A Phase 1/2 study of durvalumab alone or in combination with AXAL in recurrent/ persistent or metastatic cervical or human papillomavirus (HPV)+ squamous cell cancer of the head and neck (SCCHN): Preliminary Phase 1 results

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INTRODUCTION

- Targeting of oncogenic HPV using immunotherapeutics presents an attractive strategy for improving survival in patients with advanced cervical and oropharyngeal cancers associated with HPV infection.
  - The success of such approaches may be enhanced by a combination of immune checkpoint blockade and tumor-selective vaccination
- Axalimogene filolisbac (AXAL or ADXS11-001) is a live, irreversibly attenuated, nonpathogenic *Listeria monocytogenes (Lm)*-listeriolysin O (LLO) immunotherapy developed for the treatment of HPV-associated cancers.[1-3]
  - AXAL secretes an HPV E7 tLLO fusion protein that stimulates adaptive and innate immunity, resulting in the activation and release of HPV-specific cytotoxic T cells and reduction of tumor-associated immune tolerance[1]
- Durvalumab (MEDI4736) is a selective, high-affinity human immunoglobulin G1 monoclonal antibody that blocks programmed cell death protein 1 ligand 1 (PD-L1) binding to PD-1 (IC_{50} 0.1 nM) and CD80 (B7.1; IC_{50} 0.04 nM).[4]
  - Targeting and blocking the inhibitory effects of PD-L1 with durvalumab is an important immunotherapeutic approach designed to boost antitumor immune responses in patients with cancer
- Studies in mouse models have demonstrated that antibodies directed against PD-L1 or PD-1 exhibit antitumor activity.[5-7]
- Preclinical studies have shown that a combination of AXAL with immune checkpoint inhibitors enhances AXAL antitumor activity.[8,9]
- The present Phase 1/2 trial (NCT02291055) has been initiated to determine the safety, tolerability, and efficacy of the AXAL + durvalumab combination in patients with recurrent/metastatic cervical or HPV+ SCCHN, and the safety and efficacy of durvalumab monotherapy in recurrent/metastatic cervical cancer.
- Herein, preliminary safety and efficacy results of the Phase 1 Part A dose escalation are reported.

OBJECTIVES

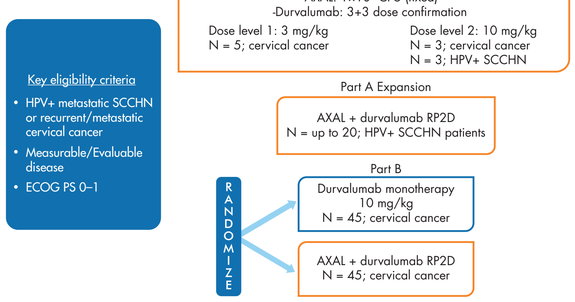
- The primary objectives of the Phase 1 Part A dose escalation are to determine the safety/tolerability and establish the combination recommended Phase 2 dose (RP2D) of AXAL (1×10^9 colony-forming units [CFU] every 4 weeks [Q4W]) and durvalumab (3 mg/kg [dose level 1] or 10 mg/kg [dose level 2] Q2W) in patients with HPV+ metastatic SCCHN or recurrent/metastatic cervical cancer.
  - Part A also includes an expansion cohort (N = 20) at the RP2D in patients with HPV+ metastatic SCCHN
- The primary objectives of the Phase 2 Part B are to evaluate safety and tumor response of durvalumab monotherapy and AXAL + durvalumab combination therapy at the RP2D in patients with recurrent/metastatic cervical cancer.

METHODS

STUDY DESIGN

- This is a Phase 1/2 study that is divided into 2 parts (**Figure 1**).
- Phase 1 Part A:
  - Dose-escalation (3+3 design), open-label, multicenter study in patients with HPV+ metastatic SCCHN or recurrent/metastatic cervical cancer
  - Dose-limiting toxicities (DLTs) were evaluated for a period of 28 days after the first dose for each patient
  - The dose level at which a DLT rate of <33% has been observed will be selected as the RP2D for Phase 2 Part B
    - Part A expansion consists of a cohort of 20 patients with metastatic SCCHN treated with AXAL + durvalumab RP2D combination therapy
- Phase 2 Part B:
  - Patients with recurrent/persistent or metastatic cervical cancer will be randomly assigned 1:1 to durvalumab (10 mg/kg) monotherapy or AXAL + durvalumab RP2D combination therapy
- In Phase 1 and Phase 2, per-protocol tumor imaging assessments of response are done in screening and at week 1 (± 1 week), starting at cycle 2, and then continue every 8 weeks (±1 week).

