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**Warner Huh:** Methodology, Investigation, Formal Analysis, Data Curation, Writing-Original Draft, Writing- Review & Editing, Visualization, and Supervision
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CONFLICTS OF INTEREST

Dr. Warner Huh received money for consultancy from Inovio and Antiva.
Dr. William Brady's institution received grant funding from the NCI. He received support for travel to meetings for the study or other purposes from Advaxis. He also received money paid to him from Sarah Cannon Development Innovations.
Dr. Paula Fracasso reports that she became an employee of Bristol-Myers Squibb Company (BMS) as of 5/1/14, and as such, she has stock with the company. Prior to her employment with BMS, she was a professor of Medicine and Obstetrics and Gynecology at the University of Virginia where she is now affiliated as a Visiting Professor of Medicine and Obstetrics and Gynecology. Her work on this clinical study was done while she was a Professor at the University of Virginia and no aactivities in this work have any relationship to her work at BMS.
Dr. Don Dizon received monies for consultancy from Clovis, Regeneron and AstraZeneca. His institution received grants/pending grants from Bristol Myers Squibb, Kazia, Tesaro and Lilly.
Dr. Matthew Powell received monies for consultancy from Merck, Tesaro, Clovis Oncology, AstraZeneca, Abbvie, Janssen and Eisai. He also received payment for lectures, including service on speakers bureaus from Merck, Tesaro, Clovis Oncology and AstraZeneca.
Dr. Bradley Monk's institution received Grant money from Advasix and Genentech. He received money from Advaxis, Genentech and Genmab for consulting free or honorarium. He received fee for participation in review activities such as data monitoring boards, statistical analysis, end point committees and the like from Advaxis. Dr. Monk also received money paid to him for consultancy from Advaxis, Genentech and Genmab. His institution has grants/grants pending from Advaxis, Genentech and Genmab. He received payment for lectures, including service on speakers bureaus from Genentech as well as payment for development of educational presentations. He also has received money from Advaxis for stock/stock options.
Dr. Charles Leath's institute received grant money from the NIH. His institution also received grants/grants pending for contracted research for recurrent cervical cancer from Agenus.
Dr. Erin Crane received New Investigator Travel Award from NRG. She received money from Tesaro/GSK for Speaker's Bureau.
Dr. Michael McHale received money for advisory board consultancy from Eisai. He also received money for payment for lectures, including speakers bureau, from Tesaro.
Dr. Carol Aghajanian reports personal fees from Tesaro, personal fees from Immunogen, grants and personal fees from Clovis, personal fees from Mateon Therapeutics, grants from Genentech, grants from AbbVie, grants from AstraZeneca, personal fees from Eisai/Merck, outside the submitted work.

# Phase II Study of Axalimogene Filolisbac (ADXS-HPV) for Platinum-Refractory Cervical Carcinoma: an NRG Oncology/ Gynecologic Oncology Group Study

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## Abstract

**Objective:** Women with persistent, recurrent, and/or metastatic cervical cancer have a poor prognosis. Even with the availability of cisplatin plus paclitaxel and bevacizumab, median overall survival (OS) is only 17.0 months, with median post-progression survival of approximately seven months. We studied the therapeutic vaccine, Axalimogene filolisbac (ADXS-HPV), in women who had progressed following at least one prior line of therapy (Gynecologic Oncology Group protocol 265/NCT01266460).

**Methods:** Volunteers ≥18 years with advanced cervical cancer and GOG performance status score of 0 or 1 were eligible for participation in this 2-stage, phase II trial. In stage 1, women received up to three doses of ADXS-HPV ($1\times10^9$ colony-forming units in 250 mL IV over 15 minutes every 28 days) and were monitored for tumor progression. In stage 2, women were treated until progression, intolerable adverse events (AEs), or voluntary withdrawal of consent. Co-primary endpoints were safety and proportion of volunteers surviving ≥12 months. An estimated, combined (stages 1+2) 12-month OS of 35% was calculated from historical GOG cohorts to declare ADXS-HPV sufficiently active in this platinum-pretreated population. Secondary endpoints were OS and progression-free survival (PFS).

**Results:** Among 50 evaluable volunteers, the 12-month OS was 38% (n=19). Median OS was 6.1 months (95% CI: 4.3–12.1) and median PFS was 2.8 months (95% CI: 2.6–3.0). The most common treatment-related AEs were fatigue, chills, fever, nausea, and anemia. The majority of AEs were grade 1 or 2 and resolved spontaneously or with appropriate treatment.

**Conclusion:** At the dose and schedule studied, ADXS-HPV immunotherapy was tolerable and met the protocol-specified benchmark for activity required to warrant further investigation in volunteers with cervical carcinoma.

### Keywords

Recurrent cervical cancer; metastatic; HPV; Listeria; Immunotherapy

## INTRODUCTION

Invasive cervical cancer is the fourth most common cancer in women and is associated with approximately 8% of all cancer deaths in women worldwide.[1] Persistent infection with the human papilloma virus (HPV) is associated with greater than 90% of all cervical cancers[2], and HPV-16 and HPV-18 are most prevalent common genotypes, (53% and 13% of global invasive cases, respectively).[3]

The current treatment strategy for persistent/recurrent metastatic cervical cancer (PRmCC) includes a platinum-based doublet chemotherapy with or without bevacizumab although median overall survival (OS) is still only 13.3 or 17 months, respectively.[1,4] The median survival of women with metastatic cervical cancer whose cancer has progressed after ≥1 line of systemic- chemotherapy is approximately 7 months.[5,6] For these volunteers with PD-L1 positive tumors, pembrolizumab has been approved for use in the United States with an overall response rate of 14.3% (95% CI, 7.4%−24.1%), although this option is not yet available in other parts of the world.

