Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Protocol Number: H-54674
Status: Approved
Initial Submit Date: 11/8/2023
Approval Period: 2/5/2024 - 12/26/2024

Section Aa: Title & PI

A1. Main Title

A PHASE 2 STUDY OF HPV L1 VACCINE IN COMBINATION WITH IMIQUIMOD AND METFORMIN IN CERVICAL, VAGINAL, AND VULVAR CANCERS

A2. Principal Investigator

Name:	JAN SUNDE	Phone:	7137986848
Id:	206551	Fax:	832 8259356
Department:	OB-GYN: ADMINISTRATIVE	Email:	sunde@bcm.edu
Center:		Mail Stn:	125084

A3. Administrative Contact

Name:	KENESHIA LANE	Phone:	
Id:	232877	Fax:	
		Email:	232877@bcm.edu
		Mail Stn:	

A3a. Financial Conflict of Interest

Does any member of study personnel (Investigator (including investigator's spouse and/or dependent children)) that are involved in the design, conduct, or reporting of the research have a Significant Financial Interest (SFI) that would reasonably appear to be affected by the research for which funding is sought and/or associated with an entity/business that would reasonably appear to be affected by the research?

No

Section Ab: General Information

A4. Co-Investigators

Name:	MICHELLE LUDWIG	Phone:	7135663757
Id:	183182	Fax:	713 5663758
Department:	RADIATION ONCOLOGY	Email:	msludwig@bcm.edu
Center:		Mail Stn:	BCM711
Name:	SHELLY SHARMA	Phone:	9013555672
Id:	188978	Fax:	
Department:	RADIATION ONCOLOGY	Email:	shellys@bcm.edu
Center:		Mail Stn:	BCM360
Name:	SIMONE HERNANDEZ RUANO	Phone:	8328244190
Id:	191164	Fax:	832 8257946
Department:	OB-GYN: ADMINISTRATIVE	Email:	shruano@bcm.edu
Center:		Mail Stn:	BCM610

Name:	KATHLEEN PENNINGTON	Phone:	8328244190
Id:	191410	Fax:	832 8257946
Department:	OB-GYN: ADMINISTRATIVE	Email:	kapennin@bcm.edu
Center:		Mail Stn:	BCM610
Name:	TRACILYN HALL	Phone:	7137982452
Id:	195219	Fax:	
Department:	OB-GYN: ADMINISTRATIVE	Email:	trhall@bcm.edu
Center:		Mail Stn:	125084
Name:	BERKLEY ANDERSON	Phone:	
Id:	198728	Fax:	
Department:	OB-GYN: ADMINISTRATIVE	Email:	bakingma@bcm.edu
Center:		Mail Stn:	
Name:	ANTHONY COSTALES	Phone:	7137983495
Id:	208504	Fax:	
Department:	OB-GYN: ADMINISTRATIVE	Email:	costales@bcm.edu
Center:		Mail Stn:	125084
Name:	CLAIRE HOPPENOT	Phone:	7137985165
Id:	231402	Fax:	
Department:	OB-GYN: ADMINISTRATIVE	Email:	231402@bcm.edu
Center:		Mail Stn:	125084
Name:	JON FUSON	Phone:	
Id:	246863	Fax:	
Department:	OB-GYN: ADMINISTRATIVE	Email:	u246863@bcm.edu
Center:		Mail Stn:	

A5. Funding Source:

Baylor College of Medicine (Internal Funding Only)

A6a. Institution(s) where work will be performed:

Baylor St. Luke's Medical Center (BSLMC)
Harris Health System- Smith Clinic

A6b. Research conducted outside of the United States:

Country:
Facility/Institution:
Contact/Investigator:
Phone Number:

If documentation of assurances has not been sent to the Office of Research, please explain:

A7. Research Category:

Cancer - Adult

A8. Therapeutic Intent

Does this trial have therapeutic intent?
Yes

A9. ClinicalTrials.gov Registration

Does this protocol/trial require registration on ClinicalTrials.gov due to it: meeting the definition of an Applicable Clinical Trial, being required under the terms and conditions of an award, or being proposed to be published in ICMJE journals?
Yes

Who will be responsible for registering and maintaining the registration of this Applicable Clinical Trial?
The BCM PI will register the trial because either:

- the trial is BCM PI-initiated,

- BCM is the lead site of this multicenter trial, or,
- the industry sponsor has instructed the BCM PI to register the trial, or,
- registration of this trail is required as a term and condition of the reward by the funding agency.

ClinicalTrials.gov Identifier:
NCT

Section B: Exempt Request

B. Exempt From IRB Review

Not Applicable

Section C: Background Information

Each year in the United States, about 13,000 new cases of cervical cancer are diagnosed and about 4,000 women die of this cancer. Hispanic women have the highest rates of developing cervical cancer, and Black women have the highest rates of dying from cervical cancer (Cervical Cancer Statistics CDC, 2023). HPV is thought to be responsible for more than 90% of anal and cervical cancers (Cancers Associated with Human Papillomavirus (HPV), 2023). Despite our best efforts, persistent/recurrent disease continues to occur in 30-40% of locally advanced cervical patients in clinical trials and in our patient population at Ben Taub (SGO2023) (SGO202302).

Radiation has been the mainstay for treatment of locally advanced cervical and vulvar cancer for over a century, with addition of chemotherapy as a radiation sensitizer following an NCI Clinical Announcement in 1999. Recently, immunotherapy has been added in patients positive for PD-L1 in advanced stage cancers (1,2).

