Abstract # 5529

ADXS11-001 IMMUNOTHERAPY: 12 MONTH SURVIVAL AND SAFETY DATA FROM A PHASE 2 STUDY IN RECURRENT CERVICAL CANCER

Robert Petit[1] and Partha Basu[2]
[1]Advaxis, Inc., Princeton NJ, [2]Chittaranjan National Cancer Institute, Kolkata, India

ABSTRACT

Background: ADXS11-001 immunotherapy is a live attenuated Listeria monocytogenes (Lm) bioengineered to secrete a HPV-16-E7 fusion protein targeting HPV transformed cells. The Lm vector serves as its own adjuvant and infects antigen presenting cells (APC) where it cross presents, stimulating MHC class I and II pathways resulting in specific T-cell immunity to tumors. Here we describe final 12 month overall survival data associated with ADXS11-001 administration in Lm-LLO-E7-015, a randomized P2 study conducted in India in 110 patients with recurrent cervical cancer; previously treated with chemotherapy, radiotherapy or both.

Methods: Patients were randomized to either 1 cycle (3 doses) of ADXS11-001 at 1 x 109 cfu or 4 doses of ADXS11-001 at 1 x 109 cfu with cisplatin chemotherapy. Naproxyn and oral promethazine were given as premedications and a course of ampicillin was given 72 hours after infusion. Patients received CT scans at baseline and 3, 6, 9, 12 and 18 months. The primary endpoint is overall survival.

Results: As of May 17, 2013, the trial has completed enrollment and 110 patients received 264 doses of ADXS11-001. The percentage of patients at 12 months is 36% (39/110) and at 18 months is 22% (16/73). The response rate was 11% (6 CRs and 6 PR/110) with tumor responses observed in both treatment arms. 33 additional patients had stable disease > 3 months, for a disease control rate of 41% (45/110). Survival and tumor responses were not due to an over-representation of patients with non-aggressive disease or to patients receiving inadequate prior treatment. Activity was observed against all high risk HPV strains detected. Two Grade 3 serious adverse events and 104 mild-moderate adverse events possibly related/related to ADXS11-001 treatment have been reported in 41% (45/110) of patients. The non-serious adverse events consisted predominately of transient, non-cumulative flu-like symptoms associated with infusion that either self-resolved or responded to symptomatic treatment.

Conclusions: ADXS11-001 can be safely administered to patients with advanced cancer alone and in combination with chemotherapy. ADXS11-001 is well tolerated and presents a predictable and manageable safety profile. The addition of cisplatin to ADXS11-001 in this study did not significantly improve tumor responses or overall survival. Objective tumor responses included CR's and apparent prolonged survival with minimal adverse experiences. Average duration of response in both treatment groups was 10.5 months. The 36% 12 month survival and 11% response rate observed in this recurrent disease setting is encouraging and suggests that ADXS11-001 is an active agent in recurrent cervical cancer.

Lm-LLO IMMUNOTHERAPY

- ADXS11-001 is a live attenuated bioengineered Listeria monocytogenes (Lm) LLO immunotherapy for the treatment of HPV-associated cancer

- ADXS11-001 secretes an antigen-adjuvant fusion protein consisting of a truncated fragment of the Lm listeriolysin (tLLO) fused to HPV16-E7

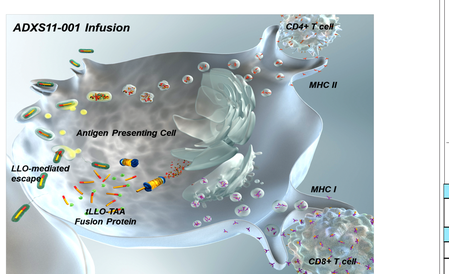
- Lm-LLO immunotherapy redirects the potent inherent cellular immune responses to Lm toward cells expressing the tumor associated antigen (TAA)

- TLm-LLO immunotherapy provides a comprehensive system for generating a cellular immune response:

