258P NECVAX-NEO1, a bacteria-based personalized neoepitope vaccine combined with PD-1/PD-L1 checkpoint inhibition in a phase I, open-label, multicenter study: safety, immunogenicity and early efficacy signals. NCT05354323

Study sponsored by:

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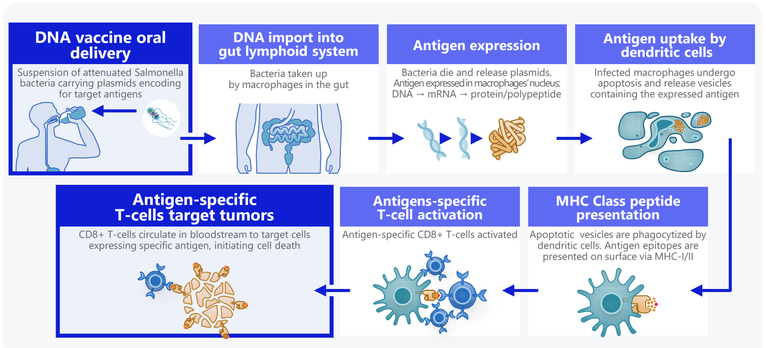
* The first author declares no conflicts of interests.

Background

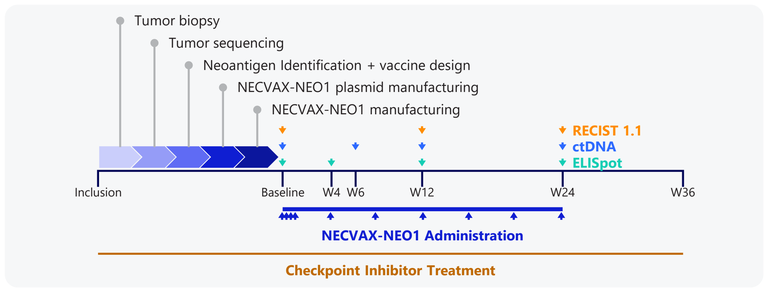
Personalized neoepitope-based cancer vaccines aim to elicit robust and specific immune responses against tumor cells by targeting patient- and tumor-specific mutations. Advances in next-generation sequencing, bioinformatics, and AI-based prediction algorithms have enabled the identification of highly immunogenic class I and II neoepitopes, leading to clinical trials that demonstrate feasibility, safety, and induction of durable T-cell responses in multiple tumor types.
NECVAX-NEO1 is a novel oral, Salmonella Ty21a–based vaccine platform designed to deliver up to 15 patient-specific neoepitopes predicted and ranked by the NEC Immune Profiler software. The attenuated Salmonella Ty21a vector carries an expression plasmid encoding minimal (9–10-mer) and extended (27-mer) epitopes linked by proteasome-optimized sequences to enhance intracellular processing and HLA presentation. NECVAX-NEO1 aims to induce potent $CD4^+$ and $CD8^+$ T-cell responses against tumor-specific antigens, promoting adaptive antitumor immunity and improved disease control.
Here, we present final clinical and immunogenicity data of NECVAX-NEO1-LT trial *, supporting the feasibility of AI-guided, oral neoepitope vaccination to activate tumor-targeted immune responses in patients with advanced solid tumors.



* Vaitiekus, D. et al. (2024, December). *Oral DNA vaccination targeting personalized neoantigens in immune checkpoint inhibitor treated solid tumor patients: Interim results* (Poster 160P). Presented at the ESMO Immuno-Oncology Congress 2024, Geneva, Switzerland.

Trial Information

NECVAX-NEO1-LT is an open-label, phase I multicenter, clinical trial of NECVAX-NEO1 in addition to anti-PD-1 or anti-PD-L1 monoclonal antibody checkpoint inhibitor monotherapy in patients with solid tumors. Based on the pharmacodynamic effects of NECVAX-NEO1 and checkpoint inhibitors, a synergistic activity of both agents in terms of immune response and clinical response is expected. The trial design is as follows:



Inclusion criteria

- Male and female cancer patients aged 18-75 years old, with measurable disease according to RECIST 1.1, treated for at least 3 months with anti PD-1/PD-L1 as first- or second-line monotherapy for one of the following tumor types: NSCLC, cutaneous melanoma, urothelial carcinoma, RCC or SCCHN.
- Adequate bone marrow, hepatic and renal function, with ECOG ≤ 2 and with life expectancy of at least 6 months.

