AIM2CERV in High-Risk, Locally Advanced Cervical Cancer

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Gynecologic Cancer InterGroup
Cervix Cancer Research

Research Grants Paid to Institution

- Amgen
- Array
- Eli Lilly
- Genentech
- Janssen Pharmaceuticals/Johnson & Johnson
- TESARO, Inc.
- Morphotek

Speaker's Bureaus/Honoraria

- AstraZeneca
- Genentech/Roche
- Janssen Pharmaceuticals/Johnson & Johnson
- Myriad

Consulting/Advisory Board

- Advaxis
- Amgen
- AstraZeneca
- Bayer
- Biodesix
- Clovis
- Genentech/Roche
- Gradalis
- Insys
- Mateon (formally OxiGENE)
- Merck
- Pfizer
- Tesaro

Axalimogene Filolisbac (AXAL):
Lead HPV Targeted Cancer Immunotherapy

PRODUCT

Axalimogene Filolisbac (AXAL) is a live attenuated Listeria monocytogenes (Lm) vector system that secretes an antigen-adjuvant protein (Lm-LLO) targeting HPV

PROFILE

AXAL is designed to improve clinical outcomes in HPV-associated tumors such as Cervical, Anal, and Head & Neck Cancers through a highly-targeted, generally well-tolerated immune-mediated response warranting further study.

