ADVAXIS
Lm-LLO Immunotherapies

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SITC 2012 Annual Meeting

October 27, 2012

Conflict of Interest:

Disclosure: Full Time Employee of Advaxis, own shares of stock

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Why Listeria?

- ***Ideal system for a cellular immune response***

- ***Powerful Innate Immunity:***
  - ***Expresses multiple PAMPs (multiple "adjuvants")***
  - ***Activates external and internal TLRs and NOD-like proteins***
  - ***Creates TH-1 "Immunotype"***

- ***Grows intracellularly in APC (circulating and in tissue-based)***
  - ***Facilitated phagocytosis***
  - ***Escapes Phago-lysosome via LLO***
  - ***Bridges innate and adaptive immunity,***

- ***Advaxis Constructs Secrete Fusion Protein: tLLO-TAA within APC***
  - ***"Programs" APCs In Situ***

- ***Adaptive Immunity***
  - ***Cross presents to MHC I and II pathways***
  - ***Enables Activated T-cell Proliferation***

- ***Microenvironment***
  - ***Facilitates infiltration of CD4+ and CD8+ T cells***
  - ***Specifically reduces immune tolerance within tumors (Tregs, MDSCs)***
  - ***Antigen Spreading***

- ***Vector can be cleared with antibiotics***

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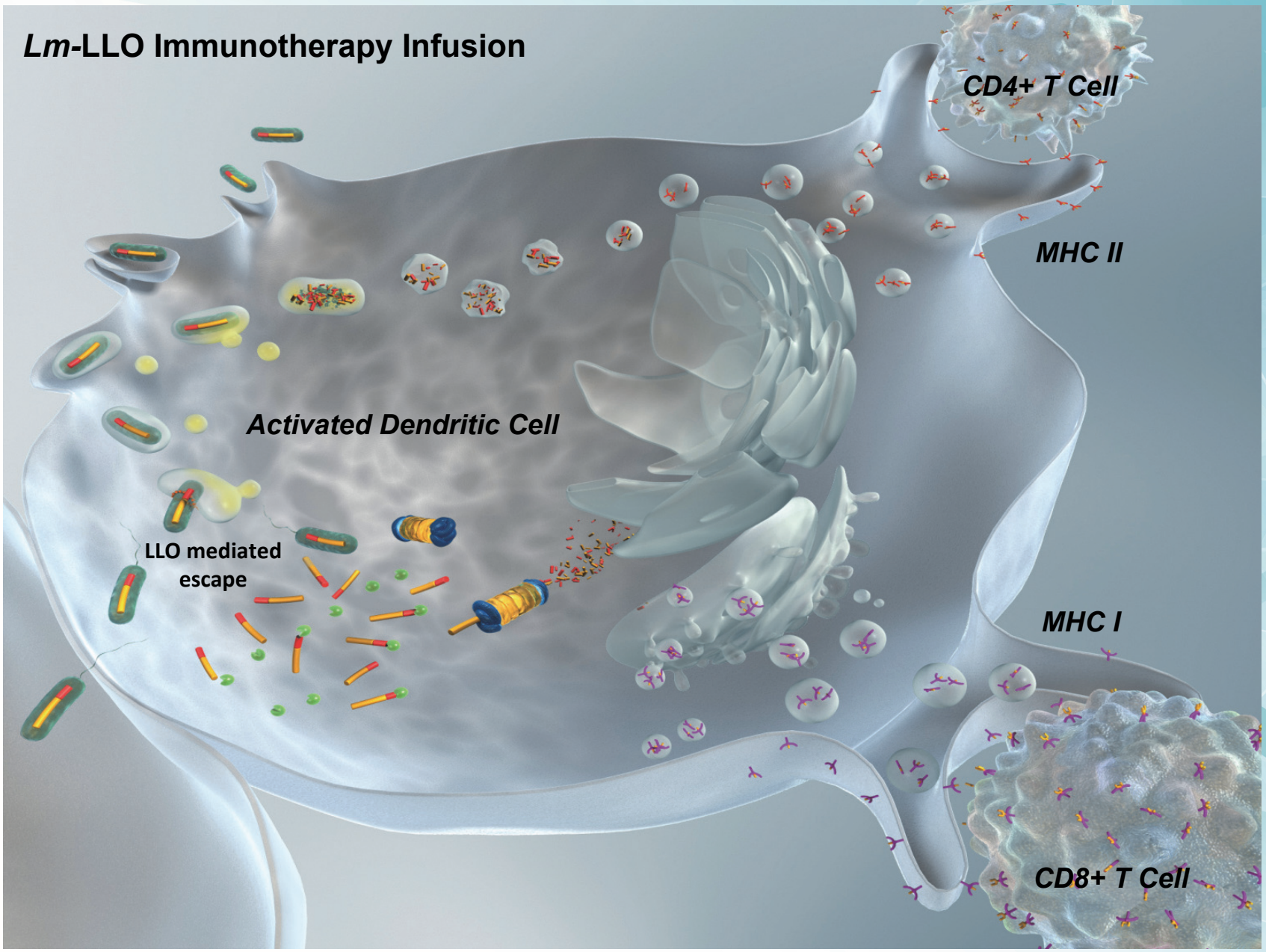
Unique Life Cycle of *Lm* in APC