  - Powerful innate immunity: TLRs, NOD-1, 2, PAMP; no adjuvant required
  - Access to APC: Cross presents tumor antigen
  - Powerful Adaptive immunity: Antigen specific CD4+, CD8+ T cells
  - Reduction of immunologic tolerance (Tregs and MDSCs) in the tumor microenvironment
  - Vector can be cleared with antibiotics

Life Cycle of *Lm* in APC

APC processing, antigen delivery, direction, and re-direction of cellular immunity



MECHANISM OF ACTION

Live attenuated Lm bioengineered to secrete an antigen-adjuvant fusion protein (antigen + tLLO) stimulate a profound innate immune response and are selectively phagocytized by antigen presenting cells (APC). Fragments from Lm are processed via the MHC class II generating antigen specific CD4+ T cells. Some Lm secrete LLO which enables them to escape into the cytosol where they secrete antigen-LLO fusion proteins. Fusion protein antigens are presented via MHC class I to generate activated CD8+ T cells. The activated T cells find, infiltrate tumors and destroy the tumor cells. Simultaneously, immunologic tolerance in the tumor microenvironment mediated by Treg cells and MDSCs is reduced enabling better tumor cell destruction. Thus Lm-LLO agents stimulate innate and adaptive tumor-specific immunity while simultaneously reducing immune tolerance to tumors resulting in improved survival and tumor responses.

LIVE ATTENUATED LISTERIA MONOCYTOGENES

- Attenuation: Genetically Engineered
- **Loss of bacterial virulence due to 10,000 to 100,000 fold attenuation**
  - Deletion of Δ prfA (with D133y complementation) results in reduction of bacterial virulence factors
  - Recombination and restoration of virulence not possible
- Secretes HPV-E7 protein fused with highly immunogenic, non-toxic tLLO fragment.

- tLLO agents are nonpathogenic, consisent with BSL-1 and RG1 agents
- According to:
  - US Centers for Disease Control (import and shipping permits)
  - German ZKBS (manufacturing)
- Published data has shown that there is no difference in the kinetics of clearance in wild-type or IFN-γ knockout mice.
- SCID mice clear *Lm*-LLO agents at doses 100,000x the LD_{50} of wild-type *Lm* in normal mice.

Lm-LLO-E7-015

A Randomized Phase 2 Study to Assess the Safety and Efficacy of ADXS-HPV +/- cisplatin Treatment for Recurrent Cervical Cancer

- 22 Sites throughout India

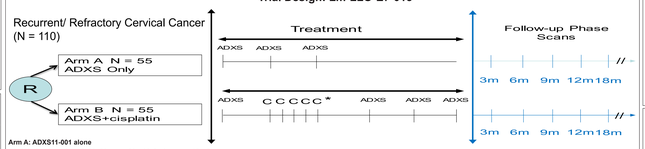
- N=110:
- Women 18-60 years of age with recurrent or refractory cervical cancer who have recurred after prior therapy (radiation therapy +/- chemotherapy)
- ECOG performance status 0-2
- Randomized - 2 groups of 55 patients receiving: ADXS11-001 or ADXS11-001+ cisplatin

- Primary objective:
- To determine the safety and efficacy of ADXS11-001 +/- cisplatin

- Efficacy Endpoints:
- Primary efficacy endpoint is overall survival
- Secondary efficacy enpoints are Tumor Response (RECIST 1.1) and PFS

Immunologic Evaluations:
- Serum cytokines, HPV specific T cells, PBMC phenotyping

Trial Design: Lm-LLO-E7-015



Arm A: ADXS11-001 alone
- 1x10⁹ cfu x3 on days 0, 28, 56 as an 80 ml infusion over 15 minutes

Arm B: ADXS11-001 + cisplatin
- ADXS11-001 = 1x10⁹ CFU as an 80 ml infusion over 15 minutes on days 0, 88, 106, 134
-*cisplatin = 40 mg/m2 x5 weekly on days 30, 37, 44, 51, 58