Figure 1. Study design



Median follow-up time*, days (range)	84 (16–369)
Median number of AXAL doses (range)	2 (0–7)
Median number of durvalumab doses (range)	6 (1–23)

*Data cut-off 10/1/16

CFU, colony-forming units; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; RP2D, recommended Phase 2 dose; SCCHN, squamous cell cancer of the head and neck.

INTERVENTIONS

- For combination therapy:
  - Patients will receive AXAL Q4W and durvalumab Q2W in each 8-week treatment cycle
    - When treatments are administered simultaneously, durvalumab (3 or 10 mg/kg) will be administered first in 250 mL saline over 60 minutes, followed 30 minutes later with the pretreatment prophylactics (nonsteroidal anti-inflammatory drugs, antiemetic, and antihistamine). AXAL will be administered 30 minutes later in 100 mL saline over 60 minutes
    - All patients will receive a 7-day course of oral antibiotic (trimethoprim/ sulfamethoxazole or ampicillin) 72 hours after AXAL administration
- For durvalumab monotherapy:
  - Patients will receive 10 mg/kg in 250 mL of normal saline infused over 60 minutes Q2W

STATISTICAL CONSIDERATIONS

- Sample size:
  - In Phase 1 Part A, up to 12 evaluable patients will be needed to determine the RP2D following the standard 3+3 dose-escalation design
    - An additional 20 patients are planned for the dose-expansion cohort
- Statistical methods:
  - Descriptive statistics will be used to summarize and evaluate the outcomes
  - All patients who received at least 1 dose of AXAL and/or durvalumab will be included in the safety analyses

RESULTS

PATIENT DEMOGRAPHICS

- To date, 11 patients are enrolled in Phase 1 (AXAL + durvalumab 3 mg/kg: N = 5; AXAL + durvalumab 10 mg/kg: N = 6).
  - Baseline characteristics are shown in **Table 1**
  - Median number of doses of AXAL or durvalumab, as well as follow-up time, are shown in **Figure 1**

Table 1. Patient demographics

	N = 11
Age, median (range)	52 (34–68)
ECOG PS, n (%)	
0 / 1	10 (91) / 1 (9)
Race, n (%)	
White / Other	7 (64) / 4 (36)
Gender, n (%)	
Male / Female	2 (18) / 9 (82)
Primary cancer, n (%)	
Cervical	8 (73)
HPV+ SCCHN	3 (27)
Prior lines of systemic therapy, n (%)	
0	3 (27)
1	4 (36)
2	0 (0)
3	2 (18)
≥4	2 (18)
Prior biologic/targeted therapy, n (%)	
Bevacizumab	6 (55)
Cetuximab	1 (9)
Other	1 (9)

ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; SCCHN, squamous cell cancer of the head and neck.

DOSE ESCALATION

- No DLTs have been observed (**Table 2A**).
- Adverse events (AEs) were reported in 100% of patients, and treatment-related AEs (TRAEs) were reported in 10 patients (91%) (**Table 2A**).
  - Grade 3 TRAEs were experienced in 3 (27%) patients, and 1 patient (9%) experienced a grade 4 TRAE
- The most frequent TRAEs were chills and/or rigors, fever, nausea, hypotension, diarrhea, fatigue, tachycardia, and headache (**Table 2B**).
  - Grade 3 chills and/or rigors were reported in 2 patients, grade 3 diarrhea in 1 patient, and 1 patient experienced grade 4 hypotension
- The RP2D was declared at durvalumab 10 mg/kg Q2W + AXAL 1×10^9 CFU Q4W.

Table 2. Summary of AEs, TRAEs (A), and TRAEs (worst grade) occurring in ≥2 patients (B)

A

All AEs	All Patients (N = 11) n (%)	3 mg/kg DURVA + AXAL (N = 5) n (%)	10 mg/kg DURVA + AXAL* (N = 6) n (%)
DLT	-	-	-
SAE	6 (55)	1 (20)	5* (83)
AE	11 (100)	5 (100)	6 (100)
AE leading to treatment discontinuation	1** (9)	-	1** (17)
Deaths	4 (36) *(all due to PD)*	1 (20)	3 (50)
TRAEs†			
SAE	2 (18)	-	2 (33)
AE	10 (91)	5 (100)	5 (83)
Grade 1	7 (64)	3 (60)	4 (67)
Grade 2	6 (55)	3 (60)	3 (50)
Grade 3	3 (27)	1 (20) Chills and/or rigors (×2)	2 (33) Chills and/or rigors, ↓WBC, diarrhea, shortness of breath
Grade 4	1 (9)	-	1 (17) Hypotension