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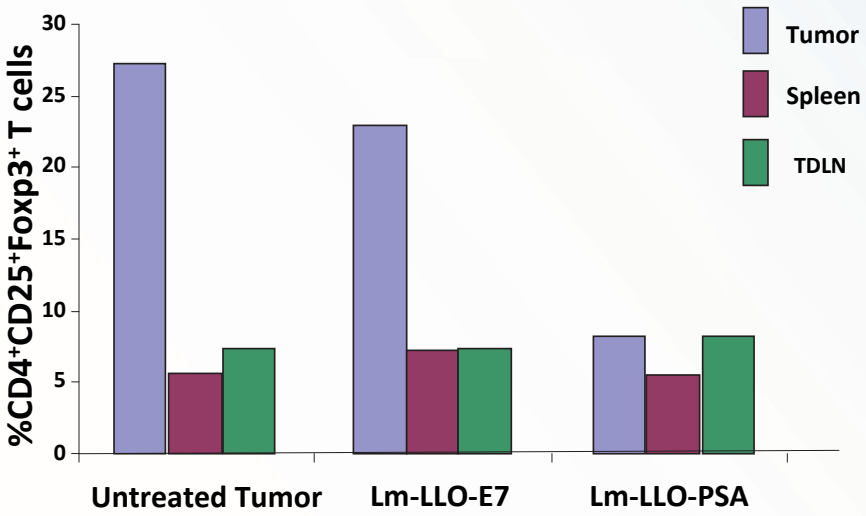
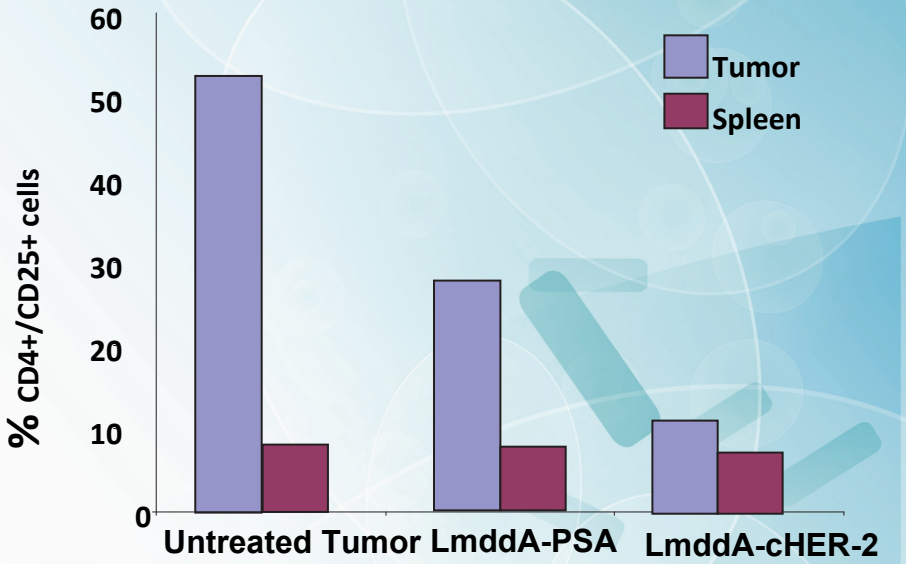
Treg Reduction in Tumor Microenvironment

PSA Tumor Model



Advaxis data on file

HER2 Tumor Model



Shahabi et. al. CGT 2011

Reduction of Tregs occurs specifically in the tumors and not in spleen or tumor draining lymph node (TDLN)

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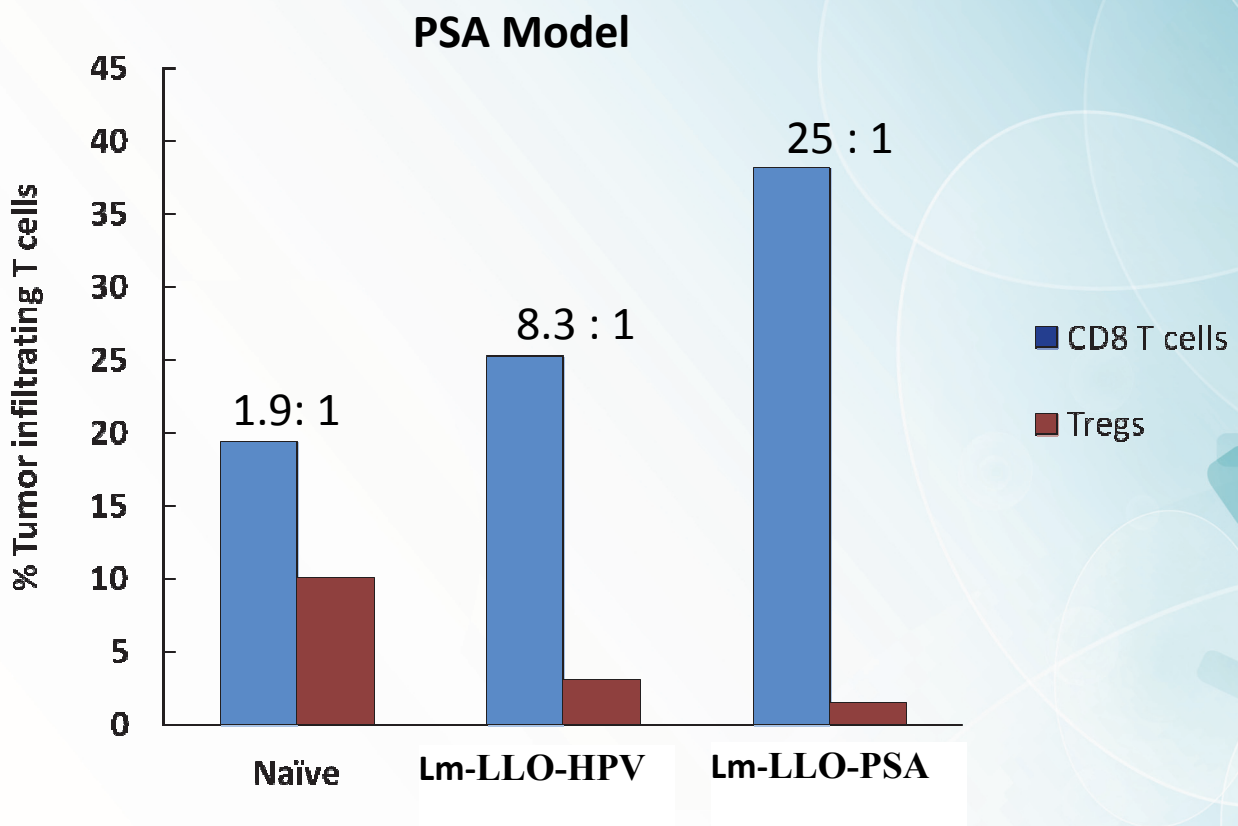
CD8^{+}:Treg Ratio in Tumors of *Lm*-LLO Treated Animals