Exclusion criteria

- Previous malignant diseases, active infections, organ transplantations or small intestine resection surgery.
- Patients in other clinical trials, in chronic concurrent therapies or treated with live vaccines within 30 days prior to trial treatment.
- Previous reported immune-related checkpoint inhibitor side effects or hypersensitivity to the IMP or persistent toxicity related to prior therapy.

Patient Disposition and Baseline Characteristics

Patient disposition

22 screened and consented

Excluded (n=16)
- Failed eligibility at Screening (n=8)
- Failed eligibility at Baseline (n=2)
- Insufficient tumor biopsy material (n=6)

6 initiated NECVAX-NEO1 treatment

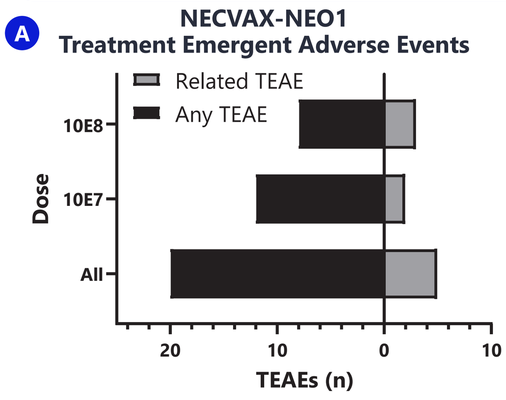
Discontinued treatment (n=1)
- PD at W12 (n=1)

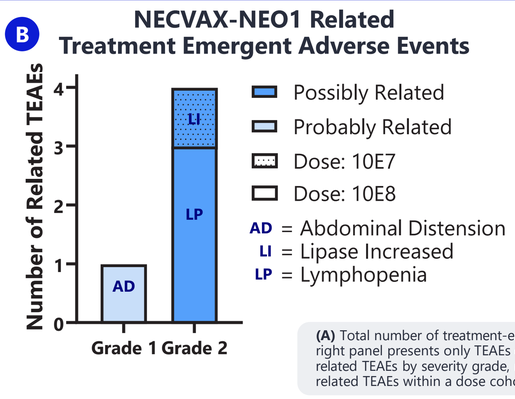
5 survival Follow-up

Patient characteristics at Baseline

Characteristics	Dose 10^7 CFU	Dose 10^8 CFU	Total
n	3	3	6
Age (years)			
mean (SD)	69.7 (6.8)	60.7 (15.9)	65.2 (12)
median (IQR)	72 (13)	65 (31)	68.5 (12)
Sex			
Female	0 (0)	1 (33.3)	1 (16.7)
Male	3 (100)	2 (66.7)	5 (83.3)
Weight (kg) at BL			
mean (SD)	113.7 (41,5)	83.7(9,1)	98.7 (31,5)
median (IQR)	133.0 (76)	85.0 (18)	88.5 (59)
Height (cm) at BL			
mean (SD)	178.3 (10,4)	171.7 (6,5)	175.0 (8,6)
median (IQR)	175.0 (20)	172.0 (13)	173.5 (8)
Race			
Not Hispanic or Latino	3 (100)	3 (100)	6 (100)
ECOG status at BL			
0	2 (66.7)	1 (33.3)	3 (50.0)
1	1 (33.3)	2 (66.7)	3 (50.0)
Tumor type			
Melanoma	1 (33.3)	0 (0)	1 (16.7)
RCC	2 (66.7)	2 (66.7)	4 (66.7)
SCCHN	0 (0)	1 (33.3)	1 (16.7)
Cancer Disease Stage at Screening			
IB	1 (33.3)	0 (0)	1 (16.7)
III	0 (0)	1 (33.3)	1 (16.7)
IV	1 (33.3)	2 (66.7)	3 (50.0)
Other	1 (33.3)	0 (0)	1 (16.7)

