ADVAXIS *Lm*-LLO Immunotherapies

Early Therapeutic Vaccine Clinical Trial Development

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Disclosure: Full Time Employee of Advaxis, owns stock in Advaxis

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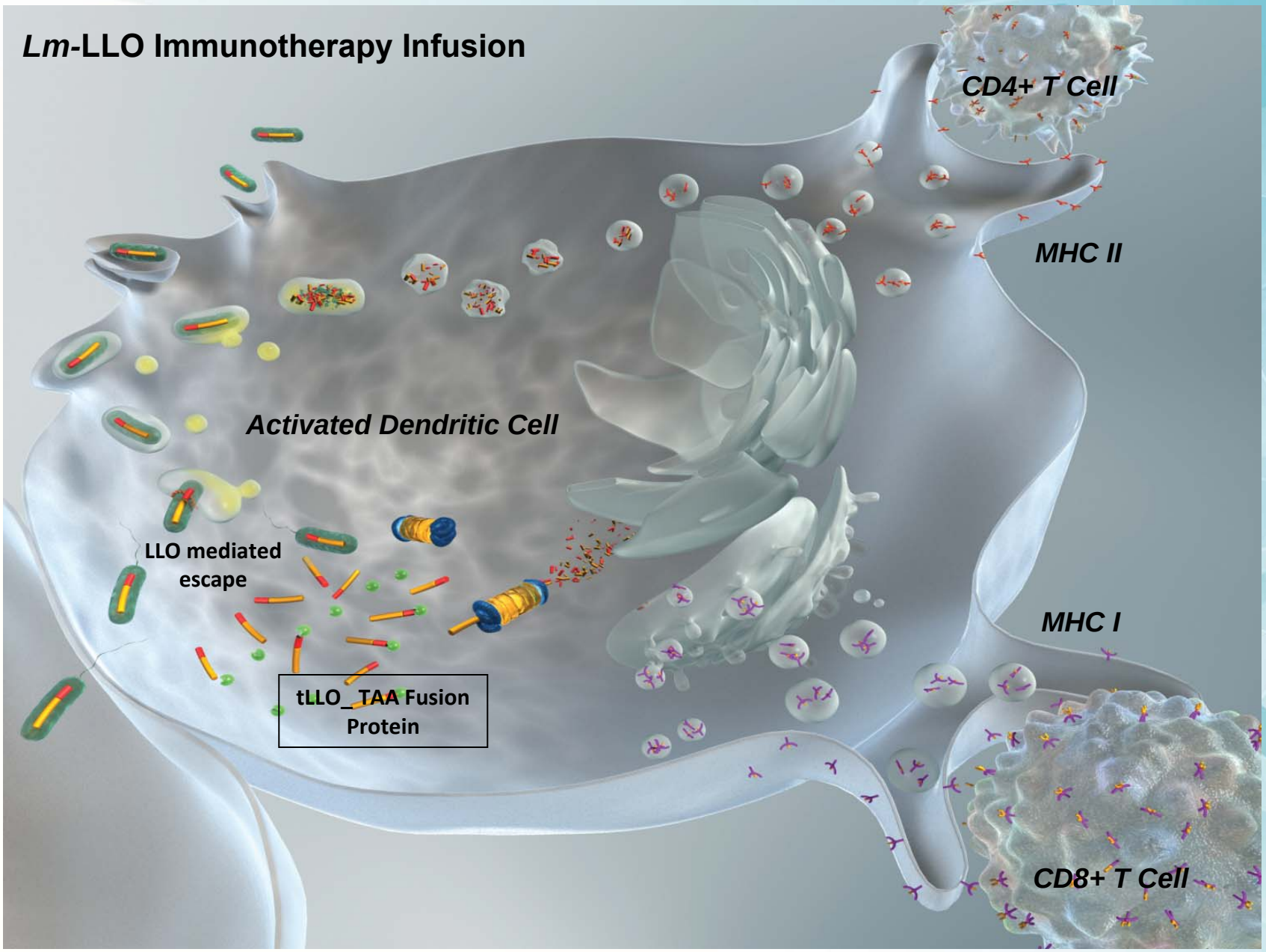
Unique Life Cycle of *Lm* in APC



