A DOSE-ESCALATION TRIAL OF GM-CSF-GENE TRANSDUCED ALLOGENEIC PROSTATE CANCER CELLULAR IMMUNOTHERAPY IN COMBINATION WITH A FULLY HUMAN ANTI-CTLA4 ANTIBODY (MDX-010, IPILIMUMAB) IN PATIENTS WITH METASTATIC HORMONE-REFRACTORY PROSTATE CANCER (MHRPC)

W. Gerritsen, A. J. van den Eertwegh, T. D. de Gruijl, G. Giaccone, R. J. Scheper, N. Sacks, I. Lowy, E. Stankevich, K. Hege;
VU University Medical Center, Amsterdam, The Netherlands; Cell Genesys Inc, South San Francisco, CA; Medarex, Inc., Bloomsbury, NJ

ABSTRACT

Introduction: A Phase 1 trial is underway to study the GM-CSF-secreting immunotherapy for prostate cancer (GVAX® immunotherapy (IT)) and ipilimumab in mHRPC patients (pts). Ipilimumab is a monoclonal antibody (ab) specific to the CTLA-4 receptor on T cells that augments immune responses by blocking inhibitory CTLA-4/B7 interactions.

Methods: Eligible pts had mHRPC and were chemo-naïve. All pts received 500 million (m) cells of GVAX IT on day 1 followed by bi-weekly intradermal injections of 300 m cells for a 24 week (wk) period. Ipilimumab was administered every (q) 4 wks starting on day 1. Pts were enrolled in cohorts of 3; each cohort was assigned an escalating dose of ab: 0.3, 1, 3 or 5 mg/kg. PSA is measured q 4 wks, and tumor assessments q 12 wks.

Results: Twelve pts completed treatment (tx). Common adverse events (AE) included injection site reaction (100% of pts) and flu-like symptoms including fever (58%). No PSA declines nor inflammatory AE occurred at the lower doses. One pt developed a Grade 3 dose-limiting alveolitis in the 5 mg/kg group. Five of six patients at the higher doses (3 and 5 mg/kg) developed Grade 2 or 3 immune mediated endocrinopathy, consistent with hypophysitis manifested by adrenal insufficiency and/or hypothyroidism; all were successfully treated with standard hormone replacement. Two pts requiring Synthroid were tapered off after recovery of thyroid function which occurred within 6 months. Five pts attained PSA reductions that qualify as partial responses by NCI criteria, with 4 durable at 2-6 months following end of tx. Four pts had stable disease on bone scan for at least 3 months. Immunomonitoring studies demonstrate T cell and dendritic cell activation, more pronounced at higher doses.

Conclusions: The GVAX IT and ipilimumab combination appears active in mHRPC. Pts developed endocrinopathies and an alveolitis, events previously seen with the ab; resolution of hypothyroidism has occurred in two pts who have ongoing PSA responses. There was an association between tumor response and immune-mediated AE. Tx of up to16 additional pts is planned.

BACKGROUND

GVAX™ Immunotherapy

- GVAX refers to a platform of using whole tumor cells that are modified to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate an immune response against cancer.
- GVAX immunotherapy for prostate cancer includes two allogeneic cell lines, LNCaP and PC-3, that contain many common antigens found in metastatic prostate cancer.
- The secretion of GM-CSF, a potent immune stimulant, induces dendritic cell growth, maturation and recruitment necessary for an immune response.
- Activated dendritic cells would then present prostate cancer antigens to T-Cells in the lymph node. This should initiate a polyvalent anti-tumor immune response.

MDX-010 (Ipilimumab)

- Ipilimumab is a fully human IgG1k anti-CTLA-4 monoclonal antibody.
- Ipilimumab is specific to the CTLA-4 receptor on T-cells and augments immune responses by blocking the inhibitory CTLA-4/B7 interactions.
- Combination Therapy with a *B16-GM-CSF* transduced cell line (mGVAX) and an anti-CTLA-4 antibody demonstrated improved survival in mice injected with a *B16* melanoma cell line.

METHODS

Study Design: Phase 1/2, open-label, dose escalation, single-center clinical trial

Patients: Asymptomatic, metastatic hormone-refractory prostate cancer (HRPC) with PSA > 5 and no prior chemotherapy or immunotherapy.