B

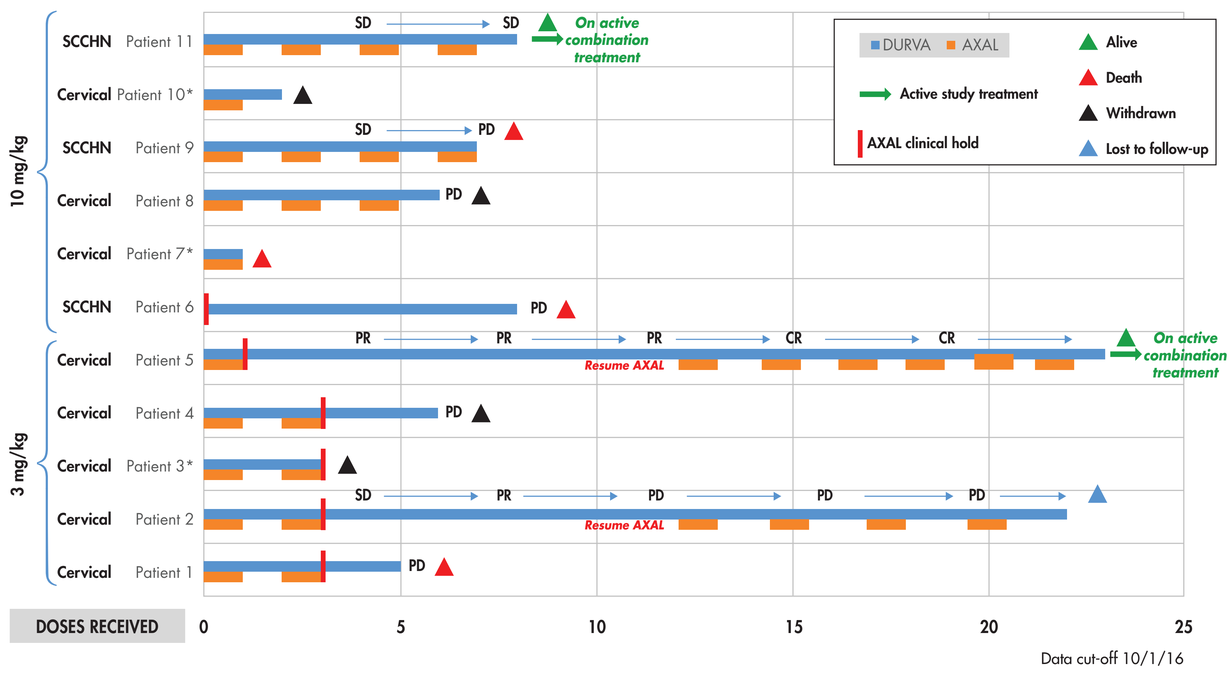
TRAE†	Any Grade n (%)	Worst Grade: Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Chills and/or rigors	9 (81)	2 (18)	5 (45)	2 (18)	-
Fever	5 (45)	2 (18)	3 (27)	-	-
Nausea	4 (36)	2 (18)	2 (18)	-	-
Hypotension	3 (27)	2 (18)	-	-	1 (9)
Diarrhea	2 (18)	1 (9)	-	1 (9)	-
Fatigue	2 (18)	2 (18)	-	-	-
Tachycardia	2 (18)	-	2 (18)	-	-
Headache	2 (18)	1 (9)	1 (9)	-	-

*N = 1 patient who received durvalumab alone. **Grade 3 diarrhea.
†AXAL and/or durvalumab related.
NOTE: Chills and/or rigors represents any report of rigors, chills, rigors/chills, chills/rigors.
TRAEs occurring in N = 1 patient, all grade 1 unless otherwise noted: bladder pain, cold sweat, decreased appetite, decreased WBC (grade 3), dizziness, dysuria, increased ALP, itching, leg edema (grade 2), muscle aches/cramps (grade 2), rash, shortness of breath (grade 3), tongue sore, and vomiting.
AEs, adverse events; ALP, alkaline phosphatase; DLT, dose-limiting toxicity; DURVA, durvalumab; PD, progressive disease; SAE, serious adverse event; TRAEs, treatment-related adverse events; WBC, white blood cells.

EFFICACY

- In total, 11 patients were enrolled and 10 received combination therapy, 7 of whom had a post-baseline scan (**Figure 2**).
- Median follow-up time was 84 days (range: 16–369) in all patients, and best responses for the AXAL + durvalumab treated population are displayed in **Figure 2**.
  - One patient with cervical cancer in the AXAL + durvalumab 3-mg/kg cohort achieved complete response (CR) and 1 patient with cervical cancer achieved partial response (PR) but subsequently experienced disease progression, and 2 patients with SCCHN in the AXAL + durvalumab 10-mg/kg cohort have achieved stable disease (SD) for at least 8 weeks (1 patient remains in SD and is still receiving treatment and 1 subsequently progressed)
  - Images depicting the ongoing CR in a patient with >12 months follow-up are shown in **Figure 3**

Figure 2. Summary of treatment received and best response in patients in the Part A dose-escalation phase



* No response assessment was made because a post-baseline scan was not obtained prior to elective withdrawal from study.