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Advaxis Lm-tLLO Immunotherapy

Live-Highly Attenuated *Lm*- based Bacterial Vector

Strong Innate Immune Effects

- TLRs; NOD-like Receptors; CpG sequence; LLO-PAMP
- APC Activation ; pro-inflammatory cytokines and chemokines
- Upregulation of myelopoesis and myeloid maturation

} No Adjuvant Required

Strong Adaptive Immune Effects

- Generates large numbers of antigen specific activated $CD4^+$, $CD8^+$, T cells

Alteration of Tumor Microenvironment

- Reduces both Tregs and MDSC in tumors but not in normal tissues
- Upregulation of chemokine expression in tumor tissue & chemokine receptors on T-cells
- Resulting in large ratio shift of CTLs over Tregs and MDSCs in tumor microenvironment

In the Clinic, ADXS-HPV: 193 patients / 485 doses

Well Tolerated:

Transient Low Grade Cytokine Release Syndrome Symptoms (33%)
<3% SAEs

Clinical Endpoints:

Prolong survival (Primary EP)
Tumor Responses : CR's PR's
Immunotherapy Tumor Response Patterns

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Advaxis Clinical Pipeline

	Clinical Pipeline			
Construct	Indication	Pre	Phase 1	Phase 2
ADXS-HPV	Cervical Cancer, **India**			
ADXS-HPV	Cervical Cancer, **US,** GOG			
ADXS-HPV	CIN 2/3, **US**			
ADXS-HPV	Head & Neck Cancer, **CRUK**			
ADXS-HPV	Anal Cancer, **US** BrUOG			
ADXS-PSA	Prostate Cancer			
ADXS-cHER2	Canine Osteosarcoma, **US** Penn			

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Regulatory Challenges

- Immunotherapy may be a new concept
  - "therapeutic vaccine" is a challenging term (immunotherapy – better accepted)
- Questions over "attenuation" of live vector
  - Additional safety testing may be required
- Mistrusting of data from other countries
  - May require studies in other countries first
- May create new barriers to initiation:
  - "Blue Ribbon" panel, late stage disease - only
- **Patient Compensation (India)**

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India DCGI – Compensation Rules (1/30/2013)

- Controversial Definitions: trial related injury or death
  - Failure of investigational product to provide intended therapeutic effect
  - Use of placebo in a placebo controlled trial
  - Violation of approved protocol the investigator
  - Adverse effect due to concomitant medication
  - Any clinical trial procedures involved in the study
- Death: Compensation Amount determined by Ethics Committee and DCGI
- Paid within 30 days of SAE

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Patient Considerations

- Living conditions – access to follow-up care
- Co-morbid infectious disease
  - Tuberculosis, HIV, parasitic infection
- Age uncertainty
- Travel and Logistics – surprisingly difficult
- Attitudes about death
- Treatment vs. Experiment
- Following for O.S. may be difficult

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Investigator/Site Considerations

- Inconsistency of facilities
- Hospitalization practices
- Sample processing and storage
- Site Staff education about immunotherapy
- Staff turnover
- Allied professionals not participating in "research"
- Seen as "treatment" instead of experiment
- **Immune-Related Response Criteria***

