A Pilot Study of Ribavirin for Patients with Recurrent/Metastatic (R/M) Human Papillomavirus (HPV)-Related Malignancies

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This will be a single center pilot study for 12 patients, designed to evaluate the efficacy of ribavirin monotherapy for patients with recurrent and/or metastatic (R/M) HPV-related malignancies. The study will be conducted in the Head and Neck Service.

Study subjects will self-administer ribavirin 1400 mg PO BID (total dose, 2800 mg/day). All patients will complete pill diaries to document administration of study drug. Cycle length is 28 days with continuous dosing.

Toxicities will be graded according to NCI CTCAE version 4.

Clinic visits for safety assessments and routine laboratory studies will occur weekly in Cycle 1, in weeks 1 and 3 of Cycle 2, and on Week 1 of subsequent cycles. Cross sectional imaging (CT or MRI) is obtained at baseline and q2 cycles and at End-of Treatment (EOT). Response assessments will follow RECIST 1.1 criteria.

Patients may remain on study until disease progression or unacceptable toxicity. Research biopsies at time of progression will only be obtained in subjects who have had an initial radiographic response.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective: To obtain a preliminary efficacy assessment for ribavirin monotherapy among patients with R/M HPV-related malignancies

Secondary Objectives:
(1) To describe overall survival and progression-free survival;
(2) To describe the safety and tolerability of ribavirin in this patient population
(3) To explore Gli-1 expression, as detected by immunohistochemistry (IHC) in pre-treatment archived pathology samples, as a candidate biomarker for efficacy of ribavirin in these cancers;
(4) Among subjects who initially respond to ribavirin, to explore if subsequent acquired resistance is associated with increased Gli-1 expression.

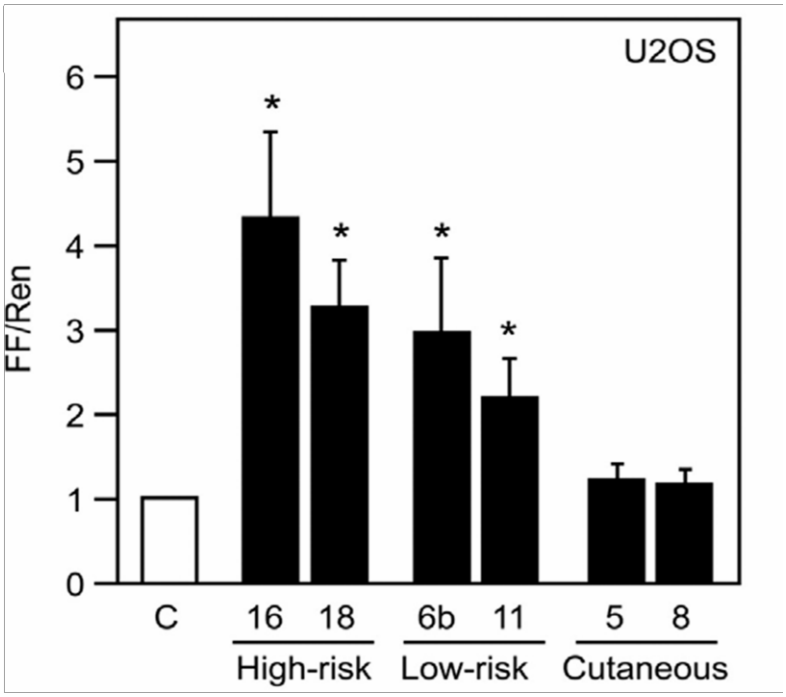
3.0 BACKGROUND AND RATIONALE

Rationale for targeting eIF4E in HPV-related cancers
Viruses have developed myriad ways to co-opt the host cell protein translational apparatus in a way that favors virus production [1, 2]. In the case of high risk human papillomavirus (HPV) strains, this has oncogenic implications. The HPV E6 viral oncoprotein, in addition to its well-established interaction with p53, also directly activates cap-dependent protein translation. We propose that impinging on E6-driven aberrant cap-dependent protein translation represents a new line of attack against HPV-related cancers.