Axalimogene filolisbac (ADXS-HPV, Princeton, NJ, USA) is a live attenuated, recombinant *Listeria monocytogenes (Lm)* bacterium. It has been bioengineered to secrete an antigen-adjuvant fusion protein that includes a truncated fragment of listeriolysin O (tLLO) fused to the full-length E7 peptide of HPV-16 (tLLO-HPV-16 E7). There is rapid take-up of ADXS-HPV by antigen presenting cells, which then culminates in HPV-specific effector T-cells that infiltrate the tumor microenvironment. ADXS-HPV mechanism of action involves a rapid take-up of ADXS-HPV by antigen presenting cells, which subsequently stimulate innate

immunity, culminating in HPV-specific effector T-cells that infiltrate the tumor microenvironment and destroy tumor cells.[7] Preclinical and clinical evidence shows that ADXS-HPV is active against multiple high-risk HPV types. Although designed to target HPV type 16-associated cancers, ADXS-HPV successfully elicited immunologic response in volunteers infected with HPV types other than type 16 in an initial Phase 1 dose escalation study in 15 women with PRmCC previously treated with chemoradiation or surgery.[8]

The objective of this study was to evaluate the safety and 12-month OS of ADXS-HPV in women with recurrent/metastatic cervical cancer who have received ≥1 prior lines of systemic chemotherapy (including bevacizumab).

## METHODS

### Study Oversight

The study was sponsored by the National Cancer Institute, which provided ADXS-HPV without charge. All the authors wrote the manuscript and take responsibility for the accuracy and completeness of the reported data and for the fidelity of the study to the protocol.

### Study design

GOG-0265 is a single-arm, open-label, two-stage, phase 2, multicenter trial with a safety run-in conducted at 15 clinical sites within the United States (NCT01266460). Co-primary endpoints were safety of ADXS-HPV, and the frequency of volunteers who survived for ≥12 months post-treatment (i.e., 12-month OS rate). Secondary endpoints were objective response rate (ORR), OS and PFS. Exploratory endpoints included associations between the presence and types of high-risk HPV, and measures of clinical response and serum cytokine levels (to be published separately).

### Volunteers

Eligible volunteers were ≥18 years old with measurable squamous/non-squamous metastatic cervical cancer (≥1 target lesion by RECIST v1.1) and GOG performance status (PS) of 0/1. All volunteers had received ≥1 prior line of systemic chemotherapy (excluding radiosensisitzing chemotherapy received as a part of their primary curative treatment), including prior treatment with bevacizumab or other biologic/targeted therapies. Volunteers were required to have adequate bone marrow and organ function defined as: platelet count ≥75,000/mcl, absolute neutrophil count (ANC) ≥1,000/mcl; lymphocyte count ≥700/mcl; hemoglobin count ≥9 g/dL or ≥5.6 mmol/L; creatinine ≤1.5x institutional upper limit normal (ULN) or measured creatinine clearance ≥50mL/min; total bilirubin ≤1.5x ULN, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3x ULN, alkaline phosphatase ≤2.5x ULN, neuropathy ≤Grade 1. All volunteers provided written, informed consent prior to study entry in compliance with according to institutional, state, and federal guidelines.

### Treatment

ADXS-HPV at $1\times10^9$ CFU was administered as a 80-mL infusion over 15 minutes. In stage 1 (including the safety run-in of 6 women), volunteers received a maximum of 3 doses of

ADXS-HPV in 28day intervals unless they demonstrated clinical progression, confirmed radiologic disease progression, intolerable toxicity, or the patient refusal. In stage 2, volunteers were allowed to continue beyond three doses of ADXS-1101 on a 28-day schedule. A pre-treatment medication regimen consisting of an antihistamine, anti-inflammatory, and antiemetic was administered along with a 7-day course of oral antibiotics starting approximately 72 hours after each ADXS-HPV infusion to ensure *Lm* clearance. The study schema is depicted in Figure 1.

### Statistical considerations and sample size determination

The study was powered to detect a 15% increase in 12-month survival (35%, at a one-sided significance level of 0.10, compared to 20% expected based on analyses of prior GOG trials in this population.[9–18] Based on a Simon two-stage design[19], the target sample size was 27 volunteers in Stage 1 and 36 volunteers in Stage 2 (63 volunteers in total). The study was designed to proceed to Stage 2 enrollment if the conditional power at the end of stage 1 was ≥20%. On October 1, 2015, during the conduct of Stage 2 of the trial, the FDA placed the study on a clinical hold which precluded both enrollment of additional patients as well as the continuation of the investigational agent for those patients enrolled on study. Secondary to this unplanned interruption of investigational agent, a subsequent decision was made the exclude the patients initially enrolled in Stage 2, as they were unable to complete therapy per protocol and replace them with 37 patients in order to complete Stage 2 which would have resulted in a total sample size of 90 patients eligible for toxicity. However, this replacement did not occur and this manuscript reports on the outcome of 54 patients as the subject replacement did not occur.

### Evaluation criteria

The evaluation of tumor response was based on immune-related Response Evaluation Criteria in Solid Tumors (ir-RECIST v1.1).[20] Radiographic imaging was performed at baseline (pre-treatment), at 12 weeks, then every 8 weeks for the first 6 months, and every 3 months thereafter. Best overall tumor response was recorded as either complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The ORR [CR + PR] and disease control rate (DCR [CR + PR + SD]) were also calculated.

PFS was defined as the duration of time from study entry to disease progression or death, whichever occurred first. OS was defined as the duration of time from study entry to death or date of last contact.

Adverse events (AEs) were graded according to the expanded NCI CTCAE v4.0.[21] Dose limiting toxicities (DLT) were determined for subjects in the Safety Lead-In in Stage 1 28 days following the completion of treatment (Day 84). Dose limiting hematologic toxicities were defined as dose delay > 3 weeks due to failure to recover counts, febrile neutropenia, grade 4 neutropenia for greater than 7 days, and grade 4 thrombocytopenia or clinically significant bleeding associated with grade 3 thrombocytopenia. Dose limiting non-hematologic toxicities were defined as non-hematologic grade 3 or 4 toxicity with the exception of: 1) Grade 3 or 4 nausea, vomiting, constipation, diarrhea resolving to Grade 1 or less after adequate medical intervention or 2) Grade 3 or 4 transaminitis resolving to

Grade 1 or less in ≤ 7 days. Other DLT defining events included bacterial meningitis, clinical sepsis requiring ICU admission and/or pressors, documented persistent listeremic event (positive blood culture for Listeria at ≥ 72 hours from dosing, or Grade 3 or 4 hypotentsion warranting therapeutic intervention, or a treatment delay of greater than 14 days. There were no dose modifications allowed during study treatment and subjects with any dose delay of more than 14 days were removed from study.

