary endpoints:
  - Treatment-related Adverse Events
  - Cytokine release
  - Circulating auto-antibodies

Pharmacodynamics

- Objective response
- Tumor response and duration of response
- Time to event (Progression Free Survival, Overall Survival)
- hTERT specific CD4 and CD8 T cell responses (IFN-γ ELISpot)
- Polarization of anti-hTERT immune response (Luminex®)
- Peripheral Blood cell populations phenotyping (Flow Cytometry): T cell subsets, Treg, Monocytic-MDSC, Immune Checkpoint molecules expression (PD-1, Tim-3, TIGIT)

RESULTS

SAFETY

Characteristic	INVAC-1 Dose level: EP 100 µg n=3	EP 400 µg n=3	EP 800 µg n=14	Tropis® 800 µg n=6	Overall (n=26)
Gender					
Female n (%)	2 (66.7)	2 (66.7)	7 (50.0)	4 (66.7)	**15 (57.7)**
Male n (%)	1 (33.3)	1 (33.3)	7 (50.0)	2(33.3)	**11 (42.3)**
Age (years)					
Mean (SD)	59.0 (10.1)	57.3 (14.4)	57.5 (13.6)	52.5 (13.3)	**56.5 (12.7)**
Median (range)	57 [50; 70]	49 [49; 74]	60 [31; 74]	52 [34; 67]	**58 [31; 74]**
Disease duration (months)					
Mean (SD)	59.4 (53.8)	29.7 (17.1)	58.8 (47.2)	71.4 (88.3)	**58.4 (55.8)**
Median (range)	34.5 [22.5; 121.1]	37.5 [10.1; 41.6]	42.5 [9.3; 162.4]	33.9 [15.3; 244]	**39.0 [9.3; 244]**
Tumor metastases					
Patients, n (%)	2 (66.7)	3 (100.0)	8 (57.1)	1 (16.67)	**14 (53.8)**
Treatment lines					
1 Line, n (%)	1 (33.3)	0 (0.0)	1 (7.1)	3 (50.0)	**5 (19.2)**
2 Lines, n (%)	0 (0.0)	1 (33.3)	4 (28.6)	1 (16.7)	**6 (23.0)**
≥3 Lines, n (%)	2 (66.7)	2 (66.7)	9 (64.2)	2 (33.3)	**15 (57.7)**
ECOG score					
0	3	1	9	1	**14**
1	0	2	5	5	**12**

Table 1: Demographic characteristics of enrolled patients

	Grade 1	Grade 2	Grade 3	Overall
Injection site reaction	13*	4*	0	17*
Gastro intestinal disorders (Diarrhea, constipation, pain, vomiting…)	15	4	0	19
General disorders Fatigue	8	8	0	16
Blood and lymphatic system disorders Lymphopenia and lymphocyte count decrease	9	3	0	12
Anemia	4	2	1	7
Respiratory disorders Cough	6	1	0	7
Metabolic disorders AESI : Hyperglycemia	5	1	0	6

Table 2: Number of patients reporting the most frequent AE by grade regardless causality (AE reported for at least 10% of patients). Patient may have experienced the sane AE several times and may have encountered different Aes. Grade is the maximum reported per patient for the AE. (*) only occurred in EP cohort

- **INVAC-1 administration ID (either with EP or by Tropis®) was safe and well-tolerated in all dose cohorts**
- **Only one grade 3 Serious AE was reported - No DLT was defined**
- **No death was reported within 28 days after the last dose of study treatment whatever the number of cycles the patients received (up to 9 cycles)**
- **Most common study treatment-related AEs were fatigue and EP-related AEs**

CLINICAL RESPONSE

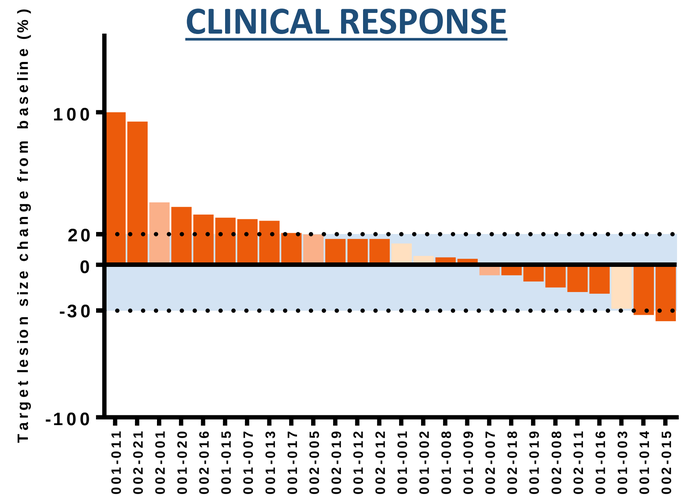


Figure 1: Best response for target lesions by patient. Target lesions were evaluated by CTScan. Area in light blue corresponds to Stable Disease (SD). All dose cohorts are represented: 100 µg (light orange), 400 µg (orange) and 800µg EP + Tropis® (dark orange)

