Modi-1, anti-citrullinated neoepitope vaccine alone and combined with checkpoint inhibitors in patients with Head and Neck, Breast, Renal and Ovarian Carcinoma: Protocol for the ModiFY Phase I/II Basket Clinical Trial

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Background

- Stressful conditions in the tumor microenvironment induces autophagy
- High levels of calcium within autophagosomes activates peptidylarginine deaminase enzymes which convert arginine residues within polypeptides to citrulline and alters proteolytic cleavage (figure 1).
- In the presence of inflammation, the MHC-II pathway presents these new citrullinated peptides to CD4 T cells.
- Modi-1 vaccine comprising three citrullinated, TLR-1/2 adjuvanted peptides (AV-Vim415cit, AV-Vim28cit and AV-Eno241cit) induces and expands a population of activated CD4 T cells. On reaching the tumor site the CD4 T cells release proinflammatory cytokines including, INFγ, which upregulates MHC class II and the same, but endogenous, modified peptides are presented on the tumor cell surface. This likely causes a positive feed-forward loop with killing of tumor cells (figure 2).

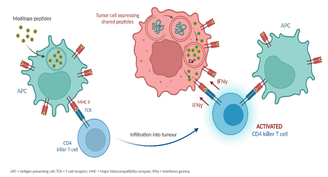

Figure 1. Citrullination

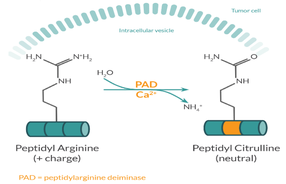

Figure 2. Mechanism of action

Study Schema

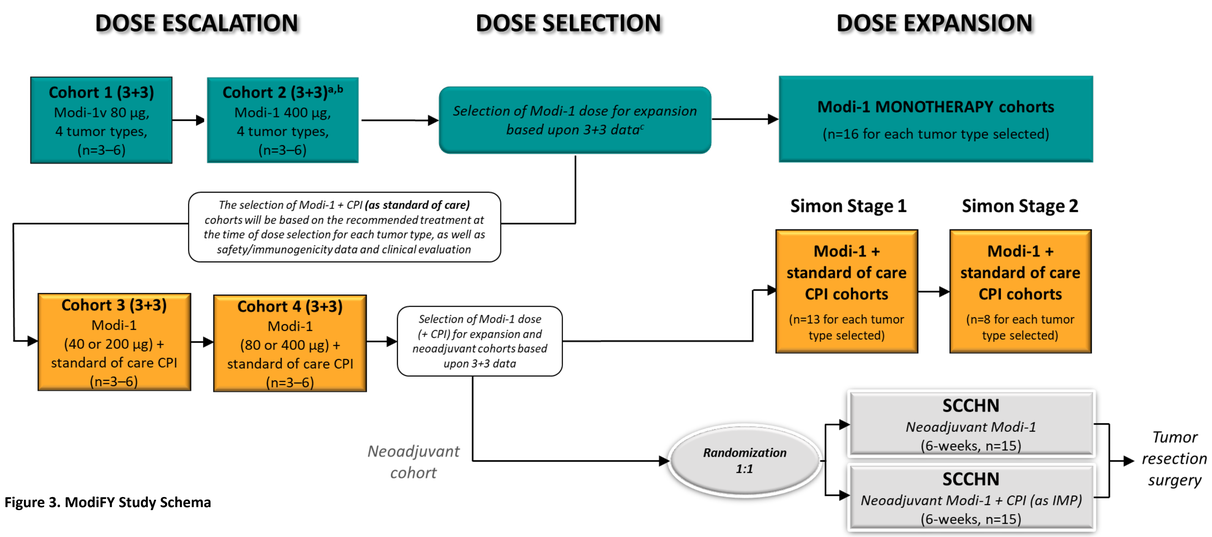

Figure 3. ModiFY Study Schema

Study Design

This is a Phase 1/2 multicenter, multicohort, open-label basket study of the Moditope® vaccine, Modi-1, in patients with advanced TNBC, SCCHN, HGSOC, or RCC. Eligible patients will be recruited and vaccinated initially to the 3+3 dose escalation cohorts, firstly in the vaccine monotherapy sub-study followed by vaccine in combination with standard of care checkpoint inhibitors. Upon establishing the safe dose of Modi-1, the tumor cohorts will be expanded for each of the target tumor type in the vaccine monotherapy and vaccine plus checkpoint inhibitors sub-studies. A separate cohort of patients with squamous cell carcinoma of the head and neck who are undergoing curative intent resection, will be randomized 1:1 to receive neoadjuvant therapy with either Modi-1 alone or Modi-1 with pembrolizumab (figure 3).

