4049

Addition of algenpantucel-L immunotherapy to standard of care (SOC) adjuvant therapy for pancreatic cancer

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Introduction

Pancreatic cancer remains one of the most difficult cancer types to treat with overall five year survival of ~ 5%. In the US, up to 25% of patients undergo surgical resection in an attempt to improve overall survival or to cure the patient. However, patients rarely achieve a long term survival outcome. The prognosis of pancreatic cancer patients in the United States is very closely tied to their stage of disease at diagnosis.

Stage	Survival (%) 1-year	2 –year	3 -year	Median Survival (mo)
IA	71.3	50.2	40.7	24.1
IB	67.3	45.4	35.3	20.6
IIA	60.7	34.9	23.8	15.4
IIB	52.7	23.8	14.4	12.7

This table represents expected overall survival in US patients based on 20,000+ patients (10,11), which is not directly comparable to studies outside of the US. In Europe ~ 5% of pancreatic cancer patients are subject to surgical resection, compared to ~20-25% in the U.S. and up to 40% in Japan (12). In the United States the majority of surgically treated patients undergo adjuvant therapy with chemotherapy or chemo-radiation; however, despite modest improvements in disease free survival (DFS), little or no progress has been achieved in changing overall survival. Therefore, improved novel therapies are greatly needed for patients with this devastating cancer. Immunotherapy is emerging as one of the novel treatment paradigms and with the recent approvals of Sipuleucel-T and Ipilimumab a much greater belief in immune therapy has emerged. Our view is that an optimal time to employ immunotherapy is when a minimal disease state exists in a patient with an intact immune system. Pancreatic cancer is a logical target given that even after complete surgical resection the recurrence and death rates are extremely high. Our group is developing adjuvant immunotherapy for patients in this setting and we are now reporting long term 2 and 3 year overall survival from our ongoing Phase 2 clinical trial. This adjuvant immunotherapy is based upon a novel technology that has been developed over the past ten years that is now being developed for patients with a variety of cancer types including pancreatic, melanoma, lung, prostate and renal cell cancer.

Algenpantucel-L immunotherapy

- A major barrier to xenotransplantation from lower mammals into primates or humans is immunity to α(1,3)galactosyl epitopes present in the organs of lower mammals, a phenomenon known as hyperacute rejection (1,2).
- α(1,3)galactosyltransferase (αGT) is expressed by lower mammals but not in humans or other Old World primates.
- Humans anti-αGal Ab can reach 1-2% of total circulating human antibodies.
- Whole cell tumor vaccines expressing αGal epitopes are significantly more effective than their αGal-negative counterparts as curative immunotherapy against established tumors in animal models (3-6)
- Algenpantucel-L consists of stably transduced human pancreatic cancer cell lines (HAPa-1 and HAPa-2) expressing the murine αGT gene .

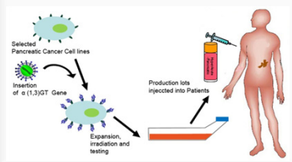


Figure 1. Algenpantucel-L description

Algenpantucel-L Immunotherapy is comprised of two human pancreas ductal adeno-carcinoma cell lines transduced with a retroviral vector expressing the murine αGT gene (HAPa1 and HAPa2). Product is irradiated for safety and administered as a series of intradermal injections.

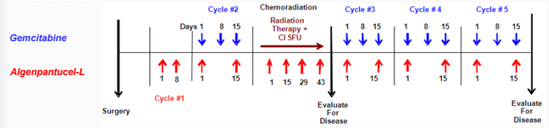
Study Design

Objectives

- **Primary:** 12 Month DFS in resected pancreas cancer patients who receive gemcitabine + 5FU-XRT (RTOG-9704) along with Algenpantucel-L
- **Secondary:** Assess overall survival (OS) and toxicity

Protocol

- 70 patient (69 evaluable). Open-label, dose finding, multi-institutional Phase 2 Study
- Dose: 100 million (N=43) or 300M (N=26) cells injected intradermally up to 14 vaccinations



Patients characteristics

Stage	N	IIB	IIA	IB	IA
NLG0205	69	81%	15%	3%	1%
RTOG-9704	221	68%	NR*	NR	NR

	Age Median	Node(+) Stage 2B	Local Invasion	CA19-9 ≥180 U/mL	Tumor ≥ 3 cm	T. Grade G3/G4	Resection Type %Whipple
NLG-0205	62	81%	90%	18%	66%	36%	86%
RTOG-9704	61	68%	NR	14%	61%	30%	85%

* NR: Not Reported

Safety & Immunological Correlative Studies

Adverse events (CTCAE 3.0)

- No serious grade 4 adverse events reported and Grade 3 events possibly attributable to vaccine were lymphopenia (6%), skin rxn/ pain (3%) and leukopenia/neutropenia (3%).
- The most frequent adverse events attributed to the algenpantucel-L immunotherapy are skin reactions at injection sites (51%).

Immunological Correlative Studies

➢ *Eosinophilia (N=69 patients)*

- In addition to eosinophilic infiltrates at the injection site in all tested patients, 70% developed eosinophilia, with 30% showing persistent eosinophilia for up to 2 years.