- **58 % of patients (15 patients) experienced disease stabilization for 1.8 to 9.9 months (4/15 patients SD > 6 months)**
- **No complete regression but 2 patients (800 µg cohort) presented unconfirmed partial regression**
- **Median PFS = 2.7 months**
- **Median OS = 15 months, One-year survival = 65.4%**

CORRELATION BETWEEN CLINICAL AND IMMUNOLOGICAL RESPONSE

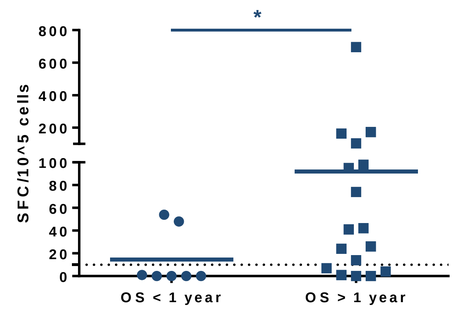


Figure 5: Anti-hTERT CD4 T cell response after 2 cycles of INVAC-1 according to one-year survival. Mean of triplicate is plotted for each patient with OS <1 year (n=7) and >1 year (n=17) – line represents IFN-γ SFC mean. Positivity threshold (>10 SFC/10^5 cells) is represented by dotted line. (*) p<0.05, Mann-Whitney non parametric unpaired U test

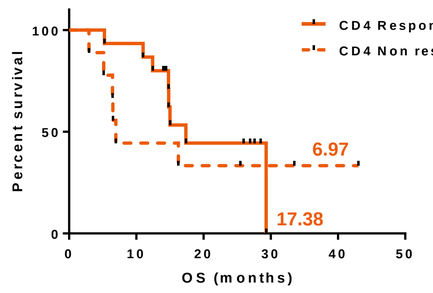


Figure 6: Overall Survival (OS) up to 45 months according to patients' CD4 responder/non-responder status (IFN-γ ELISpot). Median survival are indicated for each group

- **Significantly higher hTERT specific CD4 T cell response after 2 cycles (prime/boost) of INVAC-1 in patients with OS >1 year compared to patients whose OS is <1 year**
- **hTERT specific CD4 responders showed a non-significant trend towards longer estimated OS compared to non-responders (17.38 [12.4-29.3] vs. 6.97 months [3.0-…])**