## RESULTS

### Study Conduct and U.S. FDA Intervention

The results from Stage 1 demonstrated that the conditional power was met, and patient accrual to Stage 2 was initiated in February 2015; however, in October 2015, all trials of ADXS-HPV were placed on clinical hold by the US Food and Drug Administration (FDA), for investigation of a case of presumed listerosis with a positive blood culture. Ultimately, listeriosis was ruled out in the volunteer and the hold was lifted in December 2015. At that time, 24 of the planned 36 Stage 2 volunteers had been enrolled. A preliminary analysis of Stage 2 data showed that all 24 volunteers had either reached the primary endpoint of 12-month OS or had died. As such, after consultation with the data safety monitoring committee, the enrollment was terminated after a total of 54 of the 63 subjects were enrolled. Data cut-off for this trial occurred on January 31, 2017.

### Patient population and treatment exposure

Of the 54 volunteers, 50 received ≥1 dose of ADXS-HPV during the study. The total number of volunteers enrolled and treated in Stages 1 and 2, including the distribution of ADXS-HPV doses received are presented in Figure 2. The median age was 46 years (range 29–70 years); 31 volunteers (62%) had a GOG PS of 0; 34 volunteers (68%) received ≥2 prior lines of systemic chemotherapy, and 56% of volunteers had received prior treatment with bevacizumab (Table 1).

### Safety and tolerability

All treated volunteers experienced ≥1 adverse events, and the safety findings among volunteers enrolled in stages 1 and 2 were similar and consistent. Treatment-related AEs (TRAEs) occurred in 49 volunteers (98%): in 19 women (38%) these were grade 3 in severity and 2 volunteers (4%) had possibly-related or probably-related grade 4 events (lung infection and sepsis in one patient and hypotension and cytokine release syndrome in another patient, respectively). The most common TRAEs (>30%) were chills (58%), fatigue (54%), fever (36%), headache (36%), and nausea (32%) (Table 2).

### Efficacy data – combined data from stage 1 and stage 2 of the study

Combined data from Stages I and II of this trial demonstrated a 12-month OS rate of 38% (19/50 volunteers)(Figure 3A). Twelve-month OS rate was achieved irrespective of the prior treatment history. Median OS was 6.1 months (95% CI: 4.3–12.1) (Figure 3A) and median PFS was 2.8 months (95% CI: 2.6–3.0) (Figure 3B).

Investigator-based assessment of best tumor response was reported in 39 volunteers (78%) and 11 were inevaluable. One patient (2%) had a confirmed CR, two volunteers (4%) had a confirmed PR, 5 (10%) had SD, and 32 (64%) had PD (Table 3). The ORR [CR + PR] was 6% (3/50 volunteers) and the DCR [CR + PR + SD] was 16% (8/50 volunteers). The one patient with a confirmed CR, was enrolled in June 2015, with diffuse retroperitoneal adenopathy on PET/CT imaging. She received three monthly doses of ADXS-HPV at $1\times10^9$ CFU from July to September 2015. There was no evidence of PET avid adenopathy on repeat imaging in May 2016, and the patient continues to have a complete response 34 months after completion of treatment.

## DISCUSSION

ADXS-HPV is a unique form of immunotherapy with the intent to enhance the immune response against invasive cervical cancer. ADXS-HPV stimulates the *de novo* generation of effector T cells against the HPV-expressing tumor, facilitates T-cell infiltration by altering the tumor microenvironmoent, and reduces immune suppression mediated by regulatory T cells and myeloid-derived suppressor cells. [22] Initial clinical evidence indicates that ADXS-HPV is active against invasive cervical cancer. ADXS-HPV was given as an intravenous (IV) infusion to 15 volunteers with metastatic, refractory or recurrent invasive cervical cancer previously treated with chemoradiation or surgery[23], and shown to be well tolerated at 3 separate dose levels ($1 \times 10^9$, $3.3 \times 10^9$, and $1 \times 10^{10}$ colony forming units [CFU]). Investigators reported results from a randomized, multicenter Phase II study conducted in India, in 109 metastatic cervical cancer volunteers with 0–2 prior lines of systemic therapy, who received ADXS-HPV as monotherapy or in combination with cisplatin. Results demonstrated a 12-month OS of 34.9%, an 18-month OS of 24.8% and an overall response rate of 15.9% for both treatment groups combined.[23] Although originally designed to target HPV type 16-associated cancers, ADXS-HPV successfully elicited immunologic response in volunteers infected with HPV types other than type 16 in an initial Phase 1 dose escalation study in 15 volunteers with PRmCC previously treated with chemoradiation or surgery.[8]

Most women with metastatic cervical cancer are treated with platinum-based doublet chemotherapy, with or without bevacizumab.[24] Cisplatin doublets have demonstrated superior efficacy over single-agent platinum[25–27] and cisplatin/paclitaxel with bevacizumab continues to be the primary platinum-based chemotherapy strategy for women with metastatic cervical cancer. Bevacizumab was approved in 2014 by the FDA based on GOG-0240,[4] which reported a statistically significant improvement in median OS of 3.7 months for bevacizumab combined with chemotherapy versus chemotherapy alone. Although a significant advancement in this setting, metastatic cervical cancer continues to be incurable. Cost concerns with bevacizumab may limit its widespread use. Furthermore, volunteers with recurrent disease will typically have received radiation therapy with radiosensitizing cisplatin, and thus, may have a limited response to further cisplatin treatment. Drug and treatment development in advanced or recurrent cervical cancer is highly challenging as the median OS, irrespective of whether the patient has received bevacizumab, is only 7 months.[28] However, there have been recent immunotherapeutic treatment advancments in advanced cervical cancer including the recent approval of pembrolizumab for PD-L1 positive cervical cancer,[29] and three ongoing phase 3 randomized

clinical trials with nivolumab and cemiplimab (NCT03635567, NCT02921269, and NCT03257267). In 2018, the FDA approved pembrolizumab for the treatment of volunteers with advanced, PD-L1–positive cervical cancer. This decision was based on 98 women with metatstic cervical trial enrolled in the Keynote-158 trial. With a median follow-up of 11.7 months, the objective response was 14.3% (95% CI, 7.4%−24.1%) in 77 PD-L1– positive volunteers previously treated with ≥1 line of chemotherapy in the metastatic setting. The overall response included a complete response rate of 2.6% and a partial response rate of 11.7%. Over 90% of responders had a response duration of 6 months or longer and the median duration of response was not reached.