NECVAX NEO1 is safe and well tolerated

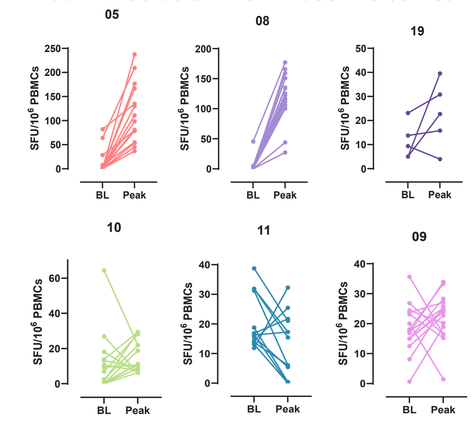


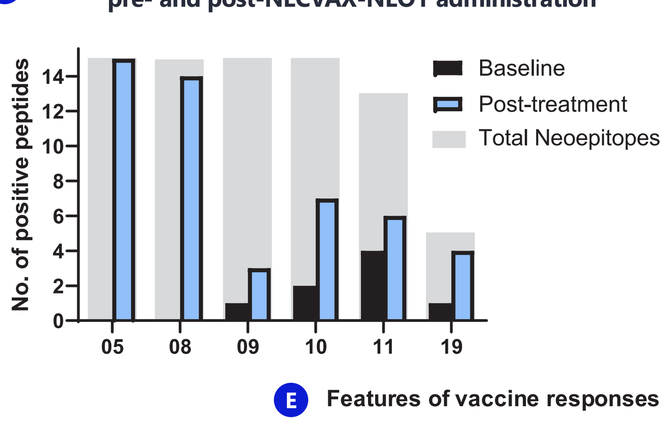


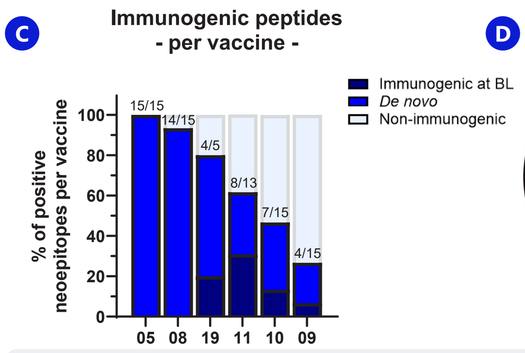
NECVAX-NEO1 is safe and well tolerated.

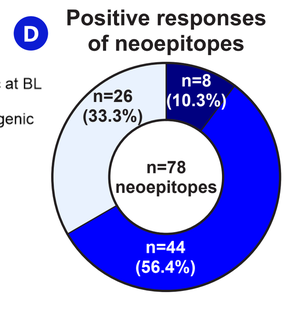
(A) Total number of treatment-emergent adverse events (TEAEs) across dose levels. The left panel shows all TEAEs, while the right panel presents only TEAEs considered related to the investigational medicinal product (IMP). **(B)** Distribution of IMP-related TEAEs by severity grade, relatedness and dose level by preferred term. Each bar represents the total number of IMP-related TEAEs within a dose cohort, subdivided by CTCAE grade to highlight the overall safety profile and severity pattern.

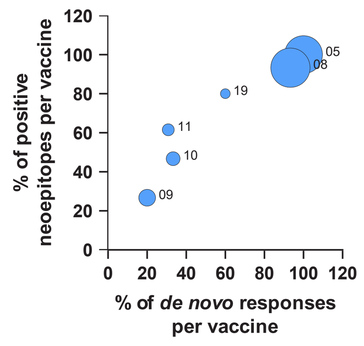
NECVAX-NEO1 triggered a strong immune response in 50% of patients





