Analysis of Prognostic Variables in Phase 2 Trials of GVAX® Immunotherapy for Prostate Cancer in Metastatic Hormone Refractory Prostate Cancer (mHRPC)

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ABSTRACT

Background. GVAX® immunotherapy for prostate cancer is comprised of two allogeneic prostate carcinoma cell lines (PC-3 and LNCap) genetically modified to secrete GM-CSF. This immunotherapy has been tested in 114 patients (pts) with mHRPC in two separate, non-concurrent multi-center Phase 2 trials, G-9803 and G-0010. A validated model that accounts for prognostic factors and predicts individual survival probabilities can enhance interpretation of observed patient survival (Halabi, et al. Prognostic model for predicting survival in men with HRPC. JCO, 2003;21(7):1232-7)).

Methods. Eligible pts were chemotherapy-naïve with radiologic evidence of HRPC. Pts in both trials were treated for 24 wks. Doses (in millions of cells) ranged from 100 monthly to 500 prime/300 boost bi-weekly. Median survival was estimated by the Kaplan-Meier method. For each patient a predicted survival was estimated by entering his baseline characteristics into the Halabi nomogram: LDH, PSA, alkaline phosphatase, Gleason sum, ECOG Status, and presence/absence of visceral disease. The median value of the predicted survivals was then calculated.

Results. All patients have completed treatment. The median survival for the 34 pts in G-9803 was 26.2 months, compared with a median survival of 19.5 months predicted by the Halabi, et al. nomogram (p=0.01, log-rank test). The median survival in G-0010 for pts receiving the dose employed in on-going Phase 3 trials has not been reached and will meet or exceed the current median follow-up in these patients of 24.1 months. A similar comparison of observed vs. predicted survival will be presented for G-0010 when the median survival is attained. The predicted survival for this group is 22 months.

Conclusion. The median survival of mHRPC pts treated with GVAX® immunotherapy for prostate cancer in G-9803 exceeds that predicted by a validated nomogram, and probably cannot be explained by subsequent chemotherapy use alone. A Phase 3 program is underway that is studying the immunotherapy either alone or in combination with docetaxel versus docetaxel in metastatic HRPC patients, with survival as the primary endpoint.

INTRODUCTION

Patients with metastatic HRPC are a heterogeneous population, and survival times are influenced by patient and tumor characteristics. A validated model that considers prognostic factors in order to predict individual survival probabilities can enhance interpretation of observed survival of patients in non-randomized trials.

Halabi, et al., developed a pretreatment prognostic model by examining the relationship between patient characteristics and overall survival during 6 different trials that enrolled 1101 patients with mHRPC. Seven characteristics that were significantly associated with survival were identified in the "learning" group of 760 patients : lactate dehydrogenase (LDH), PSA, alkaline phosphatase, hemoglobin (Hgb), Gleason sum, ECOG Performance Status (PS), and presence/absence of visceral disease. The Halabi nomogram was developed based on these 7 factors. The prognostic model was subsequently validated in a group of 341 patients with 6 of 7 characteristics (not visceral disease) significantly associated with survival.[1]

Several other studies identified these factors and several additional factors associated with survival duration in patients with HRPC. These include: age, bone pain, anemia, weight loss, anorexia, obstructive symptoms, previous hormone response, and levels of acid phosphatase, prolactin, and pretreatment serum testosterone.[2-5]

OBJECTIVE

The objective of this analysis was to undertake a retrospective comparison of the median survival times predicted by the Halabi nomogram with the observed median survival time in two similarly designed, phase 2 studies of an investigational immunotherapy for prostate cancer.

The investigational immunotherapy is based on the GVAX® platform of whole tumor cells genetically modified to secrete GM-CSF. The rationale for employing a GM-CSF-transduced tumor cell immunotherapy is to use the whole tumor cell as the source of antigen while the secreted GM-CSF, a potent immune stimulant, induces dendritic-cell growth, maturation and recruitment.