DEVELOPMENT STATUS

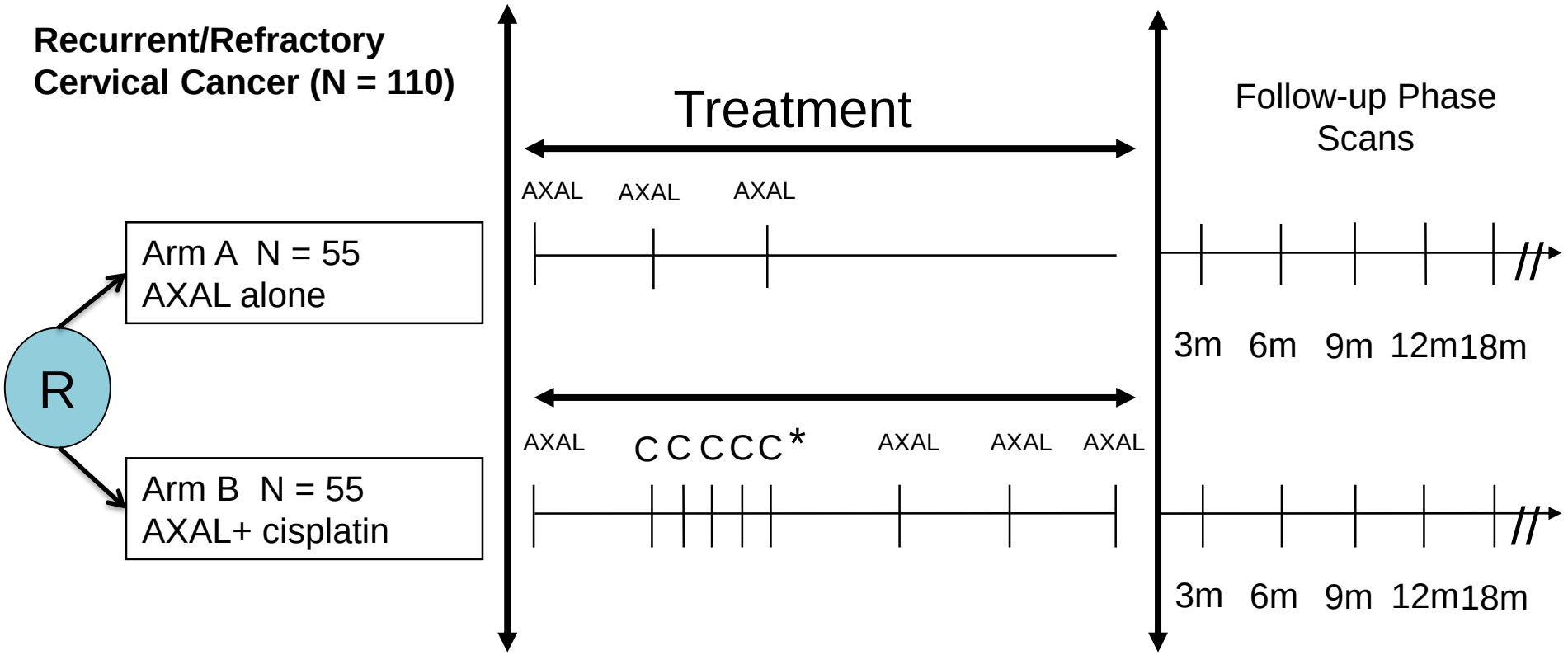
Phase 3 in cervical cancer

- FDA SPA and Fast-Track designation as adjuvant therapy for high-risk cervical cancer
- Has been well tolerated with established adverse event management in earlier phase trials

Studies in other cancers settings: Head and neck and anal cancers

- Head and neck cancer in combination with durvalumab
- Anal cancer phase 1/2 adjuvant study (RTOG; Orphan indication) and phase 2 in metastatic (FAWCETT)

Axalimogene Filolisbac (AXAL) Phase 2 Study in Indian Patients



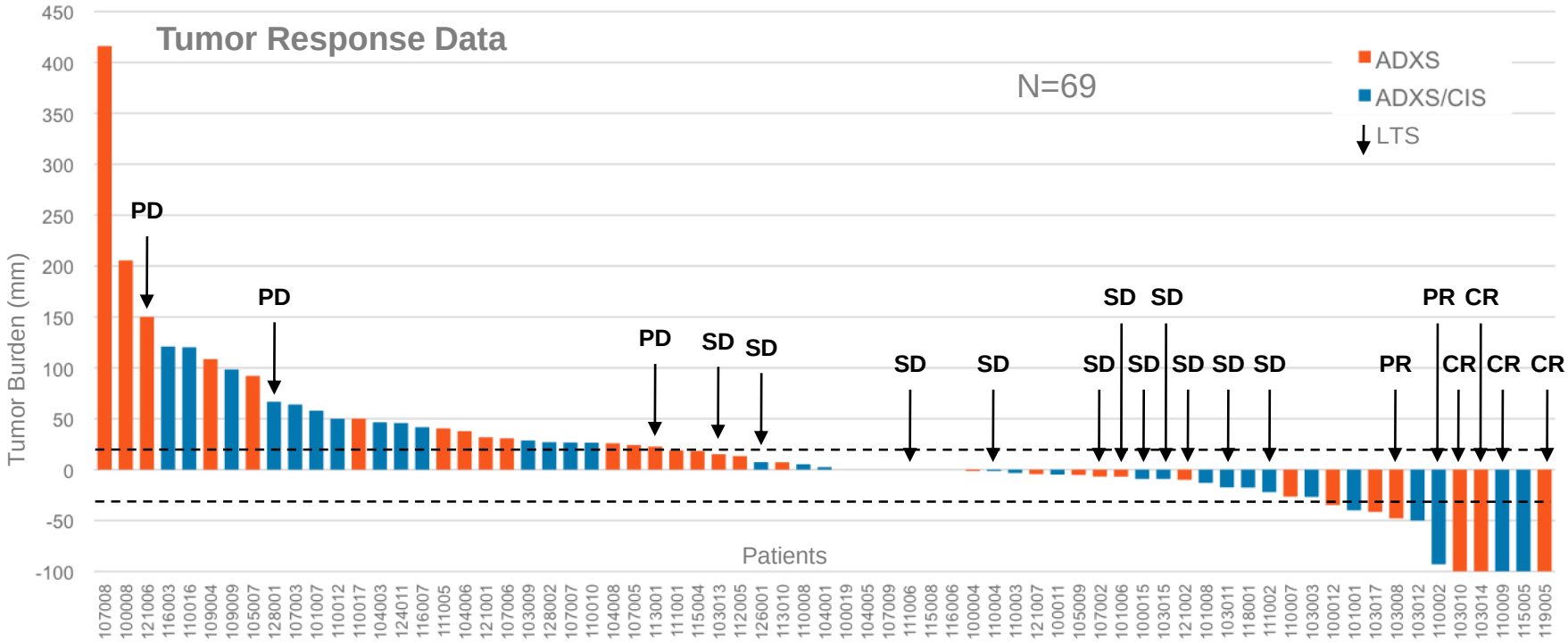
Arm A: Axalimogene alone:

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

Arm B: Axalimogene + cisplatin:

- $1x10^9$ CFU as an 80 ml infusion over 15 minutes on days 0, 88, 106, 134
- *cisplatin = 40 mg/m^2 x5 weekly on days 30, 37, 44, 51, 58

Phase 2 Study in Indian Patients: Tumor Response Data & Long-Term Survivors (LTS)

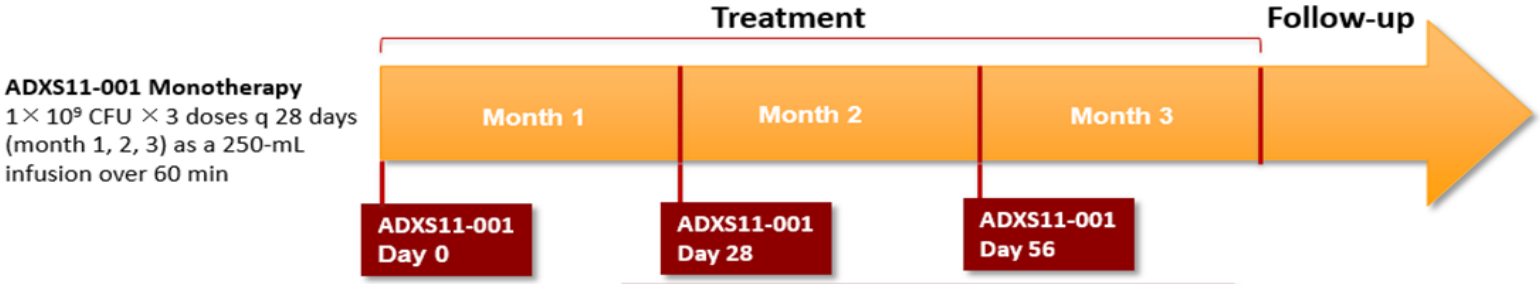


Data Presented at ASCO 2014
Basu et al. 2014; J Clin Oncol 32:5s (suppl; abstr 5610).

LTS included patients with tumor shrinkage and those who experienced increased tumor burden as best tumor response overall

GOG/NRG Study-0265 - Study Design and Eligibility

- N = ~63; Simon two-stage design
- ≥18 years
- Persistent/recurrent metastatic (PRmCC) squamous/non-squamous cervical cancer
- ≥1 prior line of systemic-dose therapy for PRmCC, *excluding that received as a component of primary curative treatment*
- Prior bevacizumab allowed, but not required
- GOG PS 0/1
- Measurable disease ≥1 target lesion (RECIST 1.1)



