Randomized phase II clinical trial to assess MUC1 specific immune response to L-BLP25 vaccine in addition to standard therapy in newly diagnosed high-risk prostate cancer

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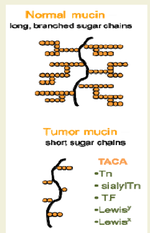
TRIAL ABSTRACT

Background: In high-risk prostate cancer, radiation therapy (RT) + androgen deprivation therapy (ADT) improve survival. Nonetheless, 10-year disease specific mortality is about 25%. L-BLP25 is a cancer vaccine containing the BLP25 lipopeptide that targets MUC1 tumor antigen. It may enhance immune targeting of cells that express MUC1 (e.g. prostate cancer). In murine models, RT synergizes with vaccine-induced anti-cancer immunity (augments T-cell mediated cancer cytolysis, up-regulates cellular Fas & co-stimulatory/adhesion molecules). ADT augments T-cell traffic to prostate. Immune response to combining the three (L-BLP25 + RT + ADT) is not known. The current trial intends to study this immune response to L-BLP25 + RT + ADT and compare it to RT+ADT alone. Using ELISPOT, prostate MRI and serial prostate biopsies, this trial may allow to study correlations of systemic immune response with changes in tumor imaging and/or tumor microenvironment after treatment with L-BLP25. This trial may provide insight into immune response biomarkers that are most appropriate in this setting.

Methods: A randomized (1:1), open-label, phase II trial of 42 pts is planned. Eligibility: Adult males with newly diagnosed high-risk prostate cancer (T3 or Gleason ≥ 8 or seminal vesicle involvement or N1 or PSA>20) and HLA-A2/A3 positivity (to allow for ELISPOT analysis). The vaccine arm will receive RT + 2-year ADT + L-BLP25. Standard arm will receive RT + 2-year ADT. L-BLP25 vaccine schedule: biweekly X 5 starting with neo-adjuvant ADT, then 6 weekly X 4 starting with RT. A single 300mg/m2 cyclophosphamide infusion (decreases suppressor T-cells) will be given 3 days before L-BLP25 to enhance immune response in the vaccine arm. The impact of L-BLP25 + RT+ADT on MUC-1-specific systemic immune response will be determined with interval peripheral blood ELISPOT assays. Pre & post-treatment multiparametric MRI with endo-rectal coil will assess prostate signal changes for correlative and predictive analysis. MRI-Ultrasound guided lesion-targeted serial prostate biopsies will be obtained to assess immune response in tumor microenvironment.

BACKGROUND: L-BLP25 MUC1 VACCINE



MUC1 is a highly glycosylated epithelial cell surface glycoprotein with role in mucosal barrier, cell-cell interaction, morphogenesis, immune regulation (Figure: Mensdorff-Pouilly et al. *Cancers* 2011)

Tumor associated mucin is oncogenic, is overexpressed in most adenocarcinomas and has exposed epitopes recognized by immune system

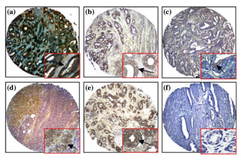


Figure 1: Over-expression of MUC1 is seen in >60% of primary prostate cancer even up to 100% with Gleason 5 score, and in 90% of the metastases (Cozzi et al. *Clin Exp Metastasis* 2005, Kirschenbaum A et al. *Molecular Urology* 1999)

LBLP25 is a liposomal therapeutic cancer vaccine designed to stimulate cellular immune response against the tumor associated antigen MUC-1

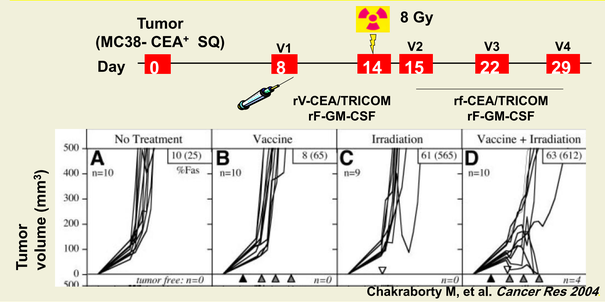
RATIONALE FOR COMBINATION THERAPIES

Vaccine + Androgen Deprivation Therapy (ADT)

- ADT increases thymic emigrants (naïve immune cells)
- ADT increased T-cell trafficking to the prostate
- ADT decreases immune tolerance to tumor antigens

Aragon-Ching JB, et al. *Front Biosci* 2007; Drake CG, et al. *Cancer Cell* 2005

Vaccine + External Beam Radiation Alters Tumor Cell Phenotype, Enhancing Immune Mediated Cell Killing



Chakraborty M, et al. *Cancer Res 2004*

OBJECTIVES

Primary Objective:

- To determine the impact of L-BLP25 vaccine in addition to standard treatment (ADT+RT) on the Muc-1-specific systemic immune response in patients with newly diagnosed high-risk prostate cancer compared to patients receiving standard treatment alone

Secondary Objectives:

- Analysis of immunologic responses (systemic and tumor microenvironment using targeted tumor biopsies)
- Evaluation of progression/recurrence status up to 24 months after randomization

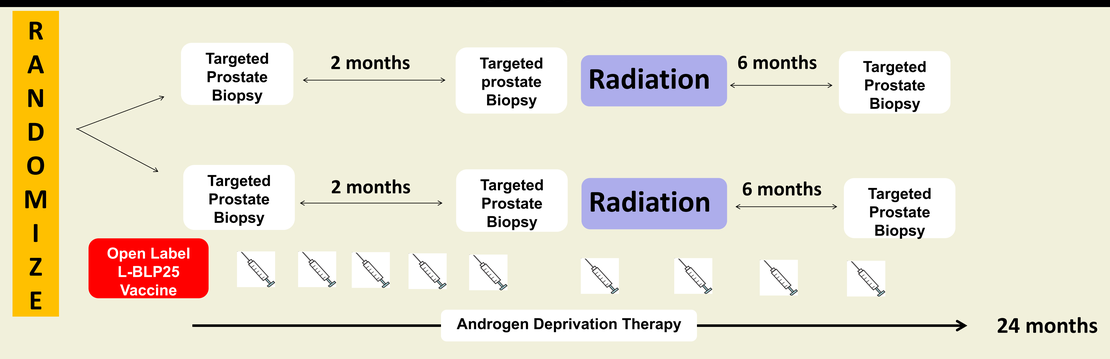
ELIGIBILITY

- Adult males with histologically confirmed newly diagnosed/untreated high-risk prostate cancer without distant metastases on CT scan or bone scan (local lymph nodes/N1 disease allowed)
- No history/clinical evidence of autoimmune disease, immuno-compromised, immunodeficiency disease
- No contraindications to MRI or RT
- Must be HLA-A2/ A3 positive for the purpose of ELISPOT immunologic monitoring

DESIGN

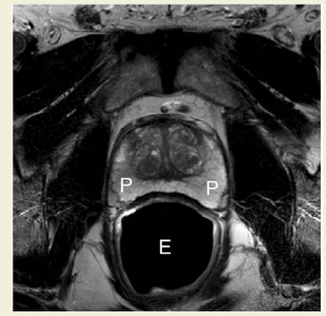
- Eligible patients will be randomly assigned to receive L-BLP25 with standard care (ADT+RT) or standard care alone
- All patients will receive neo-adjuvant/adjuvant long term ADT and RT
- Patients randomized to the vaccine arm will be administered L-BLP25 in a total dose of four 0.50 mL injections (corresponding to four 232.5 µg L-BLP25 aliquots) every 2 weeks X 5 doses starting with ADT therapy, followed by L-BLP25 injections every 6 weeks X 4 doses
- Up to 42 patients will be accrued over 2 years

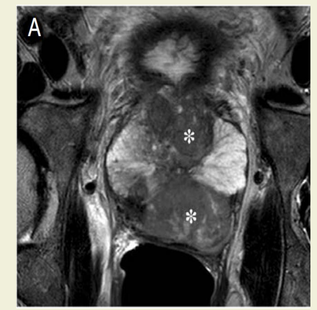
STUDY SCHEME



CORRELATIVE STUDIES: TARGETED TUMOR BIOPSIES

- Prostate multi-parameter magnetic resonance (MR) imaging will be done at baseline and periodic follow up time-points for prospective assessment of treatment induced changes





Example 1:Normal axial T2-weighted MR image of prostate peripheral zone (P) with endorectal coil (E)

Example 2: T2-weighted axial MR image of a large prostate tumor

Daar D, et al. *Radiol Technol 2011*

CORRELATIVE STUDIES: MR IMAGING

- Trans-rectal ultrasonography-MRI fusion-guided prostate lesion biopsies will be obtained at baseline, after neo-adjuvant hormone therapy (2 months) and six months after the completion of RT for the prospective assessment of:

1) Histo-pathological changes to evaluate recurrence
2) Tumor-immune microenvironment to analyze changes in local cellular immune-response

CORRELATIVE STUDIES: PERIODIC APHERESIS

- Apheresis will be done to acquire immune cells and analyze systemic antigen specific T-cell response, cytokine levels, and regulatory T-cell functions

CURRENT ENROLLMENT

- Three patients have been enrolled

TRIAL IDENTIFIER

- ClinicalTrials.gov Identifier: NCT01496131