***Lm*-LLO immunotherapies causes increased infiltration of CD8+ cells in the tumor**

Advaxis data on file

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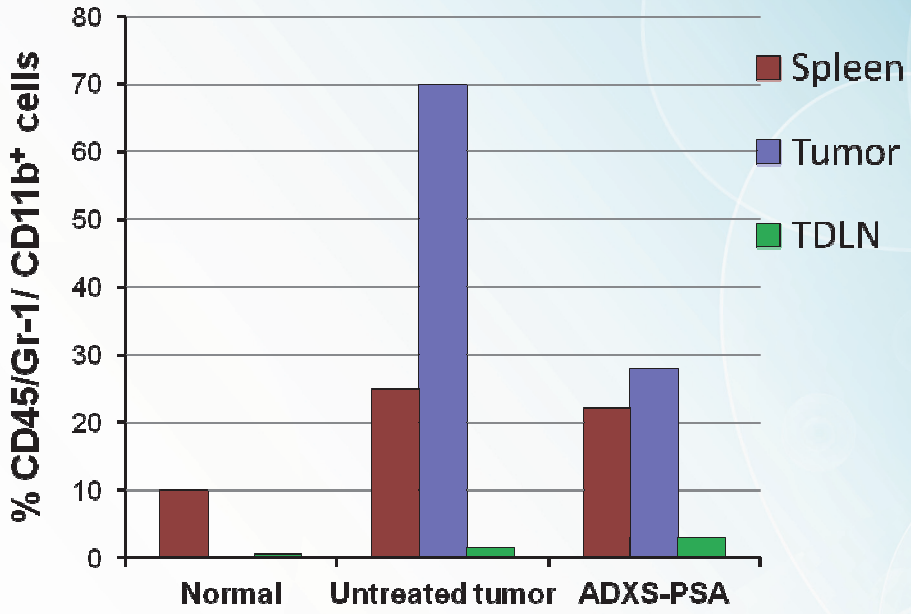
Lm-LLO Immunotherapies Decrease Myeloid Derived Suppressor Cells (MDSC) in Tumors



-*Lm* LLO immunotherapies reduce MDSC in tumor
-No effect on spleen or TDLN

Advaxis data on file

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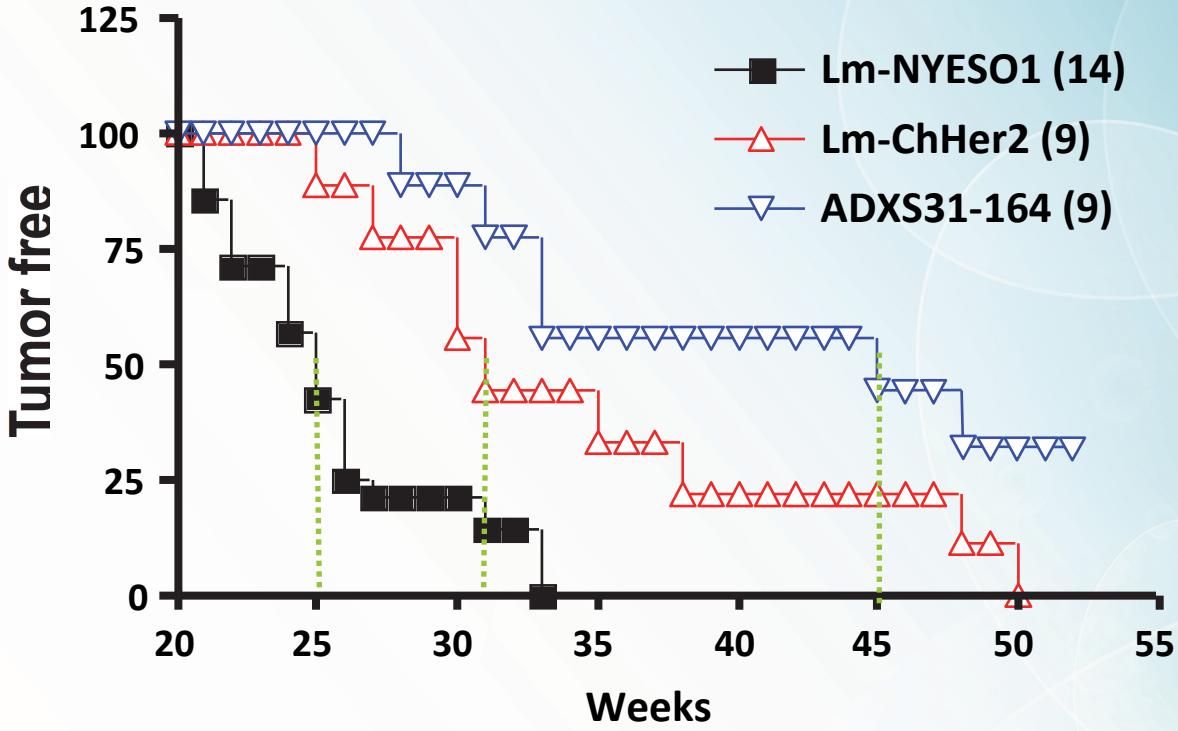
Lm-LLO Immunotherapy Can Break Immunologic Tolerance