The key regulatory step in cap-dependent translation is the binding of eIF4E (eukaryotic initiation factor 4E) to the translation initiation complex [3]. Research interest in eIF4E in oncology began with the discovery by Dr. Guido Wendel (now at SKI) that eIF4E can function as an oncogene when it is overexpressed in a murine lymphoma model [4]. It is now apparent that elevated eIF4E expression is a characteristic of HPV-related cancers. Three clinical research teams have observed that eIF4E expression progressively increases with degree of cervical pathology along the continuum from normal cervical tissue, to cervical intraepithelial neoplasia (CIN)/dysplasia, and finally to invasive cervical carcinoma [5-7]. We also observed that elevated expression of phosphorylated eIF4E is a characteristic of HPV-related tonsil squamous cell cancer in retrospective tissue microarray analysis [8].

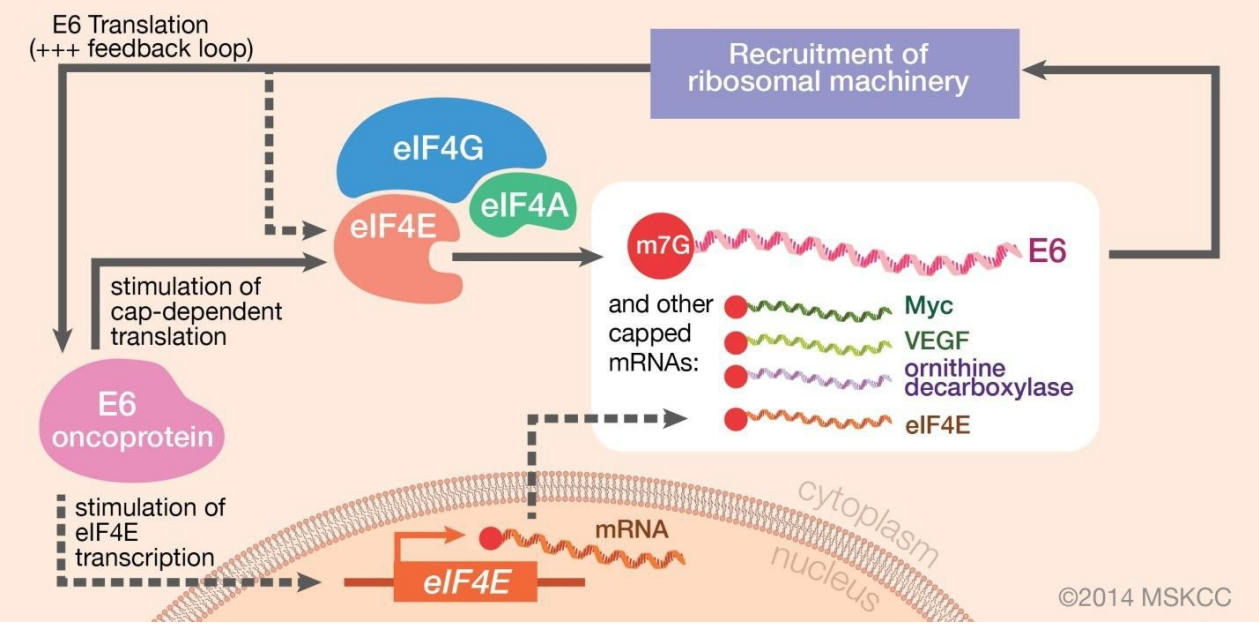
We propose that a positive feedback loop, centered at the level of protein translation, drives the expression of both E6 and eIF4E in HPV-related cancers. E6 stimulates the cap-dependent protein translation *in vitro* [9]. This effect of E6 on protein translation is a characteristic of high-risk oncogenic HPV strains. Potent stimulation of cap-dependent translation *in vitro* occurs with E6 protein from high-risk HPV16 and HPV18 strains and from low-risk HPV6b and HPV11 strains, but does not occur with E6 from non-oncogenic HPV5 and HPV8 [10] (Figure 1).

Figure 1: Mucosal but not cutaneous HPV E6 proteins increase cap-dependent protein translation. U20S cells were transiently co-transfected with the pFR-CrPV-xb bicistronic luciferase reporter construct and expression vectors for high-risk mucosal HPV E6 proteins (HPV 16, HPV 18), low risk mucosal HPV E6 proteins (HPV6b, HPV 11), cutaneous HPV E6 proteins (HPV5, HPV 8), or empty vector (C) as control. The Y axis indicates the ratio (FF/Ren) of expression of Firefly (FF) reporter, which is cap dependent, to Renilla (Ren) reporter, which is cap-independent. (Spangle. JM, Ghosh-Choudhury, N., Munger, K. 2012 J Virol 86: 7466-7472) [10].



