Gynecologic Oncology 157 (2020) 188–194

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

A first-in-human proof-of-concept trial of intravaginal artesunate to treat cervical intraepithelial neoplasia 2/3 (CIN2/3)

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HIGHLIGHTS

- Artesunate vaginal inserts are safe and tolerable in patients who have CIN2/3.
- Artesunate vaginal inserts can be self-administered, and require minimal cold chain logistics.
- Topically applied intravaginal artesunate can eliminate both CIN2/3 lesions as well as HPV.

ARTICLE INFO

Article history:
Received 21 November 2019
Received in revised form 20 December 2019
Accepted 23 December 2019
Available online 28 January 2020

Keywords:
Cancer interception
HPV high grade squamous intraepithelial lesion (HSIL/CIN2/3)
Artesunate
Histologic regression
Selfadministered

ABSTRACT

Objective. Most treatment options for cervical intraepithelial neoplasia 2/3 (CIN2/3) are either excisional or ablative, and require sequential visits to health care providers. Artesunate, a compound that is WHO-approved for treatment of acute malaria, also has cytotoxic effect on squamous cells transformed by HPV. We conducted a first-in-human Phase I dose-escalation study to assess the safety and efficacy of self-administered artesunate vaginal inserts in biopsy-confirmed CIN2/3.

Methods. Safety analyses were based on patients who received at least one dose, and were assessed by the severity, frequency, and duration of reported adverse events. Tolerability was assessed as the percentage of subjects able to complete their designated dosing regimen. Modified intention-to-treat analyses for efficacy and viral clearance were based on patients who received at least one dose for whom endpoint data were available. Efficacy was defined as histologic regression to CIN1 or less. Viral clearance was defined as absence of HPV genotype (s) detected at baseline.

Results. A total of 28 patients received 1, 2, or 3 five-day treatment cycles at study weeks 0, 2, and 4, respectively, prior to a planned, standard-of-care resection at study week 15. Reported adverse events were mild, and self-limited. In the modified intention-to-treat analysis, histologic regression was observed in 19/28 (67.9%) subjects. Clearance of HPV genotypes detected at baseline occurred in 9 of the 19 (47.4%) subjects whose lesions underwent histologic regression.

Conclusions. Self-administered vaginal artesunate inserts were safe and well-tolerated, at clinically effective doses to treat CIN2/3. These findings support proceeding with Phase II clinical studies.

1. Introduction

On a global scale, 16% of cancers are attributable to an infectious pathogen, most of which are viruses [1]. Cancers attributable to human papillomaviruses (HPVs) arise in several anatomic sites, including the cervix, vagina, vulva, anus, penis, and oropharynx. While the clinical behavior of disease originating in these individual anatomic sites differs in terms of both the kinetics of progression, as well as response to treatment, all HPV cancers are thought to arise from untreated high grade squamous intraepithelial lesions. Currently available treatments for preinvasive, intraepithelial cervical HPV lesions (HSIL/CIN2/3) are either excisional or ablative, require repeated encounters with

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https://doi.org/10.1016/j.ygyno.2019.12.035
0090-8258/

an established health care infrastructure, and can result in long-term reproductive morbidity [2]. Moreover, reported rates of recurrence after resection with uninvolved margins range from 8 to 23% [3–6]. In the United States, the burden of disease attributable to HPV is expensive; the estimated annual direct cost of preventing and treating HPV disease, not including costs of preventive vaccination, is $8.0 billion [7]. On a global level, cervical cancer is the fourth most common cancer in women. In low- and middle-income countries (LMICs), cervical cancer is the second most common type of cancer among women. Nearly 90% of deaths from cervical cancer occur in LMICs [8]. A systematic approach to early detection, in concert with a self-administered treatment, such as the one described in this paper, in a point-of-care setting could significantly improve cervical cancer outcomes for women worldwide.

Artesunate is a semi-synthetic derivative of artemisinin, a Chinese herbal medicine that has been used for centuries to treat malaria. Artemisinin-based combination therapy is now WHO-approved for first-line treatment for acute malaria [9]. The safety profile of artesunate and related compounds has been well-documented, based on experience treating >2 million patients with acute malaria, ranging from infants to adults [10]. Artesunate has been shown to be both safe and well-tolerated when administered orally, intravenously, intramuscularly, and in children <5 years of age, when formulated as rectal suppositories [11–15].