PHARMACODYNAMICS AND IMMUNOLOGICAL RESPONSE

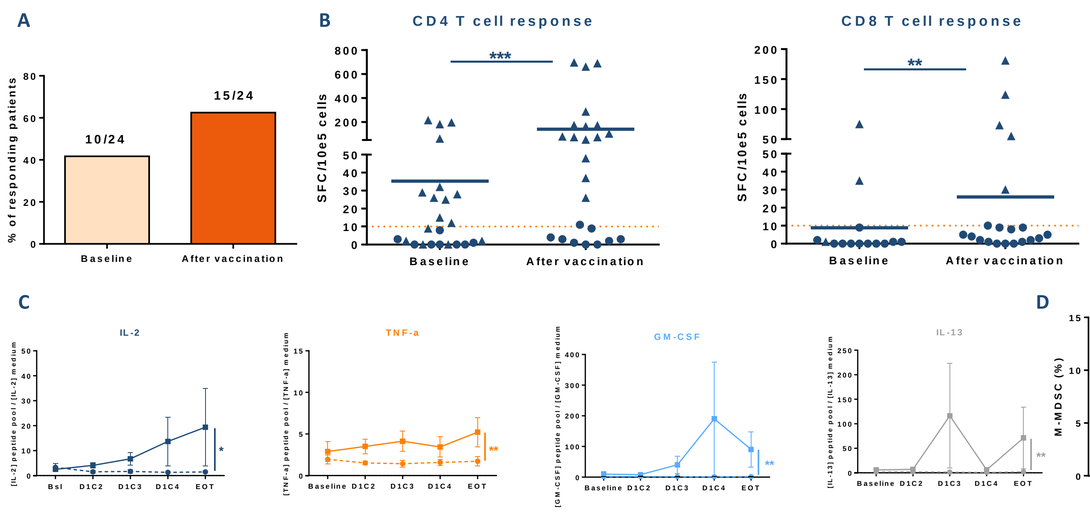


Figure 2: Characterization of INVAC-1-induced immune response. (A) Frequency of CD4 responding patients at baseline and after vaccination. Responding patients are defined by IFN-γ ELISpot response >10 SFC/10^5 cells. **(B) Anti-hTERT CD4 and CD8 T-cell responses at baseline and after vaccination.** After vaccination, each responder (triangle) or non-responder (circle) best response is showed. Orange line represents IFN-γ SFC mean. Positivity threshold (>10 SFC/10^5 cells) is represented by dotted line. (***) p<0.001, (**) p<0.01 Wilcoxon matched-pairs signed rank test. **(C) IL-2, TNF-α and GM-CSF secretion in CD4 ELISpot responders (R) versus non-responders (NR).** Dotted line: CD4 non-responders; Solid line: CD4 responders. Bsl – Baseline; D1C2 – Day 1 Cycle 2; D1C3 – Day 1 Cycle 3; D1C4 – Day 1 Cycle 4; EOT – End of Treatment. For each patient, IFN-γ ELISpot supernatant was tested in duplicate and cytokine concentration (pg/ml) was back-calculated using the appropriate regression model e.g. a 5-parameter logistic (5PL) regression curve. Ratio [cytokine in stimulated wells] / [cytokine in non-stimulated wells] were calculated for each patient and mean values +/- standard deviation (responders n=15, non-responders n=9) were plotted. Statistical comparison of cytokine ratio variations according to time for CD4 responders vs. non-responders was performed using Mann-Whitney non-parametric unpaired signed rank test. (*) p< 0.01; (**) p<0.001. **(D) Circulating tolerogenic cell populations characterization.** % of circulating Treg (left) and M-MDSC (right) are represented. Line represents mean for each time point. (*) p< 0.01, paired non parametric Wilcoxon test.

- **INVAC-1 vaccination induced a hTERT specific Th1-dominant CD4 T cell immune response in 63% of patients (15/24 evaluable) and a cytotoxic CD8 T cell response in 25% of patients (5/20 evaluable)**
- **10 patients presented pre-existing hTERT immunity, all patients showed an increased or sustained response after vaccination**
- **No modification of T cell subsets distribution nor immune checkpoint molecules expression (not shown)**
- **No vaccine-induced immunosuppression**

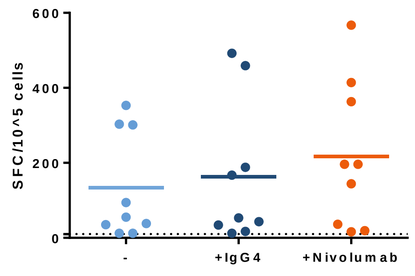


Figure 3: INVAC-1 specific CD4 T cell response in presence of anti-PD-1 (Nivolumab). Patient PBMCs (n=8) were cultured in presence or absence of Nivolumab (1µg/ml) or IgG4 control isotype before IFN-γ ELISpot assessment. Line represents IFN-γ SFC mean.

Anti-PD-1 (Nivolumab) enhances hTERT specific CD4 immune response

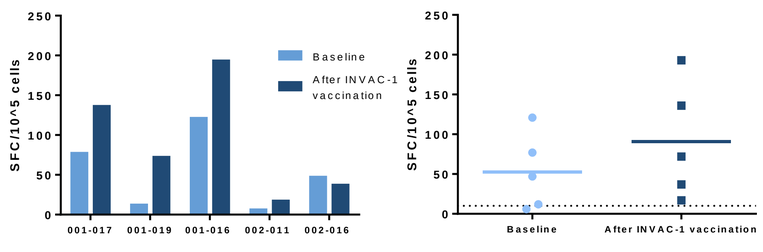


Figure 4: NY-ESO-1 specific CD4 T cell response before and after INVAC-1 vaccination. Patients (n=5) responses were evaluated by IFN-γ ELISpot.

Immune response to NY-ESO-1 was enhanced after INVAC-1 vaccination

CONCLUSIONS

- **INVAC-1** was demonstrably **safe** and **well tolerated** up to nine cycles as a single intradermal treatment (100 µg, 400 µg and 800 µg) in patients with advanced solid tumors
- **Disease stabilization** was achieved in **58% of patients**, up to 9,9 months
- **INVAC-1**, by triggering strong **anti-hTERT Th1-polarized CD4 T cell** response as well as **CD8 cytotoxic response** without immune suppression induction, demonstrated **robust immunogenicity** in patients enrolled in this study
- Patients with **OS > 1 year** showed significantly **higher hTERT specific immune response** after prime/boost INVAC-1 vaccination than patients with OS < 1 year
- Our results suggest **prolonged OS for patients presenting a INVAC-1-induced CD4 hTERT immune response** compared to non-responders (17,4 versus 7 months)
- Preliminary data suggest that **INVAC-1 could promote epitope spreading**

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