A Phase 1/2 Evaluation of ADXS11-001 *Lm*-LLO Immunotherapy, Mitomycin, 5-Fluoruracil (5-FU) and IMRT for Anal Cancer

Kimberly Perez, Howard Safran, Kara-Lynne Leonard, Thomas Dipetrillo, Nicholas Oldenburg, Adam Klipfel, Steven Schecter, Matthew Vrees, Leslie Roth, Nishit Shah, Lakshmi Rajdev, and Kayla Rosati

Brown University Oncology Group Research Consortium

This study was financially supported by:

Advaxis Inc

The Farrah Fawcett Foundation

Background

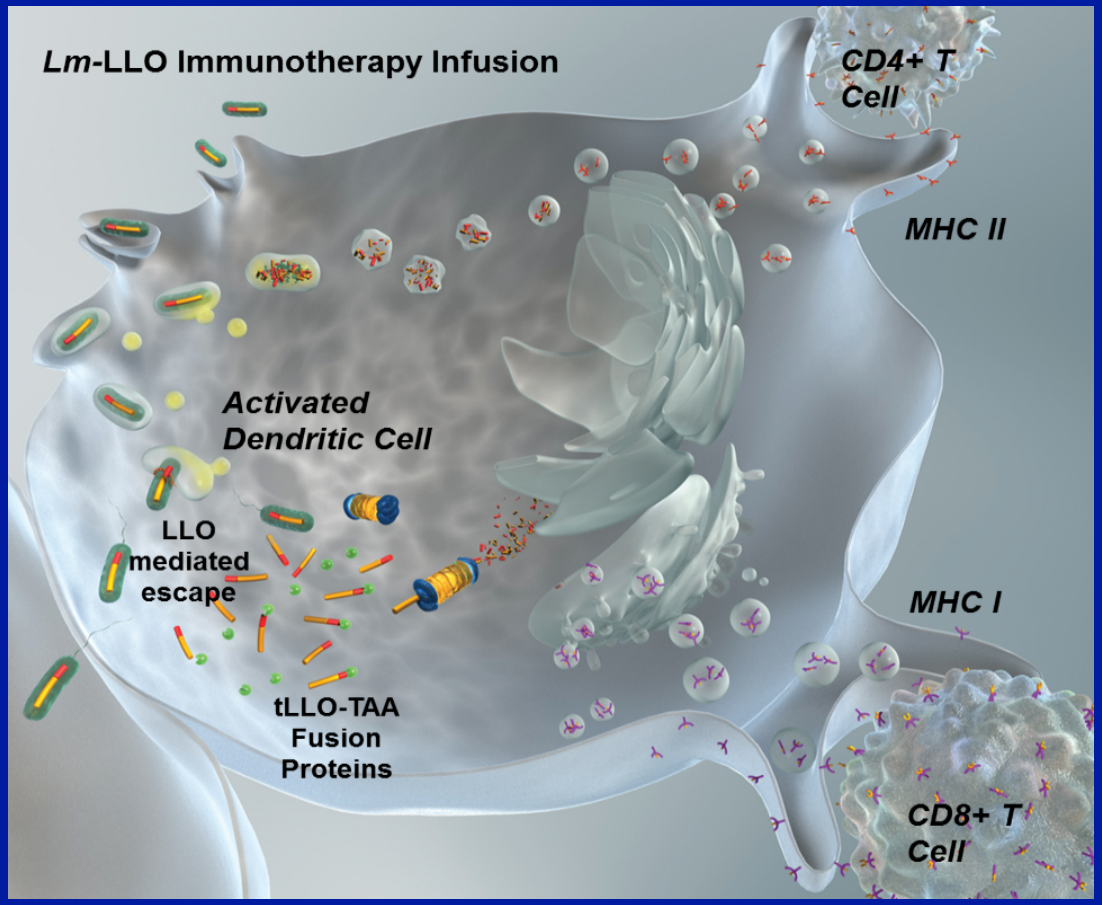
- High risk locally advanced anal cancer includes T3/4 and/or node positive disease

- Five year outcomes of RTOG 98-11 trial demonstrated a disease free survival of <40% for patients with T4N0 and/or node positive disease.