Artesunate has cytotoxic effect on human solid tumors. Early-phase clinical trials testing oral [16–18] as well as intravenous [19] administration of artesunate to patients with late-stage solid tumor malignancies have demonstrated the safety of systemically administered artesunate in human cancer patients. *In-vitro* experiments by the Schlegel group demonstrated the cytotoxic effect of artesunate on cervical cancer cell lines, with minimal effects on normal cervical cells [20]. They and others have reported the therapeutic effect of artesunate in two preclinical canine papillomavirus models [20,21]. Therefore, Frantz Frantz Viral Therapeutics, LLC and investigators in the Schlegel group at Georgetown University formed a collaboration to re-purpose artesunate for treatment of HPV-related malignancies [22].

Here we present clinical outcomes from a first-in-human proof-of-concept study to evaluate the safety, tolerability, and efficacy of self-administered vaginal artesunate inserts to treat the precursor to squamous cancers of the cervix, cervical intraepithelial neoplasia 2/3 (CIN2/3), prior to a planned, standard-of-care resection.

2. Methods

2.1. Study design and oversight

This trial was governed by an academic, investigator-initiated IND (124299) (NCT02354534). (CLT). We conducted a dose-escalation phase I study to assess the safety, tolerability, and efficacy of vaginal artesunate in women with CIN2/3, in two sites in the Baltimore, MD area: Johns Hopkins Hospital and at the Greater Baltimore Medical Center. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. The clinical trial protocol was reviewed and approved by the Sidney Kimmel Comprehensive Cancer Center Scientific Monitoring Committee, the Institutional Review Board at Johns Hopkins Hospital (IRB00045376), and by the Institutional Review Board of the Greater Baltimore Medical Center (GBMC IRB Net ID: 896491–6). All study participants gave written informed consent before undergoing screening for study eligibility and enrollment. At each visit, study participants were given diary cards to record local and general symptoms. These were reviewed by the study visit team, including the research nurses and physicians, and discussed with subjects at each visit. Patients were also instructed to contact the PI's office directly if they wished to report symptoms. All reported symptoms were classified according to CTCAEv4.0. The protocol definition for any dose-limiting toxicity was either (1) any grade 3 toxicity in any organ system, or (2) any grade 2 or higher allergic reaction/hypersensitivity reaction. A data safety and monitoring group consisting of the treating investigators and other investigators treating HPV disease arising at other anatomic sites reviewed the data regularly. All safety data, including local reactions and all other adverse events were reviewed by the Institutional Data Safety and Monitoring Board; submitted for review to the Johns Hopkins Medicine Institutional Review Board; and to the U.S. Food and Drug Administration (FDA). This manuscript was drafted by the first and last authors; all authors contributed to the reviews and revisions. The authors vouch for the accuracy and completeness of the data, and for the fidelity of the study to the protocol.

2.2. Patients

Adult, immunocompetent women who had a biopsy-confirmed tissue diagnosis of CIN2/3, a visible residual lesion, and detectable HPV were eligible for study participation. Exclusion criteria included pregnancy or breastfeeding, weight <50 kg, evidence of glandular dysplasia or adenocarcinoma *in situ*; taking immunosuppressive medication, active autoimmune disease, HIV-seropositivity, and concurrent malignancy. Eligible subjects of childbearing age had to commit to using effective adequate contraception through week 15 of the study. The full protocol is provided in the Supplementary Appendix.

2.3. Study drug

The formulation of the artesunate suppositories is confidential (Frantz Viral Therapeutics, LLC). The inserts were formulated using materials commonly found in commercially available vaginal inserts.

2.4. Procedures

Dosing regimens were chosen based on published clinical and pharmacokinetic data regarding intra-rectal administration of artesunate suppositories, including 50- and 200-mg doses in children and adults (reviewed in [23]). Within the dosing parameters of this study, the focus was on local toxicity and response. After a screening period of not >6 weeks, subjects were assigned sequentially to one of 4 treatment groups. Subjects in the first group received one treatment cycle of 50 mg inserts. Subjects enrolled in the next 3 groups received 1, 2, or 3 treatment cycles of 200 mg insert(s), at study weeks 0, 2, and 4. Each treatment cycle was comprised of 5 consecutive nightly doses of single vaginal inserts. The artesunate vaginal inserts were self-administered at bedtime using a vaginal applicator, followed by a tampon, which was removed in the morning. Subjects kept diary cards to record local vaginal reactions. Based on reported systemic adverse events from malaria patients treated with artesunate, diary cards also included neurologic symptoms, such as headaches and dizziness. These diary cards were reviewed at each study visit, and assessed real-time to determine attribution.