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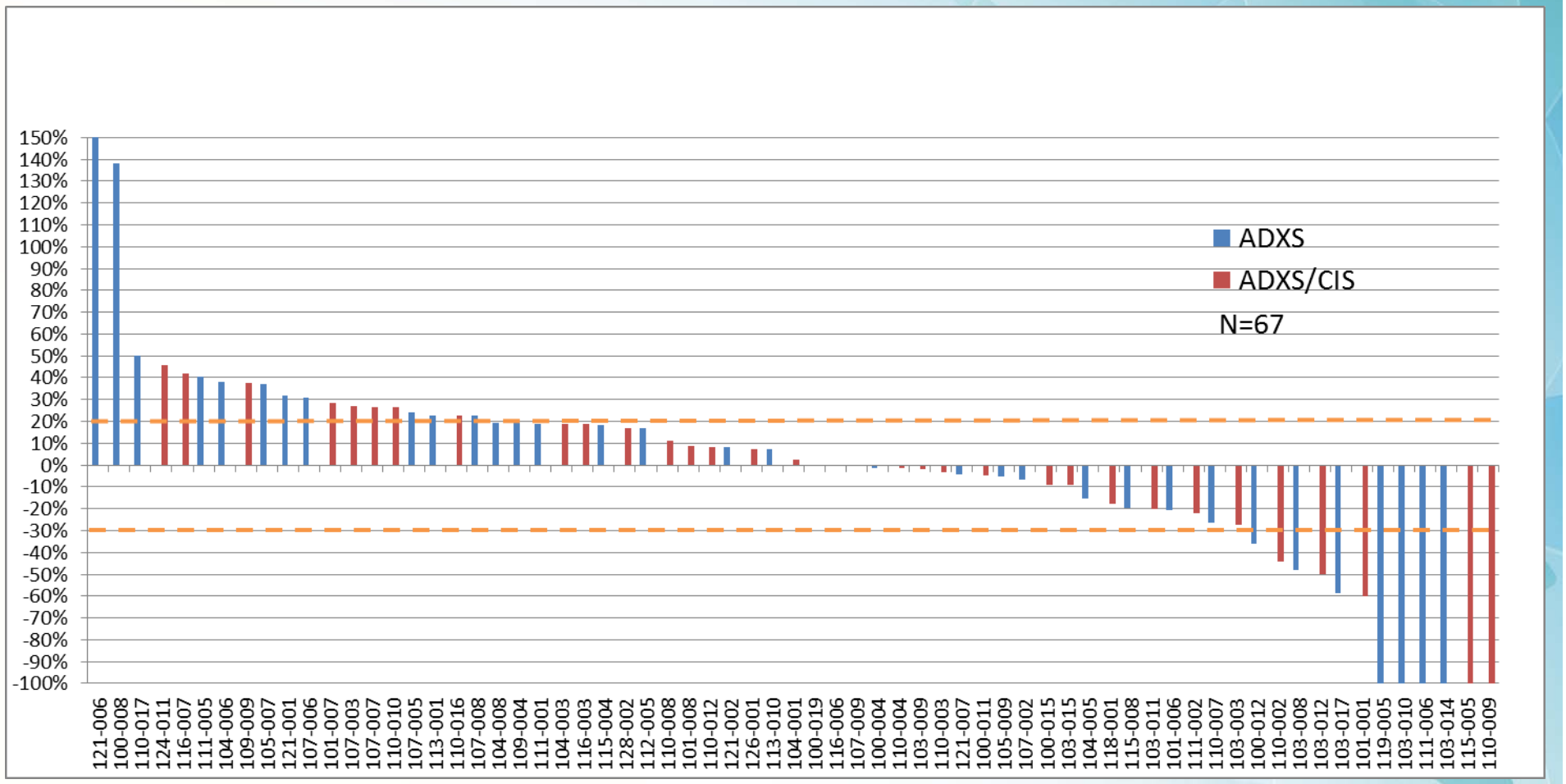
Best Response Data

(as of October 22, 2012)



Tumor reduction observed in patients infected with different high risk HPV strains including HPV 16, 18, 31, 33 and 45

