A phase I trial of a yeast-based therapeutic cancer vaccine targeting CEA: preliminary evidence of safety and immunologic activity

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Abstract

Background:
Saccharomyces cerevisiae (yeast) has been genetically modified to express CEA protein and employed as a heat-killed vector-based vaccine. Preclinical studies have shown that these modified yeast can induce a strong immune response to CEA as well as antitumor responses in a CEA-transgenic host.

Methods:
Patients (pts) were enrolled in this classic phase I design at 3 dose levels: 4, 16, and 40 yeast units (each unit $=10^7$ yeast particles). The vaccine was administered in equal doses at 4 sites subcutaneously in bilateral inguinal and anterior chest wall regions. Vaccine was administered at 2 week intervals for 3 months, then monthly. Eligible patients were required to have a serum CEA > 5 ng/ml or >20% CEA+ positive tumor block, ECOG PS 0-2, and no autoimmune history. An expansion cohort of 10 ECOG PS 0-1 pts were enrolled to focus primarily on immune response. Pts had re-staging scans at 3 months, then bimonthly. Peripheral blood was collected for analysis of immune response including ELISPOT assay, changes in the myeloid-derived suppressor cells (MDSC), natural killer cells (NK) and the effector/Regulatory T-cell ratio.

Results:
A total of 25 pts have enrolled. The most common adverse event (AE) is grade 1/2 site reaction (no grade ≥3 attributable AE). Most pts were heavily pre-treated with advanced disease where vaccine-induced immune response can be difficult to generate. Of 25 evaluable pts, 5 pts (3 colon, 1 medullary thyroid cancer and 1 NSCLC) had stable disease beyond 3 months and 2 are on-going **(11+, 8, 6+, 4, 4 months)**. All 5 pts had stabilization or declines in serum CEA after treatment. Of those 5 patients, 1 had positive ELISPOT assay, 4 had decreased CD4 effector/Treg ratio and 3 had increased NK frequency.

Conclusion:
A yeast-based vaccine targeting CEA has demonstrated safety. Additional clinical trials are required. A study in medullary thyroid cancer pts with rising tumor markers is being planned.

Study design

- Eligible patients
  - Metastatic cancer with serum CEA > 5 ng/ml or >20% CEA+ positive tumor block
  - Must have completed or had disease progression on at least one prior line of disease appropriate chemotherapy treatment
  - Dose escalation (1, 4, 10 YU per site) (n = 3 – 6 per cohort)
- Subcutaneously at 4 sites every 2 weeks x 7 courses, if no evidence of progression, then every 4 weeks until progression
- Expansion cohort HLA - $A2^+$,- $A3^+$, -$A24^+$ (n = 10)
- Primary Endpoint: Safety and tolerability
- Secondary Endpoints:
  - CEA specific T cells measured by ELISPOT
  - Effector/Treg ratio, MDSC and NK frequencies
  - Clinical response (RECIST, CEA)

Results

	N = 25	Dose level (DL)
Disease progression before 3 months	**13**	DL 1 (2 pts) DL 2 (2 pts) DL 3 (9 pts)
Disease progression at 3 months restaging	**7**	DL1 (1 pt) DL 2 (1 pt) DL 3 (5 pts)
Stable disease at 3 months *11+ months, 8 months, 6 +months, 4 months, 4 months*	**5**	DL 1 (1 pt) DL 3 (4 pts)
Patients with CEA stabilization or decline	**7**	DL 1 (1 pt) DL 3 (6 pts)
Stable disease at 3 months AND stable/decline in CEA (pt # 1, 11, 16, 21, 22)	**5**	DL 1 (1 pt) DL 3 (4 pts)

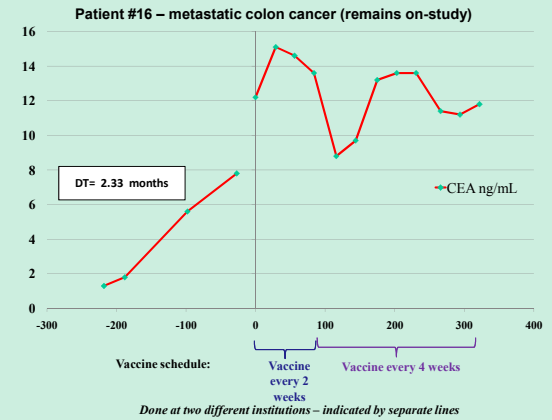
Immunological data

- ELISPOT assay (CEA and MUC1) pre - vs. post vaccination
  - positive in 3 out of 8 HLA2 positive patients (at any time point)
- Effector/Treg ratios (pre - vs. post vaccination)
  - 8 of 16 evaluable patients had increased Effector/Treg ratio
- MDSC frequency (monocytic and granulocytic)
  - 5 of 13 evaluable pts had decreased, 6 had unchanged and 2 had increased MDSC
- NK frequency
  - 6 of 13 evaluable pts had increased, 5 had unchanged and 2 had decreased NK frequency
- Anti CEA antibodies
  - Serum levels of anti-CEA in 25 patients were negative pre- and post-vaccination
- Anti Saccharomyces cerevisiae antibodies (ASCA)
  - 0/4 patients at dose level 1, 1/3 patients at dose level 2, and 6/17 at dose level 3 had increased ASCA post - vaccination

Baseline characteristics

Gender	
Male	10
Female	15
Age (median)	52 (39 - 81)
Median # of Previous Chemo	4 (1 - 6)
Tumor Types	
Colon Cancer	20
Rectal Carcinoma	2
Pancreatic Cancer	1
Non-small Cell Lung Cancer	1
Medullary Thyroid Cancer	1

CEA Stabilization and Stable Disease



Done at two different institutions – indicated by separate lines

Conclusions

- The most common adverse event was grade 1/2 site reaction, there were no grade ≥3 attributable AE
- 5 out of 25 patients had stable disease beyond 3 months with stable or declining CEA
- The patient with medullary thyroid cancer had stable disease at 3 months with positive ELISPOT assay, decreased CD4 effector/Treg ratio and increased NK frequency
- This phase I study of yeast-based vaccine targeting CEA has demonstrated safety and evidence of disease stabilization with decline in serum CEA levels
- A phase II study in medullary thyroid cancer pts with rising tumor markers (CEA and calcitonin) is being planned