Because E6 is encoded on a capped mRNA [11], it is likely that there is a positive feedback loop in which expression of E6 and expression of eI4E are mutually amplified (Figure 2). Additionally, there may be further positive feedback at the transcriptional level because E6 induces transcription of eIF4E in cell lines [5] (Figure 2).

Figure 2: Proposed positive feedback loop between he HPV E6 oncoprotein and the m7G cap-binding protein eIF4E: The E6 oncoprotein (pink) stimulates cap-dependent protein translation [9, 10], in which the binding of eIF4E to the m7G mRNA cap is a rate-limiting step [3]. Because E6 is encoded by capped mRNA [11], a positive feedback loop (solid arrowed lines) may be induced at the level of protein translation. There may also be a positive feedback loop at the transcriptional level due the ability of E6 to induce transcription of the eIF4E gene [5] (dotted arrowed lines).



Ribavirin is an antiviral agent that may be re-purposed for oncology due to eIF4E targeting

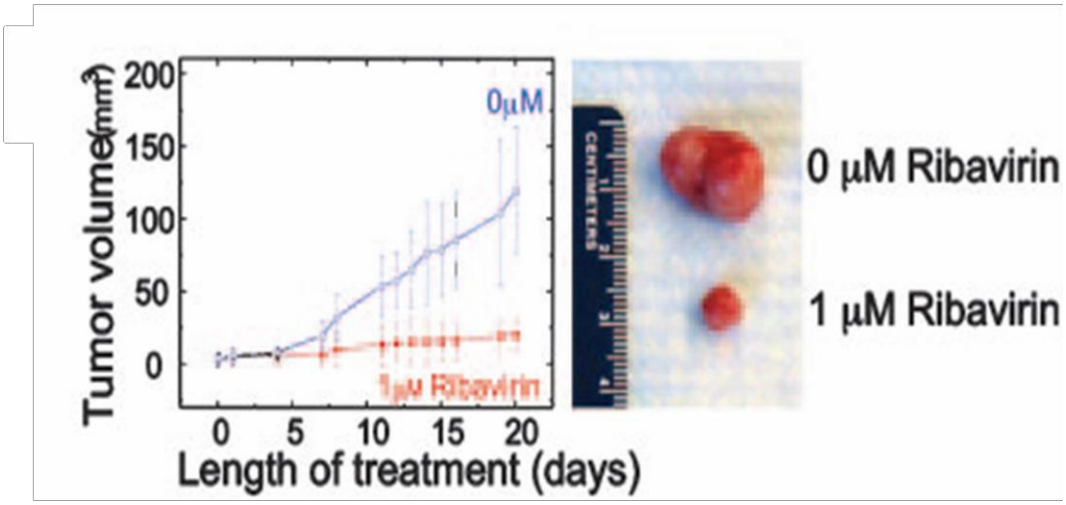
In 1972, the guanosine ribonucleotide analogue ribavirin (Virazole; 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) was reported to have broad spectrum activity against both RNA and DNA viruses [12]. The most common adverse events associated with ribavirin are mild anemia, cough, and rash. For patients treated with prolonged ribavirin, anemia usually is mild and hemoglobin remains in the normal range [13, 14]. The combination of ribavirin + peginterferon α-2b has been approved by the Food and Drug Administration as effective treatment for chronic hepatitis C [15, 16].

In the otolaryngology literature, ribavirin is known to have activity against laryngeal papillomatosis (LP), a rare HPV-related disease in which the upper airway becomes progressively occluded with benign mucosal papillomas. Repeated laser surgery for removal of lesions has been commonly applied as a management strategy. In a small pilot study, patients (3 adults, 1 child) received pre-operative ribavirin (23 mg/kg daily) on the day of laser surgery, and continued oral ribavirin at the same daily dose for an additional 6 months (only 3 months for the child). The viral strain was HPV 6 in the papillomas of three patients, and was HPV 11 in one patient. Ribavirin treatment was associated a decrease in observable disease on follow up examinations, as determined by a previously described mapping score. Ribavirin treatment was associated with an increase in the time interval between successive required surgeries by a factor of at least 2 in all patients [17]. The efficacy of ribavirin against LP was confirmed in a subsequent case report [18], and ribavirin is considered to be one treatment option for this uncommon entity [19].