30% of HER2 transgenic animals treated with ADXS31-164 did not develop tumors over a full year of observation

Shahabi et al CGT 2011

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Recurrent / Refractory Cervical Cancer

- Cervical cancer is the 2nd leading cancer killer of women
  - 454,000 cases with 275,000 deaths per year (WHO)
  - Caused by infection with oncogenic, HPV 16, 18 (>70% of Cervical Cancers)
- Once Recurrent/Refractory, treatment is palliative
- Cisplatin is the most "active" agent
  - Response Rate <30%, short duration
  - Median Survival 7-12 months
- ADXS-HPV is a live, highly attenuated *Lm* engineered to secrete tLLO-HPV16 E7 fusion protein

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Phase 2 Cervical Cancer Study

ADXS-HPV: Cervical Cancer, India **Lm-LLO-E7-15**	
Title	A Randomized, Phase 2 Study to Assess the Safety and Efficacy of ADXS11-001 with and without Cisplatin for the Treatment of Recurrent Cervical Cancer
# of patients	110
Endpoints	Safety & overall survival
Study start/completion	Nov 2010 – 2013 (LP/FV – June 2012)
# of sites and where	Multicenter 22 sites, India
Status	Enrollment completed

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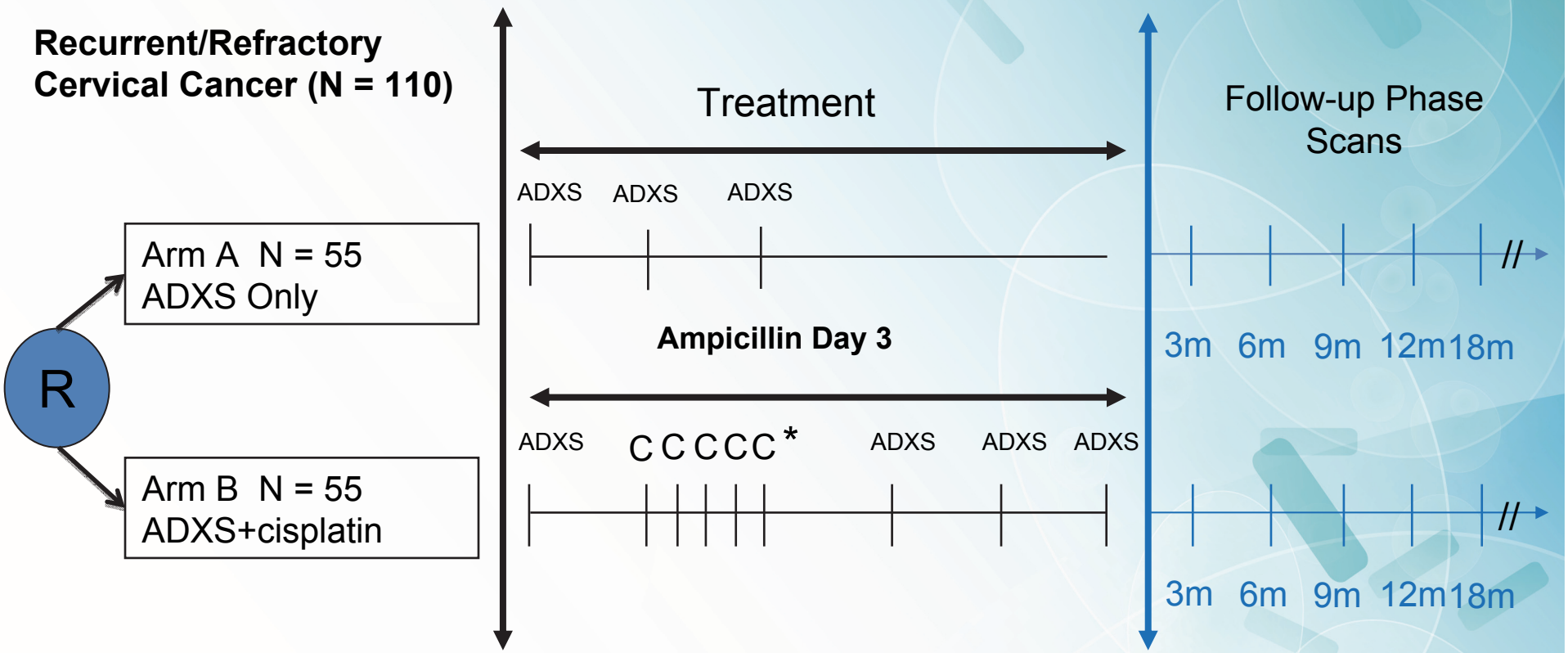
Study Design: Lm-LLO-E7-15



Arm A: ADXS-HPV alone:

•1x10^9 cfu x3 on days 0, 28, 56 as an 80 ml infusion over 15 minutes

Arm B: ADXS-HPV + cisplatin:

•ADXS11-001 = 1x10^9 CFU as an 80 ml infusion over 15 minutes on days 0, 88, 106, 134

•*cisplatin = 40 mg/m^2 weekly x5 on days 30, 37, 44, 51, 58

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Preliminary Safety Summary: Lm-LLO-E7-15

(as of October 22, 2012)