ADXS11-001

- HPV DNA is present in the majority of anal cancer
- ADXS11-0011 immunotherapy is a live attenuated *Listeria monocytogenes* (*Lm*) bioengineered to secrete an HPV-16 E7 protein fused with a truncated fragment of listeriolysin O (tLLO)
- tLLO is a virulence factor of *Lm*. It enables the bacterium to escape from the phagolysosome.
- Biosafety level 1-2. No fecal, urine shedding or person-to-person transmission; vector cleared within 24 hours with antibiotics.

ADXS11-001 Is Taken Up By Antigen Presenting Cells (APC)



- After uptake of *Lm-LLO immunotherapy*, TAA HPV-16 E7 + tLLO-fusion derived peptide is secreted and escapes phagosomes into the cytoplasm
- CD4+ and CD8+ cells activated, by MHC Class I and II presentation.
- HPV transformed tumors now “seen” as pathogen-infected and targeted by T-Cells

Advantages of ADXS11-001 as a Vector to Stimulate Cellular Immunity

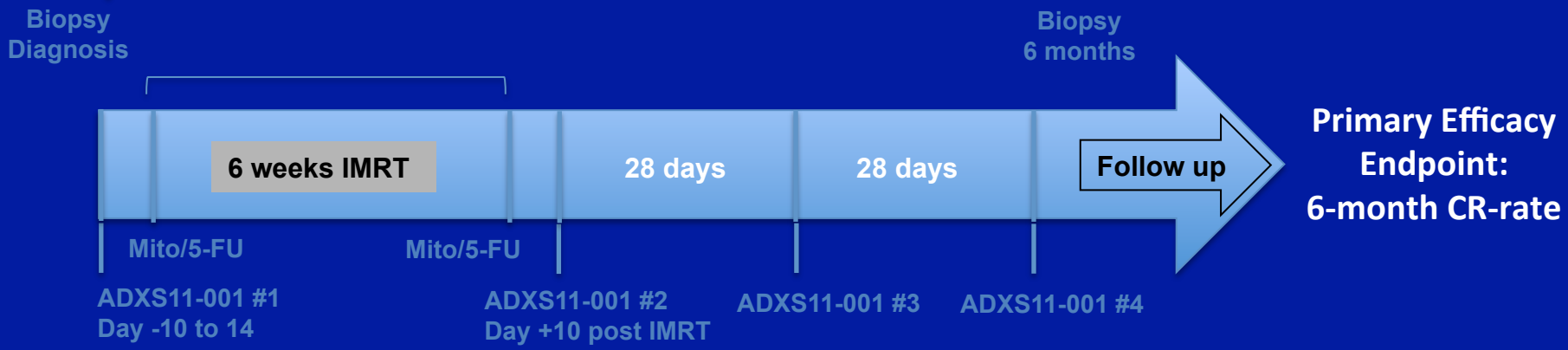
- Innate powerful immune response to *Lm*, especially to listeriolysin (tLLO). Unlike peptides or viruses, there is no immune tolerance or neutralizing antibodies
- *Lm* are taken up by APC. Since listeriolysin can break through the phagolysosome, the fusion protein tLLO-E7 is free in the cytoplasm of APC and activate MHC class I and class II immune responses
- Live vector serves as multiple adjuvants
- Makes immune system react to tumor cells as *Lm* sepsis

ADXS11-001 with mitomycin/5-FU/IMRT for Locally Advanced Anal Cancer: Brown University Study

Open Label Phase 1/2 Study

- **N = 25**
- **Primary stage II-III anal cancer**
- **High risk of recurrence**
- **HPV-positive**