Vaginal and vulvar cancers, which are also often HPV related, are very rare. Together, they account for about 7% of all gynecologic cancers diagnosed in the U.S. (Basic Information About Vaginal and Vulvar Cancers | CDC, 2023). There is little clinical trial data studying vulvar cancer and vaginal cancer since they are rare, but they are typically treated with chemoradiation, and pembrolizumab if PD-L1 positive, in the same manner as squamous cell cervical cancer. Given that all of these disease processes can be HPV related, inclusion of these patient populations is planned if an eligible patient is identified. We are just beginning to understand some of the roles of the immune system in fighting cancer, even though intratumoral injection was first reported by Dr. Coley in 1898 and termed “Coley toxin” (3). This was the first immunotherapy reported and consisted of extracts from bacteria responsible for erysipelas (Streptococcus pneumoniae and Serratia marcescens) which were injected into various skin cancers with significant success but this technique fell out of favor to radiation therapy due to toxicity and inconsistent responses (4).

This trial is designed to stimulate tumor immunity through the use of sequential, targeted vaccinations of the FDA-approved, HPV 9-valent recombinat vaccine injected during and after radiation of the tumor, in conjunction with immunity modulating imiquimod and metformin. Advanced HPV related cancers are believed to replicate under the influence of “early genes”, but the late gene, HPV-L1 protein, has been reported to have low levels of expression in advanced cervical cancers and HPV 9-valent vaccine may produce an effective anti-tumor response in cervical cancer (5). Imiquimod, an FDA-approved Toll-like receptor 7 (TLR7) agonist, has been successfully used as a vaccine adjuvant improving anti-tumor immune responses (6), and vaccines used in conjunction with radiation therapy improve the recognition and uptake of both DNA viruses and radiation induced tumor- associated antigens (neoantigens) (7). This TLR7-agonist facilitates antigen processing of tumor-specific antigens in regional lymph nodes (8).

The evaluation of combinations of immunotherapy with other treatment modalities to improve efficacy has been an active area of research in the last several years. Immunotherapy is now combined with chemotherapy in initial therapy for patients with metastatic or recurrent cervical cancer, and has been found to be synergistic with radiotherapy in a mouse model and in a recent clinical trial for locally advanced disease (9). Imiquimod, alone and with HPV vaccination, has demonstrated efficacy in eradicating pre-invasive HPV lesions of the vulva and the cervix (10, 11, 12). Investigators using preclinical models have found that intratumoral vaccination combined with radiation affects the tumor microenvironment to improve the response to treatment (13) and also improves the abscopal response (14). Additional reported unanticipated benefits of immune treatment include the finding that intramuscular HPV vaccination alone decreases recurrence of both treated pre-invasive HPV related disease and vulvar carcinoma (15,16).

Extensive work is ongoing in basic science investigating intratumoral immune response, with a few examples as noted: Imiquimod has been shown to reduce lesion size in conjunction with HPV vaccination in mice (6) and intratumoral vaccination with a HPV vaccine in a TLR vector led to a better response with lesion eradication in up to 50% of mice compared to IM vaccination (17). A recent renewed interest in intratumoral immune treatments in humans has led to multiple early phase human cancer trials, with multiple different agents, including: cervical intratumoral hydrogen peroxide based radiosensitizer treatment (18), cervical intratumoral oncolytic virus (14), melanoma intratumoral oncolytic virus (19), melanoma imiquimod intratumoral oncolytic vaccine (20), colon intratumoral influenza vaccine (21), and liver intratumoral

oncolytic virus (22) as examples. Other examples of intratumoral immunotherapy for non-malignant conditions include: intralesional HPV vaccine combined with Candida antigen, which has been used for treatment of recalcitrant warts (23), and injection of compounds such as MMR vaccine and PPD leading to clearance of common warts in 80 and 60% of patients respectively (23).

Based on published reports, the route of administration planned is not anticipated to increase the risk associated with use of the HPV vaccine (intratumoral) or the imiquimod (intravaginal) (24, 25) A large study of MVA E2 vaccinia injected directly into gynecologic lesions in 1176 females reported grade 1 toxicities only, including headaches, flu symptoms, pyrexia, chills, abdominal ache, joint pain, similar to side effects noted with many vaccines (24). A meta-analysis of 463 patients treated with intra-vaginal imiquimod for cervical intraepithelial neoplasia (CIN) reported side effects like those reported by women treated with vulvar imiquimod, such as headache/migraine (57%) followed by fatigue (56%) and myalgia (55%), while the most common local side effect was vulvar pain/pruritus in 48% (25).

Metformin is included in the planned regimen due to its immune effects. Diabetic patients treated with metformin have reduced incidence and better survival from cancer of many organs, including colorectal, liver, pancreatic, rectal, breast, prostate cancer and upper tract urothelial carcinoma (26). Metformin has been found to function in multiple ways to affect cancer growth, including the activation of adenosine monophosphate-activated kinase (AMPK), and is also thought to effect the tumor microenvironment (26; 27), and may interact with immunotherapy (28). Subcutaneous (SC) administration of vaccines has been reported to stimulate more of a cell mediated immune response (29) compared to intramuscular delivery, so the vaccine will be administered both intratumoral and SC. The timing of treatment with radiation and immunotherapy appears to be of critical importance, with radiation producing an autologous “in-situ vaccine” specific to each cancer (30).