Treatment: Patients assigned sequentially in groups of 3-6 to a dose level with a 15 patient expansion at MTD

Immunotherapy +

- Fixed Dose Level: 5 x 10^8 prime, 3 x 10^8 boost q 2 wks x 12

Ipilimumab Dose Groups

- Dose Level 1: 0.3 mg/kg q 4 wks x 6
- Dose Level 2: 1.0 mg/kg q 4 wks x 6
- Dose Level 3: 3.0 mg/kg q 4 wks x 6
- Dose Level 4: 5.0 mg/kg q 4 wks x 6

Clinical Endpoints:

- PSA Response (assessed q 4 wk x 6)
- Objective Tumor Response (assessed q 12 wk x 2)

Immunomonitoring: *(Supported in part by the Prostate Cancer Foundation)*

- Objective: Monitoring of DC and T cell functions was conducted to verify underlying scientific concepts and to correlate immune responses with clinical efficacy

Immunologic Endpoints:

- T cell naïve/memory/effector state and T_{reg} frequencies in peripheral blood
- Peripheral blood DC subset frequencies and activation status
- Tumor-specific CTL & Th responses in peripheral blood
- Tumor-specific effector CTL activity in vaccination site biopsies

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CLINICAL RESULTS

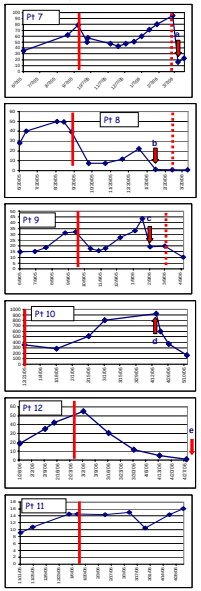
Patient Disposition

- Dose escalation cohorts: All 12 patients have completed treatment.
- Expansion cohort: Enrollment is pending

PSA Response

- A Partial PSA Response (NCI criteria) occurred in 5/6 patients on Dose Levels 3-4. Four were durable at 2-6 months following the end of treatment.
- Stable disease (<25% change) occurred in 4/6 patients on Dose Levels 1-2 and 1/6 patients on Dose Levels 3-4.
- Post-treatment declines in PSA are shown in Figure 1.

Figure 1. PSA Response over time. The start of treatment is shown by a solid red line ( ), end of treatment by a dotted red line ( ), and the occurrence of an immune-related adverse event (IRAE) by a red arrow ( ).



a: 13Mar06: SAE-Hypophysitis (7 mo)

b:03Feb06: Hypophysitis (5 mo)

c:09Feb06: SAE-Hypophysitis (5 mo)

d:04Apr06: SAE-Hypophysitis (4.5 mo)

e:23May06: SAE-Alveolitis, Low TSH (2 mo)

CLINICAL RESULTS

Objective Tumor Response

- Bone scan improvement, measurable tumor regression, and improvement in bone pain were seen in some patients.
- Bone Scan Improvement was observed in Patient 8 (3 mg/kg). See Figure 2
- Objective tumor response was observed in Patient 12 (5 mg/kg). See Figure 3
- Stable disease on bone scan was observed in 4 patients for at least 3 months.

Figure 2. Bone Scan Improvement in Patient 8 (3 mg/kg) from 15 Sept 2005 (A) to 29 March 2006 (B).

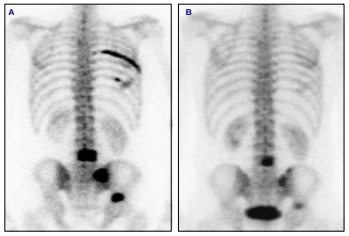
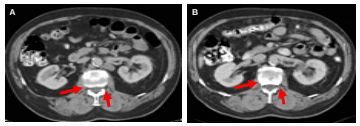


Figure 3. Objective Tumor Response in Patient 12 (5 mg/kg) from 14 Feb 2006 (A) to 16 May 2006 (B).



IMMUNE-RELATED ADVERSE EVENTS

- No immune-related adverse events (IRAE) occurred at the lower dose levels (0.3 and 1.0 mg/kg).
- IRAE's occurred in 5 of 6 patients at the higher dose levels (3 and 5 mg/kg). The times of onset are shown by red arrows in Figure 1 (above-left).
  - The IRAE's were Grade 2 or 3 endocrinopathies, consistent with hypophysitis manifested by adrenal insufficiency and/or hypothyroidism, and, in one patient on 5 mg/kg, a Grade 3 dose-limiting alveolitis accompanied by low TSH. See Table 1.
  - The endocrine-related component was successfully treated with standard hormone replacement therapy. Two patients requiring Synthroid were tapered off after recovery of thyroid function, which occurred within 6 months.
- All IRAE's were associated with PSA response, and all were delayed.