As noted above, the patient population has historically experienced a median life expectancy of approximately 7 months, making the collection of survival data practical. Because tumor measurement-based response and PFS based upon standard RECIST v1.1 criteria are inadequate surrogates for clinical benefit (including survival) in immunotherapy, time to death was selected as the primary efficacy endpoint in this study. The guiding principle was to limit the number of (essentially incurable) volunteers exposed to clinically ineffective therapy while allowing for estimation of efficacy with reasonable precision should ADXS-HPV demonstrate activity according to the protocol-specified benchmark of 35% OS at one year following treatment. Because an active second-line regimen had not been identified during the period of protocol development, a randomized trial using ineffective physician's choice chemotherapy regimens as a control arm was not considered appropriate.

Although this study was terminated early by the DSMC, available results demonstrate that ADXSHPV treatment resulted in a median OS and median PFS of 6.1 months (95% CI: 4.3–12.1) and 2.8 months (95% CI: 2.6–3.0), respectively, and a 12-month OS rate of 38%. The 12-month OS rate was 38%, which if validated in a larger trial would represent an improvement compared to the 21% rate in a historical GOG clinical study series (N = 17) in PRmCC volunteers with similar demographics [5,9–18]]; GOG/NRG Oncology Data on file, 2016) (Figure 3C).

The safety profile of ADXS-HPV was consistent with previously reported clinical experience. The commonly reported AEs in this study were related to cytokine release. The majority of events were Grade 1 and 2 and resolved either spontaneously or with appropriate medical treatment. This was commonly managed with additional intravenous fluids, antiemetics, and narcotics, and after acknowledging this toxicity, patients received prophylactic medications to reduce the inflammatory response, including intravenous fluids, antihistamines, NSAIDs, antiemetics and histamine H2-receptor antagonists. Of particular note, in October 2015 all trials of ADXS-HPV were placed on clinical hold by the US Food and Drug Administration (FDA), for investigation of an isolated safety concern (i.e., possible listerosis) that occurred in a patient who was treated on this study. This patient was found to have positive blood cultures for Listeria almost two years following her treatment and was felt to be related to retained ADXS-HPV within an implanted infusion port (and not true listeriosis). The hold was lifted in December 2015 by the FDA with changes to the treatment protocol including prolonged antibiotic therapy following treatment and an understanding that ADXS-HPV, given its attenuated form, is biologically unable to propagate, unlike the wild-type form of this bacteria. Major limitations of this study include

the decision to not complete the planned study, the absence of a control arm, and the decision during the study to treat volunteers beyond 3 doses.

In conclusion, ADXS-HPV appears both safe and active in the treatment of women with PRmCC. These results further support the evaluation of immunotherapy in general, in this agent specifically in this group of cervical cancer volunteers who clearly have limited therapeutic options. Accordingly, study of this drug has been moved to the frontline where it's efficacy and tolerability as a maintenance therapy is being evaluated in women with high-risk locally advanced cervical cancer who have completed chemoradiation plus high-dose-rate intracavitary brachytherapy. This international phase 3 study of ADXS-HPV as adjuvant treatment in high-risk locally advanced cervical cancer (AIM2CERV; NCT02853604) is actively enrolling volunteers and will provide further data to establish the future role of this novel immunotherapy in the clinical management of cervical cancer volunteers. Similar to other agents that demonstrate activity in the setting of recurrent cervical cancer, the combination of ADXS-HPV with chemotherapy may be considered as an opportunity to further evaluate this novel therapy.

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## REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359–E386. [PubMed: 25220842]
2. https://www.cdc.gov/cancer/hpv/statistics/index.htm
3. Wheeler CM, Hunt W, Joste NE, Key CR, Quint WG, Castle PE. Human Papillomavirus Genotype Distributions: Implications for Vaccination and Cancer Screening in the United States. J Natl. Cancer Instit. 2009;101(7): 475–487.
4. Tewari KS, Sill MW, Long HJ, Penson RT, Huang H, Ramondetta LM, et al. Improved Survival with Bevacizumab in Advanced Cervical Cancer. N Engl J Med. 2014;370(8):734–743. [PubMed: 24552320]
5. Monk BJ, Sill MW, Burger RA, Gray HJ, Buekers TE, Roman LD. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol. 2009;27(7):1069–1074. [PubMed: 19139430]
6. Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet. 2017 10 7;390(10103):1654–1663. [PubMed: 28756902]
7. Krupar R, et al. HPV E7 antigen-expressing Listeria-based immunotherapy (ADXS11–001) prior to robotic surgery for HPV-positive oropharyngeal cancer enhances HPV-specific T cell immunity. Presented at the 107th Annual Meeting of the American Association for Cancer Research; April 16–20, 2016; New Orleans, LA Abstract LB-095.