In a recent case study report, use of a combination of several of the treatments reported above: intratumoral HPV vaccine in combination with topical TLR7 cream, imiquimod, and oral metformin, as well as zinc, and lactobacillus acidophilus, led to regression of recurrent, chemoradiation refractory, HPV-HR positive squamous cell cervical and vulvar cancers in 2 patients, resulting in complete resolution of these incurable tumors and clearance of HPV infection (31). Of note, one of the patients, a 89-year-old African American female demonstrated an abscopal response with resolution of extensive lung metastases. Two additional patients with chemoradiation refractory vulvar cancer have subsequently been offered an off-label treatment course with a similar protocol using HPV L1 vaccine, imiquimod and metformin prior to initiation of palliative treatment for their incurable disease. One patient, who began with a 20 cm initial tumor and had a 10 cm persistent necrotic mass following chemoradiation, has had a complete response based on PET/CT imaging, and is now 12 months out from treatment initiation. A second similar vulvar cancer patient who did not present for follow-up at 3 months after chemoradiation has had progression of disease, with the responsiveness of her tumor to the novel treatment thought to be adversely affected by the delay in presentation. An additional locally advanced cervical cancer patient has received off-label treatment before and following completion of chemoradiation. Though only 5 patients have been treated with this novel protocol which uses FDA-approved medications off-label, these results are promising for treatment of persistent disease that is typically considered difficult to cure. As immunotherapy becomes incorporated into the standard of care, there remains room for improvement in these difficult-to-treat HPV related gynecologic cancers.

This window-of-opportunity study will evaluate the immune changes within the tumor microenvironment and validate why the combination immunotherapy treatment elicited such a robust immune response which led to complete resolution of the cancer, in comparison to the standard of care, chemoradiation. If the combination immunotherapy used together with chemoradiation elicits a more robust antitumor response, there is the potential that the addition of these FDA approved medications to chemoradiation could be a new standard of treatment for squamous cell carcinoma of the cervix and vulva.

References 1. Chung, H.C., 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. 37(17): p. 1470-1478. 2. Colombo, N., et al., Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. N Engl J Med, 2021. 385(20): p. 1856-1867. 3. Wiemann, B. and C.O. Starnes, Coley's toxins, tumor necrosis factor and cancer research: a historical perspective. Pharmacol Ther, 1994. 64(3): p. 529-64. 4. Marabelle, A., et al., Intratumoral immunization: a new paradigm for cancer therapy. Clin Cancer Res, 2014. 20(7): p. 1747-56. 5. Bellone, S., et al., Human papillomavirus type 16 (HPV-16) virus-like particle L1-specific CD8+ cytotoxic T lymphocytes (CTLs) are equally effective as E7-specific CD8+ CTLs in killing autologous HPV-16-positive tumor cells in cervical cancer patients: implications for L1 dendritic cell-based therapeutic vaccines. J Virol, 2009. 83(13): p. 6779-89. 6. Chuang, C.M., et al., Treatment with imiquimod enhances antitumor immunity induced by therapeutic HPV DNA vaccination. J Biomed Sci, 2010. 17(1): p. 32. 7. Cadena, A., et al., Radiation and Anti-Cancer Vaccines: A Winning Combination. Vaccines (Basel), 2018. 6(1). 8. Cho, J.H., et al., The TLR7 agonist imiquimod induces anti-cancer effects via autophagic cell death and enhances anti-tumoral and systemic immunity during radiotherapy for melanoma. Oncotarget, 2017. 8(15): p. 24932-24948. 9. Zhai, D., et al., Radiotherapy: Brightness and darkness in the era of immunotherapy. Transl Oncol, 2022. 19: p. 101366. 10. Terlou, A., et al., Treatment of vulvar intraepithelial neoplasia with topical imiquimod: seven years median follow-up of a randomized clinical trial. Gynecol Oncol, 2011. 121(1): p. 157-62. 11. Grimm, C., et al., Treatment of cervical intraepithelial neoplasia with topical imiquimod: a randomized controlled trial. Obstet Gynecol, 2012. 120(1): p. 152-9. 12. Trutnovsky, G., et al., Topical imiquimod versus surgery for vulvar intraepithelial neoplasia: a multicentre, randomised, phase 3, non-inferiority trial. Lancet, 2022. 399(10337): p. 1790-1798. 13. Morris, Z.S., et al., In Situ Tumor Vaccination by Combining Local Radiation and Tumor-Specific Antibody or Immunocytokine Treatments. Cancer Res, 2016. 76(13): p. 3929-41. 14. Zhang, X., et al., Intratumoral injection of oncolytic virus (H101) in combination with concurrent chemoradiotherapy for locally advanced cervical cancer. Int J Gynecol Cancer, 2023. 33(7): p. 1051-1056. 15. Garland, S.M., et al., Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: Post-hoc analysis from a randomized controlled trial. Int J Cancer, 2016. 139(12): p. 2812-2826. 16. Gustafson, L.W., M.

