Phase I data from TENDU-101, a first-in-human trial of a novel synthetic peptide conjugate cancer vaccine platform assessed in recurrent prostate cancer patients before salvage treatment

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Study design and safety data

A First-in-Man, Open-label, Single center, Dose-selection Study of Safety and Effect of Different Doses of TENDU Vaccine, a Therapeutic Peptide Conjugate Vaccine, in Patients with Relapse after Primary Radical Prostatectomy (TENDU-101)

Background: We have developed a synthetic drug conjugate-technology enabling cross-linking of endogenous, pre-existing circulating antibodies (Abs) to drive immunogenicity. This adjuvanting and immune cell targeting strategy was realized by employing a multi-dimensional chemistry design allowing for several identical tetanus toxin-derived B cell epitopes to be conjugated to antigenic tumor peptides intended to induce T cell responses. Here we report the first clinical results of the synthetic drug conjugate vaccine platform in the trial TENDU-101 (NCT04701021) for evaluation as therapy in prostate cancer patients.

Study overview and patient demographics:

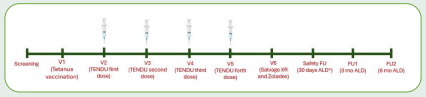
Characteristics	Number (%)
Age, median (range): 66 (55-76)	12 (100)
ECOG: 0	12 (100)
ISUP grade*: 4 / 5	6 (50) / 6 (50)
PSA (µg/mL), median (range): 0.28 (0.13-0.80)	12 (100)
PSMA PET-CT: Negative / Positive (pelvid bed)	9 (75) / 3 (25)
TENDU doses: 40 µg / 400 µg / 960 µg**	3 (25) / 3 (25) / 6 (50)

*The International Society of Urological Pathology (ISUP)
** TENDU injected in abdomen in 3 patients, 3 patients in upper arm (same as the TTd-booster dose)

Study design:
Three TENDU dose levels were investigated: 40 µg, 400 µg and 960 µg and administered 4 times with a 2-week interval. Patients were enrolled according to a dose escalation 3+3 design. All patients received a tetanus toxoid (TTd)-based vaccine injection 1 week prior to TENDU (see study overview)

The first 3 pts. were treated on the lowest dose (cohort 1), the next 3 pts. on 400 µg (cohort 2), while the next 3 pts. received the highest dose (960 µg/cohort 3.1). TENDU was administered in the abdomen. The last 3 pts. received TENDU (960 µg/cohort 3.2) in the upper arm (same arm as the TTd booster administration).

Primary objective was safety and secondary objectives were assessment of immune responses and preliminary anti-tumor responses.



Study scheme:
The patients followed the scheme to the left from screening, therapy administrations and FU meaning "Follow-Up". ALD means "After Last Dose" of TENDU.

Safety assessment:

	Any grade, n (%)	Grade 3, n (%)
Lymphocyte count decrease	9 (17.3)	1 (1.9)
Diarrhea	6 (11.5)	
Lipase increase	7 (13.5)	3 (5.8)
Anemia	4 (7.7)	
White blood cell decrease	3 (5.8)	
LHD increase	3 (5.8)	
COVID-19	2 (3.8)	
Hypertension	2 (3.8)	
Hyponatremia	2 (3.8)	
Injection site reaction	3 (5.8)	
Constipation aggravation	2 (3.8)	2 (3.8)
Hypokalemia	1 (1.9)	
Bronchial infection	1 (1.9)	
Elective anal polyp excision	1 (1.9)	
Fatigue	1 (1.9)	
Hypercalcemia	1 (1.9)	
Hypoalbuminemia	1 (1.9)	
Nocturi	1 (1.9)	
Platelet count decrease	1 (1.9)	
Wound infection leg	1 (1.9)	

All patients completed 6 months FU after the last TENDU dose and there were no discontinuations due to adverse events (AEs). In total 52 AEs were reported with the main AEs beeing decrease in lymphocyte counts, diarrhea, increase in lipase levels and anemia.