Speculum exams to assess the cervicovaginal mucosa were performed at each study visit. An interim colposcopy was done between 6 and 9 weeks after the first dosing visit. Colposcopic exams, including visual assessment, tissue biopsy, cytology, and HPV genotyping were performed at study weeks 15, 28 and 41, the final study visit. If the clinical impression, cytology, or tissue obtained at study week 15 did not raise the concern of disease progression, patients were given an option to continue conservative follow-up through week 41. At study week 15 or later, study subjects who had evidence of residual HSIL proceeded to a standard-of-care therapeutic resection; either sharply, with a cold-knife conization, or with a Loop Electrosurgical Excision Procedure (LEEP). At week 41, in study subjects who had not undergone a surgical resection, both a Pap smear and a biopsy at the site of the original diagnostic biopsy were obtained to confirm histologic regression.

All colposcopic exams were performed by either Dr. Trimble (JHH) or Dr. Levinson (GBMC). Formalin-fixed, paraffin-embedded, subject-

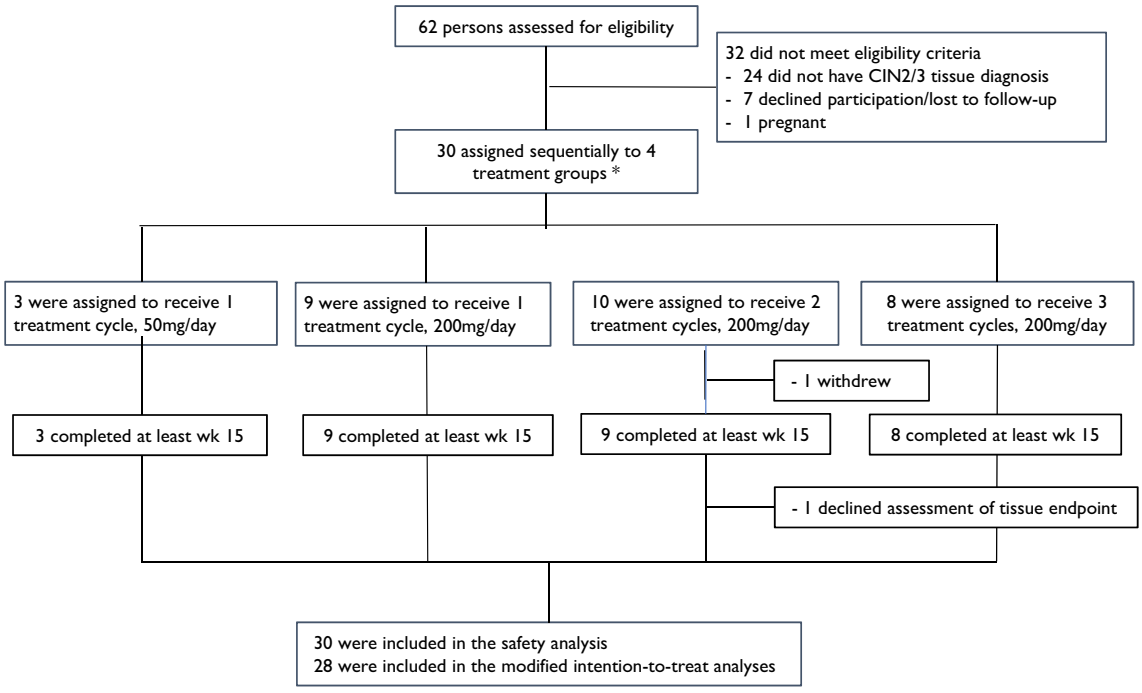

Fig. 1. Enrollment, treatment assignment, and follow-up.

