



A Phase I Dose Escalation Study of Ad GV.EGR.TNF.11D (TNFerade™ Biologic) with Concurrent Chemoradiotherapy in Patients with Recurrent Head and Neck Cancer (HNC)

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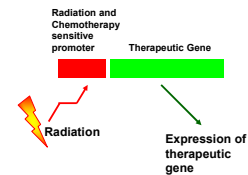
Background

- Prognosis for patients with locoregionally recurrent HNC is poor.
- Re-irradiation with concomitant chemotherapy has demonstrated long-term tumor control rates of 20-30%, but a high percentage of such patients recur within the irradiated field.
- TNFerade™ Biologic (Ad GV.EGR.TNF.11D) is a second generation replication defective adenoviral vector that carries a human TNF-α gene linked to a chemotherapy and/or radiation inducible promoter (EGR-1).
- TNF-α is a known chemotherapy and radiation sensitizer.
- Systemic administration of TNF-α is associated with severe toxicities.
- Local administration of TNFerade™ Biologic followed by chemoradiation should result in induction of regional TNF-α production and radiation enhancement without associated systemic side effects.

Combining Gene and Radiation Therapy

Goal: Achieve Spatial and Temporal Control of Gene Therapy with Radiation Sensitive Promoter

Concept: To utilize a promoter that is sensitive to radiation controlling a gene that is therapeutic



Advantages:

- The therapeutic gene is controlled (e.g. turned on only when irradiated)
- The tumor is exposed to two therapeutic modalities, gene therapy and radiation therapy

Methods

- Phase I dose escalation trial.
- Patients receive 5 days of daily radiation at 200 cGy/fx with continuous infusion fluorouracil at 800 mg/m²/day x 5 and hydroxyurea at 1000mg bid (FHX).
- TNFerade™ Biologic (Ad GV.EGR.TNF.11D) is administered in escalating doses ranging from 4x10⁹ to 4x10¹¹ PU on day 1 of each cycle by direct intratumoral injection.
- 3 to 6 patients are entered in each cohort.
- Treatment cycles are repeated every other week.

Eligibility

- Locoregionally recurrent previously irradiated HNC
- Amenable to re-irradiation with curative intent
- ECOG performance status 0-2
- Majority of disease accessible to injection
- Life expectancy greater than 12 weeks
- Normal organ and marrow function

Endpoints

Primary

- Locoregional control

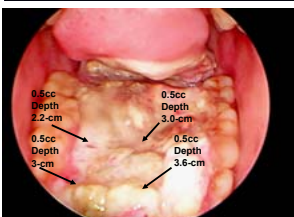
Secondary

- Objective response
- Progression-free survival
- Out of field (systemic) failure rates
- Tolerability and overall safety
- Effects of regimen on tissue biopsies
 - TNF-α mRNA levels
 - TNF-α protein levels
 - Tumor necrosis and vascular thrombosis
 - STAT1 expression

Definition of Dose Limiting Toxicity (DLT)

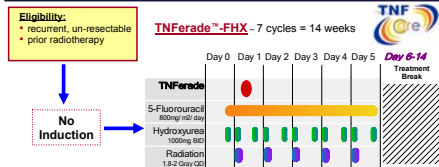
- Any grade 3 or higher non-hematologic toxicity occurring up to 2 weeks after the last administration of TNFerade™ Biologic, with the following exceptions
 - Stomatitis/dysphagia/esophagitis (unless grade 4)
 - Nausea or vomiting
 - Diarrhea
 - Direct tumor related complications
- Non-healing tissue necrosis at the injection site occurring up to 2 weeks after the last administration
- Grade 3 thrombocytopenia, neutropenia, anemia occurring during the treatment period or up to 2 weeks post administration

Injection Procedure



- TNFerade™ Biologic is given in up to four divided doses into different quadrants or sites of tumor.
- The site and depth of the injection are recorded at each treatment.
- Different sites and depths are injected during the course of treatment to increase the delivery of TNFerade™ into the entire volume of the tumor.