Gade, and J. Blaakaer, Vulval cancer and HPV vaccination in recurrent disease. Clin Case Rep, 2014. 2(6): p. 243-6. 17. Ishida, E., et al., Intratumoral delivery of an HPV vaccine elicits a broad anti-tumor immune response that translates into a potent anti-tumor effect in a preclinical murine HPV model. Cancer Immunol Immunother, 2019. 68(8): p. 1273-1286. 18. Shimbo, T., et al., KORTUC, a novel hydrogen peroxide-based radiosensitizer for the enhancement of brachytherapy in patients with unresectable recurrent uterine cervical cancer. Oncol Lett, 2023. 26(3): p. 378. 19. Curti, B.D., et al., Intratumoral oncolytic virus V937 plus ipilimumab in patients with advanced melanoma: the phase 1b MITCI study. J Immunother Cancer, 2022. 10(12). 20. Tran, C.A., et al., Intratumoral IFN-gamma or topical TLR7 agonist promotes infiltration of melanoma metastases by T lymphocytes expanded in the blood after cancer vaccine. J Immunother Cancer, 2023. 11(2). 21. Gogenur, M., et al., Neoadjuvant intratumoral influenza vaccine treatment in patients with proficient mismatch repair colorectal cancer leads to increased tumor infiltration of CD8+ T cells and upregulation of PD-L1: a phase 1/2 clinical trial. J Immunother Cancer, 2023. 11(5). 22. Heo, J., et al., Safety and dose escalation of the targeted oncolytic adenovirus OBP-301 for refractory advanced liver cancer: Phase I clinical trial. Mol Ther, 2023. 31(7): p. 2077-2088. 23. Marei, A., et al., Combined bivalent human papillomavirus vaccine and Candida antigen versus Candida antigen alone in the treatment of recalcitrant warts. J Cosmet Dermatol, 2020. 19(3): p. 758-762. 24. Rosales, R., et al., Regression of human papillomavirus intraepithelial lesions is induced by MVA E2 therapeutic vaccine. Hum Gene Ther, 2014. 25(12): p. 1035-49. 25. van de Sande, A.J.M., et al., The efficacy of topical imiquimod in high-grade cervical intraepithelial neoplasia: A systematic review and meta-analysis. Int J Gynaecol Obstet, 2023. 26. Ma, R., et al., Metformin and cancer immunity. Acta Pharmacol Sin, 2020. 41(11): p. 1403-1409. 27. Wu, Z., C. Zhang, and M. Najafi, Targeting of the tumor immune microenvironment by metformin. J Cell Commun Signal, 2022. 16(3): p. 333-348. 28. Afzal, M.Z., R.R. Mercado, and K. Shirai, Efficacy of metformin in combination with immune checkpoint inhibitors (anti-PD-1/anti-CTLA-4) in metastatic malignant melanoma. J Immunother Cancer, 2018. 6(1): p. 64. 29. Mu, J., et al., Comparative study of subcutaneous, intramuscular, and oral administration of bovine pathogenic Escherichia coli bacterial ghost vaccine in mice. Front Immunol, 2022. 13: p. 1008131. 30. Mondini, M., et al., Synergy of Radiotherapy and a Cancer Vaccine for the Treatment of HPV-Associated Head and Neck Cancer. Mol Cancer Ther, 2015. 14(6): p. 1336-45. 31. Reedy, M., S. Jonnalagadda, and K. Palle, Case Report: Intra-Tumoral Vaccinations of Quadrivalent HPV-L1 Peptide Vaccine With Topical TLR-7 Agonist Following Recurrence: Complete Resolution of HPV-HR-Associated Gynecologic Squamous Cell Carcinomas in Two Patients. Pathol Oncol Res, 2021. 27: p. 1609922.

Section D: Purpose and Objectives

PRIMARY: The primary objective of the study is to determine the effect on 24 month progression free survival of intratumoral HPV vaccination with topical imiquimod and oral metformin for locally advanced cervical, vaginal, or vulvar carcinoma in conjunction with definitive whole pelvic radiotherapy with chemotherapy followed by brachytherapy. Although the clinical benefit of this combination of drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

SECONDARY: Assess for unanticipated toxicity of the combination of intratumoral HPV vaccination with topical imiquimod and oral metformin when administered in conjunction with chemotherapy with whole pelvic radiotherapy for cervical or vulvar carcinoma. .

Corollary Objective: Study of specific immune markers and modalities by which the combination immunotherapy boosts the immune system and works in sync with the standard of care to enhance its effects. Immune biomarker assays will be performed in cervical swab and blood samples at the beginning, middle, and end of the treatment to measure the effects of treatment on several immune markers including: CD4, CD8, NK, TNF alpha and beta, IL2, HPV viral load, TGF Beta, Ki67, IGg. We will also do blood tests to test for IGg L1 and L2, E6 and E7 and a CBC. These markers were chosen to identify specific immune changes of the three treatment groups.

Section E: Protocol Risks/Subjects

E1. Risk Category

Category 2: Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.

E2. Subjects

Gender:
Female

Age:
Adult (18-64 yrs)

Ethnicity:

All Ethnicities

Primary Language:
English, Spanish

Groups to be recruited will include:
Asymptomatic patients with chronic conditions, healthy; Patients

Which if any of the following vulnerable populations will be recruited as subjects?

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

E3. Pregnant woman/fetus

Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E4. Neonates

Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E5. Children

Will children be enrolled in the research?
No

Section F: Design/Procedure

F1. Design

Select one category that most adequately describes your research:
u) Drug, Phase II, Single Center

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.