matched tissue sections from the screening biopsy and the endpoint visits (week 15, or resection) were obtained for histologic evaluation. All tissue sections were independently reviewed by two pathologists (LM, MJD) who were blinded to timing, treatment, and clinical outcomes. Cytology was assessed at screening, as well as at weeks 6, 15, 28, and 41. Peripheral blood for future immunologic studies was obtained at the screening visit, and at study weeks. 6, 15, 28, and 41. Cervical swab specimens were collected at each vaginal exam. HPV genotyping was performed on cytologic specimens from the screening visit, and at weeks 6, 15, 28, and 41 using the PCR and reverse plot hybridization (Linear Array) of the L1 gene (Focus Diagnostics, Inc., San Juan Capistrano, CA).

2.5. Statistical analysis

The primary endpoints were safety and tolerability. All subjects who had received at least one dose of artesunate were included in the safety and tolerability analysis ($n = 30$). Safety was assessed by the absence of either related serious adverse events or dose-limiting toxicities. Tolerability was assessed by the percentage of subjects who were able to complete their designated dosing regimen.

Secondary endpoints, histologic regression and viral clearance, were assessed in the modified intention-to-treat group, defined as all subjects who had received at least one dose of artesunate, and for whom endpoint data was available. Histologic regression was defined as regression of CIN2/3 to CIN1 or less during the study window. Viral clearance was defined as HPV genotypes that were detected at screening and were subsequently undetectable at the tissue endpoint.

3. Results

Between February 25, 2015 and February 20, 2018, a total of 62 subjects were screened for eligibility, 30 of whom were enrolled, one of whom was enrolled in and completed treatment group 1 (one treatment cycle, 50 mg dose). Subsequently, she was re-assessed for eligibility for participation in the treatment group that tested two treatment cycles of 200 mg inserts. Because no endpoint data are available, this treatment cycle is not included in the modified intent-to-treat efficacy analysis. As she had received more than one treatment cycle in the second treatment group, she was analyzed as two distinct study subjects in the safety analysis (Fig. 1). Demographic and clinical characteristics at baseline are presented in Table 1. A total of 29 individual subjects received at least one dose of artesunate, 28 of whom were fully dosed and for whom we had endpoint data.

3.1. Safety/tolerability

A total of 161 events were reported in the 29 subjects who were included in the safety analysis. (Table 2, and Table S1 in the Supplementary Appendix). Local symptoms included vaginal pruritus ($n = 13$), vaginal pain ($n = 12$), vaginal discharge ($n = 8$), vaginal spotting ($n = 6$), vaginal dryness ($n = 4$), uterine cramping (n = 6), pelvic pain ($n = 1$), perineal pain (n = 1) and dyspareunia (n = 1). Systemic symptoms included mild gastrointestinal discomfort ($n = 9$), short-term tinnitus ($n = 2$), dizziness (n = 9), and headache ($n = 11$). Reported grade 2 adverse events included vaginal yeast infection (n = 6), bacterial vaginosis (n = 2), vaginal inflammation (n = 2), urinary tract infection (n = 2), and noninfective cystitis (n = 1). The following events were determined to be unrelated to the study medication: anxiety, insomnia, suicidal ideation, vaginal twitching, fever, flu-like symptoms in a patient who developed a cold, body itching, chills, and eczema flare. No subjects withdrew from the study because of intolerable side effects, and all 28 subjects included in the modified-intention-to-treat analyses were able to complete their designated dosing regimen. There were no grade 3 or 4 adverse events reported. A total of 3 subjects reported no noticeable side effects at all.

Table 1
Patient characteristics.

