Final results of a First-in-Human Phase I Study evaluating INVAC-1, an Optimized Human Telomerase 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.

In preclinical studies, INVAC-1 vaccination triggered strong and long-lasting hTERT-specific CD8+ as well as CD4+ T-cell responses and also promoted antitumor effect. Here, we report clinical and pharmacodynamics results of the first clinical study with INVAC-1 vaccine as a single agent in solid tumors.

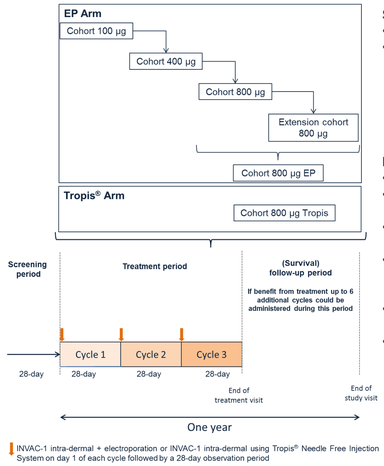
METHODS

Study design

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

Study population

- 26 patients 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.



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

Safety

- Primary endpoint: DLT
- Secondary endpoints:
  - Treatment-related AE
  - Cytokine release
  - Circulating auto-antibodies

Pharmacodynamics

- Objective response
- Tumor response and duration of response
- Time to event (PFS, OS)
- hTERT specific CD4 and CD8 T cell responses (IFN-γ ELISpot)
- Polarization of anti-hTERT immune response (Luminex®)
- Peripheral Blood cell populations phenotyping: T cell subsets, Treg, MDSC, Immune Checkpoint expression (Flow Cytometry)

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)
Med (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 (%)		2 (66.7)	3 (100.0)	8 (57.1)	1 (16.67)	14 (53.8)
Treatment lines						
1 Line		1 (33.3)	0 (0.0)	1 (7.1)	3 (50.0)	5 (19.2)
2 Lines		0 (0.0)	1 (33.3)	4 (28.6)	1 (16.7)	6 (23.0)
≥3 Lines		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

Figure 1: Demographic characteristics of enrolled patients

	Grade 1	Grade 2	Grade 3	Overall/26
Injection site reaction	13*	4*	0	17*
Gastro intestinal disorders (Diarrhea, constipation, pain, vomiting…)	15	4	0	19
General disorders Asthenia	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

Figure 2: Number of patients reporting the most frequent AE by grade regardless causality (AE reported for at least 10% of patients)

- INVAC-1 was safe and well-tolerated in all dose cohorts
- No DLT was defined
- No death was reported within 28 days after the last dose of study treatment whatever the number of cycles the patient received (up to 9 cycles)
- Most common study treatment-related AE = asthenia

CLINICAL RESPONSE

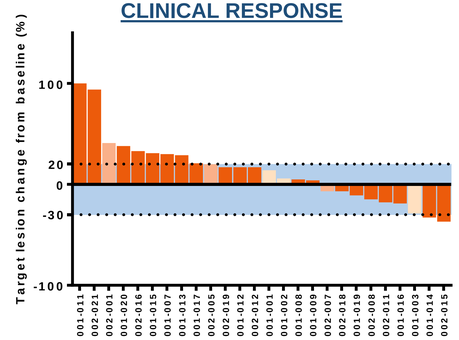


Figure 3: Best response for target lesions by patient. Area in light blue corresponds to Stable Disease (SD). All dose cohorts are represented: 100 µg (light orange), 400 µg (orange) and 800µg EP + Tropis® (dark orange)

- 58 % of patients (15 patients) experienced disease stabilization
- 2 patients (800 µg cohort) presented transient partial tumor response

CORRELATION BETWEEN CLINICAL AND IMMUNOLOGICAL RESPONSE

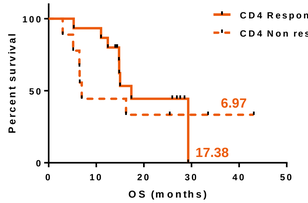
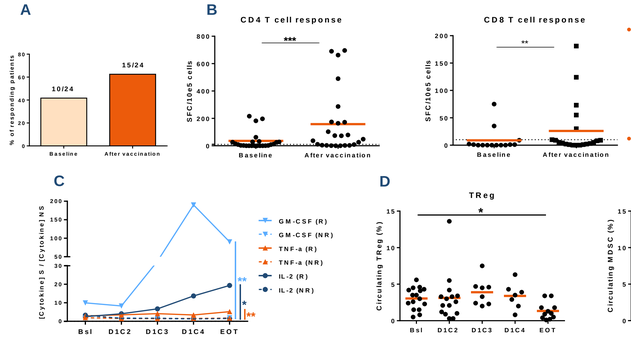


Figure 6: Overall Survival (OS) up to 45 months according to patients' CD4 responder/non-responder status (IFN-γ ELISpot). Median survival are indicated for each group

Overall survival by subgroups according to the presence or absence of an anti-hTERT CD4 specific T-cell response showed a clear (although non-statistically significant) trend towards longer estimated OS for responders compared to non-responders (17.38 [12.4-29.3] vs. 6.97 months [3.0-])

PHARMACODYNAMICS AND IMMUNOLOGICAL RESPONSE



- INVAC-1 vaccination induced a robust hTERT specific Th1 CD4 immune response as well as cytotoxic CD8 T cell response
- No immune tolerance induction

Figure 4: Characterization of INVAC-1-induced immune response. (A) Frequency of CD4 responding patients at baseline and after vaccination. (B) Anti-hTERT CD4 and CD8 T-cell responses at baseline and after vaccination. After vaccination, each patient's best response was showed. Orange line represents IFN-γ SFC mean. ***, 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).** Bsl – Baseline; D1C2 – Day 1 Cycle 2; D1C3 – Day 1 Cycle 3; D1C4 – Day 1 Cycle 4; EOT – End of Treatment. Cytokine secretion is expressed as ratio [cytokine in stimulated wells (S)] / [cytokine in non-stimulated wells (NS)] – Mean values (responders n=15, non-responders n=9) are plotted. Statistical comparison between CD4 responders and non-responders was performed using unpaired non parametric Mann-Whitney t test. (*) p< 0.01; (**) p<0.001. **(D) Circulating tolerogenic cell populations characterization.** % of circulating Treg (left) and MDSC (right) are represented. Line represents mean for each time point. (*) p< 0.01, paired non parametric Wilcoxon t test.

Preliminary data

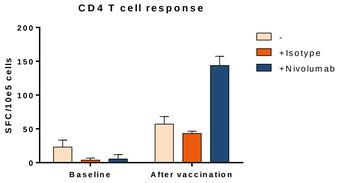


Figure 5: INVAC-1 specific CD4 T cell response in presence of anti-PD-1 (Nivolumab). Patient 01-012 PBMCs were cultured in presence or absence of Nivolumab (1µg/ml) or IgG4 control isotype before ELISpot assessment.

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

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**, showing an improved efficacy of INVAC-1 compared to most of hTERT vaccines clinically tested to date
- **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
- Our results showed **prolonged OS for patients presenting a INVAC-1-induced CD4 hTERT immune response** compared to non-responder (17,4 versus 7 months) whatever their immune status at baseline (preexisting anti hTERT immune response or not)

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