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Potential chemo-sensitization effect of tergenpumatucel-L immunotherapy in treated patients with advanced non-small cell lung cancer (NSCLC)

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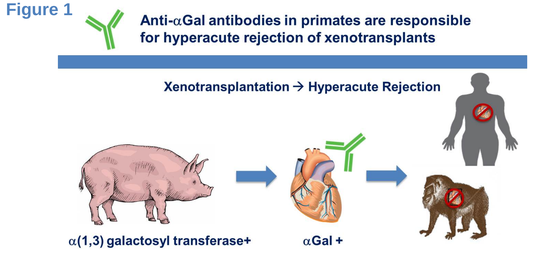
Background

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer death with an overall 5-year survival of less than 18% and less than 2% for patients with metastatic disease. Multi-drug resistance is a major obstacle for treatment. Chemo-sensitization is a process wherein tumors become more sensitive to chemotherapy. Immunotherapy has the potential to increase sensitivity of cancer cells to chemotherapy (1,2). We have completed a phase 1 study evaluating the safety of a novel immunotherapy tergenpumatucel-L in patients with advanced NSCLC. We herein report the phase 2 portion of this study, NLG0101. In addition we report here a potential chemo-sensitization effect of tergenpumatucel-L immunotherapy.

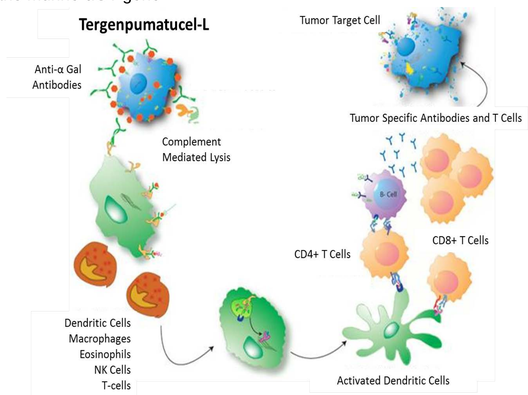
Figure 1



- The α(1,3)galactosyltransferase (αGT) gene is expressed by lower mammals, but not in humans or other Old World primates (3,4)
- Humans naturally acquire anti-αGal antibodies to levels that can reach 1% of total circulating antibodies (3,4)
- Anti-αGal antibodies responsible for HyperAcute rejection of xenotransplants (Fig 1)(4)
- Animal models demonstrate efficacy to treat tumors when αGal expressing cells are utilized (5,6,7)

Figure 2

Mechanism of action for tergenpumatucel-L immunotherapy which consists of stably transduced human lung cancer cell lines expressing the murine αGT gene



Objectives

Primary

- Assess objective tumor response rate

Secondary

- Assess survival and response duration.
- Evaluate immunological response

Methods

Clinical Protocol and Sample Collection

- Phase 2, all patients received 300 million cells per injection every 2 weeks for eight scheduled doses
- PBMC collected prior to immunization and again after the 4th & 8th immunizations Performed correlative immunologic studies including whole-cell ELISPOT assay
- Patients progressing on study monitored for response to salvage chemotherapy

Results

Clinical Response

- 28 patients were treated and evaluable for response
- 8 patients (29%) achieved stable disease (SD) ≥4 months
- 5/16 (31%) patients responded to subsequent chemotherapy

Survival (table 1)

- 11.3 month median overall survival (95% CI 3.8-21.9)
- 46% one year survival

Safety

- Well tolerated. No treatment related SAE's
- Common AE's included localized skin reactions, fatigue

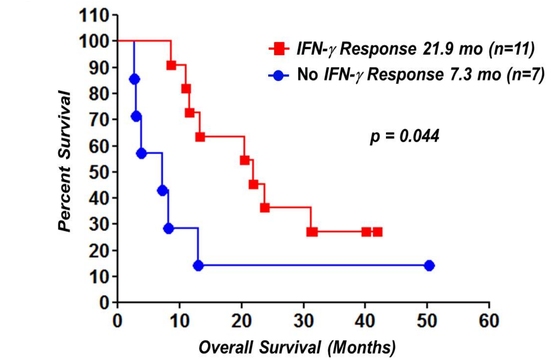
Table 1

Therapy	Overall Survival (months)	1 Year Survival
Tergenpumatucel-L	11.3	46%
Premetrexed (8)	8.3	30%
Docetaxel (9)	7.5	37%
BSC (9)	4.6	11%

Immunological Response: IFN-γ

- Evaluable clinical samples were available from 18 patients
- 11 out of 18 patients responded with increased IFN-γ release after immunization.
- Responders defined as ≥10-fold increase in IFN-γ release vs. baseline.
- Improved survival in IFN-γ responders (Fig 3)

Figure 3



Evidence of Cross-Priming to Shared Antigens

- 6/11 (55%) patients with increased IFN-γ (ELISPOT) release also showed reactivity to H522, an unrelated lung adenocarcinoma cell line that is not a component of tergenpumatucel-L

Potential Tergenpumatucel-L Chemo-sensitization

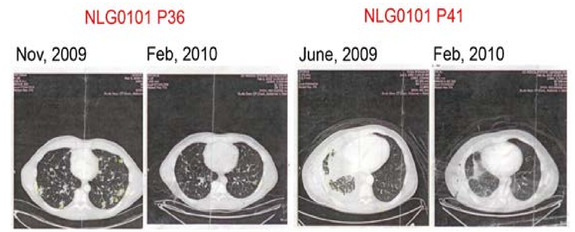
- Patients were followed for response to subsequent treatment after progressing on tergenpumatucel-L (table 2)
- 16 patients that progressed received salvage chemotherapy
  - 5/16 (31%) achieved partial response
  - 4/16 (25%) achieved stable disease

Table 2

Response	Patients (n)	Rate (%)
Partial Response	5	31%
Stable Disease	4	25%
Progressive Disease	7	44%

Patient Examples

Potential Chemo-sensitization Effect



Patient 036 received subsequent chemotherapy and had a durable partial response. Patient survived 3 years after initial progression in the trial.

Patient 041 received subsequent chemotherapy and experienced rapid partial response. Patient survived 16 months after initial progression in the trial

Conclusions

Single Agent Tergenpumatucel-L

- Encouraging 11.3 month median survival compares favorably to current standard of care of approximately 8 months
- Well tolerated, no drug related grade 4 events reported

Correlative Study Results

- Significantly improved OS in patients with elevated IFN-ɣ secretion (p=0.044)
- Acquired reactivity to CL4-H522 cell line, not part of tergenpumatucel-L, suggests antigen cross-priming to shared tumor antigens

Potential Chemo-sensitization

- Unexpected and promising results for this patient population with 31% response rate in patients receiving subsequent chemotherapy after progressing on tergenpumatucel-L
- An additional 25% of patients achieved SD

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