EXPANDED PHASE 1 COMBINATION TRIAL OF GVAX IMMUNOTHERAPY FOR PROSTATE CANCER AND IPILIMUMAB IN PATIENTS WITH METASTATIC HORMONE-REFRACTORY PROSTATE CANCER (mHRPC)

W. R. Gerritsen[1], A. J. van den Eertwegh[1], T. D. de Gruijl[1], H.P. Van den Berg[1], R. J. Scheper[1], N. Sacks[2], I. Lowy[3], E. Stankevich[3], K. Hege[2];
[1]VUMC Cancer Center, Amsterdam, THE NETHERLANDS; [2]Cell Genesys, Inc., South San Francisco, CA, USA; [3]Medarex, Inc., Bloomsbury, NJ, USA

ABSTRACT

Background: A Phase 1 trial is underway to study GVAX immunotherapy for prostate cancer [GVAX immunotherapy (GVAX IT)] and ipilimumab (Ipi) in chemonaïve mHRPC patients (pts).

Methods: Twelve pts were treated in a dose-escalation phase for 24 weeks (wks) with bi-weekly intradermal injections of GVAX IT and monthly Ipi. Pts were enrolled in cohorts of 3; each cohort received an escalating dose of Ipi: 0.3, 1, 3 or 5 mg/kg. Sixteen pts were then enrolled in an expansion cohort to be treated with GVAX IT and 3 mg/kg Ipi.

Results [As of December 2007]: Escalation Cohort: Median follow-up of 12 pts is 21.2 months (m). Five of six pts at the higher Ipi doses (3 and 5 mg/kg) developed Grade 2 or 3 immune-related adverse events (irAEs), including Grade 2 or 3 hypophysitis and Grade 3 alveolitis. Late onset PSA responses (declines > 50%) were seen in these 5 pts with response durations of 6.7, 8.6, 9.5, 13.8 (on-going), and 23.1 m. Four of these pts had stable disease on bone scan for at least 12 m, and up to 21 m. Multiple tumor-reactive antibodies (abs) induced by treatment were identified by serologic analysis (SEREX), including abs to filamin B, PSMA and NY-ESO-1. Biopsies of injection sites showed T cell infiltration and Granzyme B expression; these T cells are being tested for antigen-specific lytic activity. Expansion Cohort: Sixteen pts were enrolled, 6 have completed treatment, 10 are on-going. Three pts have experienced irAEs of Grade 1 diarrhea, Grade 3 adrenal insufficiency, and a Grade 3 hepatitis that resolved with steroids. With median follow-up of 6.5 months in the 6 pts who have completed treatment, 1 pt had a PSA response (defined as > 50% decline) and 3 obtained stable PSA, accompanied in one pt by pain relief and decrease in alkaline phosphatase.

Conclusion: The GVAX IT and ipilimumab combination is active in mHRPC in this trial. IrAEs appear manageable and may correlate with anti-tumor activity. The maximum tolerated dose of the combination is not established. Follow-up on the 16 expansion cohort pts will provide data on safety, clinical activity and immunologic correlates.

BACKGROUND

GVAX® Platform

- GVAX® (Cell Genesys) refers to a platform based on 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 prostate cancer cell lines, LNCaP and PC-3, that contain many common antigens found in metastatic prostate cancer.
- GM-CSF, a potent immune stimulant, induces the dendritic cell growth, maturation and recruitment necessary for initiation of an immune response.
- Activated dendritic cells could then be expected to present prostate cancer antigens to T cells in the lymph node, initiating a multiple-antigen anti-tumor immune response.

MDX-010 (ipilimumab)

- Ipilimumab (Medarex and Bristol-Myers Squibb) is a fully human IgG1k anti-CTLA-4 monoclonal antibody.
- In vivo studies in an animal model demonstrated that 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, open-label, dose-escalation, single-center clinical trial

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

Dose Escalation: Patients were assigned sequentially in groups of 3-6 to a dose level

Immunotherapy		Ipilimumab Dose Groups
• Fixed Dose Level: 5 x 10^8 prime, 3 x 10^8 boost q 2 wks x 12	+	• 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

Expansion: Based on safety results during dose escalation, the cohort at Dose Level 3 was expanded to include 16 additional patients.