Lm-LLO-E7-015 is designed to evaluate the safety and efficacy of ADXS11-001 +/- cisplatin. The ADXS11-001 treatment arm receives ADXS11-001 (1x109 cfu) as 3 IV infusions 4 weeks apart, each dose followed by antibiotic at 3 days post-dosing. The ADVX11-001 + cisplatin treatment arm receives ADXS11-001 as an IV infusion (1x109 cfu), followed by antibiotic beginning 3 days post-dosing, followed 4 weeks later with 5 weekly IV administrations of cisplatin (40 mg/m2) followed 4 weeks later by 3 IV infusions of ADXS11-001 one month apart with antibiotic beginning 3 days after each ADXS11-001 dose. Naproxsyn 500 mg BID, (Day -1, 0) and promethazine 25 mg PO, BID (pre-dose, 8 hours) are administered as premedications. Ampicillin 500 mg QID (Days 3-9) is administered post-infusion. Safety is assessed at every visit. Efficacy is determined from overall survival and scans taken at baseline (before the first treatment dose) and at 3, 6, 9 12, & 18 months after treatment begins. Patients who complete the study are followed for survival.

Safety Summary: *Lm*-LLO-E7-015 (as of May 17, 2013)

110 patients received 264 doses of ADXS11-001 at 1x109 cfu

AEs related (or possibly related) to study drug:
-45 patients (41%) report 104 Grade 1-2 AEs
- -21 Cytokine Release Syndrome (CRS)
  - (2 or more symptoms: fever, chills, nausea, headache, tachycar dia, hypotension, rash, and shortness of breath)
- -31 Chills/Shivering
- -4 Fever
- -2 Headache
- -2 Leukopenia
- -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 AEs (CRS with dyspnea in 1 patient; fever in 1 patient)
-0 Grade 4 AEs
-0 Grade 5 AEs

Safety Summary: *Lm*-LLO-E7-015 (as of May 17, 2013)

ALL AEs (Related and Unrelated to ADXS11-001)
- 107 patients (97%) report 617 AEs
- 68/617 were SAEs
- -15 Disease Progression
- -9 Anemia
- -9 Renal Failure (4 Obstructive Uropathy)
- -8 Death (Sudden/Unknown Cause)
- -5 Bleeding
- -3 Bowel Obstruction
- -3 Dyspnea
- -2 Vomiting
- -1 SAE each: Ascites, Deep Vein Thrombosis, Diarrhea, Gastritis, Hyperkalemia, Multi-Organ Failure, Pain, Pulmonary Embolism, Peritonitis, Psychosis, Sepsis, Urinary Tract Infection

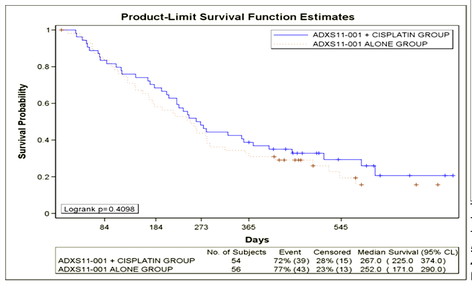
Safety: Frequency of SAEs in 110 patient Phase 2: Advaxis11-001 vs. Chemotherapy

Trial	Regimen	P. S.	%SAE
Lm-LLO-E7-015	ADXS-HPV 10^9 cfu/mo x3 / (ADXS + ADXS+CIS)	0-2	62%/(2%*)
Mannel 2000	cisplatin 75 mg/m^2 q21d + Pentoxyfylline	0-3	159.0%
Bookman 2000	Topotecan 1.5 mg/m2 dx5, q21d	0-3	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%

62% all cause SAEs were reported in both treatment arms combined. Single-agent and doublet chemotherapy regimens with activity in cervical cancer typically report one or more SAE's per patient treated (105% - 409%).

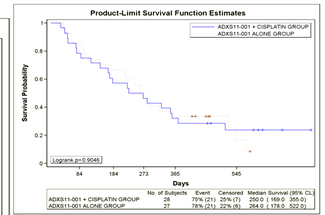
The incidence of SAEs related to ADXS11-001 was approximately 2%*. This compares quite favorably with single-agent and combination chemotherapy regimens in this disease setting.