8. Maciag PC, Radulovic S, Rothman J. The first clinical use of a live-attenuated Listeria monocytogenes vaccine: a Phase I safety study of Lm-LLO-E7 in volunteers with advanced carcinoma of the cervix. Vaccine 2009;27(30)3975–3983. [PubMed: 19389451]
9. Muggia FM, Blessing JA, Method M, Miller DS, Johnson GA, Lee RB, et al. Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92(2):639–643. [PubMed: 14766259]
10. Plaxe SC, Blessing JA Olt G, Husseinzadah N, Lentz SS, DeGeest K, et al. A phase II trial of pyrazoloacridine (PZA) in squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Cancer Chemother Pharmacol. 2002;50(2):151–154. [PubMed: 12172981]
11. Armstrong DK, Blessing JA, Rader J, Sorosky JI. A randomized phase II evaluation of bryostatin-1 (NSC #339555) in persistent or recurrent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group Study. Invest New Drugs 2003;21(4):453–457. [PubMed: 14586213]
12. Fracasso PM, Blessing JA, Wolf J, Rocereto TF, Berek JS, Waggoner S. Phase II evaluation of oxaliplatin in previously treated squamous cell carcinoma of the cervix: a gynecologic oncology group study. Gynecol Oncol. 2003;90(1):177–180. [PubMed: 12821360]
13. Brewer CA, Blessing JA, Nagourney RA, Morgan M, Hanjani P. Cisplatin plus gemcitabine in previously treated squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol. 2006;100(2):385–388. [PubMed: 16271750]
14. Rose PG, Blessing JA, Lele S, Abulafia O. Evaluation of pegylated liposomal doxorubicin (Doxil) as second-line chemotherapy of squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol. 2006;102(2):210–213. [PubMed: 16478630]
15. Garcia AA, Blessing JA, Vaccarello L, Roman LD. Phase II clinical trial of docetaxel in refractory squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. Am J Clan Oncol.2007;30(4):428–431.
16. Miller DS, Blessing JA, Bodurka DC, Bonebrake AJ, Schorge JO. Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol. 2008;110(1):65–70. [PubMed: 18455781]
17. Fiorica JV, Blessing JA, Puneky LV, Secord AA, Hoffman JS, Yamada SD, et al. A Phase II evaluation of weekly topotecan as a single agent second line therapy in persistent or recurrent carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol. 2009;115(2):285–289. [PubMed: 19726073]
18. Schilder RJ, Sill MW, Lee YC, Mannel R. A phase II trial of erlotinib in recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. Int J Gynecol Cancer. 2009;19(5):929–933. [PubMed: 19574787]
19. Simon R Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989; 10(1): 1–10. [PubMed: 2702835]
20. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 201; 18(3): e143–e152.
21. https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5×7.pdf
22. Lee SJ, Yang A, Wu TC, et al. Immunotherapy for human papillomavirus-associated disease and cervical cancer: review of clinical and translational research. J Gynecol Oncol. 2016; 27:e51.
23. Basu P, Mehta A, Jain M, Gupta S, Nagarkar RV, John S, et al. A Randomized Phase 2 Study of ADXS11–001 Listeria monocytogenes-Listeriolysin O Immunotherapy With or Without Cisplatin in Treatment of Advanced Cervical Cancer. Int J Gynecol Cancer. 2018 5;28(4):764–772. [PubMed: 29538258]
24. NCCN Guidelines Version 1.2017 Cervical Cancer. Accessible at: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf Accessed February 6,2017.
25. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. J Clin Oncol 2004;22:3113–3119. [PubMed: 15284262]

26. Long HJ 3rd, Bundy BN, Grendys EC Jr, Benda JA, McMeekin DS, Sorosky J, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: A Gynecologic Oncology Group Study. J Clin Oncol. 2005;23:4626–4633. [PubMed: 15911865]

27. Monk BJ, Sill MW, McMeekin DS, Cohn DE, Ramondetta LM, Boardman CH, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2009; 27(28):4649–4655. [PubMed: 19720909]

28. Tewari KS, Monk BJ. Gynecologic oncology group trials of chemotherapy for metastatic and recurrent cervical cancer. Curr Oncol Rep. 2005;7(6):419–434. [PubMed: 16221379]

29. Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, et al. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2019 6 10;37(17):1470–1478. [PubMed: 30943124]

## RESEARCH HIGHLIGHTS

- ADXS-HPV immunotherapy was tolerable and met the protocol-specified benchmark for activity
- Among 50 evaluable volunteers, the 12-month OS was 38%
- The majority of AEs were grade 1 or 2 and resolved spontaneously or with appropriate treatment

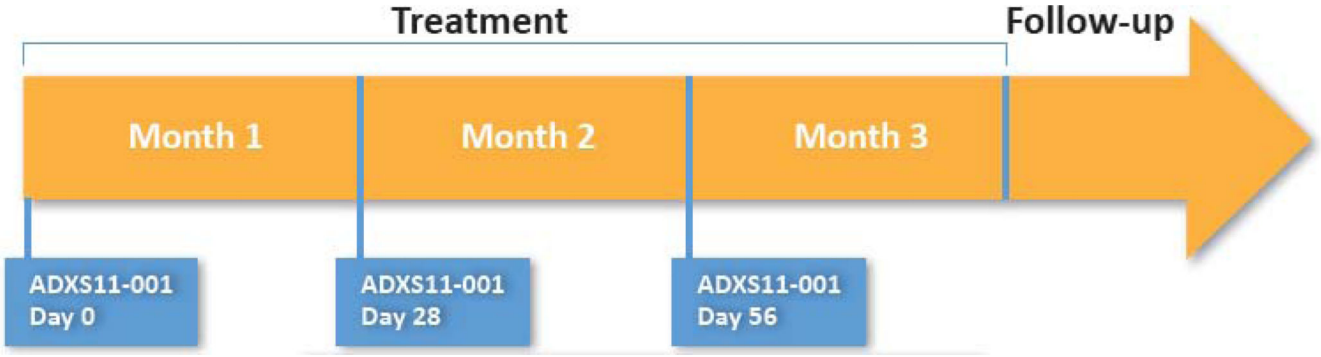



**Figure 1.**

GOG/NRG-0265 study schema

**ADXS-HPV Monotherapy** 1×109 CFU x 3 doses* q 28 days (month 1, 2, 3) as a 250 mL infusion over 60 min

*Stage 2 amended to allow continuous (>3) dosing of ADXS-HPV.