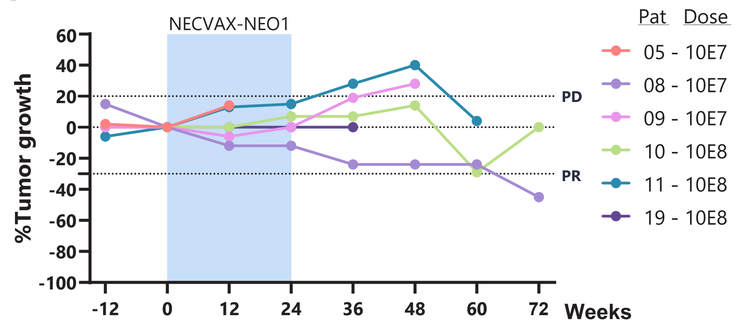


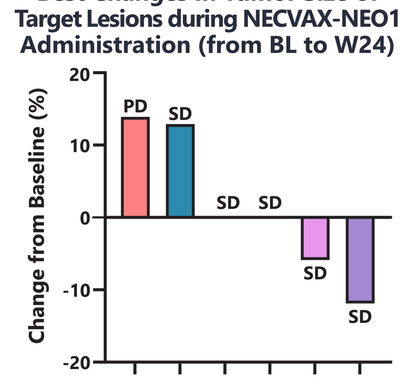


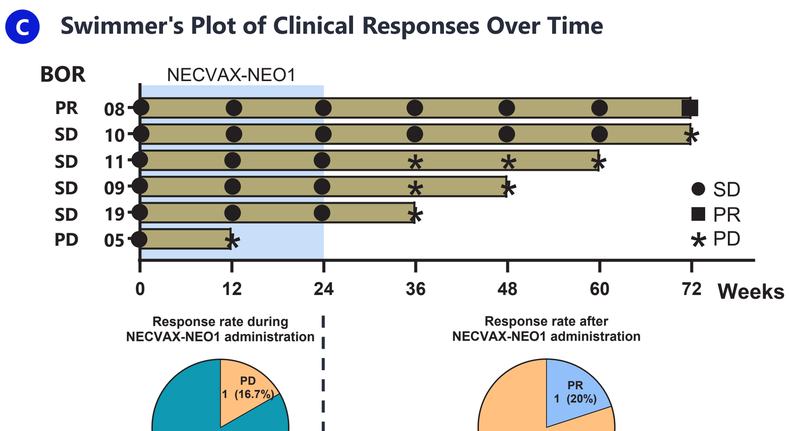


(A) Normalized IFN-γ ELISpot counts for each neoepitope at baseline (BL) and at peak immune response (Peak). **(B)** DFR-based neoepitope positive immune responses before and after vaccination. **(C)** Number and percentage of neoepitopes eliciting positive immune responses per patient. **(D)** Number and percentage of neoepitopes eliciting positive immune responses in all patients. **(E)** Scatter plot of positive neoepitope responses (Y) vs de novo responses (X), with point size indicating total magnitude. Patients 05 and 08 display the highest overall immunogenicity (high positivity and de novo responses), while 09 and 10 show lower responses. Patient 19 shows a high response profile similar to 05/08, and 11 exhibits an intermediate pattern.

NECVAX-NEO1 presented a disease control rate of 83%

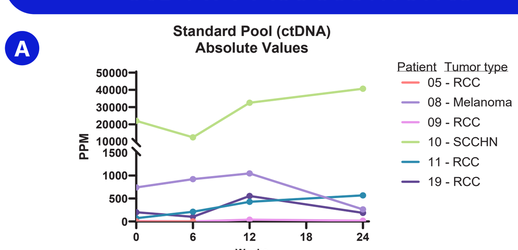


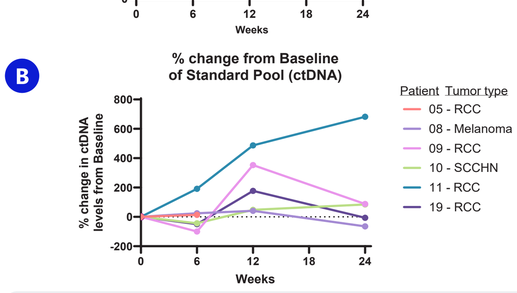




(A) Radiographic changes (%) in target lesions recorded before, during (blue shaded area), and after NECVAX-NEO1 administration for each patient. PD, progressive disease; PR, partial response. **(B)** Best percentage change in the sum of target lesion diameters during NECVAX-NEO1 administration (BL to W24) for each patient, categorized according to radiographic response. PD, progressive disease; SD, stable disease. **(C)** Upper panel: Swimmer's plot summarizing the clinical course of all patients enrolled in the study. Each bar represents an individual subject, with bar length corresponding to time on study. Patient 05 presented a new lesion at W12. Patient 10 presented PD in a non-target lesion at W72. BOR, best overall response; PD, progressive disease; SD, stable disease; PR, partial response. Lower panel: Pie charts depicting the distribution of best overall responses during NECVAX-NEO1 administration (left) and after treatment discontinuation (right). Administration of NECVAX-NEO1 is contributing to disease stabilization while removal of NECVAX-NEO1 is increasing the failure to control the disease progression.