In 2004, Dr. Alex Kentsis (now at SKI, but then working in the lab of Dr. Katherine Borden) published that ribavirin has anti-cancer activity pre-clinically that is directly related to eIF4E-targeting [20]. In xenograft experiments with an eIF4E-depedent head and neck SCC cell line (FaDu), ribavirin

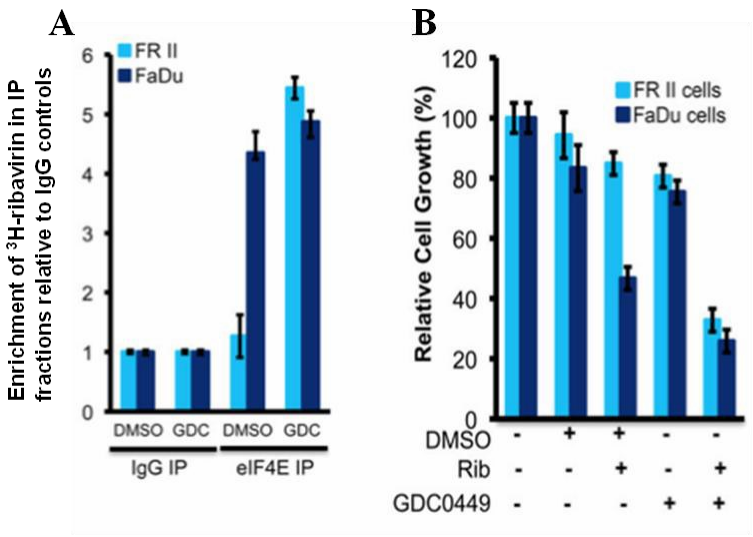
treatment (40 µg/kg daily) yielded tumor volume that was 6-fold less than in the untreated control group (Figure 3) [20]. Dr. Borden's group subsequently studied ribavirin in M4/M5 acute myeloid leukemia (AML), another tumor type that is characterized by elevated eIF4E expression. In a proof of principle trial, ribavirin demonstrated encouraging activity, with 1 complete remission, 2 partial responses, 2 blast responses, 4 stable diseases, and 2 progressive diseases among 11 evaluable patients with M4/M5 AML. [21].

Figure 3: Ribavirin activity against head and neck SCC xenograft. Mean tumor volume in nude mice engrafted with cells derived from a head and neck SCC eIF4E-dependent tumor (FaDu) as a function of treatment with daily 1 µM ribavirin orally at a dose of 40µg'kg per day (orange line) or control treatment (blue line). Photographs of tumors resected after 20 days of treatment (Kentis A, et al. 2004 PNAS 101: 18105-18110) [20].



Dr. Borden's group has moved beyond the initial description of the anticancer efficacy of ribavirin in AML, to describe recently the most common mechanism of resistance to this drug: glucuronidation of ribavirin, mediated by the sonic hedgehog factor Gli-1 [22]. Ribavirin binds eIF4E in sensitive FaDu cells, but not in FRII cells with acquired resistance (Figure 4A). RNASeq demonstrates that ribavirin-resistant FRII cells have 21-fold elevation of Gli-1 [22]. Gli-1 upregulation leads to ribavirin glucuronidation. Pre-treatment of resistant cells with GDC-0449 (vismodegib, a small molecule inhibitor of sonic hedgehog signaling upstream of Gli-1) restored sensitivity to ribavirin (Figure 4B). Conversely, forced over-expression of Gli-1 in FaDu cells conferred resistance to ribavirin [22]. This mechanism also was observed in AML patients with acquired resistance to ribavirin in a phase II trial (NCT01056523; manuscript in preparation, K. Borden, pers. comm.). These mechanistic insights into ribavirin resistance mechanism can inform the subsequent development of ribavirin in oncology.

Figure 4. Acquired Resistance to Ribavirin is associated with loss of ability of the drug to bind eIF4E. (A) ^{3}H-Ribavirin co-immunoprecipitates (IPs) with eIF4E in FaDu cells, but not in cells with acquired resistance to ribavirin (FRII cells). GDC-0449 restores ability of ^{3}H-Ribavirin to co-IP with eIF4E in FRII cells. (B) Cell growth of FRII cells and FaDu cells as a function of Gli-1 inhibition with 200nM GDC-0449 (courtesy of K. Borden, adapted from: Zahreddine HA, et al Nature 2014 May 28 Epub ahead of print) [22].