CFU, colony-forming units; GOG, Gynecologic Oncology Group

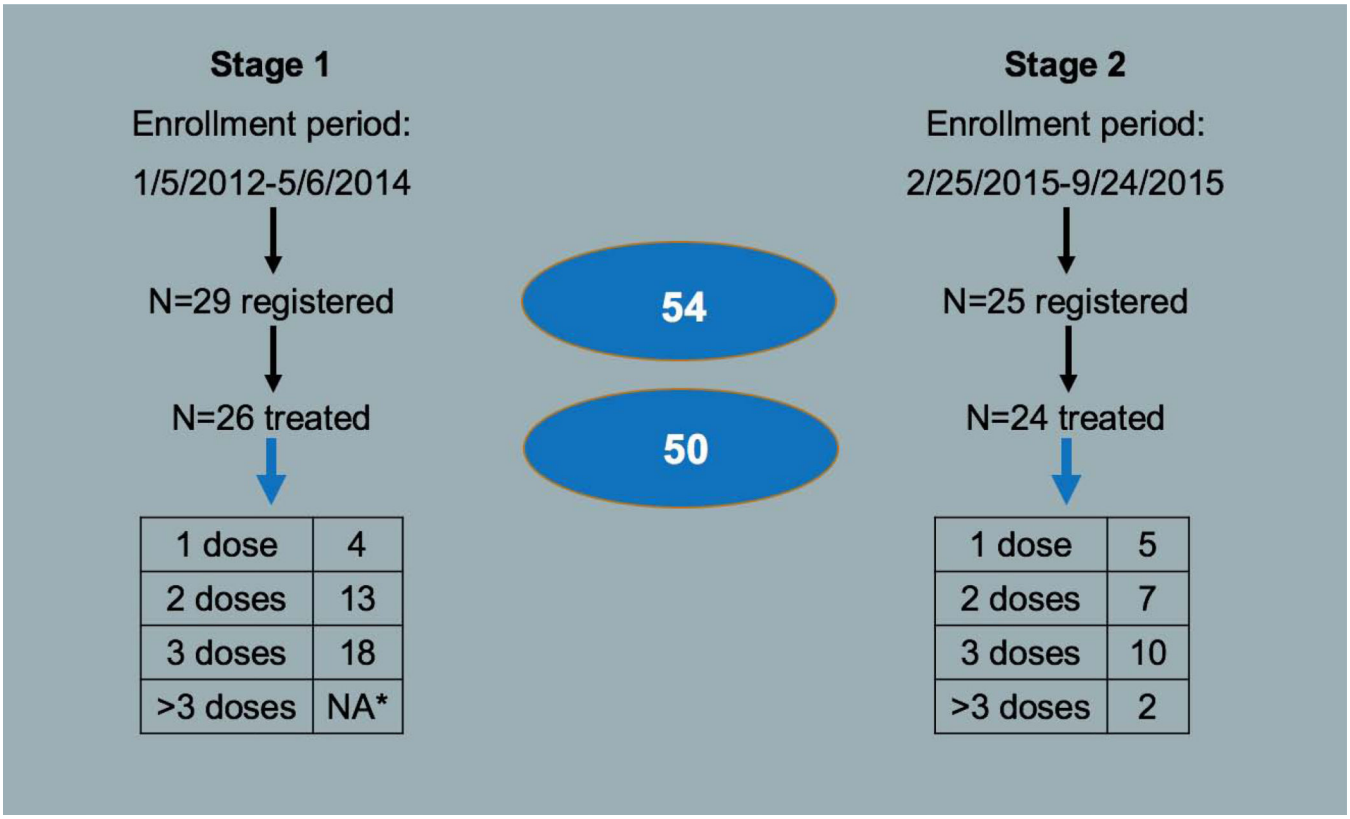



**Figure 2.**

GOG-0265 CONSORT diagram

Study complete

*Maximum of 3 doses allowed on stage 1 protocol

ADXS-HPV placed on clinical hold

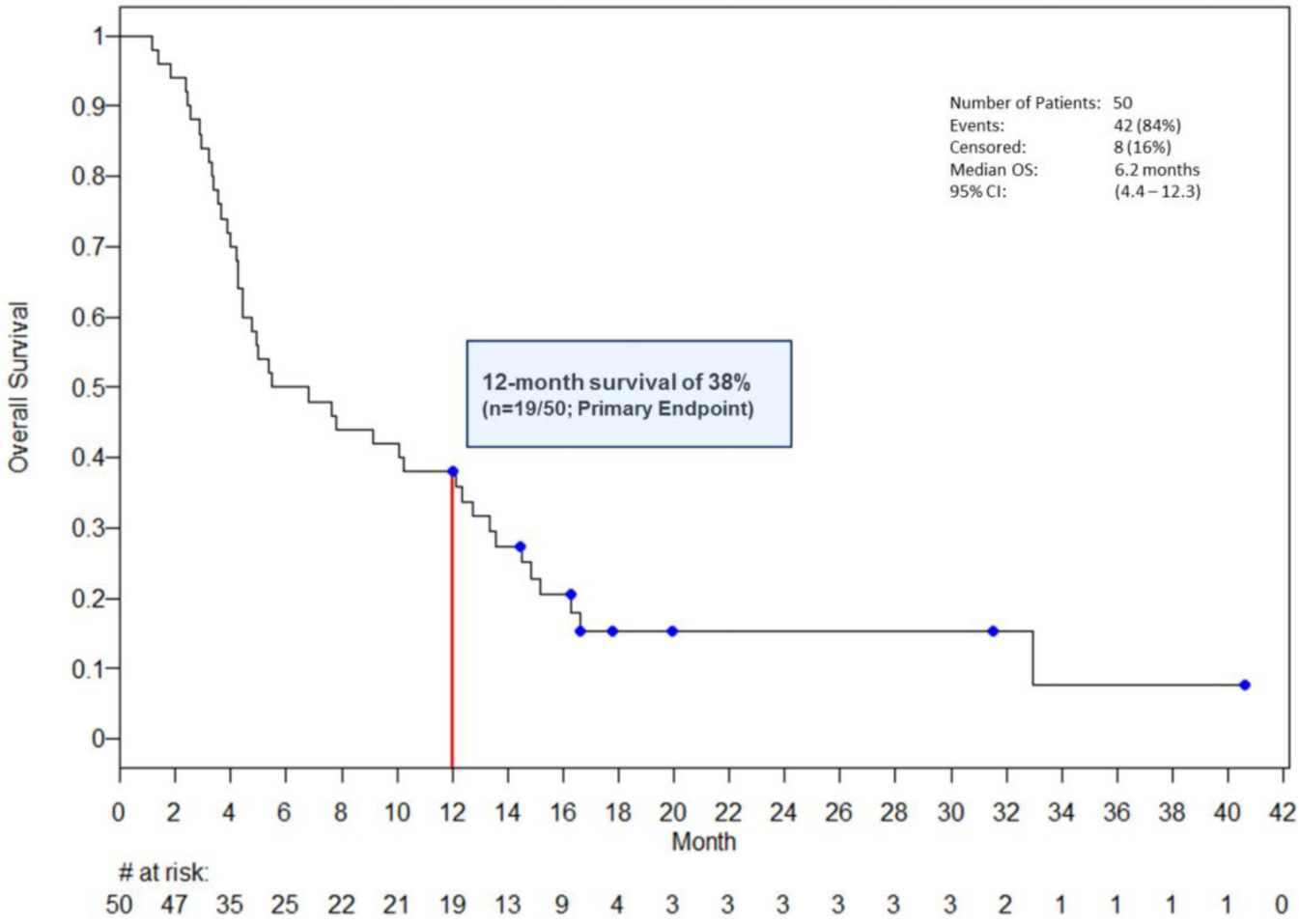
N=10 volunteers still receiving ADXSHPV at time of hold

N=4, ≥3 doses

N=6, <3 doses

GOG, Gynecologic Oncology Group; NA, not applicable

A.