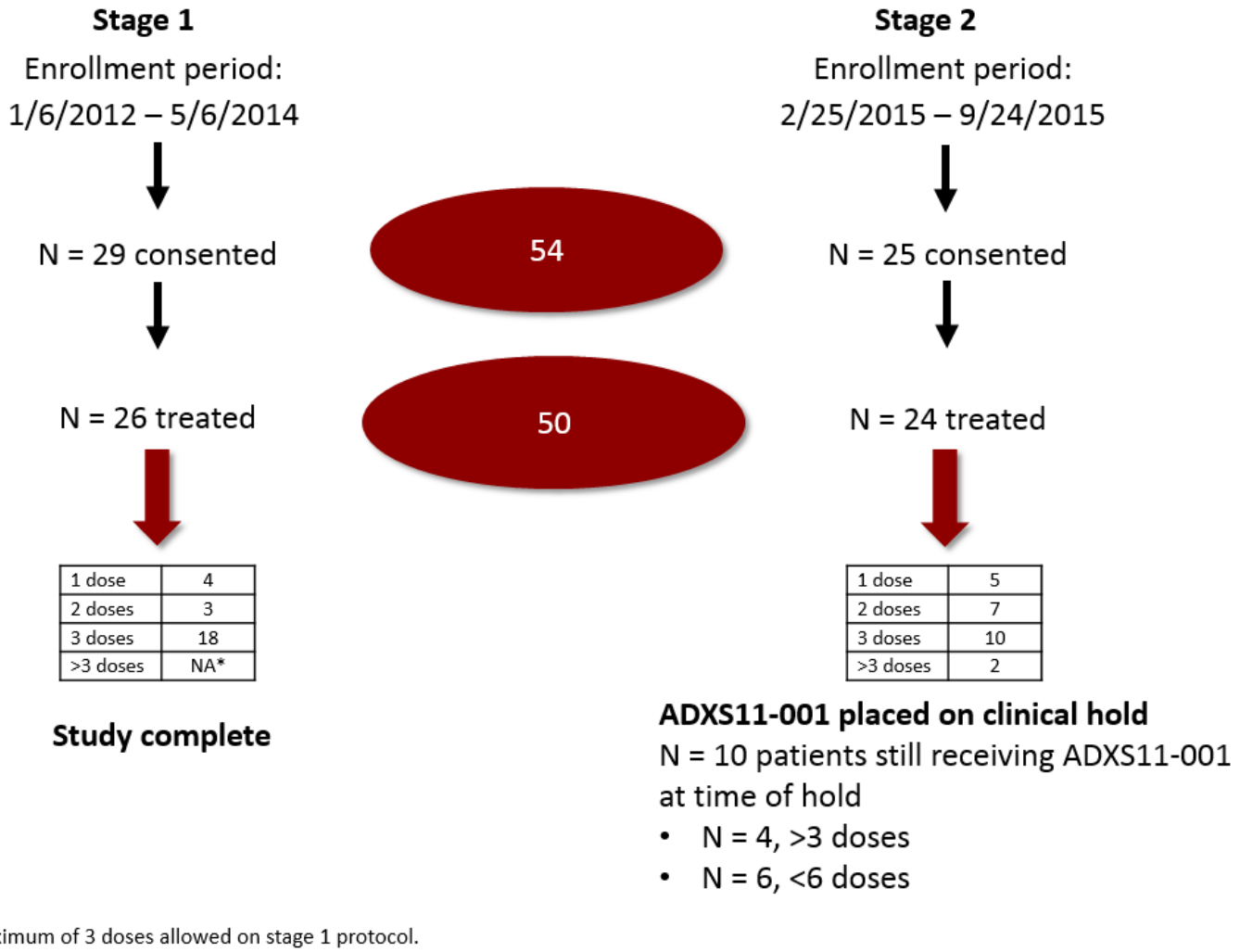
Co-primary Endpoints
- 12-month survival rate
- Tolerability/safety of ADXS11-001

Secondary Endpoints
- PFS
- OS
- ORR

*Stage 2 amended to allow continuous (>3) dosing of ADXS11-001.

https://www.clinicaltrials.gov/ct2/show/NCT01266460. Endpoints: ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.
Tewari KS, et al. *Curr Oncol Rep*. 2005;7:419-434. On October 24, 2016, Advaxis announced early closure of stage 2 which is no longer enrolling.