Endpoints:

- Safety
- Time to PSA progression and time to clinical disease progression
- Survival

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

- Immunomonitoring was designed to investigate underlying scientific concepts and to correlate immune responses with clinical efficacy. Monitoring of DC and T cell responses is ongoing.

PATIENTS

Table 1. Baseline Demographics

Cohort Dose Level	Escalation 0.3-5 mg/kg	Expansion 3 mg/kg
Number of Patients	12	16
Age (median years) Range	64 44-78	67 59-74
Metastases		
Bone	10 (83%)	9/10 (90%)
Lymph Node	6 (50%)	1/10 (10%)
Lung	0	1/10 (10%)
Measurable	3 (25%)	1/10 (10%)
Visceral	0	1/10 (10%)
Gleason Sum		
Unknown	0	4/16 (25%)
5-7	8 (67%)	6/16 (38%)
8-10	4 (33%)	6/16 (38%)
ECOG Perf.		
0	9 (75%)	13/14 (93%)
1	3 (25%)	1/14 (7%)
Time Since Dx (median mos)	34	52
PSA† (median ng/mL) Range	48 15-351	117 25-1206
Pre-treatment PSA DT <3 months	67%	44%
Alk Phos† (median U/L) Range	86 48-429	199 53-1049
LDH (median U/L) Range	209 164-282	210 140-741
Hemoglobin† (median mmol/L) Range	8.5 7.3-9.9	7.9 6.9-8.9
Halabi Predicted Survival†‡ (median mos)	19	16

†The differences between the two cohorts in PSA, Alk Phos, Hemoglobin, and Halabi predicted survival were statistically significant.

‡Halabi S, et al., J Clin Oncol 2003; 21(7): 1232-7

DOSE ESCALATION

Disposition

- 12 patients were enrolled with 3 patients at each of the 4 dose levels. All 12 patients completed the dosing phase.
- Median follow-up is 22.3 months.

Response

- PSA declines of 50% or more were seen in 5/6 patients on the 3-5 mg/kg doses. Duration of PSA response ranged from 6.3 to 24.0 months.
- Maximum change in PSA from baseline is shown in Figure 1.
- Stable disease on bone scan, including regression of lesions, was observed in 4 patients, ongoing at 12 (n=2) and 18 (n=2) months.
- Resolution of abdominal lymphadenopathy was noted in 1/3 patients with measurable disease at baseline.

Safety

- Injection site reactions occurred in 100% of patients.
- Flu-like symptoms were common.
- No immune-related adverse events (irAE) occurred at the lower dose levels (0.3 and 1.0 mg/kg). At the higher dose levels (3 and 5 mg/kg), irAEs occurred in 5 of 6 patients.
- The irAEs were Grade 2 or 3 endocrinopathies, consistent with hypophysitis manifested by adrenal insufficiency and/or hypothyroidism. One patient on 5 mg/kg had a Grade 3 dose-limiting alveolitis, which responded to treatment, accompanied by low TSH. All endocrinopathies were successfully treated with standard hormone replacement therapy. The two patients requiring Synthroid were tapered off after recovery of thyroid function, which occurred within 6 months, with one patient subsequently maintaining a PSA response.

RESULTS: EXPANSION

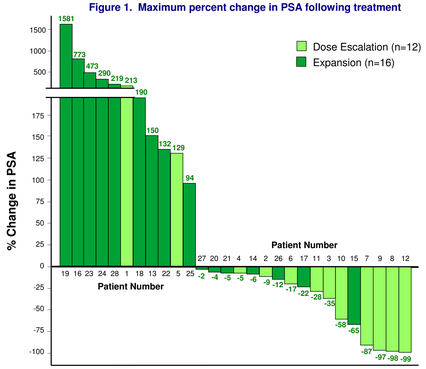
Disposition

- 16 patients were enrolled, all at Dose Level 3 (3 mg/kg), 15 have completed the dosing phase, and 1 is ongoing as of May 2008.