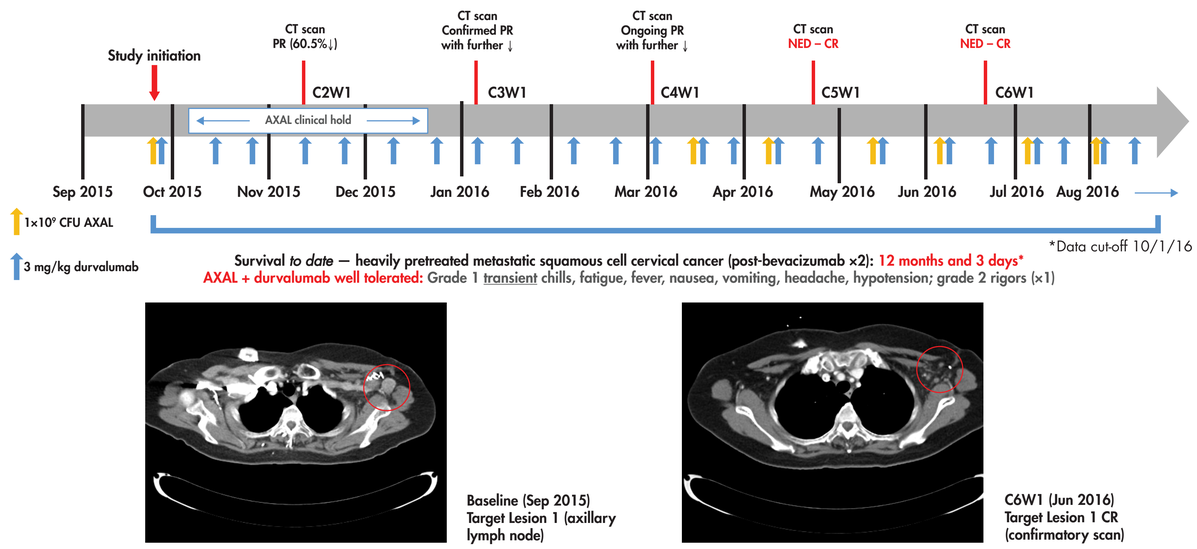
CR, complete response; DURVA, durvalumab; PD, progressive disease; PR, partial response; SCCHN, squamous cell cancer of the head and neck; SD, stable disease.

Figure 3. Case study

49-year-old Asian woman with squamous cell cervical cancer diagnosed 2011

- Prior systemic chemotherapy:
  - Cisplatin/paclitaxel/bevacizumab (Feb 2011 — Nov 2011)
  - Carboplatin/paclitaxel (Feb 2013 — Jul 2013)
  - Carboplatin/paclitaxel/bevacizumab (Jan 2015 — May 2015)

  } Best response: stable disease
- September 25, 2015 — first dose in Phase 1/2 trial of AXAL + durvalumab
  - PR after full cycle of combination treatment, CR after 4 cycles of durvalumab and 3 doses of AXAL



Survival *to date* — heavily pretreated metastatic squamous cell cervical cancer (post-bevacizumab ×2): 12 months and 3 days*
AXAL + durvalumab well tolerated: Grade 1 transient chills, fatigue, fever, nausea, vomiting, headache, hypotension; grade 2 rigors (×1)

Baseline (Sep 2015)
Target Lesion 1 (axillary lymph node)

C6W1 (Jun 2016)
Target Lesion 1 CR (confirmatory scan)

CFU, colony-forming units; CR, complete response; CT, computed tomography; NED, no evidence of disease; PR, partial response.

CONCLUSIONS

- The combination of AXAL + durvalumab appears safe and tolerable.
- Preliminary data indicate encouraging antitumor activity of the combination immunotherapy regimen.
  - The data are consistent with previously reported AXAL monotherapy activity in advanced cervical cancer, where evidence of durable CR has also been observed[10]
- Enrollment in expansion Part A and randomization to Part B of the clinical trial has commenced in HPV+ SCCHN and advanced cervical cancer, respectively.

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Brian M. Slomovitz and Marshall Posner: no potential conflicts of interest to disclose. Hagop Youssoufian: employee of Advaxis. Kathleen Moore: advisory boards of AstraZeneca, Clovis, Immunogen, Genentech/ Roche, VBL Therapeutics, Novacure, and Tesaro; publication steering committees of Advaxis and Tesaro.

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