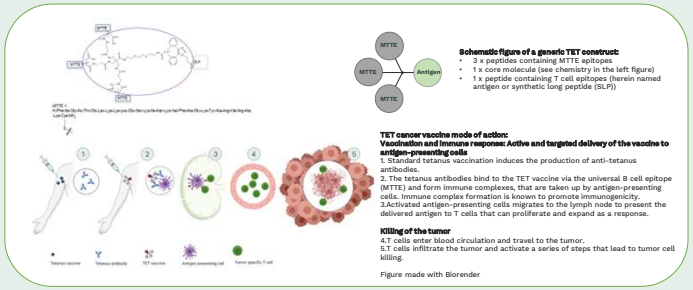
All grade 3 AEs (n=6) were in the two lowest dose levels (31% AE in cohort 1, 25% in cohort 2 and 44% in cohorts 3.1+3.2). 33 (63.5%) were mild, 13 (25%) were moderate and 6 (11.5%) were severe (grade 3). 46 (88.4%) were deemed unrelated to TENDU, 3 (5.8%) possibly related to TENDU (lipase increase) and 3 (5.8%) deemed related to TENDU (injection site reactions). The elective anal polyp excision led to constipation followed by hospitalisation e.g. noted as an AE.

Design of vaccine substance

The TENDU vaccine is based on a synthetic peptide-conjugate design that includes the Tetanus-Epitope Targeting (TET) platform. TET is a vaccine modality allowing for endogenous antibodies to bind to the vaccine conjugate to form conjugate/antibody complexes that can engage with innate receptors in the immune system to both activate and target dendritic cells.

TENDU intended for prostate cancer therapy contains four different drug substances. The drug substances are comprised of three distinct structural elements, two of them are common in all drug substances. The first common element is a Minimal Tetanus Toxoid Epitope (MTTE) peptide (marked with blue square below). Each drug substance contains three copies of the MTTE peptide, which are coupled to a central core moiety (second common element, marked with purple circle below).

The differences between the four drug substances arise from the Synthetic Long Peptides (SLPs) coupled to the central core moiety. These SLPs includes prostate-cancer specific T-cell epitopes from: PSMA (prostate membrane antigen) and PAP (prostatic acid phosphatase). Both proteins are over-expressed in prostate cancer patients and are present in the tumor micro-environment. A general structure of the drug substances and an illustration of the mode-of-action of the TET platform is shown below



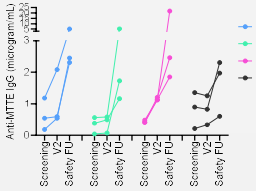
Conclusions

- Four (4) consecutive administrations of the TENDU vaccine at dose levels 40 µg, 400 µg and 960 µg, with 14 days between vaccinations, was safe and well-tolerated, as assessed by reported AEs, by the study population of 12 adult prostate cancer patients with documented progressive disease and prognostically high-risk features
- T-cell responses against incorporated CD4/CD8 epitopes in the vaccine increased from baseline in 5/6 patients with samples from pre-and post TENDU vaccination available for analysis.
- There were no trends for decrease in PSA and/or PAP protein in blood observed between dose levels based on levels of anti-MTTE antibodies or doses of TENDU, and longer follow-up was not possible due to initiation of standard-of-care therapy that impacts PSA and PAP levels. The low number of patients in the study overall and in each dose cohort call for caution in the interpretation of efficacy results.
- Co-administration of tetanus and the TENDU vaccine at the same anatomical site (arm) in cohort 3.2 (960 ug) was sub-optimal. Both the polyclonal anti-tetanus antibody response (not shown) and anti-MTTE antibody responses were lower compared to the other cohorts (1, 2 and 3.1).

In summary, the study provided valuable insight into the safety and route of administration of synthetic peptide conjugates that are targeted by pre-existing endogenous antibodies. The tetanus-including conjugates is equipped to drive immune-complex formation and can thereby provide delivery of antigens along with adjuvant signals to antigen-presenting cells through Fc receptor mediated cross-linking and internalization. A larger study is required to evaluate efficacy parameters.