This window-of-opportunity study will be offered to all eligible patients undergoing chemoradiation for cervical, vulvar, or vaginal cancer, since it is an additional treatment anticipated to enhance the response to therapy. The treatment group will be compared to a historical control. We will evaluate the immune changes within the tumor microenvironment and validate why the combination immunotherapy study elicited such a robust immune response which led to complete resolution of the cancer, in comparison to the standard of care, chemoradiation. If the combination immunotherapy used together with chemoradiation elicits a more robust antitumor response, there is the potential that the addition of these FDA approved medications to chemoradiation could be a new standard of treatment for squamous cell carcinoma of the cervix and vulva.

Inclusion Criteria:

• Participants must have histologically confirmed locally advanced or metastatic cervical carcinoma (Stage IB2-IVB), vaginal, or vulvar carcinoma (Stage II-IVB), AND not be considered a primary surgical candidate. Patients offered neoadjuvant therapy may be enrolled if they respond and receive chemoradiation. • Participants must have measurable disease, per Recist criteria. See Section 12 (Measurement of Effect) for the evaluation of measurable disease. Radiological evaluation shall occur within approximately 30 days prior to enrollment initiation and start of radiation. • Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 • Participants must be ≥ 18 years of age • Participants must have adequate organ function within 28 days of registration, defined as follows: - Absolute neutrophil count ≥ 1,500/µL - Platelets ≥ 100,000/µL - Hemoglobin ≥ 9 g/dL - Serum creatinine ≤ 1.5 x upper limit of normal (ULN) - Total bilirubin ≤ 1.5 x ULN (≤2.0 in patients with known Gilberts syndrome) OR direct bilirubin ≤ 1 x ULN - Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN unless liver metastases are present, in which case they must be ≤ 5 x ULN • Participants receiving corticosteroids may continue as long as their dose is stable for at least 4 weeks prior to initiating protocol therapy. • Participant must agree to not donate blood during the study or for 90 days after the last dose of study treatment. • Female participants of childbearing potential must have a negative serum pregnancy test within 14 days prior to registration. Females of non-childbearing potential is defined as follows (by other than medical reasons): - ≥45 years of age and has not had menses for >1 year, post-hysterectomy, post-bilateral oophorectomy, post external beam radiation of 6 Gy to the pelvis, or post-tubal ligation. • Participants must agree to not breastfeed during the study. • Participants must be able to understand the study procedures and agree to participate in the study by providing written informed consent • Participants must be eligible for chemoradiation treatment in the opinion of the treating investigator. • Participants who are HIV+ must have CD4 counts >200/dL and demonstrate documented Highly active antiretroviral therapy (HAART) compliance m. Participant must have CT (chest/abdomen/pelvis) or PET-CT, within 56 days of registration. • Participants must be newly diagnosed. • Standard chemoradiation using external beam radiation therapy

(EBRT) and brachytherapy is permitted for cervical or vaginal carcinoma, and chemoradiation with EBRT for vulvar carcinoma. A lesion must be readily accessible for intratumoral tumor injection. • ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A). • For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. • Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load. • Patients with treated brain metastases are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression. • Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

Exclusion Criteria:

• Patients who are receiving any other investigational agents. • Patients who have untreated, new or progressive brain metastases or leptomeningeal disease. • History of allergic reactions attributed to compounds of similar chemical or biologic composition to agents used in study. • Patients with uncontrolled intercurrent illness. • Patients with psychiatric illness/social situations that would limit compliance with study requirements. • Pregnant women are excluded from this study because cervical carcinoma or vulva carcinoma patients have undergone treatment rendering the patient infertile. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cervical carcinoma or vulva carcinoma, breastfeeding should be discontinued.

F2. Procedure

Treatment visits will occur during the second and fourth weeks of radiation, and then during weeks 8, 10, 12, and 16, which will occur after completing radiation.

At the treatment visit:

A blood sample will be obtained by a research nurse (10 milliliters/ 2 teaspoons)

A speculum exam will be performed and 2 small brushes (cytobrush) will be used to collect cells from the surface of the tumor. If you have a vulvar cancer, the cells will be collected from the tumor surface.

HPV 9-valent recombinant vaccine (3 milliliters/approximately ½ teaspoon) will be injected into several locations on the tumor surface, using ½ half of the single dose vaccine diluted with saline solution.

If you have cancer of the vulva, the vaccine will be injected without placing the speculum.

Imiquimod cream will be applied to the surface of the tumor at the visit.

You will then receive ½ of the vaccine dose as a subcutaneous shot.

Following the visit, you will receive 6 small doses of imiquimod cream in individual packets. These are to be applied using a vaginal applicator 3 nights per week for the next 2 weeks.

If you have cancer of the vulva, the imiquimod cream will be applied directly on the tumor surface.

You will also receive metformin 500 mg tablets, which are to be taken by mouth twice daily for the next 2 weeks.

A PET/CT test will be performed at treatment completion (week 20), then PET/CT or CT chest/abdomen/pelvis 2 years post treatment. You will have follow-up visits with a physical exam including pelvic exam every 3 months up until 2 years.

Section G: Sample Size/Data Analysis

G1. Sample Size

How many subjects (or specimens, or charts) will be used in this study?