Potential future implications: targeting eIF4E in combination therapy regimens

We now seek to develop ribavirin as an eIF4E-targeting strategy in HPV-related cancers. We envision that this approach could mature into future vertical inhibition strategies with other inhibitors of the PI3K/mTOR (phosphatidylinoslitol-3 kinase /mammalian target of rapamycin) pathway. eIF4E is downstream of mTOR in the PI3K/mTOR pathway, and there appears to be a convergence of molecular alterations on this pathway in HPV-related cancers. Mutations in *PIK3CA*, the gene encoding the catalytic subunit of PI3K, occur in approximately 25-30% of HPV related oropharynx cancers [23]. Cervical cancer studies have reported *PIK3CA* mutation rates of 14% to 31% [24, 25]. Although other anogenital cancers have been less well studied, one report demonstrated that *PIK3CA* hotspot mutations occur in 16% of anal cancers [26] and aberrant expression of eIF4E has been described in penile squamous cell cancer [27]. The convergence of molecular alterations along this pathway in HPV-related cancers suggests a strategy of blocking the pathway at upstream (PI3K) and downstream (eIF4E) locations.

The first-in-human trial of BYL719, an orally administered α-specific PI3K inhibitor, provided encouraging results against HPV-related head and neck cancer. In this phase I trial for 72 patients with advanced solid tumors harboring *PIK3CA* alterations, 2 of the 3 best radiographic

responses in the study occurred in HPV positive head and neck cancers [28]. This phase I observation has prompted further study of BYL719 against head and neck cancers (MSKCC IRB 14-

116 and 14-021 [29]). It is likely that targeting PI3K may have useful activity against other HPV-related tumors as well. However, in order to obtain deeper and more durable responses, we anticipate that combination therapy strategies will be necessary. If ribavirin demonstrates clinically useful activity against HPV-related cancers, vertical inhibition to completely shut down the PI3K/mTOR/eIF4E axis in HPV-related cancers could be achieved by combining ribavirin with a PI3K inhibitor. In view of the central role that radiation therapy plays in the clinical management of HPV related cancers , future studies could also seek to build on the preclinical observation that targeting of eIF4E with ribavirin achieves radiosensitization against cancer cell lines [30].

Preliminary Data:

To determine if ribavirin targets eIF4E in HPV-related cancers, we conducted a pilot 'window of opportunity" study to evaluate the pharmacodynamic effects of ribavirin on the expression of phosphorylated eIF4E in HPV-associated oropharynx squamous cell cancer (MSKCC IRB 10-218; NCT01268579). The primary endpoint was to determine if ribavirin reduces phosphorylated eIF4E expression in post-treatment biopsy samples, as evaluated by IHC. Patients received ribavirin for approximately two weeks, and underwent pre and post-treatment tumor biopsies. Among 6 evaluable patients, marked reductions of the expression of phosphorylated eIF4E were detected in 4 cases. One patient was inevaluable because there were no viable cells on the fine-needed aspirate of tumor after 2 weeks of ribavirin treatment, but he did have marked reduction in jaw pain during treatment period with ribavirin. The results are summarized in Table 1, and Figure 5 illustrates a representative case. IRB 10-218 was not a study for therapeutic intent; study drug was given only for 2 weeks only. IRB 10-218 provides further evidence that ribavirin targets eIF4E, strengthening the rationale for the proposed therapeutic study.

Figure 5: Example of eIF4E targeting in HPV –associated oropharynx cancer 'window-of-opportunity" study, IRB 10-218. IHC detection of phosphorylated eIF4E (Cell Signaling #9741) in pre treatment (A) and ribavirin treatment day 14 (B) surgical pathology samples in patient with newly diagnosed HPV related oropharynx SCC.

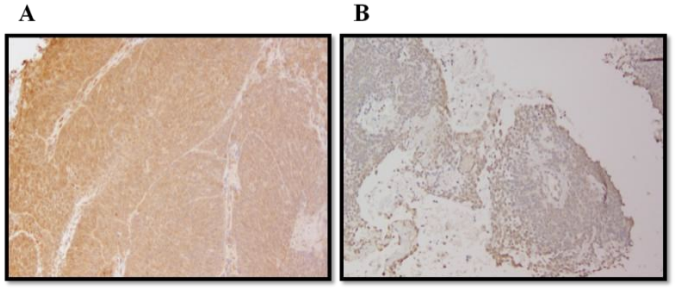


Table 1: Expression p-eIF4E (percent positive by IHC) in pre and post treatment biopsies in window-of-opportunity study IRB 10-28.

