A PHASE 3 TRIAL OF GVAX IMMUNOTHERAPY FOR PROSTATE CANCER VS. DOCETAXEL PLUS PREDNISONE IN ASYMPTOMATIC, CASTRATION-RESISTANT PROSTATE CANCER (CRPC)

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ABSTRACT

Background: A phase 3 trial comparing GVAX immunotherapy (CG1940/CG8711) to docetaxel plus prednisone was initiated in 2004. The study was designed to enroll 600 patients (pts) with a primary endpoint of superiority in overall survival. It was conducted at over 100 centers in North America and the European Union. The study was prematurely terminated based on the results of a previously unplanned futility analysis conducted by the study's independent Data Monitoring Committee (IDMC) which determined that the study had less than a 30% chance of meeting its predefined primary endpoint of improvement in overall survival.

Methods: Castration-resistant, chemotherapy-naïve men without cancer-related pain requiring opioid analgesics were eligible. CG1940/CG8711 (500 million cells prime/300 million cells boost doses q 2 weeks x 13 doses) was administered in the experimental arm (G) followed by maintenance GVAX immunotherapy (q 4 wks). Docetaxel (75mg/m^2 q 3 wks x 9 cycles) plus prednisone (10 mg daily) was given in the control arm (D+P).

Results: The study completed accrual of 626 pts in 2007, and all completed the initial 6 month treatment period. At the time of study termination the median follow-up was 66 weeks. Analysis of the dataset revealed no imbalance in patient baseline characteristics. The Halabi predicted survival (HPS) was 16 months for each arm. More than 45% of pts enrolled were Gleason ≥ 8. The median number of doses was 8 (range 1-51) for G and 9 (1-16) for D+P. Grade 3 or higher related adverse events were 8.8% on G versus 43% on D+P. The median survival was 20.7 months on G and 21.7 months on D+P, hazard ratio 1.03, 95% CI (0.83, 1.28), p=0.78, stratified log-rank test. The Kaplan-Meier (KM) curve shows G crossing above D+P at approximately 22 months. In the subset of men with HPS ≥ 18 months (n=264) median survival was prolonged on G (29.7 months) compared to D+P (27.1 months), HR 0.90 (0.61-1.33), p =0.60.

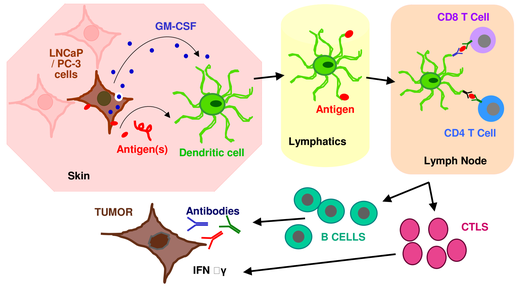
Conclusions: This randomized Phase 3 trial shows that the toxicity profile of GVAX is favorable compared to D+P. While survival was not significantly improved overall compared to chemotherapy, a late favorable effect of GVAX is suggested by crossover in the KM survival curve. Pts with HPS ≥ 18mo may have a more favorable response to immunotherapy.

BACKGROUND

Immunotherapy: the 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 (CG1940/CG8711), 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. See Figure 1 (below).

Figure 1. GVAX Immunotherapy: Proposed Mechanism of Action



- In two phase 2 studies, this immunotherapy demonstrated clinical and immunologic activity and was well tolerated. A longer median Kaplan-Meier survival time was observed with the higher dose levels of immunotherapy compared with the lower dose levels. Median survival was 34.9 months in the 10 metastatic, hormone-refractory prostate cancer (HRPC) patients on the highest dose in Study 1 and 35.0 months in the 22 metastatic HRPC patients in the high dose group in Study 2.
- The potential for efficacy with limited toxicity warranted further investigation of this immunotherapy in phase 3 trials.