Local: 85 Worldwide: 85

Please indicate why you chose the sample size proposed:

The planned cohort size will be 77 primary cervical cancer patients, the number needed for the evaluation of improvement in time to progression-free survival, with up to 8 vulvar/vaginal cancer patients, since they are rare. Members of the protocol study team have completed a comprehensive review of local control outcomes for all women treated for a locoregionally advanced cervical cancer (bulky FIGO IB3- IVA) with chemoradiotherapy to include standard of care concurrent cisplatin at the Harris Health System. Twenty-four month progression-free survival for patients who presented with FIGO IIIA-IVA cervical cancer is 67%. Since this clinical trial is enrolling an advanced stage cohort, we estimate that PFS would be 67% with standard of care and we will consider the trial a success if PFS is better than 77% at 24 months. Employing a one-sample exponential hazard rate test, and using a survival time of at least 2 years, which is consistent with the follow up time of 2 years, a sample of 77 patients are needed (alpha=10%, one-tailed, history control PFS24 m=67% vs new PDA24m=77%). Similar results are obtained for a standard one-sample log-rank test. .

Vulvar and vaginal carcinoma patients will be accrued while the trial is enrolling, in addition to the 77 cervical cancer patients, since these cancers are much more rare. An adequate number of patients for statistical comparison is not anticipated to accrue, but this data will be reported separately. Up to 8 vulvar or vaginal cancer patients are anticipated, for a total of 85 patients.

G2. Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

The primary objective will be addressed by looking at progression free survival at 24 months compared to a historical cohort with a Kaplan Meyer curve using a log-rank test to evaluate for significance.

Section H: Potential Risks/Discomforts

H1. Potential Risks/Discomforts

Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

Human Papillomavirus 9-valent Vaccine, Recombinant: The vaccine will be given intratumorally, but this is not anticipated to change the risk compared to standard vaccination, since trial of intralesional injection of HPV vaccine in nearly 1200 women found similar side effects to standard HPV vaccination. There may be some minimal discomfort during vaccine administration. Because vaccines may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. ADVERSE REACTIONS The most common (≥10%) local and systemic adverse reactions reported: injection-site pain (80-90%), injection-site swelling (23-40.0%), injection-site erythema (17-34.0%) and headache (15%).

Imiquimod: The cream will be applied topically per vagina using an applicator. There may be some discomfort during application, and there is some risk of local skin reaction of the vulva, similar to that noted with vulvar application, as reported in trials of approximately 500 women using imiquimod treatment for cervical lesions Local skin reactions in a study of external genital warts were reported as the following reactions, with the percentage of severe reactions noted in parentheses: erythema (4%), erosion (1%), excoriation/ flaking (0%), edema (1%), scabbing (0%), induration (0%), ulceration (3%), vesicles 0(0%). Remote site skin reactions were also reported. Other possible reactions included burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness, remote bleeding, burning, itching, pain, tenderness, tinea cruris, Systemic reactions included fatigue, fever, influenza-like symptoms, headache, diarrhea, myalgia.

Metformin: Common adverse reactions to metformin include GI symptoms such as diarrhea 53.2% nausea/vomiting 25.5% flatulence 12.1% indigestion 7.1% abdominal discomfort 6.4% Other symptoms such as fatigue 9.2%, headache 5.7% were reported. LACTIC ACIDOSIS is also a risk with metformin.

Blood Sample Collection: Blood sample collection (~10 ml of blood) at three time points (prior to treatment, mid treatment and 6 months post treatment) will occur in the course of usual and routine prenatal care and will not require any additional sampling or added blood draws. There is potential for transient pain, bleeding, infection, and injury to the participant during routine venipuncture for blood sample collection; however, these risks are minimal and exist at baseline with obtaining of blood samples for any medical indication, regardless of participation in proposed research.

Cervical swab collection: Two sterile disposable cytobrushes (Cytobrush Plus GT (Cooper Surgical, Trumbull, CT)) will be used to collect cells from the cervix by rotating the brush 360 with 3 to 4 full rotations against the tumor. This procedure is less invasive that what occurs during a routine gynecological care such as during a pap-smear and is not associated with any increased pain or discomfort. There is potential for transient pain, bleeding, infection, and injury to the participant during routine cervical sample collection; however, these risks are minimal and exist at baseline with obtaining of blood samples for any medical indication, regardless of participation in proposed research.

Patient Data: The use or disclosure of protected health information involves no more than minimal risk to the individuals because the data collected will be presented without any patients' identification. Each patient will receive an identifier code. Only the study team will have access to the patients' names. Patients are assigned a study ID, which is used for data entry. Biologic samples collected from participants will be marked with the same assigned study ID. All patient information will be entered into a database via that ID. There is the potential for loss of privacy, but by careful protection of the data by keeping the data on a password protected file on the PI's computer on the hospital server, this risk will also be minimal.

H2. Data and safety monitoring plan

Do the study activities impart greater than minimal risk to subjects?
Yes

NOTE: The answer to the questions in H2 requires the completion of the form: 'Section H â€“ Data and Safety Monitoring Plan' as an attachment in Section S.

H3. Coordination of information among sites for multi-site research

Is the BCM Principal Investigator acting as the SPONSOR-INVESTIGATOR for this multi-site research?
No or Not Applicable

Is BCM the COORDINATING CENTER for this multi-site research?
No or Not Applicable

Section I: Potential Benefits

Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.
The potential benefit is increased likelihood of cure, if the treatment is found to be efficacious.