110 patients received 264 doses of ADXS-HPV at $1x10^9$ cfu

Related /Possibly Related **AEs to ADXS-HPV:**

- **42 patients (30%) report 60 Grade 1-2 AEs; 2 Grade 3 AEs**
  - 17 Cytokine Release Syndrome (in 14 patients)
    - {2 or more symptoms: chills/rigors, fever, nausea, vomiting,}
  - 22 Chills/Shivering (in 17 patients)
  - 3 Fever (in 3 patients)
  - 2 Headache (in 2 patients)
  - 2 Leukopenia (in 2 patients)
  - 2 Vomiting (in 2 patients)
  - 1 AE in 1 patient each: Nausea, Vomiting, Dizziness, Eosinophil Count Increased, Hemorrhage, Hyponatremia, Lymph Node Pain, Pain in Extremity, Weight Decreased
- **2 Grade 3 AE (dyspnea, fever); <2% SAE Related to ADXS-HPV**
- **0 Grade 4 AEs**
- **0 Grade 5 AEs**

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Preliminary Safety Summary: Lm-LLO-E7-15

(as of October 22, 2012)

***TOTAL AEs* (Related and Unrelated to ADXS-HPV)**

- **100 patients (91%) report 533 AEs**
- **124/533 were SAEs**

- **23 deaths (within 30 days of last dose)**
  - 11 Disease Progression
  - 3 Renal Failure
  - 3 Pulmonary
  - 3 Cardio/Respiratory
  - 1 Multi-Organ Failure
  - 1 Peritonitis
  - 1 Unknown

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Frequency of SAEs: ADXS-HPV vs. Chemotherapy

Trial	Regimen	P. S.	%SAE
Lm-LLO-E7-015	ADXS-HPV 10^9 cfu/mo x3, or 4+CIS	0-2	62.1%
Mannel 2000	cisplatin 75 mg/m^2 q21d + Pentoxyfylline	0-3	159.0%
Bookman 2000	Topotecan 1.5 mg/m2 dx5, q21d	0-2	124.0%
Muggia 2003	Vinorelbine 30 mg/m^2 d1, d8, q21d	0-3	105.0%
Curtin 2001	Paclitaxel 170 mg/m^2 q21d	0-2	148.0%
Moore 2004	cisplatin 50 mg/m^2 q3w	0-2	134.0%
	cisplatin 50 mg/m^2 + Txl 135 mg/m^2 q3w	0-2	177.0%
Brewer 2006	cisplatin 30 mg/m^2 q3w + Gem 800mg/m^2 d1 & 8 q28d	0-2	356.0%
Monk 2009	topotecan 0.75 mg/m2 d 1, 2, 3 plus Cis 50 mg/m2 d1 Q3Wk	0-2	409.4%
	gemcitibine 1g/m2 d1 & 8 + Cis 50 mg/m2 d1 Q3Wk		324.6%
	vinorelbine 30 mg/m2 days 1 & 8 + Cis 50 mg/m2 d1 Q3Wk		384.7%
	paclitaxel 135 mg/m2 + Cis 50 mg/m2 d2 Q3Wk		364.6%

Compared to other treatments for advanced cancer; low incidence of SAEs related to ADXS-HPV (<2% SAE)

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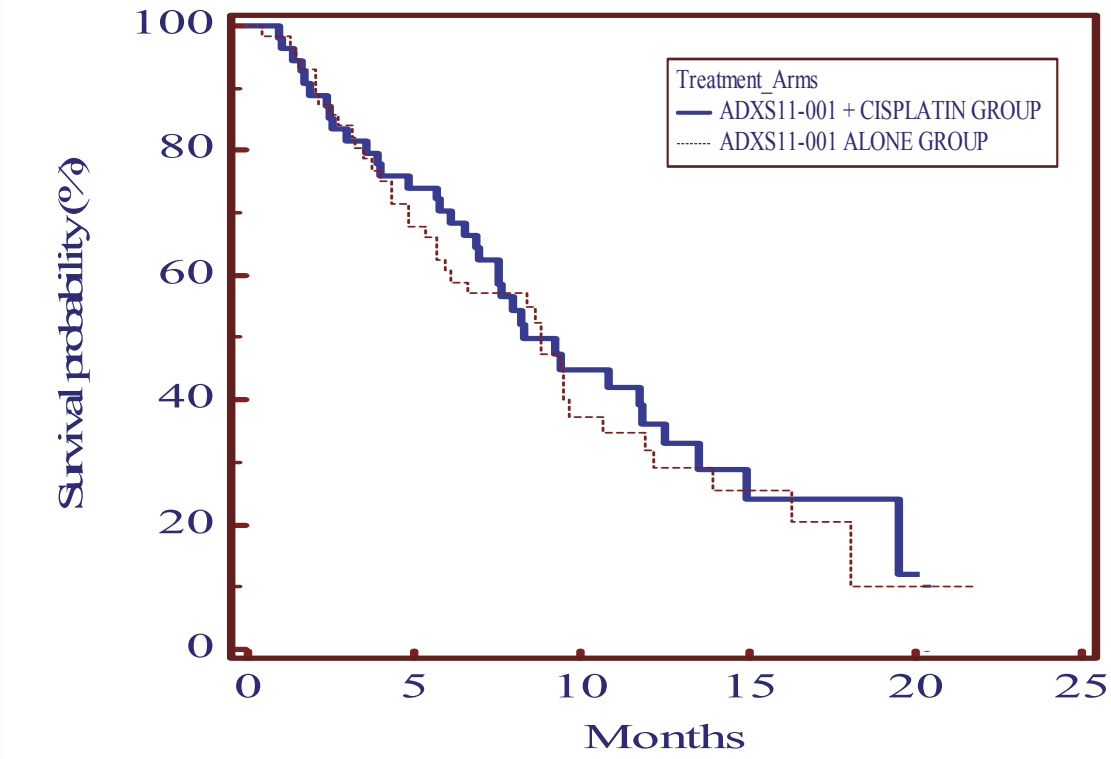
Preliminary Survival