Table 1. Summary of Immune-Related Adverse Events

Patient	Primary Event	Onset	Secondary Events
007	Hypophysitis	7 mo	Adrenal Insuff
008	Hypophysitis	5 mo	Adrenal Insuff
009	Hypophysitis	5 mo	Adrenal Insuff, Leukopenia, Hypothyroidism
010	Hypophysitis	4.5 mo	Adrenal Insuff, Hypothyroidism
012	Alveolitis	2 mo	Low TSH

IMMUNOMONITORING STUDIES

Immunomonitoring studies

- Immunomonitoring studies demonstrate T cell and dendritic cell activation, which was more pronounced at the higher dose levels.
- After one treatment, T cells were found infiltrating the injection site. The number of infiltrating T cells notably increased between the first and fifth treatment. See Figure 4. The majority of infiltrating T cells were CD4+ Th cells, far outnumbering the infiltrating CD8+ T cells. No infiltration by CD56+ NK cells was observed. An increased cytotoxic potential was indicated by an increase in scattered Granzyme B+ lymphocytes after Treatment 5.
- A rise in frequencies of HLA-DR+ activated T cells occurred at the higher dose levels (3-5 mg/kg) but not at the lower dose levels. (See Figure 5.)

Fig 4. Biopsy results from the injection site taken 48 hours after treatment (Patient 10; 200x). The insert (lower right) shows Granzyme B+ lymphocytes in the deep dermis.

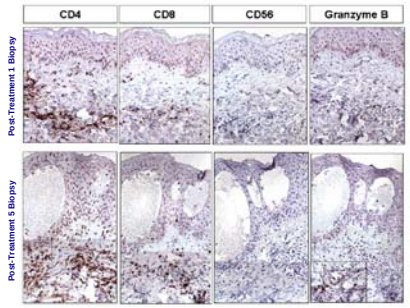
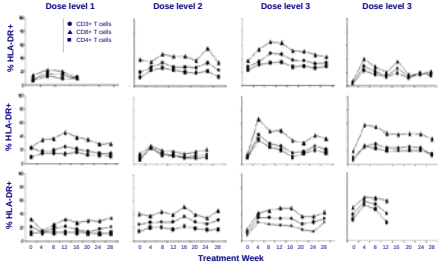


Figure 5. Immunologic response (% HLA-DR+ T cells) to treatment by dose level at Baseline and Weeks 4, 8, 12, 16, 20, 24 and 28.



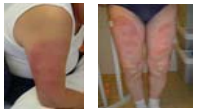
SAFETY

- Injection site reactions occurred in 100% of patients. (See Figure 5.)
- Flu-like symptoms including fatigue and fever were common.

Table 2. Treatment-Related Adverse Events (n=12)

Adverse Event*	Max Grade	Frequency (%)
Fatigue	3	75
Fever	3	58
Anorexia	1	42
Flu-like symptoms	2	33
Nausea	1	17
Bone Pain	1	8
Dry Skin	1	8

Fig 5. Injection site Reactions



Immunotherapy + MDX-010 (0.3 mg/kg)

Immunotherapy + MDX-010 (3 mg/kg) After 1 week

SUMMARY AND CONCLUSIONS

- This study demonstrated a dose response to Ipilimumab (MDX-010) in combination with a fixed dose of GVAX immunotherapy for prostate cancer (CG1940/CG8711) with regard to IRAE's and clinical activity. See Table 3.

Table 3. Summary of PSA Responses and IBE's

MDX-010 dose	Partial PSA Response	IBE
0.3 and 1 mg/kg	0/6	0/6
3 and 5 mg/kg	5/6	5/6

- A strong association between tumor response and immune-related adverse events (IRAE) was observed.
  - 100% of IRAE's were associated with PSA response
  - Additional evidence of bone scan improvement, measurable tumor regression, and improvement in bone pain was observed.
- This evidence of anti-tumor activity is unprecedented for a combination of immunotherapies in advanced prostate cancer.

CONTRIBUTORS

VU MEDISCH CENTRUM

Dept Medical Oncology
Tanja de Gruijl
Sinéad Lougheed
Helen Gall
Bob Pinedo
Beppe Giaccone
Winald Gerritsen
Fons van den Eertwegh

Dept Pathology
Saskia Santegoets
Anita Stam
Petra Scholten
Erik Hooijberg
Mary von Blomberg
Rik Scheper

CELL GENESYS, INC.
Natalie Sacks
Kristen Hege
Shirley Clift
Karin Jooss
David Rhodes
Sayeh Morali

MEDAREX
Israel Lowy
Steven Fischkoff
Elizabeth Levy

PROSTATE CANCER FOUNDATION

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