Overall Survival



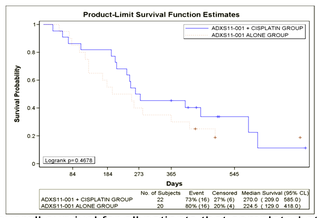
	No. of Subjects	Event	Censored	Median Survival (95% CL)
ADXS11-001 + CISPLATIN GROUP	54	72% (39)	28% (15)	267.0 (225.0 374.0)
ADXS11-001 ALONE GROUP	56	77% (43)	23% (13)	252.0 (171.0 290.0)

Overall Survival by Prior Therapy: Chemotherapy and Radiation



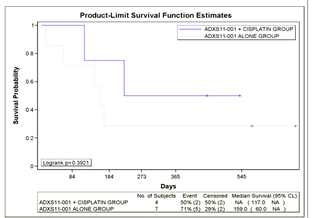
	No. of Subjects	Event	Censored	Median Survival (95% CL)
ADXS11-001 + CISPLATIN GROUP	29	76% (21)	25% (7)	250.0 (169.0 365.0)
ADXS11-001 ALONE GROUP	27	78% (21)	22% (6)	364.0 (178.0 522.0)

Overall Survival by Prior Therapy: Radiation Alone



	No. of Subjects	Event	Censored	Median Survival (95% CL)
ADXS11-001 + CISPLATIN GROUP	22	82% (18)	27% (4)	270.0 (109.0 585.0)
ADXS11-001 ALONE GROUP	20	85% (18)	30% (4)	224.5 (129.0 418.0)

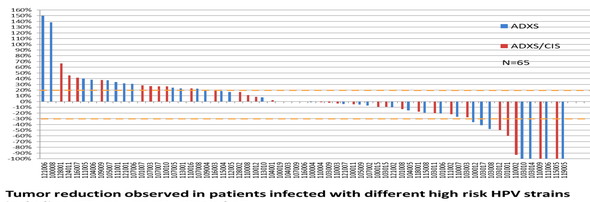
Overall Survival by Prior Therapy: Chemotherapy Alone



	No. of Subjects	Event	Censored	Median Survival (95% CL)
ADXS11-001 + CISPLATIN GROUP	4	50% (2)	50% (2)	NA (117.0 NA)
ADXS11-001 ALONE GROUP	7	71% (5)	29% (2)	159.0 (60.0 NA)

The Kaplan Meier curve on the left represents overall survival for all patients that completed at least 12 months of follow-up.
The addition of cisplatin to ADXS11-001 did not significantly improve survival (p=0.41). Median overall survival was ~260 days (8.5 months).
The 3 Kaplan Meier curves above represent relative overall survival by treatment arm and by prior therapy.
50% of patients were previously treated with combination radiation/chemotherapy;
40% of patients were treated with radiotherapy alone; and 10% of patients were treated with chemotherapy alone.
No differences in overall survival were observed based on prior therapy.

Lm-LLO-E7-15 Best Response Data (as of May 17, 2013)



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

The best overall response is shown for 65 patients. 18 patients expired prior to the 3 month evaluation and 27 patients withdrew consent or were lost to follow up over the same interval. Using RECIST criteria 20 patients had a best overall response of progressive disease, 12 patients had objective responses (6CR/6PR), and 33 patients had stable disease ≥ 3 months. Similar tumor responses were observed in both treatment groups.
Tumor responses were observed in all strains of high-risk HPV detected including HPV 16, 18, 31, 33 and 45

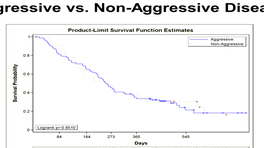
Landmark Survival

		Treatment Group	
Patients at Risk, n (%)*	Overall (N=110)	ADXS11-001 ALONE (N=56)	ADXS11-001 + CISPLATIN (N=54)
9 Months			
n	110	56	54
% alive (#)	46% (51)	43% (24)	50% (27)
12 Months			
n	110	56	54
% alive (#)	36% (39)	32% (18)	39 % (21)
18 Months			
n	73	38	35
% alive (#)	22% (16)	18% (7)	26% (9)

*Percentage is calculated from 'n' count at respective month as denominator.
n denotes the number of subjects who would have completed X months in study from the date of randomization.