ID	Race	Age	HPV at study entry				R/NR	HR (wks)	VC	VC (wks)
ART50_1	W	29		52	67		R	51	X	
ART50_2	W	37		31			NR		X	
ART50_3	W	25		51			R	28	VC	43
ART200_1_1	W	31	16				R	10	VC	10
ART200_1_2	W	35		33	58		R	22	X	
ART200_1_3	W	35	16				R	31	X	
ART200_1_4	B	23	16	35	42	52	NR		X	
ART200_1_5	W	27		54	73		R	8	VC	43
ART200_1_6	W	33		52			R	10	VC	42
ART200_1_7	W	28	16	18	62		R	8	X	
ART200_1_8	W	29	16				NR		X	
ART200_1_9	B	26		58	68		R	16	X	
ART200_2_1	W	32		51			R	10	VC	10
ART200_2_2	B	26		52	59		NR		X	
ART200_2_3	W	32	16	53			R	30	X	
ART200_2_4	W	29	16	31	42		NR		X	
ART200_2_6	A	37		58			NR		X	
ART200_2_7	W	23		82			R	6	VC	29
ART200_2_8	W	43	16				R	7	VC	15
ART200_2_9	W	27		42	66		R	6	VC	
ART200_3_1	B	39		33	83		R	6	X	
ART200_3_2	W	32	16				R	38	X	
ART200_3_3	W	50	16				NR		X	
ART200_3_4	W	32	16				NR		X	
ART200_3_5	W	24		52			NR		X	
ART200_3_6	B	39		51	83	IS39	R	6	X	
ART200_3_7	W	25	16				R	12	VC	12
ART200_3_8	A	42		33			R	9	X	

3.2. Efficacy

In the modified intention-to-treat analysis, overall, histologic regression to CIN1 or less was observed in 19/28 (68%) subjects (Fig. 2). Rates of histologic regression were >60% across all four dosing groups (Fig. 2A). Histologic regression occurred within 15 weeks in 12/19 (63.2%) of the regressors. The mean time to regression was longer in the groups that received only one treatment cycle (20.4 weeks, $n = 9$) compared to subjects who received either 2 or 3 treatment cycles (12.9 weeks, $n = 10$) (Fig. 2D). Rates of regression were similar across age groups, ranging from 57 to 88% (Fig. 2B). When segregated by HPV genotypes detected at baseline, rates of histologic regression were highest in lesions not associated with HPV16 (Fig. 2C). Lesions that did not undergo histologic regression shared at least one clinical characteristic; in each resection specimen, residual CIN2/3 was limited to the endocervical glandular compartment, not involving the ectocervix.

Clearance of HPV genotypes detected at baseline occurred in 9 of the 19 (47.4%) subjects whose lesions underwent histologic regression. In 3 of the 9, viral clearance was documented concurrently with histologic regression. In the other 6 subjects, histologic regression preceded viral clearance by intervals ranging from 8 to 35 weeks. Similar to the pattern observed with respect to time to histologic regression, we observed that time to viral clearance was longer in the subjects who had undergone one treatment cycle (mean 27.5 weeks, $n = 9$) compared to those who had received either 2 or 3 treatment cycles (mean 16.5 weeks, $n = 10$). A total of 7 of the 9 patients who had both histologic regression and viral clearance had disease associated with mono-infection with a single HPV genotype (3 HPV16, 2 HPV51, 1 HPV52, 1 HPV82). In no subject was viral clearance observed prior to histologic regression. Viral clearance did not occur in any subject who had persistent CIN2/3 at the tissue endpoint.

Table 2
Summary of reported adverse events.

Treatment group	1	2	3	4	Total
	N = 3	N = 9	N = 10	N = 8	N = 30
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with ≥1 AE	2 (66.7)	9 (100)	8 (80)	8 (100)	27 (90)
Subjects with ≥1 Related[a] AE	2 (66.7)	6 (66.7)	8 (80)	8 (100)	24 (80)
Subjects with ≥1 Serious AE	0 (0.0)	0 (0.0)	1 (10)	0 (0.0)	1 (3.3)
Subjects with ≥1 Related[a] Serious AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
All AEs	14	42	50	55	161
All Related[a] AEs	12	27	42	51	132
All Serious AEs	0	0	1	0	1
All Related[a] Serious AEs	0	0	0	0	0

N = Number in the population and dose group (denominator for percentages, where applicable).
n = Number of subjects (numerator for percentages, where applicable).
Note: A subject is counted only once within each category. If there is more than one event within the category, the worst-case assessment is tabulated.
[a] Related = Probably, Possibly, Definitely related to the study treatment. Manually calculated from the output table.