Subject #	Baseline p-eIF4E	Post Tx p-eIF4E
1[ǂ]	90%	No viable cells
2	70%	30%
3	90%	30%
4*	70-80%, strong	40-50%, weak
5*	40%	40%
6	80%	50%
7	80%	80%

[ǂ] Inevaluable, due to lack of viable cells on fine needle aspirate after 2 weeks.

*Samples for Subjects 4 and 5 were surgical pathology samples. Samples for Subjects 1, 2, 3, and 6 were fine needle aspirates. Results are scored as the percentage of tumor cells staining positively for p-eIF4E by IHC.

Dr. Katherine Borden and colleagues at the University of Montreal studied ribavirin in a phase I/II study for AML (ClinicalTrials.gov identifier NCT01056523), another malignancy that expresses high levels of eIF4E. They established that the phase II recommended dose of ribavirin in oncology is 1400 mg PO BID (K. Borden, pers. comm., clinical manuscript in preparation; correlative science data from NCT01056523 has been published [22]). As such, the ribavirin dosing for oncology studies differs from the dosing of this drug for hepatitis C [15].

We now propose a pilot “basket study” for patients with any R/M HPV related cancer (oropharynx, cervical, vulvar, vaginal, anal, and penile) for which there is not a curative-intent standard therapy option.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This will be a single-institution pilot trial. The primary endpoint is to obtain a preliminary efficacy assessment for ribavirin monotherapy among patients with R/M HPV-related malignancies. There is no randomization or dose escalation.

4.3 Intervention

Subjects will self administer ribavirin 1400 mg PO BID (total, 2800 mg/day). Cycle length is 28 days with continuous dosing. Toxicities will be graded according to NCI CTCAE version 4. Clinic visits for safety assessments and routine laboratory studies will occur weekly in Cycle 1, in weeks 1 and 3 of Cycle 2, and on Week 1 of subsequent cycles. Cross sectional imaging (CT or MRI) is obtained at baseline and q2 cycles and at End-of Treatment (EOT). Response assessments will follow RECIST 1.1 criteria. Patients may remain on study until disease progression or unacceptable toxicity. At time of progression of disease, research biopsies will only be obtained in patients who had initial radiographic response.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Ribavirin
Availability and Administration:

Generic ribavirin is commercially available as 200 mg, 400mg, and 600 mg tablets, which will be orally administered by the patients themselves. Ribavirin will be purchased from the hospital pharmacy. Tablets are supplied in bottles of 84 capsules (200 mg each). Ribavirin is available as blue-colored (shade depending on strength), capsule-shaped, film-coated tablets. Medication labels will comply with US legal requirements and be printed in English. The storage conditions for study drug will be described on the medication label. Ribavirin tablet should be taken with food (but it will not be considered a protocol violation if a subject takes dose on an empty stomach).

Pharmacology:

Ribavirin oral tablet administration is characterized by rapid absorption with a t_{max} of approximately 2 hours, followed by rapid distribution and long terminal phases. Mean γ-phase half-life has been reported to be in the range of approximately 30 - 61 hours after a single dose, and 274 - 296 hours following multiple doses. Mean bioavailability is approximately 30 - 50%. Apparent plasma clearance is approximately 20 L/h. Population based pharmacokinetic models have identified factors associated with lower apparent clearance of ribavirin (female gender, higher age, and low body weight), but taken together these factors account for less than 30% of the variability in clearance [31-34].

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

1. Recurrent and/or metastatic HPV-related carcinoma of the cervix, anus, vagina, vulva, penis, or oropharynx. The cancer diagnosis must be confirmed by slide review in the MSKCC Department of Pathology. HPV positive status must be demonstrated by HPV in situ-hybridization (ISH) and/or by p16 immunohistochemistry (IHC).
   Note: For cervix squamous cancer, HPV ISH test or p16 IHC test is not required, because all cervix squamous cancers are presumed to be HPV-associated.

2. Adults (≥ 18 years of age)

3. ECOG performance status of 1 or better

4. Measurable disease according to RECIST 1.1 criteria

5. Availability of archived tumor tissue for correlative studies (5 unstained slides)

6. Adequate organ function, as follows:
   Adequate bone marrow reserve: absolute neutrophil count (ANC) ≥ 1.5 X 10^9/L, platelets ≥ 160 X 10^9/L, hemoglobin ≥ 10 g/dL

   Hepatic: total bilirubin within ULN (upper limit of normal); alkaline phosphatase (AP), aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.0 X ULN

   Renal: Serum creatinine ≤ 1.3 mg/dL. Patients with serum creatinine > 1.3 mg/dL may be eligible if creatinine clearance (CrCl) ≥ 55 mL/min based on the standard Cockroft and Gault formula.