ADXS11-001
1x10^9 cfu x 4 (1 prior to chemoRT and 3 post, q 28 days) as a 500 ml infusion over 30 min



- **Premeds with Naprosyn (500 mg BID, day -1 & 0) & Promethazine (25 mg BID, predose 8 hr)**
- **Ampicillin is given day 3-9 after each ADXS11-001 dose**

Objectives

- To evaluate the safety of the addition of ADXS11-001 to standard chemoradiation for patients with anal cancer
- To evaluate the 6-month clinical complete response rate for patients with anal cancer treated with ADXS11-001, mitomycin, 5-FU and IMRT

Statistical Considerations

- Goal Accrual = 25
- Based on the Simon's two-stage design, the null hypothesis that the true response rate is 50% (p0) will be tested against a one-sided alternative. In the first stage, 16 patients will be accrued. If there are 10 or fewer responses in these 16 patients, the study will be stopped early for futility

Major Eligibility Criteria

- Newly diagnosed locally advanced anal cancer
- Stages: T $\geq$ 4cm or node +
- PS 0-1
- Staging by CT/MRI or PET scan
- No significant cardiac or pulmonary disease
- Adequate bone marrow and renal function
- No HIV thus far

Patient Characteristics (N=11)

Age, years	No.
<50	1
≥50 but <75	9
Median	62
Range	37-71
Sex	
Male	5
Female	6
Stage	
II	4
III	7
Lymph node involvement	
N0	6
N1	0
N2	1
N3	4

ADXS11-001 Related Toxicities

Adverse Event	Grade 2	Grade 3	Grade 4
Flu-like Symptoms	1		
Migraine	1		
Hypotension	1		
HypoK*		1	
Chills/rigors	3	2	
Nausea	2		
Back pain	1	1	
Fever	2		

Acute Grade 3 toxicities related to ADXS11-001:

- Chills/rigors (N=2)
- Back pain (N=1)
- All toxicities were within 24 hours of dosing

*These AEs occurred during dosing time point but are also included with overall AEs.