4. Discussion

In this first-in-human clinical trial testing vaginal artesunate inserts to treat CIN2/3, treatment was well-tolerated and safe. First, and foremost, the study design was within the standard of care. The likelihood of progression to cancer was virtually nil. Based on data from a single, unethical longitudinal study in which treatment was withheld from women diagnosed with CIN3, in patients whose lesions progressed to cervical cancer, the time to progression was estimated to be between 10 and 15 years [24–26]. We chose the dosing regimens based on clinical and pharmacokinetic data from systemic administration of artesunate, using rectal administration as the closest comparator, in both children and adults (reviewed in [27]). Although we did not expect dose-limiting toxicities with topical administration, the study design included a small run-in cohort of subjects treated with 50 mg inserts. No local or systemic dose-limiting toxicities were observed in any study patients.

The clinical setting of CIN2/3 was informative. In this timeframe, some pre-invasive HPV lesions undergo histologic regression, and some do not. In this study, we observed histologic regression in two-thirds of treated patients, and clearance of detectable virus in nearly half of those who had regressed. This level of treatment effect is clinically relevant. In a prospective study of similar patients who had biopsy-confirmed CIN2/3 and underwent close observation for 15 weeks prior to a planned, standard-of-care therapeutic resection, we previously reported that a subset underwent spontaneous regression. No lesions progressed to carcinoma. Histologic regression occurred in 20.5% of CIN2/3 associated with only HPV16. The rate of regression of CIN2/3 associated with mixed infections that included HPV16 and other genotypes was higher, 29.2% [28]. In some patients, the endogenous immune response was capable of eliminating $HPV16^+$ CIN2/3.

Regression of CIN2/3 lesions can be enhanced by non-surgical treatment. In a report of subjects who had $HPV16^+$ CIN2/3 and underwent heterologous DNA-prime, TA-HPV boost vaccination targeting HPV16 antigens, we observed a 46% rate of histologic regression in the first 12 patients enrolled in this Phase I protocol [29]. Because tissue-based analyses of resection specimens obtained at study week 15 suggested that we were censoring the endpoint, subsequent study protocols were designed with this observation in mind. In a separate study testing treatment of CIN2/3 with VGX-3100, a therapeutic DNA vaccine targeting HPV16 and 18 administered with electroporation, we reported a 49.5%