Response

- Stable PSA disease was seen in 7/16 (44%) patients. The median duration of stable disease was 5.6 months (range 3.7-10.6 months).
- The maximum change in PSA from baseline is shown in Figure 1. PSA kinetic changes included delayed declines after initial progression.
- Of 12 patients with identified bone lesions at baseline, 5 have ongoing stable disease, with 2 stable at 3 months, 2 stable at 6 months, and 1 stable at 9 months.
- No objective responses were seen in measurable disease.

Figure 1. Maximum percent change in PSA following treatment



Treatment-Related Adverse Events – Expansion Cohort

- Injection site reactions occurred in 100% of patients, similar to those previously reported for GVAX immunotherapy for prostate cancer.
- Flu-like symptoms including fatigue and fever were common. (See Table 2.) The maximum grade reported for treatment-related adverse events was Grade 4 for hypophysitis, Grade 3 for fatigue, diarrhea and hepatitis; Grade 2 for fever, rash, flu-like symptoms, nausea, malaise, colitis, pruritus and injection site reaction; and Grade 1 for the rest.

Table 2. Adverse Events Reported as Related to One or Both Agents in > 1 patient (n=16)

Fatigue	12 (75%)
Fever	8 (50%)
Rash	6 (38%)
Flu-like symptoms	6 (38%)
Nausea	4 (25%)
Malaise	4 (25%)
Headache	3 (19%)
Colitis	3 (19%)
Diarrhea	3 (19%)
Anorexia	2 (13%)
Eye pruritus	2 (13%)
Hyperhidrosis	2 (13%)
Pruritus	2 (13%)
Vomiting	2 (13%)
Hypophysitis	2 (13%)

Immune-Related Adverse Events

- Interim data as of May 2008.
- All events similar to those previously reported for ipilimumab.
- Two patients developed hypophysitis manifested by adrenal insufficiency and/or hypothyroidism. The endocrine-related component was successfully treated with standard hormone replacement therapy.
- One patient was diagnosed with Grade 3 auto-immune hepatitis.
- Two patients were diagnosed with low-grade colitis; both resolved without high dose steroids.

RESULTS: EXPANSION

PSA Kinetics and irAEs

- The association of favorable PSA kinetics and irAEs observed in prior studies with ipilimumab was seen in some patients in this study and not in others. Several examples are shown below.

Figure 2. PSA response over time in Patient 015

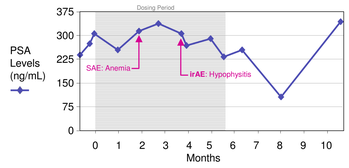


Figure 3. PSA response over time in Patient 026

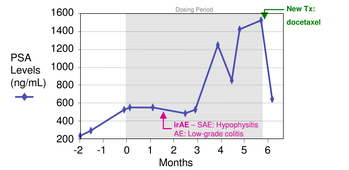


Figure 4. PSA levels over time in Patient 016

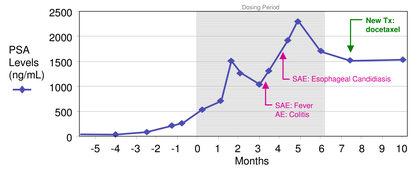
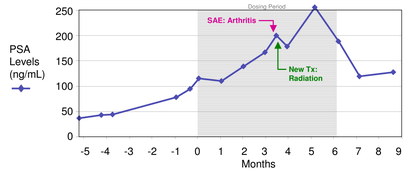