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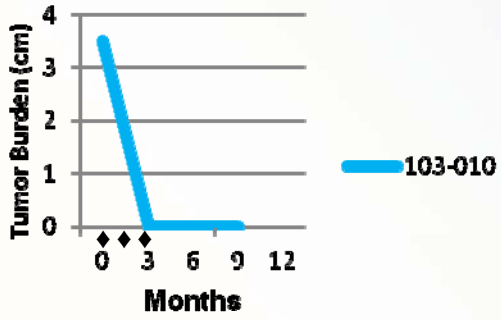
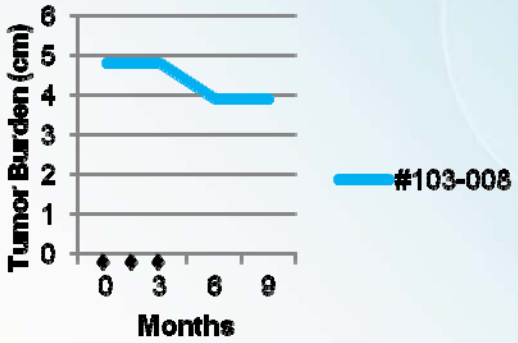
ADXS-HPV: Clinical Patterns of Response

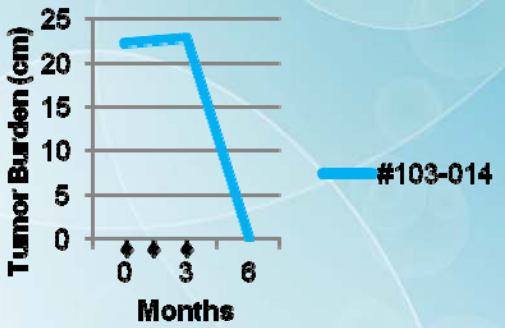
A. Immediate Response



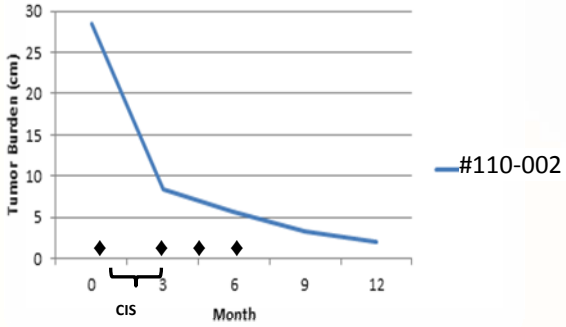
B. Durable Stable Disease



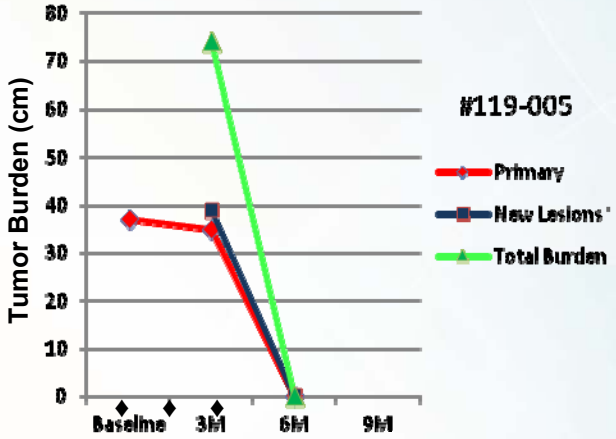
C. Reponse after Initial Tumor Burden Increase



D. Continuing Decrease Over Time



E. Response After New Lesions



♦ = ADXS11-001 Dosing

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Infrastructure

- Power Grid Fluctuations
- Telephone access not always possible
- No “social security” number
- No tumor registry or historical data
- No such thing as “overnight shipping”
- Patient access to sites between scheduled visits may not be possible
- Survival Follow-Up In Person (Site Staff)

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Conclusions

- Early immunotherapy trials in a global setting have many challenges
- Extraordinary efforts/time may be required to seek initial regulatory permissions. Regulations may change significantly.
- Differences in patient populations and logistic challenges need to be considered
- Patient and investigator education about the object of immunotherapy
- Patient/Staff understanding of the nature of immunologic responses is critical for patient retention
- Data consistency in multi-national studies will be a difficult challenge
- When these challenges are met, immunotherapy can be well accepted.

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-Thank You-