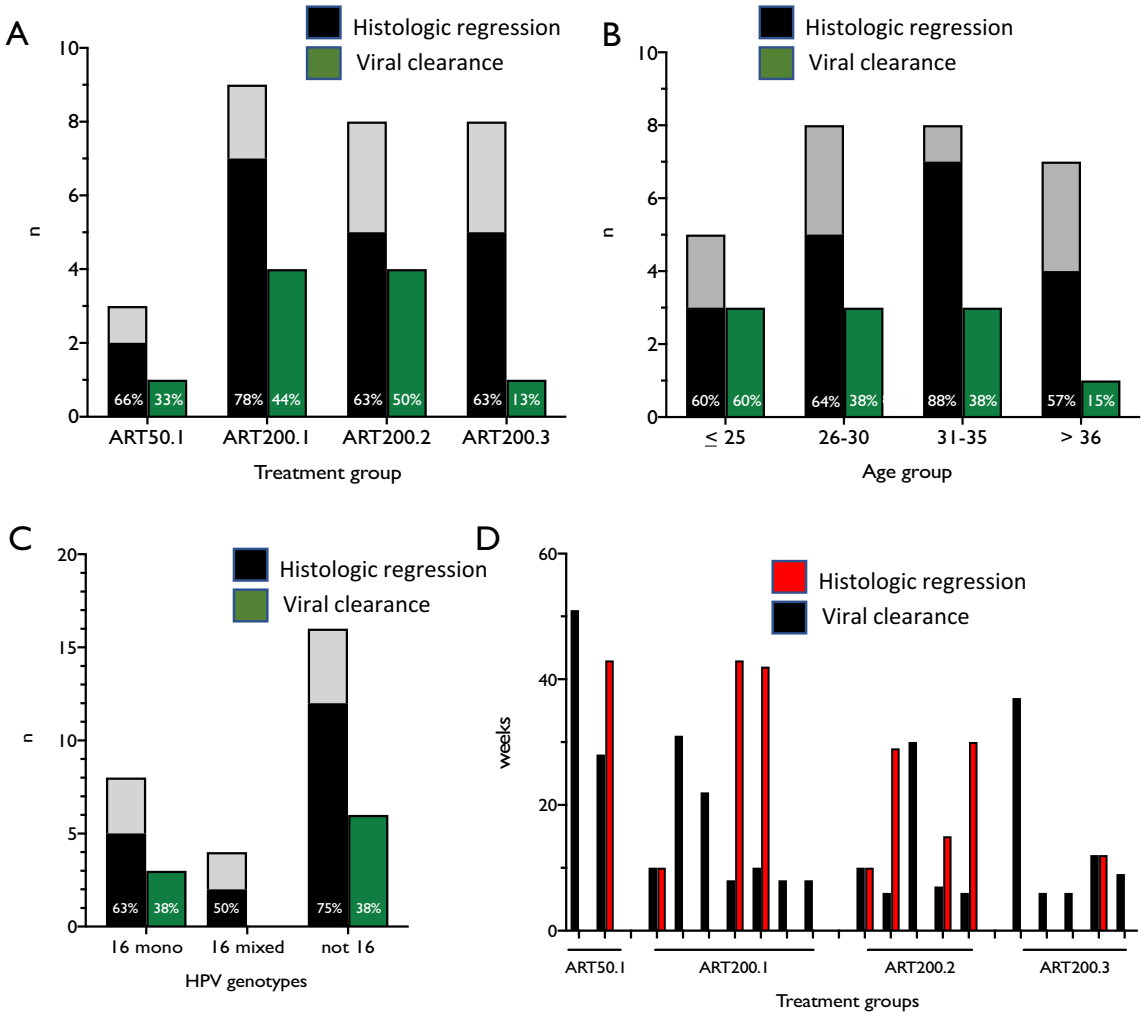

Fig. 2. Rates of histologic regression and viral clearance.

rate of histologic regression, and concomitant histologic regression and viral clearance in 40.2% of vaccinated subjects [30]. No lesions progressed to invasive carcinoma during the study windows of either of these protocols. Altogether, these observations identified CIN2/3 as a therapeutic target that was likely to be informative in proof-of-principle treatment trials with similar study windows. Given the small size of this Phase I study, we opted to use a binary endpoint of CIN2/3 *vs.* no CIN2/3. In future Phase II and Phase III trials with larger statistical power, histologic evaluations will explore the distinction between CIN2 and CIN3.

Our observation that in non-regressors, residual CIN2/3 was restricted to the endocervical canal suggests that initially, artesunate cytotoxicity is mediated by direct contact. It also suggests that mechanisms that induce clinical responses may differ between the ecto- and *endo*-cervical compartments. In addition to being relatively inaccessible compared to the ectocervix, residual endocervical disease would also have been at least intermittently covered by mucus produced by the glands themselves. In some subjects whose lesions regressed, in many of the pre-treatment biopsies, HSIL involved endocervical glands; however, diagnostic pre-treatment biopsies had to have been taken in a manner such that residual HSIL was visible on the ectocervix after the biopsy; in other words, the squamocolumnar junction was ectocervical.

Two observations suggest that cell death mediated by artesunate may have immunomodulatory effects in the mucosal microenvironment. First, while rates of histologic regression were similar across the four treatment groups, the time to regression was longer in the groups that received only one treatment cycle. This observation suggests that there may be an initial treatment effect that induces cell death that renders the cell contents immunologically visible. Artesunate-mediated cytolysis may then elicit an adaptive immune response recognizing HPV antigens. An HPV-specific T-cell response could conceivably target residual disease, in a now pro-inflammatory microenvironment. Second, in 6 of 9 subjects who had both histologic regression and viral clearance, histologic regression was not concurrent with, but preceded viral clearance by weeks (range 15–35 weeks). This sequence of observations is also congruent with generation of either an innate pro-inflammatory microenvironment as a result of an immunogenic cell death, or the induction of an adaptive immune response specific for HPV antigens, or both.

Going forward, this approach will provide an opportunity to learn about the immunobiology of artesunate-mediated cell death in pre-invasive HPV disease originating in different anatomic sites. Because the pre-invasive lesions are accessible, it will be possible to assess the contributions of tissue-specific microbiota to shaping the nature of the response to treatment, in longitudinal, subject-matched samples. The observation that vaginal artesunate eliminates a clinically significant proportion of CIN2/3 lesions also suggests that it could be a useful adjunct for patients who have dysfunctional immune responses, such as transplant recipients, those who have autoimmune disorders, or persons living with human immunodeficiency virus.