All patients have been on study for at least 12 months.
Final 12 month overall survival of 36% with a (current) 18 month survival of 22% is notable in this disease setting.
Patients continue to be followed for survival.
Overall survival observed with ADXS11-001 is consistent with an active agent in recurrent cervical cancer.

Overall Survival: Aggressive vs. Non-Aggressive Disease



	No. of Subjects	Event	Censored	Median Survival (95% CL)
Aggressive	87	78% (68)	22% (19)	268.0 (222.0 318.0)
Non-Aggressive	23	78% (18)	22% (5)	264.0 (159.0 405.0)

80% (87/110) of the patients in this trial had aggressive disease (defined as recurrence ≤2 years from initial diagnosis). 35% (30/87) of patients with aggressive disease survived 12 months and 39% (9/23) of the non-aggressive disease survived 12 months. Aggressive disease had no impact on overall survival.

Duration of Response (PFS) by Treatment Group

Patient#	Response	Duration in Months Average (Range)
103-010	CR	12
119-005	CR	9
111-006	CR	*9
103-014	CR	*6
103-008	PR	>18
100-012	PR	9
		10.5 months (6-18+)

Patient#	Response	Duration in Months Average (Range)
110-009	CR	>3.8
115-005	CR	12
110-002	PR	>18
103-001	PR	9
103-012	PR	3
103-003	PR	3

Duration of Stable Disease (PFS) by Treatment Group

#Patients	Treatment	Average PFS (Range)
N = 14	ADXS11-001 ALONE	**6 months (3-12)**
N = 19	ADXS11-001 +CISPLATIN	**4.1 months (3-12)**

* Lost to follow-up

The table above represents duration of response (PFS) by treatment group. Average duration of response after 12 months minimum follow-up is 10.5 months in both treatment groups. In patients with stable disease, there is an apparent difference based on treatment group as patients treated with ADXS11-001 alone had an average PFS of 6 months compared to patients treated with ADXS11-001 + cisplatin had an average of PFS of 4.1 months.

Responsiveness of Disease and Treatment Group

Recurrence	Response/Duration of Response	Overall (N=110)	Treatment Group: ADXS11-001 ALONE (N=56)	Treatment Group: ADXS11-001 + CISPLATIN (N=54)
Aggressive				
	Complete Response	4.5% (4/87)	6.8% (3/44)	2.3% (1/43)
	Partial Response	4.5% (4/87)	4.5% (2/44)	4.6% (2/43)
	Stable Disease	31.0% (27/87)	27.3% (12/44)	34.8% (15/43)
Non-Aggressive				
	Complete Response	8.6% (2/23)	8.3% (1/12)	9.0% (1/11)
	Partial Response	8.6% (2/23)	8.3% (1/12)	9.0% (1/11)
	Stable Disease	26.1% (6/23)	16.6% (2/12)	36.4% (4/11)

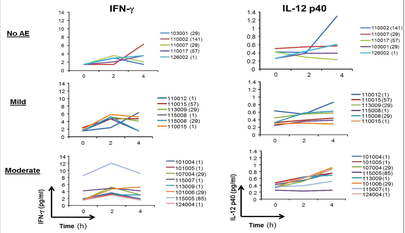
Percentage is calculated by taking respective column header group count as denominator.

The above table is a summary of CR, PR, and Stable Disease by aggressive disease defined as recurrence ≤ 2 years vs. non-aggressive disease defined as recurrence > 2 years per RESIST guidelines
For aggressive and non-aggressive disease, the response rates were 9.2% (8/87) and 17.4% (4/23) respectively. Stable disease >3 months was 31% for aggressive disease and 26% for non-aggressive disease.
Disease control rates of > 3 months were 44% (37/80) for aggressive disease and 43% (10/23) for non-aggressive disease.Tumor responses are not restricted to patients with non-aggressive disease.