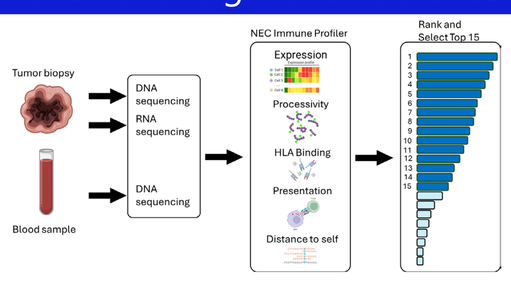
ctDNA Assessments

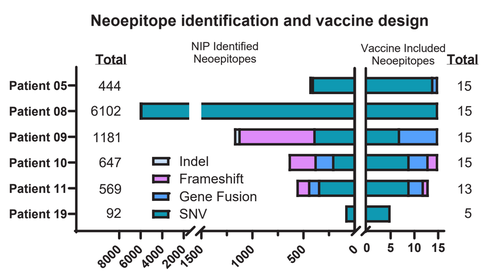




(A) Baseline ctDNA shedding varied across patients: patient 10 showed the highest levels, followed by patient 08, whereas patients 05, 09, 11, and 19 exhibited minimal shedding, limiting longitudinal analysis. These patterns align with reported ctDNA dynamics (Husain H et al. JCO Precis Oncol. 2022). **(B)** Percentage change in ctDNA levels from Baseline (week 0) during NECVAX-NEO1 administration. Responders (patients 05, 08, and 19) showed ctDNA reduction or stabilization, while non-responders (10, and 11) displayed progressive increases consistent with persistent or advancing minimal residual disease. Patient 09 shows an early spike followed by a late decline in ctDNA, suggesting a transient molecular response without durable clinical benefit.

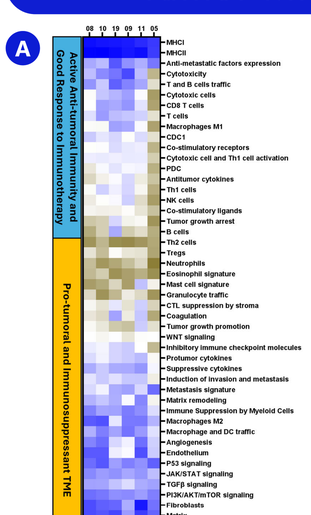
Vaccine design and features

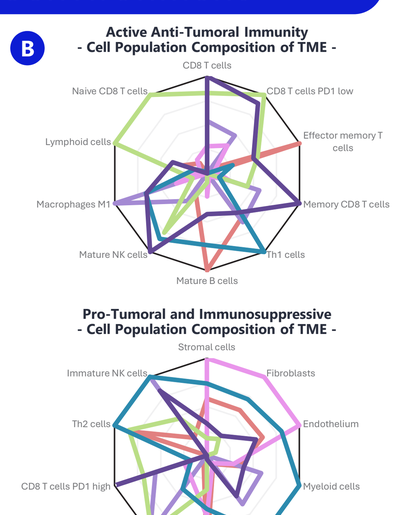




(A) Schematic representation of the NECVAX-NEO1 design process. Sequencing data from tumor biopsies and blood samples are processed through the AI-based NEC Immune Profiler (NIP) to identify and rank candidate neoepitopes based on predefined immunogenicity features. Up to 15 top-ranked neoepitopes are incorporated into the final personalized vaccine. **(B)** Left: Number and type of candidate variants. Right: Number and type of neoepitopes selected for inclusion in the final vaccine design.