Schema



TNFerade™ Biologic dose levels: 1) 4x10⁹, 2) 4x10¹⁰, 3) 4x10¹¹ PU

Tumor biopsies: pre-treatment, cycle 2 (2 days post injection), and post treatment

TNFerade™ Biologic qPCR Assay Development

- Used to determine specific TNF-α expression encoded by TNFerade™ contrasted to TNF-α made from inflammatory cells
- A qPCR assay based on SYBR Green detection method
- Expression of TNF-α encoded by TNFerade™ can be detected in A549(lung), PC3 (prostate) and U87 (glioblastoma) tumor cells when grown in the hind-limbs of athymic nude mice when injected with 2.2x10⁹ PU of AD.EGR.TNF and irradiated with 2gy for 5 days
- Assay will be used to detect expression of TNF-α encoded by TNFerade™ in human tumor biopsy samples

Results: Demographics

Mean Age, years (range)	59.4 (37, 71)
Mean ECOG Performance Status (range)	1 (0:1, 1:7, 2:2)
% Male	60%
% Previous Radiation Treatment	100%
% Previous Chemotherapy	90%
% With Original Treatment	90%
% At Time of Recurrence	50%
% Previous Surgery for HN Lesion	70%

Results: Adverse Events

Adverse Events of Interest	4x10 ⁹ (n=6)				4x10 ¹⁰ (n=3)				4x10 ¹¹ (n=1)			
	1	2	3	4	1	2	3	4	1	2	3	4
Mucositis	1 (17%)	5 (83%)			3 (100%)							1 (100%)
Dermatitis	2 (33%)	3 (50%)			1 (33%)	1 (33%)	1 (33%)					1 (100%)
Hand and Foot Syndrome	1 (17%)	1 (17%)			1 (33%)							1 (100%)
Anemia	4 (67%)	1 (17%)			3 (100%)							1 (100%)
Neutropenia					1 (33%)							
Thrombocytopenia												
Pneumonia			4 (67%)		1 (33%)							
Fever	2 (33%)				2 (66%)							
Fatigue	4 (67%)	2 (33%)			1 (33%)							1 (100%)
Serifinal Bleed*					1 (17%)							
Spontaneous Pneumothorax					1 (17%)							

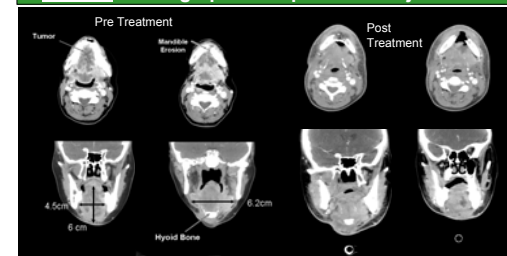
*Dose Limiting Toxicity
Each subject was counted one time for each event at the highest NCI CTCAE Grade

Results: Treatment Response

Patient ID	Dose Group (PU)	Baseline M1 Disease	Previous Chemo	Previous Surgery	Best Response		Duration of Response (Months)	Site of Progression	Survival (Months)	Cause of Death
					Clin	Path				
1	4x10 ⁹	Yes	Yes	No	PR	NE	4.9	Local and systemic	4.9	Metastatic disease
2	4x10 ⁹	No	No	Yes	CR	CR	6.3	Local with salvage surgery	10.5	Vascular complications 2 months post surgery
3	4x10 ⁹	Yes	Yes	Yes	PR	CR	4.1	Local and systemic	9.8	Anoxic brain injury
4	4x10 ⁹	No	Yes	Yes	CR	NE	5.4	NA	5.4	Pneumonia
5	4x10 ⁹	No	Yes	Yes	PR	PR	12.6	Systemic	12.6	Failure to thrive and metastatic disease
6	4x10 ⁹	No	Yes	No	PR	PR	Disease free	NA	9.1 +	NA
7	4x10 ¹⁰	No	Yes	Yes	PR	PR	Disease free	NA	7.0 +	NA
8	4x10 ¹⁰	No	Yes	Yes	PR	CR	4.0	Local with salvage surgery	7.0 +	NA
9	4x10 ¹⁰	No	Yes	No	SD	SD	Disease persistence	NA	7.0 +	NA
10	4x10 ¹¹	No	Yes	Yes	CR	CR	Disease free	NA	5.3 +	NA

CR-Complete Response, PR-Partial Response, SD-Stable Disease

Results: Radiographic Response – Subject 008



Conclusions

- TNFerade™ Biologic up to 4x10¹⁰ PU can be safely added to concomitant chemoradiotherapy
- Final dose escalation to 4x10¹¹ PU is currently in progress
- Toxicity profile to date is consistent with that observed with concomitant chemoradiotherapy alone
- Response activity has been observed
- Induction of TNF-α in tumor tissues will be evaluated

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