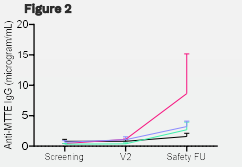
Immune responses

Figure 1



Drug exposure data (antibody responses against MTTE):
- The concentration of anti-MTTE Abs increased from screening to V2 (after administration of a pre-conditioning tetanus vaccination) in most patients (less clear for cohort 3.2) (Figure 1).
- The levels of anti-MTTE Abs in blood increased further after TENDU vaccination (Safety FU) in all patients (Figure 1).
- The highest levels of IgGs specific for MTTE after the therapy completion was found in one patient per dose level in cohorts 1, 2 and 3.1 (Figure 1).
- On an aggregated level, cohort 3.1 displayed the most apparent increase in anti-MTTE levels compared to the other cohorts, mainly driven by one patient (Figure 1 and 2).

Figure 2



Material and Methods:
- Anti-MTTE antibodies were evaluated by ELISA using biotinylated MTTE peptides coated on streptavidin plates. The amount of circulating anti-MTTE antibodies was calculated by preparing a standard curve using a recombinantly produced chimeric anti-MTTE IgG1 antibody.

Figure 3

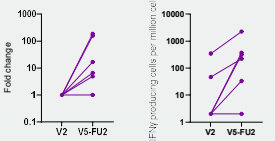
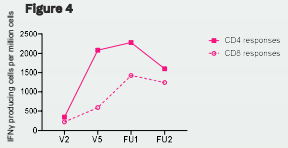


Figure 4



T cell response data:
- 6 patients had available T cell readouts pre- and post TENDU treatments. In 5 out of 6 individuals, an increase in T cell responses were detected (Figure 3).
- The best responder based on anti-MTTE levels in blood in cohort 3.1 showed a durable CD8 (dotted line) and CD4 (filled line) response to the vaccine over time (Figure 4).

Material and methods:
- PBMCs were isolated from patient whole blood samples at V2, V5, Safety, FU1 and FU2 taken before TENDU injection and were cultured with 10µM SLPs derived from the TENDU vaccine for 12 days. Cells were restimulated for 22h with the epitope mixes covering CD4 or CD8 epitopes of the vaccine and IFNg-producing cells were analyzed using ELISpot. A response was deemed present when the mean spot count of stimulated cells exceeded mean spot count + 2x SD of the unstimulated cells.

Circulating tumor cell data and PAP levels

Figure 5

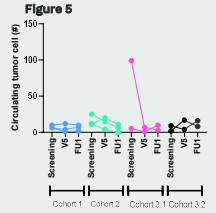
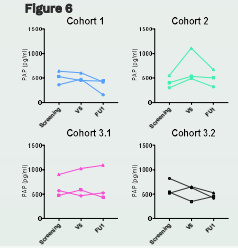


Figure 6



Preliminary anti-tumor data:
- Three patients (from cohorts 1, 2 and 3.2) had a positive PMSA PET/CT at screening. At V5, 2 out of 2 tested remained positive.
- Circulating tumor cells were assessed at screening, V5 (i.e. after three doses of TENDU) and FU1. The total number of detected circulating tumor cells are summerized and plotted on the left (Figure 5).
- PAP levels did not change during the course of the TENDU vaccination (Figure 6).

Material and methods:
- PSMA-PET/CT images were assessed as positive (including location) or negative
- Circulating tumor cells were captured with the GILUPI CellCollector® coated with anti EpCAM antibodies, inserted into the blood vessel for 30min. Captured cells were stained with Hoechst, anti-PDL1, anti-PSMA or anti-PSAP and examined by microscope evaluation. Cells with intact morphology, a positive stain for Hoechst and a minimum of one of the tumor markers, were considered tumor cells.
- Circulating PAP and PSA (not shown) levels were measured by a standardized clinical routine assay.

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