(as of October 22, 2012)



Number at risk

Group: ADXS11-001 + CISPLATIN GROUP						
	54	39	16	5	1	0
Group: ADXS11-001 ALONE GROUP						
	56	38	14	6	1	0

Preliminary survival data suggests no difference between treatments

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Preliminary Phase 2 Data Compared to Historical Controls

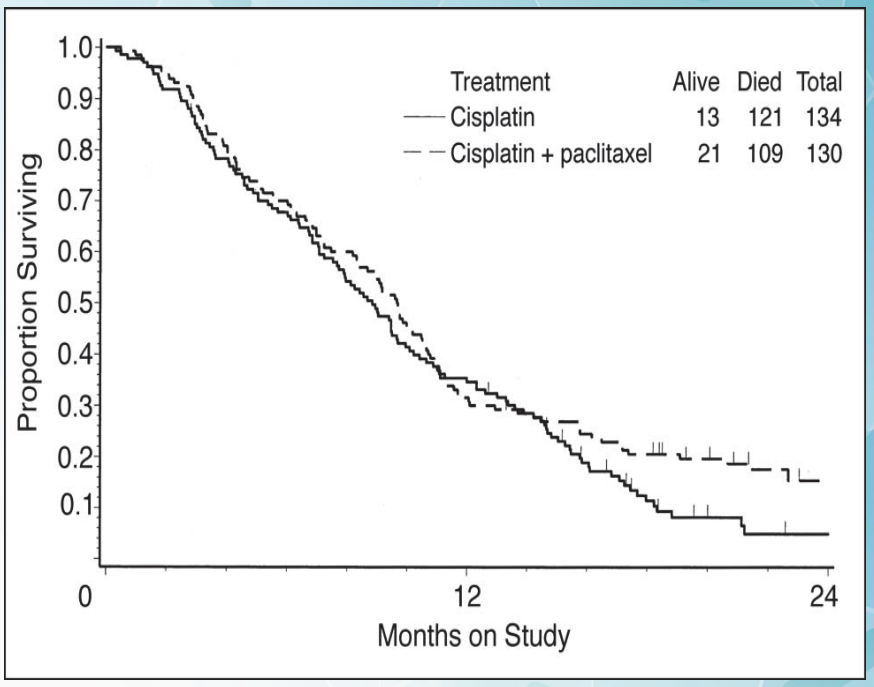
Lm-LLO-E7-15
Preliminary Landmark Survival Data
(as of October 22, 2012)

	6 mo.	9 mo.	12 mo.	18 mo.
# Alive/N	71/109	39/88	23/70	6/36
% Survival	65%	44%	33%	17%

Published Phase 2 single agent trials report 12 months survival of 0-22% *

**NCCN Guidelines:*
Plaxe SC, et. al., 2002, Cancer Chemother Pharmacol; 50: 151-4.
Garcia AA, et. al., 2007, Am J Clin Oncol; 30: 428-431.

GOG Phase 3 Trial Cis +/- Paclitaxel



Published Phase 3 study with most active single agent (cisplatin)

Moore, et. al. 2004 J Clin Oncol 22:3113-3119

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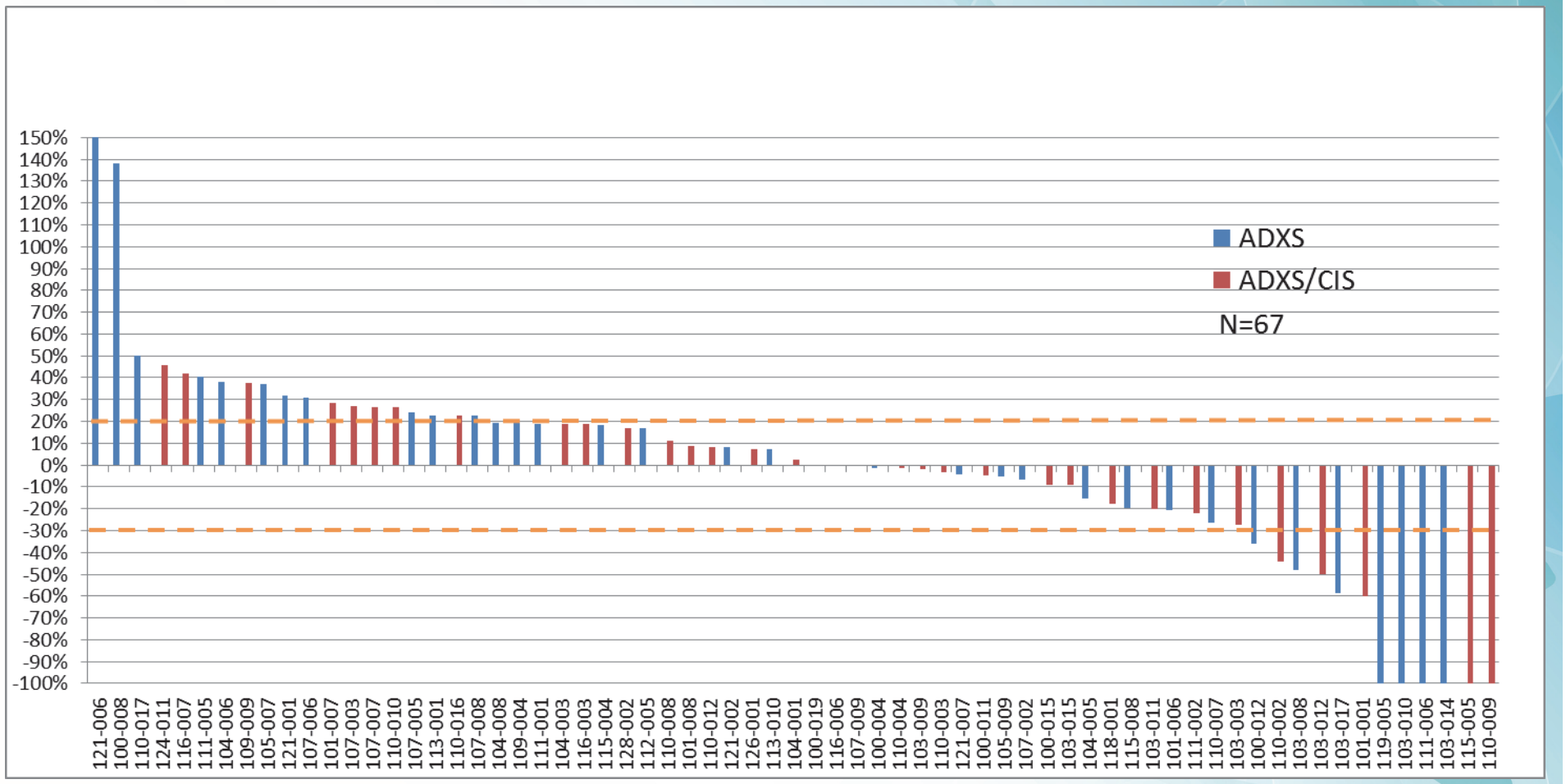
Best Response Data