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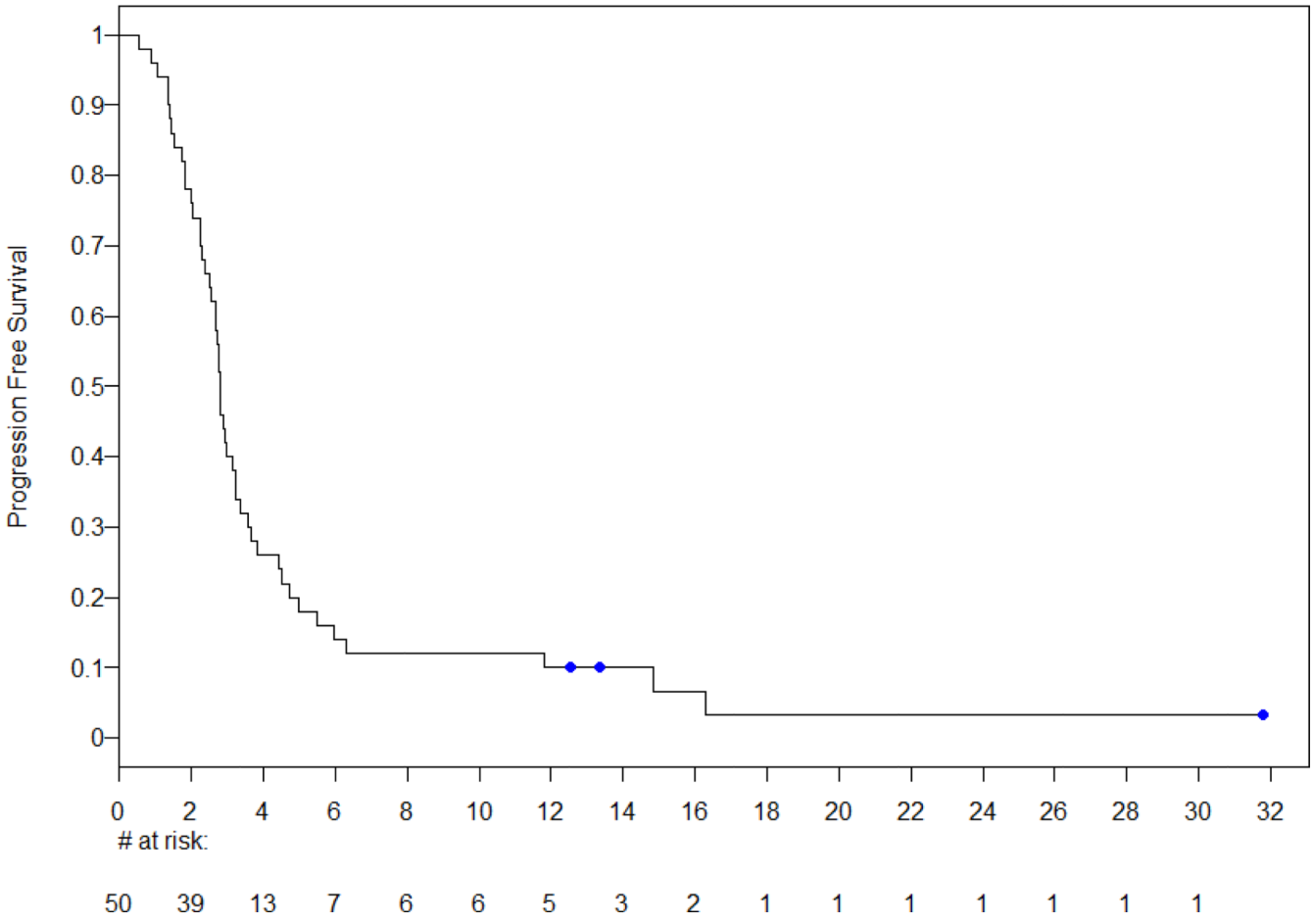

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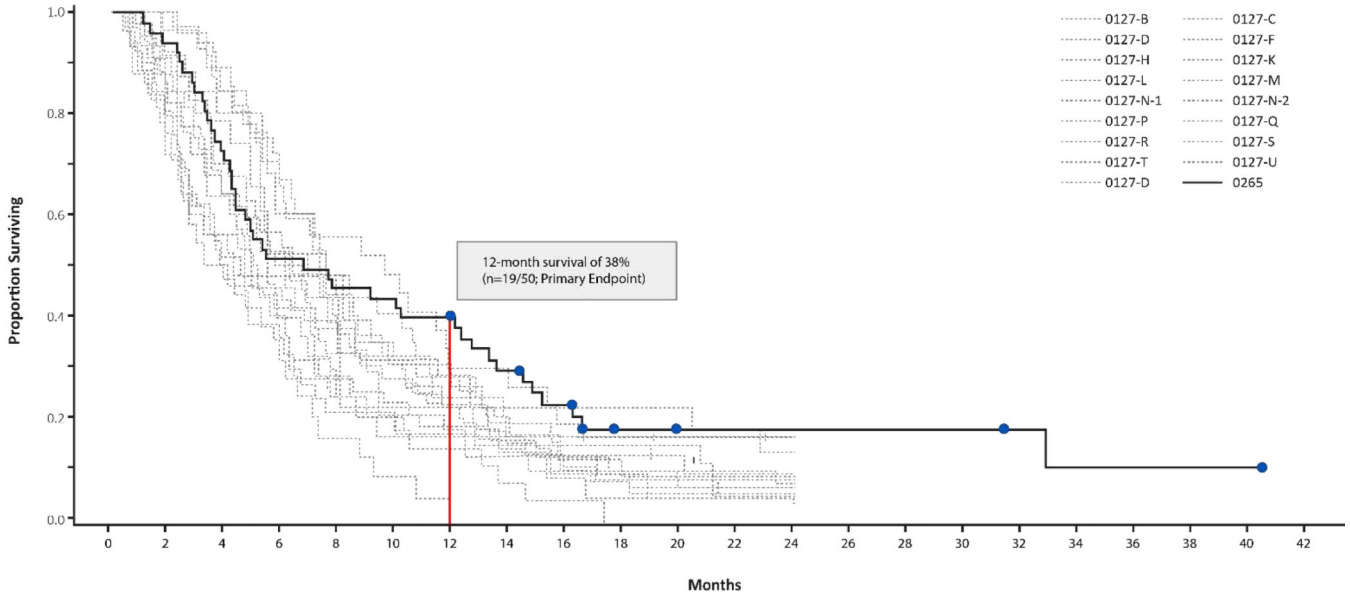