GOG/NRG Study-0265 - CONSORT Diagram



*Maximum of 3 doses allowed on stage 1 protocol.

https://www.clinicaltrials.gov/ct2/show/NCT01266460. Endpoints: ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.
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GOG-0265: AXAL Safety Profile

Stage 1 Adverse Event Summary* (n = 26)			
AE	**Grade 1–2**	**Grade 3**	**Grade 4**
Patients with ≥1 TRAE, n (%)	24 (92)	4 (15)	1 (4)**
TRAEs occurring in ≥10% of patients			
Fatigue	15 (58)	-	-
Chills	14 (54)	-	-
Fever	11 (42)	-	-
Nausea	10 (39)	-	-
Headache	9 (35)	-	-
Hypotension	7 (27)	2 (8)	-
Vomiting	6 (23)	-	-
Cytokine release syndrome	5 (19)	3 (12)	-
Myalgia	5 (19)	-	-
Abdominal pain	4 (15)	-	-
General pain	4 (15)	-	-
Flu-like symptoms	3 (11)	-	-
AST elevation	3 (11)	-	-

*Combined safety results being analyzed
**The observed grade 4 TRAE recorded in 1 patient (lung infection and sepsis) was considered possibly related to treatment.
AST, aspartate aminotransferase.

Huw W, et al. ASCO 2016. Abstract 5516.

Phase 3 AIM2CERV Studies AXAL as Adjuvant Monotherapy to Prevent Disease Recurrence in High-Risk Cervical Cancer

- HRLACC
- FIGO stage I–II with positive pelvic nodes
- FIGO stage III–IVA
- Any FIGO stage with para-aortic nodes

Treatment with cisplatin* (at least 4-wks exposure) and radiation (minimum 40-Gy external beam radiation therapy)

Baseline tumor imaging must be performed within 28 days prior to the first study treatment infusion

Randomize

Placebo IV
Up to 1 year
N=150

Axalimogene Filolisbac
(1 X 10^9 CFU)
Up to 1 year
N=300

Primary Endpoint:

DFS

- Special Protocol Assessment (SPA)
- Fast Track Designation
- Orphan Status

GOG Gynecologic Oncology Group

AIM2CERV – Axalimogene Filolisbac Immunotherapy Following Chemo/Radiation in Patients who have High Risk Locally Advanced Cervical Cancer (HRLACC)

CFU, colony-forming unit; DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; HRLACC, high-risk locally advanced cervical cancer; IV, intravenous; AIM2CERV – Axalimogene Filolisbac Immunotherapy Following Chemo/Radiation in Patients who have High Risk Locally Advanced Cervical Cancer (HRLACC)

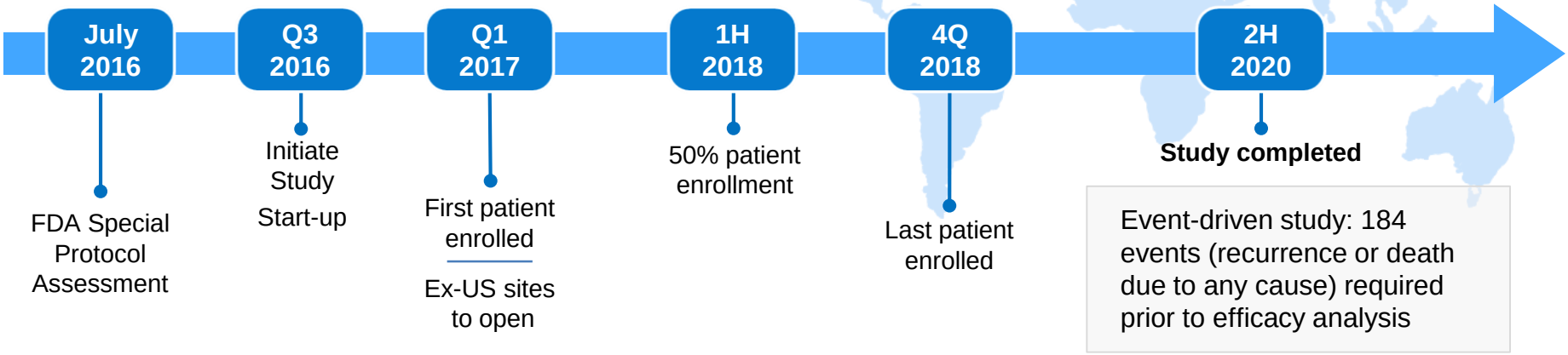
1. Herzog T, et al. SITC 2016. Poster 145.