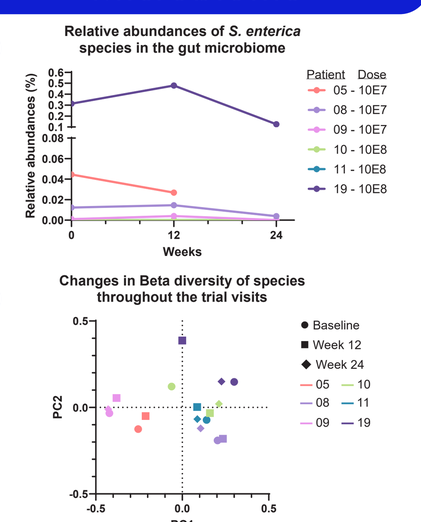
Tumor Microenvironment





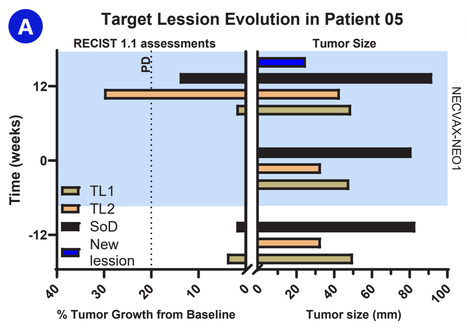
(A) Heatmap of gene-expression signatures associated with active anti-tumoral immunity or pro-tumoral/ Immunosuppressive TME when overexpressed. Values are shown as ssGSEA scores, a variation of GSEA (Subramanian et al., 2005). **(B)** Spider plots representing TME cellular composition using min–max–normalized variables. The upper plot reflects active anti-tumoral immunity, while the lower plot shows pro-tumoral/ immunosuppressive components.

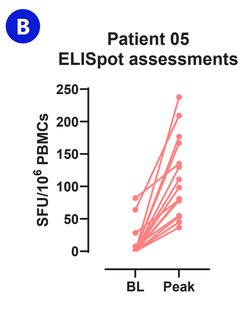
Microbiome

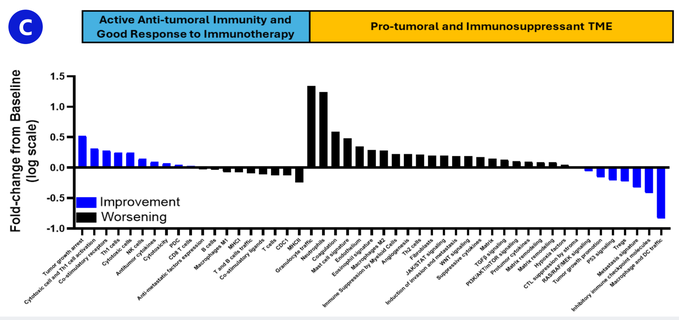


(A) Relative abundance of *S.enterica* species in the gut microbiome showing no changes along the trial visits after NECVAX-NEO1 vaccination. **(B)** Beta diversity (sample to sample variation) of the gut microbiome of the patients at different time points assessed by PCoA analysis with Bray-Curtis distances. Each patient tends to cluster together regardless of the time points, which seems to indicate that the gut microbiome is not affected by the vaccination.

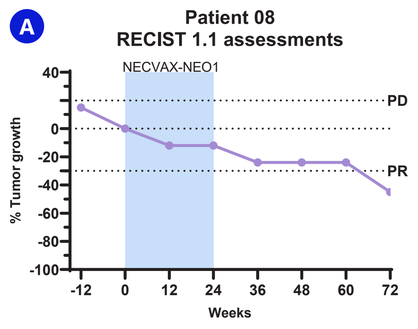
Showcases

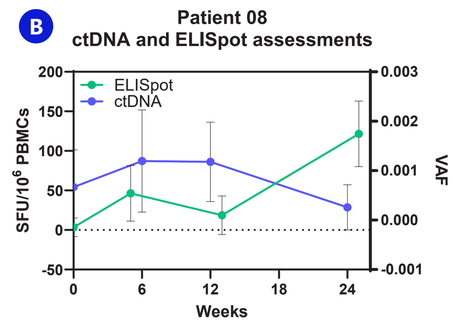


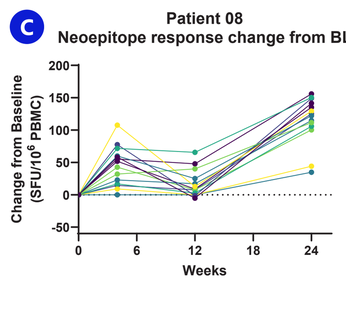


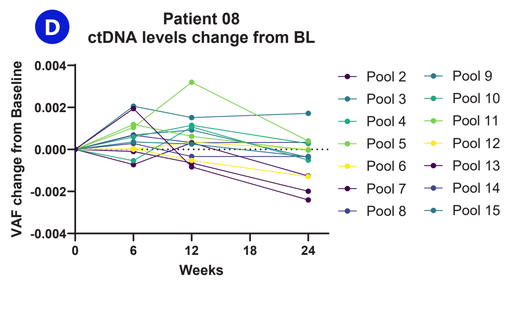


Patient 05 represents an immune responder case exhibiting progressive disease (PD) and passed away 104 days after the last dose of NECVAX-NEO1. Although the overall change in the sum of diameters (SoD) of target lesions was <20%, one target lesion demonstrated a >30% increase in size and a new lesion of 25 mm appeared at W12 **(A)**, indicating localized progression, despite the presence of a robust vaccine-induced immune response **(B)**. TL = Target Lesion; SoD = Sum of Diameters. **(C)** A second biopsy, obtained prior to patient withdrawal, was subjected to TME analysis. A clear enhancement of pro-tumoral and immunosuppressant TME can be observed.