7. Ability to swallow oral medication.

8. Patients of childbearing potential must have a negative serum pregnancy test within 14 days of treatment. Patients must agree to use a reliable method of birth control during and for 6 months following the last dose of study drug.

9. At least one prior systemic therapy regimen for R/M HPV-related carcinoma

6.3 Subject Exclusion Criteria

1. History of hemolytic anemia or thalassemia

2. Current treatment or known prior treatment with ribavirin

3. Active infection or serious underlying medical condition that would impair the patient's ability to receive protocol treatment.

4. Current therapeutic anticoagulation with Coumadin (warfarin)

5. Known brain metastases

7.1 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team here at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discus the study and their potential for enrolling in the research study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of the medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of 1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; 2) conversing with patients regarding possible enrollment; 3) handling of PHI contained within those records and provided by the potential subjects; and 4) maintaining information in a screening log of patients approached.

8.1 PRETREATMENT EVALUATION

- Complete medical history including current medications, physical examination including evaluation of ECOG performance status within 14 days prior to therapy.
- Pathology review at MSKCC
- The following laboratory studies will be obtained within 14 days prior to therapy: Complete blood count with white blood cell differential and platelet counts; Comprehensive profile (including electrolytes, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, albumin, and glucose); prothrombin time and activated partial thromboplastin time
- Serum pregnancy test for women of childbearing potential within 14 days prior to therapy.
- Electrocardiogram within 8 weeks prior to therapy
- Baseline cross-sectional imaging of the known sites of disease (CT or MR) within 4 weeks prior to therapy

9.0 TREATMENT/INTERVENTION PLAN

9.1 Clinical Plan

Study subjects will self-administer ribavirin 1400 mg PO BID (total dose, 2800 mg/day).

Ribavirin should be taken with food, not in a fasting condition.

All patients will complete pill diaries to document administration of study drug. Patients should be instructed to bring completed pill diaries and all pill bottles to each visit.

Cycle length is 28 days with continuous dosing. Clinic visits for safety assessments and routine laboratory studies will occur weekly in Cycle 1, in weeks 1 and 3 of Cycle 2, and on Week 1 of subsequent cycles (± 3 days). Although clinic visits and lab tests should generally occur on the same day each week to facilitate continuity with providers, there is no requirement regarding the day of the week of these visits.

Toxicities will be graded according to NCI CTCAE version 4.

Cross sectional imaging (CT or MRI) is obtained at baseline and q2 cycles. Imaging scans will be scheduled to occur in the last week (± 2 days) of each even-numbered cycle. However, after completion of cycle 4, the interval between scans may be increased to q3 cycles, at the discretion of the investigator.

Response assessments will follow RECIST 1.1 criteria (See Section 12).

Patients may remain on study until disease progression or unacceptable toxicity. There will be a post-treatment visit 30 days (± 7 days) from last dose of drug for patients who maintain active follow up. If a patient is unable to attend the post-treatment visit due to medical or logistical issues or lost to follow-up, this will not be a protocol violation.

9.2 Immunohistochemistry (IHC)

Anti Gli-1 antibody (Glioma associated oncogene 1; H-300 rabbit polyclonal, Santa Cruz Biotechnology, sc-20687) has been used extensively for IHC in studies of cervix cancer and head and neck cancer [35, 36] and will be optimized for IHC in our Pathology Core. Formalin-fixed paraffin-embedded (FFPE) slides will be prepared in the Department of Pathology according to standard practices, and will be analyzed by Dr. Nora Katabi. Archived FFPE pre-treatment tumor samples will be processed for IHC detection of Gli-1 and scored by the study pathologist (scale 0-3 dichotomized to low/high).

For any patients who initially experience a radiographic response to ribavirin by RECIST 1.1 (confirmed or unconfirmed), at time of subsequent disease progression a research tumor biopsy will be obtained (unless such biopsy is deemed to pose unacceptable safety risk). Gli-1 expression will be assessed by IHC, in an effort to explore if increased Gli-1 expression (compared with pre-treatment tissue) may be associated with acquired resistance to ribavirin in patients with HPV-related malignancies. These post-treatment biopsies should generally be obtained within 2 weeks of the last dose of ribavirin, although it will not be considered a violation if the biopsy occurs outside of this time window. The gauge of the needle will be at the discretion of the interventional radiologist, although 18 gauge is preferred.