AIM2CERV by the Numbers

450 Patients

~20 Countries

~150 Global sites



Event-driven study: 184 events (recurrence or death due to any cause) required prior to efficacy analysis

Estimated timeline

Timeline is based on current estimates.
FDA, US Food and Drug Administration.

AIM2CERV Study Objectives

Primary Objective

- Disease free survival (DFS)

Secondary Objectives

- Safety and Tolerability
- Overall Survival (OS)

Exploratory Objectives

- Association between HPV subtypes and efficacy
- Patient Reported Outcomes (PROs)

Key Inclusion Criteria

- Histological diagnosis of squamous cell, adenocarcinoma or adenosquamous carcinoma of the cervix who have undergone definitive therapy with a curative intent
- Subjects may have:
  Stage IB2, IIA2, IIB with any of the following pelvic lymph node metastases criteria:
  - Biopsy proven pelvic node(s)
  - 2 or more positive nodes by MRI/CT ≥1.5cm shortest dimension
  - 2 or more positive pelvic nodes by PET with standard uptake value ≥2.5

-or- All Stage IIIA, IIIB, IVA

- Any FIGO stage with para-aortic lymph node metastases criteria (defined by 1 of the following):
- Biopsy proven para-aortic node(s)
- 1 or more positive para-aortic node(s) by MRI/CT >1.5 cm shortest dimension
- 1 or more positive para-aortic node(s) by PET with SUV >2.5

Key Exclusion Criteria

Subjects:

- Who have not achieved disease-free status
- With FIGO stage IVB
- Who have undergone a previous hysterectomy (partial / subtotal can participate)
- Who have implanted medical device(s) that pose a high risk for colonization and/or cannot be easily removed
- Who are receiving, plan, or anticipate on receiving PI3K or TNFα
- Have a contraindication (sensitivity or allergy) to trimethoprim/sulfamethoxazole and ampicillin

Investigational Product

Drug Product ADXS11-001 (Axalimogene filolisbac)

- ADXS11-001 for infusion is free flowing isotonic, aqueous, cream colored suspension at pH of 6.0-7.9 supplied in a DIN 2R glass vial (4mL). It is supplied at a concentration of 1.16 x 10^10 cfu/mL with total volume of 1.2 mL; each vial contains excess fill of 0.2 mL to ensure recovery of label claim of 1.16 x 10^10 cfu.
- ADXS11-001 for infusion is diluted with 0.9% Sodium Chloride Injection, USP (normal saline) to achieve dose in 250 mL volume for IV infusion

Stability and Handling ADX11-001

- Aseptic technique must be strictly observed throughout preparation, using Class II biologic safety cabinet with laminar flow
- Store frozen at -80 (± 10) ° C
- Prior to preparation, thaw at room temperature at or below 25ºC (77ºF) for 5-10 minutes
- 6 hour stability (vial from freezer through duration of infusion)

Investigational Product

ADXS11-001 Stability and Handling (continued)

- Do not use lines with an in-line filter
- Do not administer as IV push or bolus
- Do not combine, dilute or administer as an infusion with other medicinal products
- Do not co-administer other drugs through same infusion line
- ADXS11-001 and all other IV study medications must be administered through a temporary line, which will be removed prior to discharge
- Prevent accidental use of an existing portacath/infusion port -
- Preprinted stickers stating ‘DO NOT USE PORTACATH/INFUSION PORT’ will be supplied to site and attached to all study medication IV bags.