Concurrent Chemotherapy and Radiation Associated Toxicities

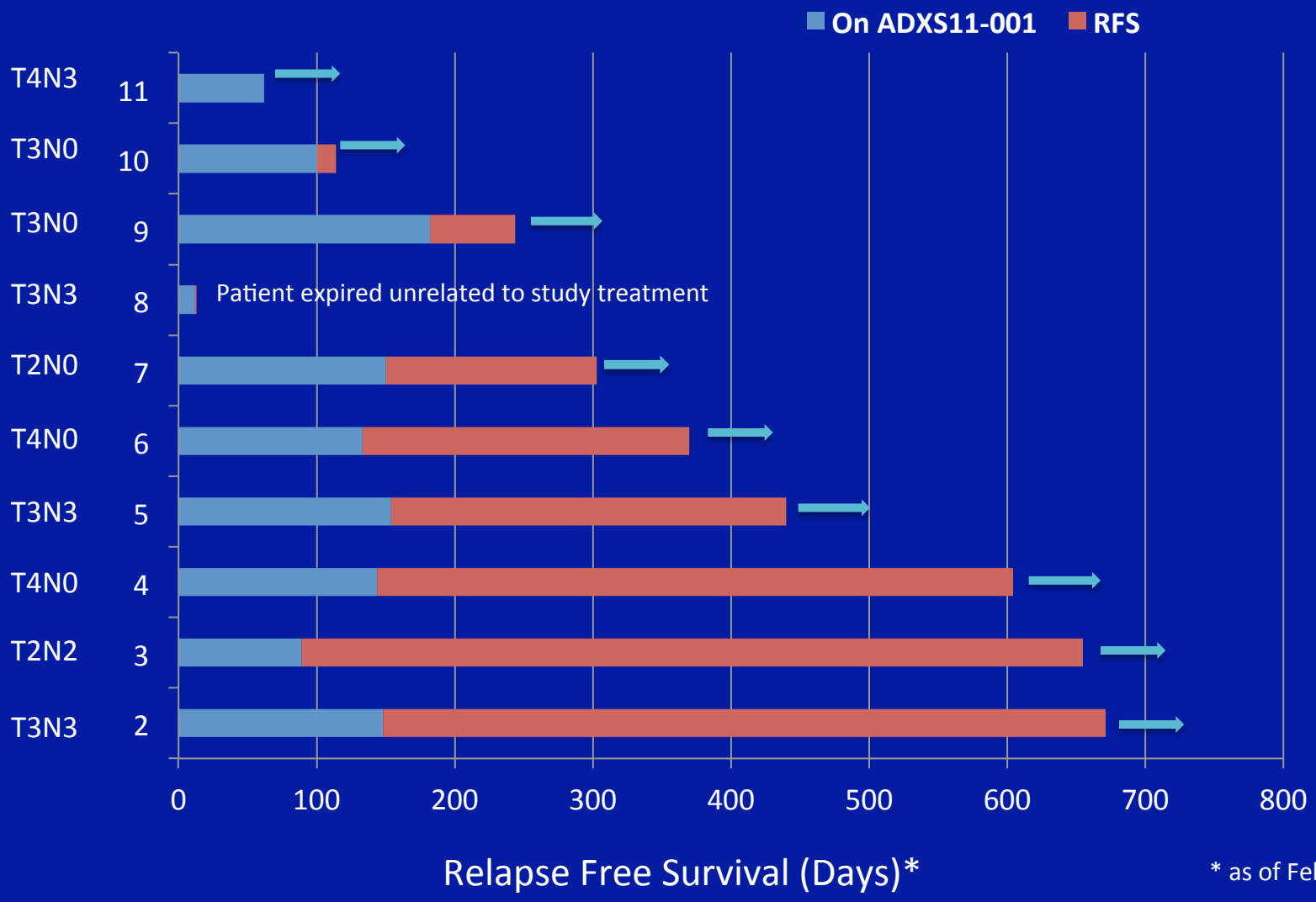
Side Effects	Grade 3	Grade 4	Grade 5
Anal mucositis	1		
ANC	1	2	
Anemia	3		
Perianal pain	1		
Catastrophic cardiac, pulmonary or massive CVA			1
Dehydration	2		
Diarrhea	2		
Fatigue	1		
GI bleed/rectal bleed	2		
HypoK	3		
Hyponatremia	1		
Lymphopenia	3	3	
Mucositis	2		
Pain – back	1		
Thrombocytopenia	3	2	
Sm intestinal infection	1		
Leukopenia	1	2	
Weakness	1		
Weight loss	1		

- One patient had unrelated Grade 5 cardiovascular event during 5-FU infusion

Initial Data

- 10 patients treated on study since April 2013
- ADXS11-001 did not worsen the toxicity profile due to chemoradiation
- Thus far, all patients who have completed treatment:
  - Had complete response
  - None have developed recurrence

Preliminary RFS Data



* as of Feb 15, 2015

Note: Patient #1 enrolled but was never treated on study

Conclusion

- Well tolerated immunotherapy given with standard concurrent chemoradiation
- Thus far, preliminary efficacy promising in this sample of high risk patients
- Development of an international Phase 2/3 study is in discussion.

Next Steps for ADXS11-011 in Anal Cancer

- Locally Advanced
  - Phase 2/3 Study Planned
    - Double Blind, Placebo controlled study of 5FU/MMC + radiotherapy +/- ADXS11-011 in patients with locally advanced high risk anal cancer

- Metastatic
  - Phase 2 *(conducted by Advaxis)*
    - Monotherapy Study of ADXS11-001 in subjects with persistent/ recurrent, loco-regional or metastatic anal cancer or HPV+ squamous cell cancer of the rectum
    - *This Study is in the process of recruiting sites. If interested in participating please contact : Ann Kennedy* ann.kennedy@inventivhealth