METHODS

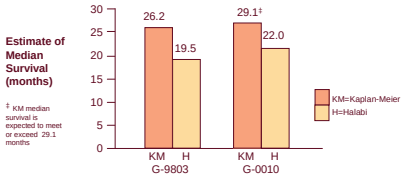
- **Study Design**: Patients from two separate, multi-center, open-label, dose escalation, phase 1/2 clinical trials were included in this analysis. These trials enrolled HRPC patients with radiologic evidence of metastatic disease, no bone pain, no prior chemotherapy or immunotherapy.
- **Treatment:** Patients received immunotherapy for 24 weeks or until disease progression. The immunotherapy was comprised of two allogeneic prostate cancer cell lines that had been genetically modified to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF). Following manufacture of the transduced cell lines, cells were lethally irradiated to prevent further cell division.
- **Dose Levels**: Each dose level consisted of 50% LNCaP and 50% PC-3 cells.
  - G-9803: 500 million cell prime injection followed by 100 or 300 million cells q14d (n=34)
  - G-0010 Low Dose: 100-200 million cells q28 days (n=33)
  - G-0010 Middle Dose: 200 million cells q14 days (n=25)
  - G-0010 High Dose: 300 or 500 million cell prime injection followed by 300 million cells q14 days (n=22)
- **Survival Analysis**: A predicted survival was estimated for each patient by entering his baseline characteristics into the Halabi nomogram: PSA, alkaline phosphatase, Hgb, LDH, Gleason sum, ECOG PS, and presence/absence of visceral disease. The median value of the predicted survivals was then calculated and compared with the observed median survival as estimated by the Kaplan-Meier method. Only data from the high dose groups were included in this analysis of prognostic factors since these were the doses selected for further development and phase 3 studies.

BASELINE CHARACTERISTICS

Study		G-9803	G-0010
Number of Patients		34	22
Gleason Sum	2-4	9%	5%
	5-7	50%	45%
	8-10	32%	36%
Visceral Disease	Yes	3%	9%
	No	97%	91%
ECOG PS	0	82%	82%
	1	18%	18%
	2	0	0
PSA	median	50	28
	range	4-1207	6-2107
Alk Phos.	median	98	76
	range	47-739	30-249
Hgb	median	12.7	13.4
	range	9.3-16.0	11.8-15.5
LDH	median	Not collected†	155
	range	--	115-229

†LDH was not collected in the G-9803 Study. Therefore, the median LDH value from the Halabi population (225; range 173-409) was used for the Halabi calculation of predicted survival in the G-9803 study group.

HALABI SURVIVAL PREDICTION



Observed (KM) vs. Predicted (H)

- In the G-9803 Study, the median survival for the 34 patients based on a Kaplan-Meier analysis was 26.2 months. The median survival predicted by the Halabi nomogram was 19.5 months.
- In the G-0010 Study, the median survival for the 22 patients in the High Dose Group has not been reached. The estimated Kaplan-Meier median survival for these patients is expected to meet or exceed 29.1 months based on the patients still in follow-up. Four patients have withdrawn consent for further follow-up and thus were censored in the analysis. The median survival predicted by the Halabi nomogram was 22.0 months.

DISCUSSION

- The observed median survivals in both trials exceeds that predicted by the Halabi nomogram.
- The nomogram was based on a patient population with a range of characteristics which encompasses the characteristics of the immunotherapy study groups.
- Consistent results in 2 separate, multi-center clinical trials suggest the potential of this immunotherapy for prostate cancer to improve overall survival of patients with mHRPC.
- The suggestion provided by this retrospective analysis that immunotherapy based on the GVAX® platform may have clinical benefit is being tested in two ongoing randomized phase 3 trials. The first Phase 3 trial (VITAL-1) is currently enrolling patients in North America and will randomize 600 asymptomatic, metastatic HRPC patients to either immunotherapy at the highest dose (500 prime / 300 boost bi-weekly) or docetaxel/prednisone. The second Phase 3 trial (VITAL–2) is currently enrolling patients in North America and Europe and will randomize 600 metastatic HRPC patients with bone pain to either immunotherapy plus docetaxel or docetaxel/prednisone alone. Survival is the primary endpoint in both trials.

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