Describe potential benefit(s) to society of the planned work.
Worldwide approximately 300,000 women die from cervical cancer annually, with 4000 of those deaths occurring in the United States. Worldwide, women from lower and middle income countries are disproportionately affected. In the United States, Hispanic women have the highest rates of developing cervical cancer, and Black women have the highest rates of dying from cervical cancer. HPV is thought to be responsible for more than 90% of anal and cervical cancers (Cancers Associated with Human Papillomavirus (HPV), 2023). Despite our best efforts, persistent/recurrent disease continues to occur in 30-40% of locally advanced cervical patients in clinical trials and in our patient population.

Treatment with radiation has been the mainstay for treatment of locally advanced cervical and vulvar cancer for over a century, with addition of chemotherapy as a radiation sensitizer following an NCI Clinical Announcement in 1999. Recently, immunotherapy has demonstrated benefitin patients positive for PD-L1 in advanced stage cancers.

Vaginal and vulvar cancers, which are also often HPV related, are very rare. Together, they account for about 7% of all gynecologic cancers diagnosed in the U.S. There is little clinical trial data studying vulvar cancer and vaginal cancer since they are rare, but they are typically treated with chemoradiation, and pembrolizumab if PD-L1 positive, in the same manner as squamous cell cervical cancer. Given that all of these disease processes can be HPV related, inclusion of these patient populations is planned if an eligible patient is identified.

Radiation is available in a number of countries worldwide, including low and middle income countries. If effective, this treatment can be utilized in those settings immediately, since we are utilizing medications that are approved in many countries and are somewhat readily available thus reducing the rate of HPV related cervical, vaginal and vulvar cancers annually.

This treatment could also be considered for any HPV induced cancer, expanding the potential patient population further

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.
There is minimal risk with these widely used medications, and there are 4-5 additional clinic visits to apply the treatment. There is the potential to improve the cure rate for difficult to treat cancers, a benefit to the patients if the treatment improves progression free survival

Section J: Consent Procedures

J1. Waiver of Consent

Will any portion of this research require a waiver of consent and authorization?
No

J1a. Waiver of requirement for written documentation of Consent

Will this research require a waiver of the requirement for written documentation of informed consent?
No

J2. Consent Procedures

Who will recruit subjects for this study?

PI
PI's staff

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.

All patients undergoing chemoradiation for cervical, vaginal, or vulvar carcinoma at BCM sites (Smith Clinic and Dan L Duuncan Comprehensive Cancer Center - DLDCCC) will be identified as candidates by their Gynecologic oncology (Gyn Onc) providers at their initial visit and/or at tumor board presentation. All Gyn Onc providers are listed as investigators for this study and will be able to discuss the procedure with patients. Research coordinators will then evaluate the patients for eligibility for the study. The trial will be discussed with patients in the weeks before starting radiation and offered to them by the physician. A copy of the consent form will be provided and all efforts will be made to provide the patient with time to decide on the trial without delaying their standard of care treatments. It will be explained that this treatment is not required to receive standard chemoradiation, and that participation is completely optional and will not otherwise affect the standard care that they receive. We will discuss the rationale for the study based on case reports where these experimental treatments have cured a small number of patients. It will also be explained that the medications themselves are well known and widely used, with a known safety profile that is overall well tolerated.

Are foreign language consent forms required for this protocol?
Yes

Which of the following ways will you document informed consent in languages other than English?
A full-length informed consent document

J3. Privacy and Intrusiveness

Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?
No

J4. Children

Will children be enrolled in the research?
No

J5. Neonates

Will non-viable neonates or neonates of uncertain viability be involved in research?
No

J6. Consent Capacity - Adults who lack capacity

Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?
No

J7. Prisoners

Will Prisoners be enrolled in the research?
No

Section K: Research Related Health Information and Confidentiality

Will research data include identifiable subject information?
Yes

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
Yes

Specific information concerning alcohol abuse:
No

Specific information concerning drug abuse:
No

Specific information concerning sickle cell anemia:
No

Specific information concerning HIV:
No

Specific information concerning psychiatry notes:
No

Demographic information (name, D.O.B., age, gender, race, etc.):
Yes

Full Social Security #:
No

Partial Social Security # (Last four digits):
No

Billing or financial records:
No

Photographs, videotapes, and/or audiotapes of you:
No

Identifiable biospecimens
Yes

Other:
No

At what institution will the physical research data be kept?
BCM

How will such physical research data be secured?
Secure storage

At what institution will the electronic research data be kept?
BCM

Such electronic research data will be secured via BCM IT Services- provided secured network storage of electronic research data (Non-Portable devices only):
Yes

Such electronic research data will be secured via Other:
No

Will there be anyone besides the PI, the study staff, the IRB and the sponsor, who will have access to identifiable research data?
No

Please describe the methods of transmission of any research data (including PHI, sensitive, and non-sensitive data) to sponsors and/or collaborators.
A Data Safety Monitoring Committee will review data for unanticipated adverse events. There is currently no plan to share research data with non-BCM personnel. For data to be transmitted between study personnel will be transmitted via BCM's encrypted/secure email system. All personnel are BCM employees and therefore have access to the BCM secure network. Any data files with patient information will be password protected and stored on the secure BCM server to ensure patient data security.

Will you obtain a Certificate of Confidentiality for this study?
No

Please further discuss any potential confidentiality issues related to this study.
All treatments will take place at BCM affiliated facilities, so no potential confidentiality issues are anticipated.