(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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CR and PR Responses
(October 22, 2012)

Patient #	First Line Tx	Stage	Tx Arm	Tumor Burden (mm)						Tumor Decrease
				Baseline	3 mo.	6 mo.	9 mo.	12 mo.	18 mo.	
Complete Responses										
103-014	CT	IVB	ADXS	223	228	0	N/A	N/A	N/A	100%
115-005	RT	IIB	ADXS + CIS	30	0	0	0	0	EXP. 15 mo.	100%
110-009	CT + RT	IB	ADXS + CIS	23	0	0	0	0	N/A	100%
103-010	CT	IVA	ADXS	35	0	0	0	0	DP 15 mo.	100%
119-005	RT	IIIA	ADXS	37	35	0	N/A	N/A	N/A	100%
111-006	RT	IV	ADXS	16	16	0	N/A	N/A	N/A	100%
Partial Responses										
110-002	RT	IVB	ADXS + CIS	284	84	56	34	20	36 EXP. 20 mo.	93%
101-001	CT + RT	IVB	ADXS + CIS	50	42	44	20	EXP. 11.5 mo.	-	60%
103-012	CT + RT	IVB	ADXS + CIS	18	9	25	WC 10/22/12	N/A	N/A	50%
103-008	RT	IVA	ADXS	48	48	39	39	25	N/A	48%
103-017	CT + RT	IVB	ADXS	106	62	exp. 3.1 mo.	-	-	-	41%
100-012	CT + RT	IVB	ADXS	164	107	105	105	exp. 9.5 mo.	-	36%

N/A = not available, scan has not occurred; EXP = expired; DP = disease progression; WC = withdrew consent

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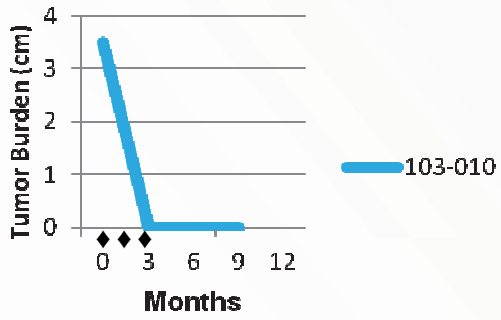
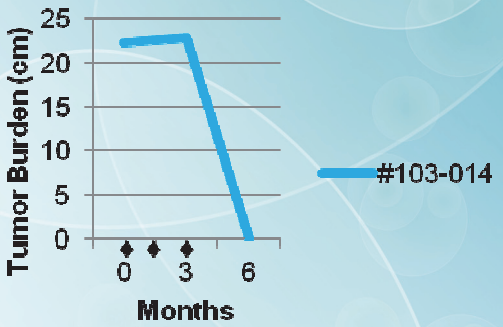
ADXS-HPV: Clinical Patterns of Response