In the unresectable disease population, Modi-1 will be administered intradermally on five dosing occasions during the first 25 weeks and six subsequent booster doses over the next 18 months for a total of twelve vaccine doses over 2 years of treatment. The Phase IIa expansion cohorts of the master protocol is designed with a Simon two-stage methodology, with an interim analysis for futility based on RECIST 1.1 imaging criteria.

The neoadjuvant sub-study in resectable SCCHN, will comprise two doses of Modi-1 over 3 weeks and in the Modi-1+ pembrolizumab arm patients will receive an additional dose of pembrolizumab.

Fully recruited cohorts

	Cohort 1 80 µg/peptide (n=3)	Cohort 2 400µg/peptide (n=3)	Cohort 3 200µg/peptide (n=3)
Male	0	0	2
Female	3	3	1
Median age (range)	60 (57-65)	71(62-81)	60 (58-69)
Cancer type			
HGSOC	3	2	0
SCCHN	0	1	3
Concomitant Checkpoint Inhibitor	NA	NA	Pembrolizumab n=2 Nivolumab n=1
RECIST Response at Week 8	SD=1 PD=2	PR=1 SD=1 PD=1	Timepoint not reached

Table 1. Baseline characteristics

Results

As of February 2023, 3 pts received Mod1-1v (vimentin only) 80 µg/peptide and 3 pts received Modi-1 at 400 µg/peptide (vimentin + enolase peptides) as part of the monotherapy dose escalation. A further 3 pts received Modi-1 at 200 µg/peptide in combination with a checkpoint inhibitor (table 1).

No DLTs were observed, enabling enrolment into the monotherapy expansion cohorts. 20 pts have received Modi-1(v) (3 pts Modi-1v 80 µg/peptide, 17 Modi-1 400 µg/peptide): 16 had HGSOC, 2 TNBC, 2 SCCHN with 53 doses received; 2 pts have been treated beyond 24 weeks.

All pts had skin reactions consistent with a delayed-type hypersensitivity reaction at injection sites.

Vaccinations have been well tolerated with 71 adverse reactions in 15 pts reported. All were Grade 1 or 2 except for four Grade 3 reactions in 3 pts (anemia, fatigue, and injection site reactions). There have been no SAEs. Elevation in anti-CCP antibodies has not been seen.

In the recruited cohorts, the best overall response by RECIST v1.1 included 1 PR (SCCHN), 2 SD and 3 PD. The imaging timepoint in cohort 3 (Modi-1+CPI) was not reached in February 2023.

Discussion

This study is currently ongoing and recruiting patients in the Phase IIa sub-study investigating Modi-1 monotherapy in the dose expansion tumor cohorts. In tandem , patients are being screened for Modi-1 + standard of care checkpoint inhibitor (Cohort 4). This master protocol aims to address the safety, tolerability, cellular immune response , tumor response (RECIST) of Modi-1 when given alone and in combination with standard of care checkpoint inhibitors in patients with advanced SCCHN, RCC, HGSOC and TNBC.

Additionally, a sub-study in patients with SCCHN scheduled to have curative intent resection, the study will enable the identification and profiling of TILs in resected tumor tissue. The pathological tumor response will also be recorded from the resected samples. The patients recruited to this sub-study will be randomized to receive neoadjuvant treatment with either Modi-1 alone or in combination with pembrolizumab.

The master protocol basket study with surrogate efficacy and immunology endpoints will inform the subsequent development pathway of Modi-1 as multiple target tumor types are being reviewed simultaneously within a single master protocol.

The tumor response in patients is being assessed using RECIST 1.1 and iRECIST. Early week 8 imaging data in the Modi-1 alone dose escalation and expansion cohorts is encouraging ,demonstrating the potential for Modi-1 to stabilize and shrink tumors in a sub-group of patients that have otherwise exhausted most lines of therapy.

The safety, efficacy and immunology will continue to be evaluated in approximately 138 patients treated with Modi-1 within this master protocol.

Conclusions

Modi-1 is well tolerated, and the early monotherapy efficacy data are encouraging. Safety and early efficacy data are supportive of the current ongoing sub-studies with Modi-1 in combination with standard of care checkpoint inhibitors.

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