Figure 5. PSA levels over time in Patient 020



Adrenal Androgens and PSA

- The primary hormone that stimulates the growth of prostate cancer is dihydrotestosterone, which is produced primarily by the testes and also by the adrenal glands. The inhibition of adrenal androgen synthesis may result in disease response even in men who are refractory to standard androgen ablation therapies. To evaluate whether onset of adrenal insufficiency was correlated with observed PSA kinetic changes, the adrenal androgens Androstenedione (Andro), DHEA and DHEA-S were assayed at baseline and every 4 weeks in all patients.
- Adrenal androgen levels (including DHEA, DHEA-S, and Andro were below the lower limits of normal (LLN) in several patients. Levels declined from baseline in nearly all patients and dropped by at least 50% in 10 patients, including two patients with undetectable levels who developed clinical hypophysitis. See Table 3.
- The relationship between adrenal androgen suppression and PSA activity was investigated after 5 patients in the escalation cohort had both hypophysitis and PSA declines of 50% or more. The relationship in the expansion cohort is inconsistent as shown in Figures 6-9.

Table 3. Adrenal Androgen Levels

Baseline Levels	
All 3 Labs >LLN	10 (63%)
DHEA <LLN	1 (6%)
DHEAS <LLN	5 (31%)
Andro <LLN	2 (12%)
Post-treatment Drop of ≥50%	
DHEA	8 (50%)
DHEAS	5 (31%)
Andro	7 (44%)

Figure 6. PSA, Andro, and DHEA over time in Patient 015

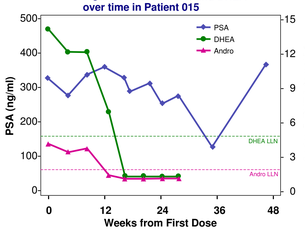


Figure 7. PSA, Andro, and DHEA over time in Patient 027

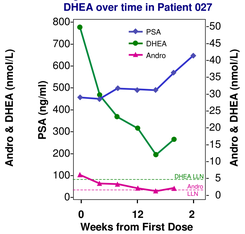


Figure 8. PSA, Andro, and DHEA over time in Patient 024

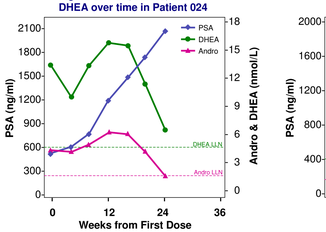
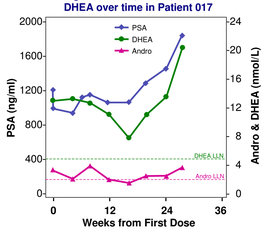


Figure 9. PSA, Andro, and DHEA over time in Patient 017



SUMMARY AND CONCLUSIONS

- This study has treated 28 patients with 4 different doses of ipilimumab (MDX-010) in combination with a fixed dose of GVAX immunotherapy for prostate cancer, including 19 treated with 3 mg/kg of ipilimumab. The expansion cohort appeared to have a poorer prognosis based on traditional risk factors than the escalation cohort.
- The side effects of combination treatment were manageable and included irAEs similar to those previously observed with ipilimumab. The rate of hypophysitis (32% of the 22 patients at Dose Levels 3-4) was lower than originally observed at these dose levels in the escalation cohort alone (83%). Additionally, a high proportion of patients had declines in adrenal androgens following treatment.
- Signals of clinical activity included PSA and radiologic changes. An inconsistent relationship between anti-tumor activity, hypophysitis and adrenal androgen suppression was observed.
- Delayed declines in PSA were observed. This pattern of late effects is consistent with observations in other immunotherapy trials.
- Further evaluation of the combination of GVAX immunotherapy for prostate cancer and ipilimumab at doses higher than 3mg/kg is warranted.

CONTRIBUTORS

VU MEDISCH CENTRUM

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

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

BRISTOL-MYERS SQUIBB

KWF KANKER BESTRIJDING

PROSTATE CANCER FOUNDATION

MEDAREX
Israel Lowy
Steven Fischkoff
Elizabeth Stankevich

CELL GENESYS, INC.
Natalie Sacks
Kristen Hege
Shirley Clift
Erik Holte
Vinkey Moroak
Jia Ma
Tim Pinkerton

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