METHODS

- **Objective**: This trial was initiated to test the hypothesis that GVAX immunotherapy for prostate cancer could prolong survival in asymptomatic, metastatic CRPC patients compared to docetaxel and prednisone.
- **Study Design**: Phase 3, randomized, controlled clinical trial conducted at over 100 centers in North America and the European Union
- **Patients**: Men with castration-resistant, metastatic prostate cancer without cancer-related pain that requires opioid analgesics and without prior chemotherapy or immunotherapy were eligible.
- **Randomization**: Patients were randomly assigned to one of two treatment arms. Randomization was stratified by ECOG performance status (0 vs. 1 or 2), Gleason score (≤ 7 vs. ≥ 8) and alkaline phosphatase (≤ upper limit of normal vs. > upper limit of normal, based on central laboratory normal ranges).
- **Treatments**: The two treatment arms were:
  - GVAX Immunotherapy for Prostate Cancer (G)
    - Fixed dose of 5 x 10^8 prime, 3 x 10^8 boost q 2 wks x 12
    - Duration: 24 weeks or until disease progression
    - Maintenance: 3 x 10^8 q 4 wks until death or new treatment
  - Docetaxel plus prednisone (D+P).
    - Docetaxel 75 mg/m^2 q 3 wks x 9 cycles plus prednisone 10 mg/d
    - Duration: 24 weeks or until disease progression
- **Endpoints**: The primary endpoint is duration of survival. Adverse events were collected and graded by NCI Toxicity Grade.
- **Statistical Analysis:** The Kaplan-Meier methodology was used to estimate the median survival time for each treatment arm. The hazard ratio was estimated using a stratified Cox regression model. Formal hypothesis testing for this analysis used a stratified log-rank test to determine whether survival was prolonged in the G Arm compared with the D+P Arm.
- **Futility Analysis**: Due to early termination of another trial comparing combination immunotherapy plus chemotherapy to chemotherapy in more advanced patients (symptomatic HRPC), a futility analysis was undertaken to estimate the probability of meeting the primary endpoint in this trial.

INTERIM ANALYSES

- In January 2008, an interim analysis was conducted by the independent Data Monitoring Committee (IDMC) for this clinical trial. Based on their undisclosed analysis, the IDMC recommended continuation of the trial.
- In October 2008, a previously unplanned futility analysis was conducted to determine the probability of meeting the predefined primary endpoint of prolonged survival. The futility analysis found a less than 30% chance of meeting the primary endpoint, and the trial was terminated.

PATIENTS

Table 1. Baseline Demographics

	Arm G	Arm D+P
No. of Patients	311	310
Age (median years)	71	71
Range	48-93	44-95
Metastases		
Bone	265 (85%)	250 (81%)
Lymph Node	140 (45%)	144 (46%)
Lung	31 (10%)	43 (14%)
Measurable	169 (54%)	178 (57%)
Visceral	40 (13%)	40 (13%)
Gleason Sum		
Unknown	32 (10%)	23 (7%)
2-4	5 (2%)	8 (3%)
5-7	125 (40%)	135 (43%)
8-10	149 (48%)	144 (46%)
ECOG Perf.		
0	218 (70%)	213 (69%)
1	90 (29%)	85 (27%)
2	2 (1%)	11 (3%)
Time Since Dx (median mos)	68	73
PSA† (median ng/mL)	75	67
Range	0-5502	0-5076
Alk Phos† (median U/L)	108	112
Range	30-3468	30-6524
LDH (median U/L)	196	203
Range	102-1224	89-3479
Hemoglobin (median g/dL)	13	13
Range	8-16	7-17
Predicted Survival‡ (median mos)	16	16

† PSA=prostate specific antigen; Alk Phos = alkaline phosphatase
‡ Predicted survival time was based on the Halabi nomogram, a validated model using 7 prognostic factors to predict survival time for patients with metastatic HRPC.

- There was no significant difference between the two treatment arms with respect to these baseline prognostic factors.

DISPOSITION

- The study randomized 626 patients and 621 patients were included in the efficacy analysis. Treatment was administered to 585 patients, and 585 were included in the safety analysis.