Relative Increase in Cytokines and Chemokines Post-Dose

Cytokine	Relative Fold Increase (2h)	Relative Fold Increase (4h)
IL-6	34.00	32.68
IL-8	22.50	12.80
IL-10	28.47	33.78
IL-18	0.57	0.63
MIP-1 α	3.00	2.10
MIP-1β	28.68	18.63
MCP-1	35.52	23.94
TNF-α	19.21	11.78
TNF-R2	1.94	1.84

Preliminary Association of Cytokines with Adverse Events

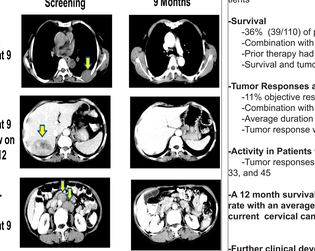


A relative 2-3 fold increase in IFN-γ and IL-12 levels in the patients exhibiting varying degree of adverse events

The table on the left represents a subset of the clinical samples that have been analyzed thus far and shows relative increases in some cytokines and chemokines at 2 and 4 hours. More than a 15-fold increase is observed in the level of cytokines (IL-6, IL-8, IL-10 and TNF-) and chemokines (MIP-1 , MIP-1 and MCP-1) post-administration of ADXS11-001, indicating strong stimulation of innate immunity.

The graphs on the right represent a subset of the clinical samples that have been analyzed thus far. There appears to be a 2-3 fold increase in IFN- and IL-12 levels associated with increased severity of CRS symptoms. There is no apparent association of cytokine levels or CRS symptoms with tumor response.

Case Study: Patient 110-002



Patient 110-002 enrolled with 284mm (sum of linear measures) of disease at 10 sites, including liver, lung, & peri-aortic nodes. The patient was previously treated with surgery and radiation (EBRTx25), and recurred within 1 year with metastatic disease. She was randomized to receive ADXS/CIS. At 3 months she had 94mm of tumor at 5 sites, at 6 months 56mm of tumor at 3 sites, at 9 months 34mm at 2 sites, and at 12 months 20mm in a single peri-aortic node not amenable to biopsy.

CONCLUSIONS

-ADXS11-001 is Well Tolerated in Patients with Refractory Cervical Cancer
- -Well tolerated with predominately mild transient AE's associated with infusion. 2 Grade 3 SAEs out of 110 patients

-Survival
- -36% (39/110) of patients are alive at 12 months; 22% (16/73) of patients are alive at 18 months
- -Combination with cisplatin in this trial did not improve survival or tumor response
- -Prior therapy had no effect on survival or tumor response between treatment groups
- -Survival and tumor response are not attributable to the inclusion of patients with less aggressive disease

-Tumor Responses are Equivalent in Both Treatment Groups
- -11% objective response rate including CRs and PRs, disease control rate of 41% for ≥3 months
- -Combination with cisplatin did not improve the response rate
- -Average duration of responses ~10.5 months
- -Tumor response was not affected by prior therapy or aggressiveness of disease

-Activity in Patients with Various Different High Risk HPV Strains
- -Tumor responses observed in patients infected with all high risk HPV strains detected, including HPV16, 18, 31, 33, and 45

-A 12 month survival of 36% with an 18 month survival of 22% (preliminary), and an 11% objective response rate with an average 10.5 month duration after 1 cycle of treatment is consistent with an active agent in recurrent cervical cancer.

-Further clinical development includes optimization of the ADXS11-001 dose and schedule including multiple cycles of treatment, use in combination, and sequencing with other agents. The optimal dose and schedule will be used in future registration studies.

Dr. Robert Petit, PHD; petit@advaxis.com
Dr. Partha Basu MD, DNB; basupartha@hotmail.com
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