Section L: Cost/Payment

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.
Research procedures will be the application of 6 doses of HPV vaccine, requiring a clinic visit with the Gynecologic Oncology provider. These visits and medications will be covered by the institution/trial which is sponsored by the BCM Gynecologic Oncology division. All other visits and imaging are standard of care.

The study medications, including HPV vaccine, metformin and imiquimod, and vaginal applicators (if needed) will be provided at no cost to the study participants. The study sponsor (BCM Division of Gyn Oncology) will be providing these items.

After finishing the treatments, the patient will receive standard follow up care, which includes a PET/CT test about 3 months after treatment completion and follow up visits every 3 months for 2 years that include a physical/pelvic exam and evaluation of symptoms. They will also have a routine CT scan or PET scan (per doctor's preference) at 1 and 2 years after finishing treatment. Insurance will be billed for all standard of care visits and testing, and the patient will be responsible for any co-pays for these visits.

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.

Dollar Amount:
0

Distribution Plan:

Section M: Genetics

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.

Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family member's confidentiality?

Section N: Sample Collection

SAMPLE: Blood

What is the purpose of the sample collection?
Evaluate immune response

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.
10 mL (2 teaspoons) blood in EDTA-coated tubes at each of the 3 treatment visits (prior to initial treatment, mid treatment, and 6 months post treatment initiation). Peripheral blood samples will be collected in EDTA-coated tubes and peripheral blood mononuclear cells (PBMCs) will be isolated from the blood using the standard procedure with LymphoprepTM (Stemcell technologies, Cambridge, MA) density gradient centrifugation for use in flow cytometry analysis.

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:
Clinical Labs

Will the sample be stripped of identifiers?
No

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?
N/A

Will sample material be sold or transferred to any third parties? Will the information be de-identified?
N/A

If sample will be banked for future use:

Where will the sample be banked and for how long?
N/A

Does the banking institution have an approved policy for the distribution of samples?
N/A

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?
Yes

Will samples be made available to the research subject (or his/her medical doctor) for other testing?
No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?
No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?
Yes

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?
Data collected from samples will be password protected and stored on the BCM secure serve. If a subject revokes authorization their data will be deleted.

Will study data or test results be recorded in the subject's medical records?
No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?
Specific test results will not be released, since they are assessing immune response over time to determine the effect of the treatment on the immune response. Overall study results can be shared with the patients.

Please identify all third parties, including the subject's physician, to receive the test results.
None

SAMPLE: Other 1: Tumor cytobrushing

What is the purpose of the sample collection?
Two sterile disposable cytobrushes (Cytobrush Plus GT (Cooper Surgical, Trumbull, CT)) will be used to collect cells from the cervix by rotating the brush 360 with 3 to 4 full rotations against the tumor. Study of specific immune markers and modalities by which the combination immunotherapy boosts the immune system and works in sync with the standard of care to enhance its effects. Immune biomarker assays will be taken at the beginning, middle, and end of the treatment to measure using flow cytometry.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.
N/A

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:
Other: Provider

Will the sample be stripped of identifiers?
No

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?
No

Will sample material be sold or transferred to any third parties? Will the information be de-identified?

No

If sample will be banked for future use:

Where will the sample be banked and for how long?
Sample will not be banked

Does the banking institution have an approved policy for the distribution of samples?
N/A

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?
Remaining tissue will be stored in our -80 freezer located in our laboratory. Samples will be stored with a study ID and all patient identifiers will be removed. All samples will be disposed upon study publication.

Will samples be made available to the research subject (or his/her medical doctor) for other testing?
No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?
No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?
yes

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?
Data collected from samples will be password protected and stored on the BCM secure serve. If a subject revokes authorization their data will be deleted.

Will study data or test results be recorded in the subject's medical records?
No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?
Specific test results will not be released, since they are assessing immune response over time to determine the effect of the treatment on the immune response. Overall study results can be shared with the patients.

Please identify all third parties, including the subject's physician, to receive the test results.
N/A

SAMPLE: Tissue

What is the purpose of the sample collection?
Baseline evaluation of immunity prior to initiation of treatment

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.
N/A

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:
Pathology

Will the sample be stripped of identifiers?
No

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?
No

Will sample material be sold or transferred to any third parties? Will the information be de-identified?
No

If sample will be banked for future use:

Where will the sample be banked and for how long?
No

Does the banking institution have an approved policy for the distribution of samples?
N/A

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?
Stored in pathology

Will samples be made available to the research subject (or his/her medical doctor) for other testing?
No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?
No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?
yes

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?
yes

Will study data or test results be recorded in the subject's medical records?
No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?
Results of the overall study will be shared with the subject

Please identify all third parties, including the subject's physician, to receive the test results.
N/A

Section O: Drug Studies

Does the research involve the use of ANY drug* or biologic? (*A drug is defined as any substance that is used to elicit a pharmacologic or physiologic response whether it is for treatment or diagnostic purposes)
Yes

Does the research involve the use of ANY gene transfer agent for human gene transfer research?
No

O1. Current Drugs

Drug : Human Papillomavirus 9-valent Vaccine, Recombinant (Gardasil9)

Drug : imiquimod 5% cream (Aldara)

Drug : metformin

Is this study placebo-controlled?
No

Will the research involve a radioactive drug?
No

Section P: Device Studies

Does this research study involve the use of ANY device?

No

Section Q: Consent Form(s)

HPV 9-valent vaccine, recombinant; imiquimod; and metformin (HPV VIM) Trial

Section R: Advertisements

None