This novel treatment approach for preinvasive, intraepithelial disease is a strategy poised to address a new priority for cancer research; that is, the ‘interception’ and treatment of incipient malignancies [31–34]. While this proof-of-principle clinical trial demonstrates a clinical

response in the treatment of CIN2/3, much remains to be done. In addition to validation of these findings in a larger trial (NCT04098744), clinical trials testing topically applied artesunate in the clinical settings of preinvasive HPV lesions in the anus (AIN2/3) (NCT03100045) and for vulvar intraepithelial neoplasia (VIN2/3) (NCT03792516) are ongoing.

In the end, in either high- or low-resource settings, an effective, self-administered treatment option for preinvasive HPV disease would provide many advantages over current treatment modalities. In high-resource settings, many women would prefer to avoid having surgery, if possible, as many women affected by this disease are young and desire future fertility. A topical option would obviate the potential sequelae of surgery, which include cervical stenosis, cervical incompetence and increased risk for pre-term birth [35,36]. In settings with limited human and financial resources, a non-surgical, self-administered treatment for preinvasive cervical HPV disease, with minimal shipping and storage requirements, would truly change the landscape of care.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.12.035.

Funding

Frantz Viral Therapeutics, LLC designed, formulated, and supplied the artesunate vaginal inserts, which they provided free of charge, and provided partial financial support for study management and real-time specimen processing.

CRediT authorship contribution statement

Cornelia L. Trimble: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision.**Kimberly Levinson:**Investigation, Resources, Writing - review & editing, Project administration. **Leonel Maldonado:**Validation.**Michael J. Donovan:**Validation.**Katharine T. Clark:**Writing - review & editing.**Jie Fu:**Validation, Investigation.**Maria E. Shay:**Project administration, Data curation.**Mary Elizabeth Sauter:**Investigation, Resources.**Stephanie A. Sanders:**Investigation, Resources. **Peter S. Frantz:**Writing - review & editing.**Mihaela Plesa:**Data curation, Writing - original draft, Writing - review & editing, Supervision.

Declaration of competing interest

Dr. Trimble's institution reports grants from Frantz Viral Therapeutics, LLC, for the conduct of the study. Dr. Trimble reports consulting fees from Inovio, Merck, Vedantra Pharmaceuticals, Janssen, and GlaxoSmithKlein; grants from Inovio Pharmaceuticals, Stand Up to Cancer, The Commonwealth Foundation, Hoffman-La Roche, and the Dana Foundation; and board participation for the Australian Cancer Research Foundation and the Scientific Advisory Board of the Keystone Symposia, outside the submitted work.

Dr. Levinson's institution reports grants from Frantz Viral Therapeutics, LLC during the conduct of the study.

Dr. Maldonado reports nothing to disclose.

Dr. Donovan reports nothing to disclose.

Ms. Clark reports nothing to disclose.

Dr. Fu's institution reports grants from Frantz Viral Therapeutics, LLC during the conduct of the study.

Ms. Shay's institution reports grants from Frantz Viral Therapeutics, LLC during the conduct of the study.

Ms. Sauter's institution reports grants from Frantz Viral Therapeutics, LLC during the conduct of the study.

Ms. Sanders' institution reports grants from Frantz Viral Therapeutics, LLC during the conduct of the study.

Mr. Frantz reports personal fees from Frantz Viral Therapeutics, LLC and outside the submitted work, and being related to the CEO of Frantz Viral Therapeutics, LLC. He is the Vice President of Amarex, which received fees from FVT during the conduct of the study.

Ms. Plesa reports personal fees and, her institution reports grants from Frantz Viral Therapeutics, LLC during the conduct of the study.

Acknowledgements

We thank the patients who participated in this study, and their families. The concept of the use of artesunate to treat HPV-related malignancies was developed by Dr. Richard Schlegel and colleagues at Georgetown Medical Center, who conducted both *in vitro* and animal studies that supported the rationale for the clinical translation of artesunate [22].

The suppository formulation for drug delivery was developed by Frantz Viral Therapeutics, LLC in collaboration with Buderer Drug Co. We thank Dr. Jerome Belinson for many helpful discussions, and Marsha Tanner Wilson, MPH for editing the manuscript.

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