**Figure 3.**

Survival of volunteers treated in both stages of the study A. 12-month OS rate overall, and B. PFS overall.

**Table 1.**

Baseline demographics and clinical characteristics

| | Stage 1 (n=26) | Stage 2 (n=24) | Overall (n=50) |
|---|---|---|---|
| Median age (range), years | 46 (33–66) | 46 (29–70) | 46 (29–70) |
| Race - white, n (%) | 18 (69) | 19 (79) | 37 (74) |
| Histology- n (%) | | | |
| Squamous | 16 (62) | 14 (58) | 30 (60) |
| Adenocarcinoma | 8 (31) | 9 (38) | 17 (34) |
| Adenosquamous | 2 (7) | 1 (4) | 3 (6) |
| GOG PS, n (%) 0 vs 1 | 16 (62) vs 10 (38) | 15 (62) vs 9 (38) | 31 (62) vs 19 (38) |
| FIGO stage at diagnosis, n (%) | | | |
| IA | 0 | 1 (4) | 1 (2) |
| IB | 11 (42) | (29) | 18 (36) |
| IIA | 3 (11) | 0 | 3 (6) |
| IIB | 6 (23) | (33) | 14 (28) |
| IIIB | 2 (8) | 2 (8) | 4 (8) |
| IVN | 4 (16) | 6 (25) | 10 (20) |
| Prior lines of systemic-dose therapy, n (%) | | | |
| 1 | 9 (35) | 7 (28) | 16 (32) |
| 2 | 13 (50) | 14 (58) | 27 (54) |
| 3 | 4 (15) | 3 (12) | 7 (14) |
| Prior bevacizumab, n (%) | 10 (38) | 20 (83) | 28 (56) |

FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; GOG, Gynecologic Oncology Group; PS, performance status.

**Table 2.**

Treatment-related adverse events (TRAEs) reported in volunteers treated in stage 1 and stage 2 of the study (≥10% of volunteers)

| Preferred term | Grade 1 – 4 n (%) | Grade 1 – 2 n (%) | Grade 3 n (%) | Grade 4 n (%) |
|---|---|---|---|---|
| **Volunteers with ≥1 TRAE, n (%)** | 49 (98) | 28 (56) | 19 (38) | 2 (4)* |
| **TRAEs occurring in ≥10% of volunteers** | | | | |
| Chills | 29 (58) | 29 (58) | 0 (0) | 0 (0) |
| Fatigue | 27 (54) | 27 (54) | 0 (0) | 0 (0) |
| Anemia | 25 (50) | 20 (40) | 5 (10) | 0 (0) |
| Fever | 18 (36) | 18 (36) | 0 (0) | 0 (0) |
| Headache | 18 (36) | 18 (36) | 0 (0) | 0 (0) |
| Hypotension | 17 (34) | 11 (22) | 5 (10) | 1 (2) |
| Nausea | 16 (32) | 16 (32) | 0 (0) | 0 (0) |
| Vomiting | 14 (28) | 13 (26) | 1 (2) | 0 (0) |
| AST increased | 11 (22) | 11 (22) | 0 (0) | 0 (0) |
| GGT increased | 11 (22) | 9 (18) | 2 (4) | 0 (0) |
| Myalgia | 11 (22) | 10 (20) | 1 (2) | 0 (0) |
| Cytokine release syndrome | 10 (20) | 4 (8) | 5 (10) | 1 (2) |
| Alanine aminotransferase increased | 8 (16) | 8 (16) | 0 (0) | 0 (0) |
| Alkaline phosphatase increased | 8 (16) | 7 (14) | 1 (2) | 0 (0) |
| Flu like symptoms | 8 (16) | 8 (16) | 0 (0) | 0 (0) |
| Sinus tachycardia | 8 (16) | 7 (14) | 1 (2) | 0 (0) |
| White blood cell decreased | 8 (16) | 7 (14) | 1 (2) | 0 (0) |
| Anorexia | 6 (12) | 6 (12) | 0 (0) | 0 (0) |
| Dizziness | 6 (12) | 6 (12) | 0 (0) | 0 (0) |
| Abdominal pain | 5 (10) | 5 (10) | 0 (0) | 0 (0) |
| Dyspnea | 5 (10) | 4 (8) | 1 (2) | 0 (0) |

*The observed grade 4 TRAEs recorded in 2 volunteers (lung infection and sepsis, same patient; hypotension and cytokine related symptoms, same patient) were considered possibly related or probably related to treatment. AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; TRAE, treatment related adverse event.

**Table 3.**

Investigator assessment of tumor best response in stage 1 and stage 2 of the study, and overall

| Tumor best response, n (%) | Stage 1 (n=26) | Stage 2 (n=24) | Overall (n=50) |
|---|---|---|---|
| **PR** | 0 (0) | 1 (4) | 1(2) |
| **SD** | 3 (12) | 2 (8) | 5 (10) |
| **ID** | 18 (69) | 14 (58) | 32 (64) |
| **NE** | 5 (19) | 6 (25) | 11 (22) |

PR, partialresponse; NE, not evaluable; PD, increasing disease; SD, stable disease.