A. Immediate Response

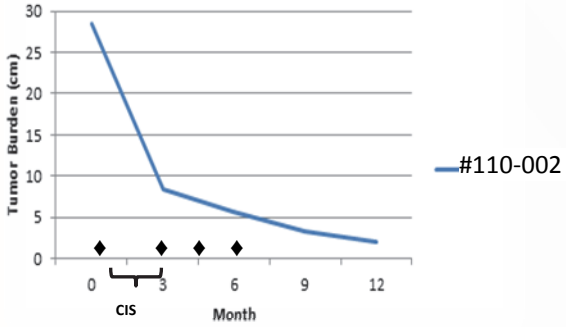


B. Durable Stable Disease

C. Response after Initial Tumor Burden Increase

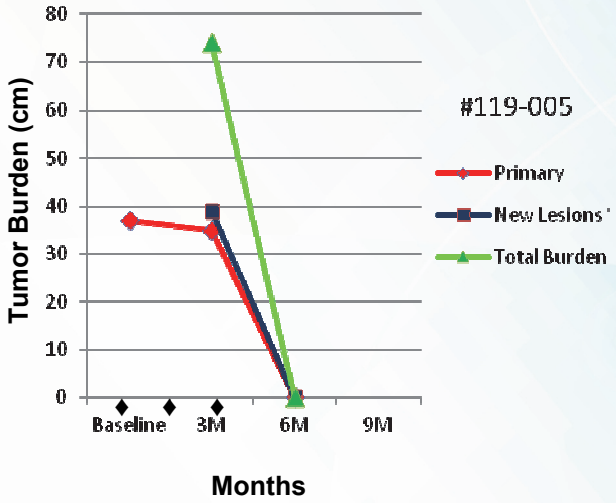


D. Continuing Decrease Over Time



♦ = ADXS11-001 Dosing

E. Response After New Lesions



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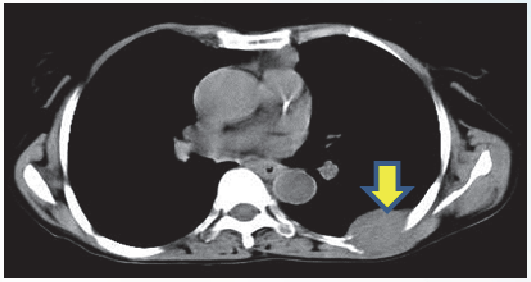
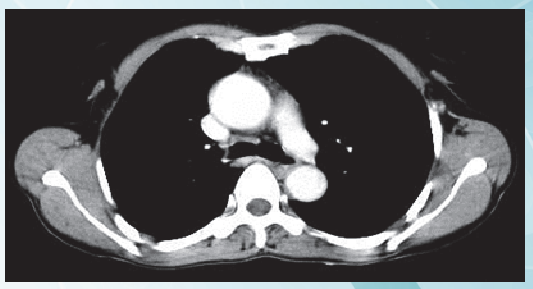
Case Study: Patient 110-002

Patient #	First Line Tx	Stage	Tx Arm	Tumor Burden (mm)						Tumor Decrease
				Baseline	3 mo.	6 mo.	9 mo.	12 mo.	18 mo.	
110-002	RT	IVB	ADXS + CIS	284	84	56	34	20	36	93%

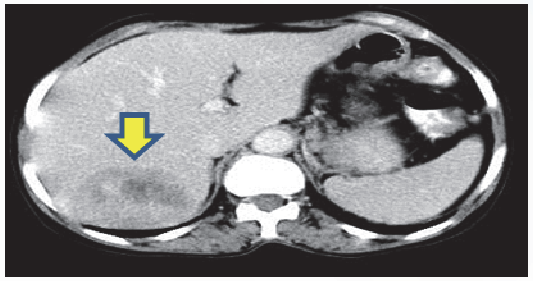
Screening **9 Months**

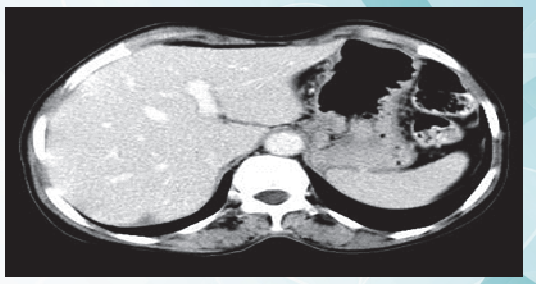
Resolution of lung metastasis on CT



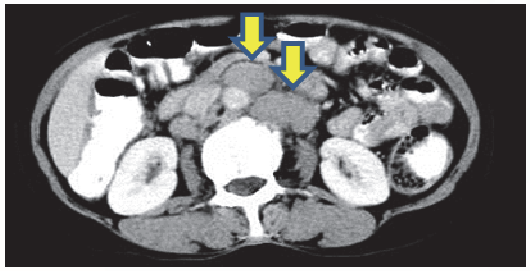


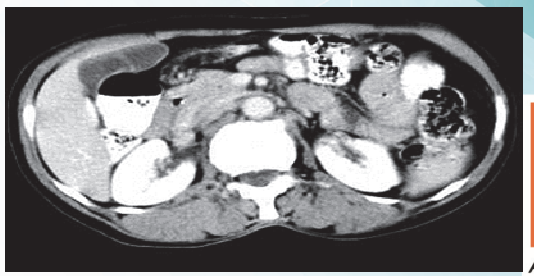
Resolution of liver metastasis on CT





Resolution of para-aortic lymph node metastasis on CT





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Summary

ADXS-HPV, a live highly attenuated *Listeria* based *Lm*-LLO immunotherapy directed against HPV, is well tolerated and appears to have therapeutic activity in recurrent/refractory cervical cancer. The addition of Cisplatin had no effect on survival or tumor response

***Lm*-LLO Immunotherapies:**

- **Active vector – no additional adjuvant required**
- **Stimulate comprehensive innate and adaptive immune responses**
- **Result in generation of antigen-specific T cell responses, and their infiltration at the site of disease**

–Break tolerance and suppresses tumor defenses, can induce antigen spreading

–Can delay progression or resolve tumors

ADXS-HPV

Safety

–Well-tolerated and manageable safety profile. Suitable for earlier stage disease

–AEs predominately cytokine-release syndrome - Grade 1/2 transient, non-cumulative, that self resolve or respond to symptomatic treatment (< 2.0% *related* SAEs)

–Incidence and severity of AEs lower than chemotherapy

Efficacy

–Complete and partial tumor responses; and (apparent) durable stable disease observed

–Patterns of tumor response similar to those seen with other effective immunotherapies

–Can be combined with chemotherapy

–Activity against different high risk HPV strains including HPV16, 18, 31, 33, and 45

–Broad potential against HPV-associated dysplasia and malignancies

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Lm-LLO Immunotherapies

-Thank You-