Protocol ADXS001-02 – Regions, Countries & Sites

- Study will be conducted in US, Latin America, Europe, and Asia-PAC regions
- A total of 18 countries and ~ 150 sites are planned to participate

Country	Sites Selected
Argentina	7
Brazil	9
Canada	6
Chile	3
Denmark	3
Korea	7
Malaysia	5
Mexico	4
Netherlands	2
Poland	3
Romania	4
Russia	10
Serbia	6
Spain	18
Sweden	3
Taiwan	6
Ukraine	10
US	42

Protocol ADXS001-02 – Primary CRO and Study Vendors

inVentiv Health Clinical

- Global CRO responsible for Project Management, Monitoring, Pharmacovigilance and Regulatory

GOG Foundation

- Responsible for Data Management and Site Contracting/budgeting (US only)

RadMD

- Central Radiology Imaging

Covance

- Central Clinical Laboratory for HPV Genotyping

Suvoda

- Interactive Response Technology

Almac

- Drug Distribution

AIM2CERV Steering Committee

Dr. Floor Backes
- Ohio State University Wexner Medical Center

Dr. Larry Copeland
- Ohio State University Wexner Medical Center

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- University of Cincinnati Cancer Institute

Dr. Warner Huh
- University of Alabama at Birmingham

Dr. Katie Moore
- Stephenson Cancer Center - Oklahoma University Health Sciences Center/Oklahoma Health Center

Dr. Brad Monk
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- Vall d´Hebron University Hospital (Spain)

Dr. Sharad Ghamande, MD
- GRU Cancer Center

Dr. Mansoor Raza Mirza
- Dept. of Oncology, Rigshospitalet, Copenhagen University Hospital

Top reasons for screen failures to date

- FIGO Stage IB2, IIA2, IIB **without** pelvic lymph node metastases (most common)
- Implanted medical device
- Diagnosed with FIGO Stave IVB
- Medical history or condition deemed exclusionary by the investigator
- Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial

Protocol ADXS001-02 – Study Challenges

Study Start-Up Challenges

- Contracting process – can this be done in parallel or does this need to be done in sequence
  - If in sequence, can something be implemented at the site level to switch to a parallel process?
- Institutional Review Board (IRB) - Central vs. Local IRB – local IRBs tend to take longer to approve the study
- Sites with additional internal institutional boards that are required to review and approve the protocol
- Institutional Biosafety Committees (IBCs) - Central vs. Local IBC
- Sites new to the IBC process take longer to get up and running with assembling an IBC at their site for the 1st time
- Site having the resources and being educated on how to handle a Biosafety Level 2 (BSL-2) product

Protocol ADXS001-02 – Study Challenges

Recruitment Challenges

- Subset of rare cancer limits potential patients
- Majority of sites are new to Advaxis and new to the technology, which makes it more challenging for sites to convince patients to participate in the study
- Difficulty convincing patients to undergo additional treatment (after CCRT)
- Patient enrollment is time dependent on CCRT treatment
  - Patients need to be 10 weeks post CCRT to be eligible for this study, so identifying patients who are in various stages of treatment (just diagnosed, in the middle of treatment, or completing CCRT) and tracking them until they are 10 weeks out is critical to the success of this stud
- Patients must be considered disease-free at the time of enrollment
- Sites identifying patients in study site database that are newly diagnosed or currently in CCRT ahead of the Site Initiation Visit

Protocol ADXS001-02 – Study Challenges

Trial Challenges

- SPA approval limits our ability to make any significant protocol changes
- Majority of sites are new to Advaxis and new to the technology
- Long term antibiotic treatment (6 months) following last infusion
- Requirements of drug (e.g. pharmacy handling of BLS2 agent)
- Blinded versus unblinded teams at study site
  - Ensuring that sites have clearly identified blinded and unblinded teams at the site to ensure that the blind in maintained throughout the entire study
  - Resources – Sites knowing who their resources are and who to call for what questions
- Protocol/Infrastructure for management of treatment-related AEs
  - Managing Cytokine Release Symptoms
    - Pre-medication Regimen
    - IV Fluids
    - Treatment of symptoms

Contact Us

For questions regarding the study, please contact:

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