➢ *Anti-CEA antibodies (Ab) (N=33 patients)*

- 43% of patients increased anti-CEA Ab (>20%). The pattern of response was similar in both dose cohorts.

➢ *Anti-mesothelin Ab (N=36 patients)*

- 25% of patients increased anti-mesothelin Ab (>20%). The pattern of response was similar in both dose cohorts.

Overall Survival

Time points (years)	NLG0205 Overall Survival	Expected** Overall Survival	Percent Increase In Survival
1	86%	63%	37%
2	51%	32%	59%
3	42% *	19%	121%

•Based on Kaplan-Meier estimate
**Brennan et al nomogram

Survival Analysis

- The primary endpoint was reached with 1- year DFS of 62% (p=0.02, Median DFS 14.1mo)
- The secondary endpoint, OS at 12 months, was 86%. (Median OS 24.1 mo)

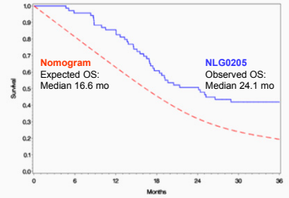


Figure 3. The Kaplan-Meier plot (Blue Line) of actual study data (Median Follow up 33 months) and projected survival based on the prognostic Brennan *et.al.* Nomogram* of. (Red Line) are shown.

* Key prognostic variables (age, gender, nodal status, nodal ratio, resection margin, tumor grade, tumor stage, surgical type, splenectomy +/-, local invasion, weight loss) of each patient in NLG0205 trial were used to predict survival by the Brennan et.al. Nomogram (8).

Potential chemosensitization effect of algenpantucel-L immunotherapy

There is a limited role for chemotherapy in recurrent resected pancreatic cancer due to lack of response rates reported in literature with occasional partial responses but no complete responses. Three pancreatic cancer patients on algenpantucel-L therapy developed recurrent disease and consequently received either FOLFIRINOX, Gemcitabine + Capecitabine + Erlotinib or Gemcitabine + Taxotere. Interestingly, all 3 patients experienced durable (6-36M), complete responses (CR). Algenpantucel-L may hold chemosensitizing effects by immunostimulation, rendering patients more sensitive to following chemotherapy.

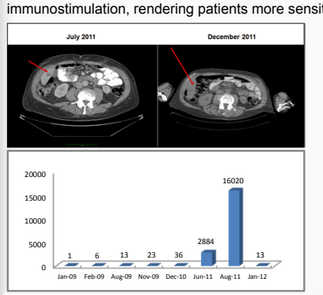


Figure 4. Case report #1 . Patient RM is a 54 year-old male diagnosed with Stage IIB in Dec 2010. After resection the patient received chemotherapy plus algenpantucel-L under compassionate use (4M) before disease recurrence in Jul 2011 (liver mets by CT/PET with elevated CA19-9). The patient was started on FOLFIRINOX two weeks later with complete radiologic (CT/PET) and biochemical response by Dec 2011.

Figure 5. Case Report #2. Pt. SLV w/ Stage IIA pancreatic cancer received Algenpantucel-L/ Gem/ 5-FU/ XRT on the NLG0205 study (initial Dx Jan 2009). Rapid rise of CA-19-9 and recurrence was confirmed CT/PET in Aug 2011. The patient achieved CR after Gem/ Xeloda/ Tarceva, confirmed by CT/PET and CA 19-9 in Dec 2012.

Conclusions

- Our study of adjuvant Algenpantucel-L in patients with high risk, surgically treated pancreatic cancer demonstrates one, two and three year overall survival of 86%, 51% and 42% respectively. These demonstrate improvements of 37%, 59% and 121% over predicted one, two and three outcomes respectively based upon nomogram analysis of these same patients.
- Over the 33 month median follow up period of the study, the percentage improvement in overall survival rate compared to nomogram analysis increased over time. These data are consistent with recent studies of active immunotherapies (Sipuleucel-T and Ipilimumab) in that immune benefits appear greater in some patients over time.
- Prominent eosinophil responses have been observed with the majority of patients demonstrating measurable increases in peripheral blood eosinophilia.
- Increase in either anti-α(1,3)galactosyl, anti-mesothelin and anti-CEA antibodies have been observed in the majority of patients.
- Unusual anecdotal observations have been made with 3 patients who had already failed chemotherapy and progressed after treatment with Algenpantucel-L. In all cases, using different chemotherapy regimens, complete responses occurred upon re-treatment and none of these 3 patients have recurred with 6 to 36 months of follow up.
- Algenpantucel-L immunotherapy has an excellent safety profile. Most AEs were related to injection site reactions.
- Despite NLG0205 patients having greater lymph node involvement than the RTOG9704 population (81% *vs.* 68% LN+), they showed better and one year OS (86% vs 69%).
- Based on the validation of the 6th edition AJCC pancreatic cancer staging system by Bilimoria *et.al.* (10) and the prognostic criteria described by Brennan *et.al.* (8), the predicted 12-month overall survival for the patients in NLG0205 would be 55-63 mo compared to the observed survival of 86%.
- Based upon these encouraging results a Phase 3 trial began in May of 2010 and patients are now been enrolled at over 50 cancer centers in the US. For information concerning patient referral please call (515)296-5555.

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