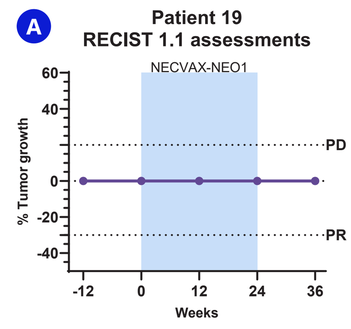


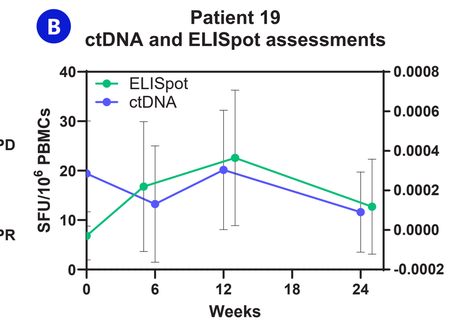


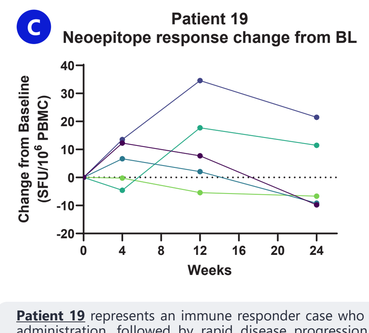


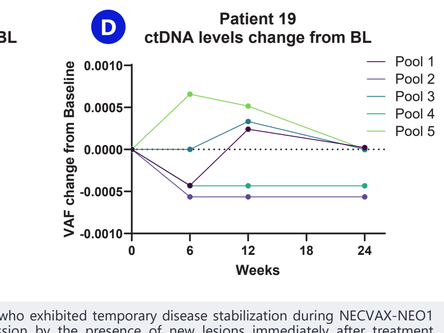


Patient 08 represents an immune responder case exhibiting stable disease during NECVAX-NEO1 administration and subsequently achieving a partial response after trial completion **(A)**. This patient demonstrated a strong concordance between immunological and molecular biomarkers during the course of vaccination **(B)**. As the immune response against the selected neoepitopes increased, the levels of tumor-specific circulating tumor DNA (ctDNA) initially plateaued and subsequently declined, indicating an effective antitumor response to NECVAX-NEO1. Figures **(C)** and **(D)** illustrate the parallel evolution of these parameters: panel C depicts the progressive enhancement of the immune response against individual neoepitopes, while panel D shows the corresponding decrease in ctDNA molecules associated with each specific neoepitope, highlighting the direct relationship between vaccine-induced immunity and tumor molecular clearance.









Patient 19 represents an immune responder case who exhibited temporary disease stabilization during NECVAX-NEO1 administration, followed by rapid disease progression by the presence of new lesions immediately after treatment discontinuation **(A)**. Detailed monitoring of biomarker dynamics revealed an increased immune response to the vaccine-derived neoepitopes, concomitant with a decrease in tumor-specific ctDNA levels, followed by a loss of control of the immune response **(B)**. Figures **(C)** and **(D)** explains the parallel evolution of these parameters: panel C depicts the progressive enhancement of the immune response against neoepitopes 2 and 4, together with clearance of ctDNA variants of the same neoepitopes (panel D). On the other hand, loss of responses towards neoepitopes 1, 3 and 4 correlate with an increase of ctDNA variants of the same neoepitopes.

Conclusion

- **NECVAX-NEO1** has been shown to be **safe and well tolerated** in combination with immune checkpoint inhibitors at doses of 10^7 CFU and 10^8 CFU.
- **NECVAX-NEO1 can trigger strong immune responses** and biomarker changes, **presenting an 83.3% of disease control rate** in solid tumor patients.
- The **NEC Immune Profiler** AI-based technology **is able to identify immunogenic tumor-specific neoepitopes.**
- **Two more studies** are currently being run in **TNBC patients neoadjuvant** treatment **and CPI treated solid tumors**.