Table 2. Patient Disposition

	Arm G	Arm D+P
No. of patients randomized	311	310
No. who received treatment	307	278
No. who completed initial treatment phase (24 weeks)	113	170
No. who received maintenance therapy	81	na
Reasons for discontinuation		
Progressive disease	63%	31%
Adverse event	22%	37%
Patient request	8%	11%
Investigator decision	4%	15%
Death	2%	4%
Other	2%	3%

SAFETY

- Immunotherapy (G) was well-tolerated in comparison to chemotherapy (D+P), with a lower rate and smaller range of adverse events.
- All Grade 1-2 treatment-related adverse events occurring in ≥ 10 patients in Arm G are shown in Table 1. The 15 most prevalent Grade 1-2 treatment-related AEs in Arm D+P are shown in Table 1; additional Grade 1-2 treatment-related AEs that occurred in ≥ 10 patients in Arm D+P included leukopenia, neutropenia, decreased appetite, hyperglycaemia, dizziness, headache, hypoaesthesia, peripheral sensory neuropathy, lacrimation increased, flushing, dyspnea, epistaxis, stomatitis, dry skin, rash, arthralgia, myalgia, pain in extremity, mucosal inflammation, edema, and pyrexia.
- Injection site reactions occurred in 99% of Arm G patients. These were expected and were not reported as adverse events in most cases.

Table 3. The most common Grade 1-2 Treatment-Related Adverse Events by Arm. Adverse events common to both treatments are in green.

Arm G # of Treated Patients	307	Arm D+P # of Treated Patients	278
Anemia	8 (3%)	Alopecia	122 (44%)
Anorexia	13 (4%)	Anemia	56 (20%)
Arthralgia	16 (5%)	Anorexia	28 (10%)
Asthenia	16 (5%)	Asthenia	38 (14%)
Back Pain	10 (3%)	Constipation	33 (12%)
Chills	23 (7%)	Diarrhea	52 (19%)
Dysgeusia	11 (4%)	Dysgeusia	58 (21%)
Fatigue	75 (24%)	Edema, periph.	36 (13%)
Headache	14 (5%)	Fatigue	129 (46%)
Influenza-like Illness	20 (7%)	Insomnia	22 (8%)
Malaise	9 (3%)	Nail Disorder	34 (12%)
Myalgia	9 (3%)	Nausea	75 (27%)
Nausea	22 (7%)	Neuropathy, periph.	24 (9%)
Pruritis	16 (5%)	Paraesthesia	20 (7%)
Pyrexia	34 (11%)	Vomiting	23 (8%)

Grade 3-5 Adverse Events

- Treatment-related adverse Events of Grade 3, 4 or 5 were reported in 25 (8%) patients in Arm G and 121 (44%) patients in Arm D+P. See Table 4.

Table 4. Grade 3-5 Treatment-Related Adverse Events that occurred in ≥3 patients in a Arm.

	Arm G	Arm D+P
No. of Treated Patients	307	278
Anemia	2 (1%)	4 (1%)
Asthenia	3 (1%)	6 (2%)
Blood Glucose Increased	0	3 (1%)
Dehydration	1 (<1%)	3 (1%)
Diarrhea	1 (<1%)	6 (2%)
Fatigue	7 (2%)	15 (5%)
Febrile Neutropenia	0	21 (8%)
Leukopenia	0	12 (4%)
Neutropenia	0	42 (15%)
Hyperglycemia	0	7 (3%)
Hypotension	0	4 (1%)
Nail Disorder	0	3 (1%)
Paraesthesia	0	3 (1%)
Pneumonia	0	3 (1%)
Pyrexia	0	3 (1%)
Syncope	0	4 (1%)
Vomiting	2 (1%)	3 (1%)

Serious Adverse Events

- The serious adverse events (SAE) that were reported in Arm G did not reveal an unexpected pattern of acute toxicity attributable to treatment. In Arm G 13 patients (4.2%) had related SAEs as compared to 47 (16.9%) in the D+P Arm. The SAEs observed in Arm D+P were consistent with the known pattern of toxicity of docetaxel chemotherapy.
- The majority of deaths in this trial were due to prostate cancer progression as expected in this advanced stage population. The deaths that were reported as treatment-related SAEs in Arm G were unique events, and do not indicate a pattern of fatal toxicity that can be attributed to the immunotherapy.

SURVIVAL ANALYSIS

Figure 2. Kaplan-Meier Estimates of Survival (weeks).
Analysis Stratified by Randomization Factors (ECOG, Gleason Score, and Alkaline Phos.)

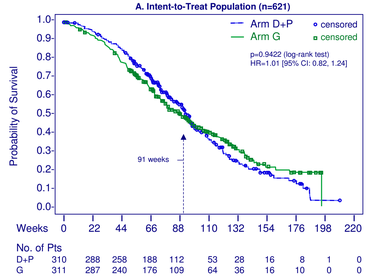
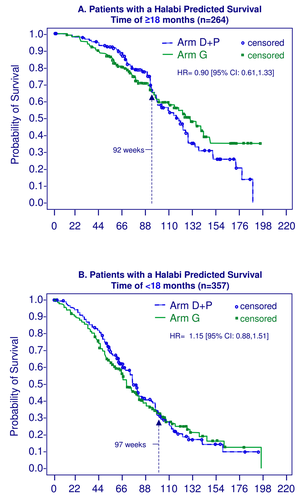


Figure 3. Kaplan-Meier Estimates of Survival (weeks).
Analysis Stratified by Randomization Factors (ECOG, Gleason Score, and Alkaline Phos.)



Survival

- The median survival was 20.7 months for patients randomized to Arm G and 21.7 months for patients randomized to Arm D+P. The median follow-up on the 621 patients was 17.1 months. The Kaplan-Meier curve is shown in Figure 2.
- The intent-to-treat analysis of overall survival was performed on a dataset of 621 patients containing 371 deaths, less than the 400 pre-specified to obtain 80% power. The Kaplan-Meier curves appear to show no meaningful difference in the pattern of survival between the two arms. The hazard ratio was 1.01, 95% CI (0.83, 1.28), p=0.78 (stratified log-rank test) suggesting no difference between the two treatment arms.
- The Kaplan-Meier curve for Arm G crosses above the Arm D+P curve at approximately 21 months, suggesting a late possibly favorable effect of the immunotherapy.
- Additional survival analyses were conducted to determine whether some subgroups of patients may show greater benefit from immunotherapy. In the subgroup of patients with a predicted survival time ≥ 18 months at baseline, based on the Halabi nomogram, the hazard ratio was 0.90 [95% CI: 0.61,1.33]. This suggests that immunotherapy may provide a survival benefit compared to chemotherapy in this patient group.
- In Arm G, 69% of patients received subsequent docetaxel following immunotherapy, and 26% had either no additional therapy or had treatments not established to have an impact on survival in metastatic HRPC. Data on subsequent therapies was not available for 5% of patients.

DISCUSSION

- This phase 3, randomized, controlled trial compared GVAX immunotherapy for prostate cancer (G) with docetaxel and prednisone (D+P) in 621 asymptomatic, metastatic HPRC patients.
- The immunotherapy was well tolerated. Adverse effects of chemotherapy were more frequent and generally of higher grade than with immunotherapy. The safety profile of the immunotherapy was similar to the profile observed in earlier Phase 1/2 trials of an allogeneic, GM-CSF-secreting, prostate cancer immunotherapy.
- At median follow-up of 17.1 months, the median survival time was similar in the two Arms: 20.7 in Arm G and 21.7 in Arm D+P (p=0.78). A late favorable effect of immunotherapy is suggested by the curves crossing at approximately 21 months (91 weeks) in the Kaplan-Meier survival curve, which is consistent with previously observed patterns of response to immunotherapy.
- Exploratory analyses suggest a hypothesis that patients with a predicted survival time of at least 18 months, based on the Halabi nomogram, may benefit from immunotherapy.

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