Post-treatment biopsies will not be obtained in patients who do not initially respond to ribavirin.

(*Note:* Pharmacokinetics (PK) will not necessary for this study. PK for standard dosing of ribavirin was established in the 1980s, and PK for escalated ribavirin dosing in cancer was investigated in NCT00559091, NCT01056523, NCT01056757, and NCT01309490.)

10.0 EVALUATION DURING TREATMENT/INTERVENTION.

		Cycle 1	Cycle 2	Cycle ≥3	Post Treatment[d]
	Baseline	Weeks 1, 2, 3 and 4	Weeks 1 and 3	Week 1	
History and Physical	X	X	X	X	X
CBC, Comp panel	X	X	X	X	X
PT/aPTT	X				
Serum Pregnancy Test	X				
EKG [a]	X				
Radiologic Assessment (CT or MRI)[b]	X		X	X	
Archival Tissue	X				
Research biopsy					X[c]
Adverse Event and Concomitant Medications Monitoring		Continuous Monitoring for Adverse Events			
Ribavirin		Continuous BID dosing			

[a] Baseline EKGs to be performed within 8 weeks prior to treatment

[b] Radiologic assessments occur at baseline (within 4 weeks of starting treatment) and q2 cycles. Imaging scans will be scheduled to occur in the last week (± 2 days) of each even-numbered cycle. However, after completion of cycle 4, the interval between scans may be increased to q3 cycles, at the discretion of the investigator.

[c] Research biopsy at time of progression of disease is only for patients who experience initial radiographic response. When done, every effort should be made to obtain the research biopsy within 2 weeks of the last dose of ribavirin.

[d] The post treatment evaluation should occur 30 days (± 1 week) after the last dose of ribavirin, for patients who maintain active follow up. The one exception is the post-treatment biopsy for patients who had previously responded (see footnote b)

11.1 TOXICITIES/SIDE EFFECTS

11.2 General Considerations

Ribavirin Toxicities:
Hematologic: anemia, thrombocytopenia, leukopenia, lymphopenia
Gastrointestinal: anorexia, nausea, diarrhea
Hepatic: elevated liver function tests
Pulmonary: dyspnea, cough
Reproductive: may be teratogen
Constitutional: fatigue, musculoskeletal pain
Dermatologic: alopecia, pruritus, rash
Neurologic: headache, dizziness
Endocrine and metabolic: hyperuricemia

The listed ribavirin toxicities include those side effects described in the treatment of hepatitis C in which ribavirin may be given in combination with peginterferon alfa [13-16], and those side effects described in other settings including oncology research in which ribavirin was given at doses up to 1400 mg po BID [37][17, 21].
Even when the patient meets criteria for continued treatment at full dose per the protocol, the investigator retains the discretion to delay the next treatment and/or reduce ribavirin dose if there are safety concerns and/or logistical issues. Any dose reductions not specified in the protocol should be discussed with the principal investigator.

Doses that have been reduced for toxicity must not be re-escalated.

Treatment delays of up to 21 total days per cycle are allowed in a given cycle. Any patient who requires a treatment delay of >21 days, for medical and/or logistical reasons, in a given cycle should be removed from study.

If an investigator feels that a patient requires a dose reduction and/or dose delay other than those specified herein, this may be allowed after communication with the Principal Investigator, and would not be considered protocol violation. If the Principal Investigator is unavailable, Co-PI or designated covering investigator may address such issues as they arise.

Dose modifcation guidelines in this section are only for those adverse events thought to be at least possibly related to ribavirin.

Dose Modification Scheme

Dose Level	AM/PM Dose	Total Daily Dose
Full Dose	1400 mg PO BID	2800 mg
Dose Level Minus 1	1000 mg PO BID	2000 mg
Dose Level Minus 2	800 mg PO BID	1600 mg
Dose Level Minus 3	600 mg PO BID	1200 mg

11.3 Hematologic Toxicity Management

Hemoglobin

The most common toxicity requiring dose reduction for ribavirin is anemia.

For any patient who experiences a fall in hemoglobin of > 3 g/dL (from Day 1 value; or from the hemoglobin value at the time of the previous dose reduction) and/or a drop in hemoglobin level to < 8.0 g/dL, ribavirin dose will be decreased by one dose level.

Packed Red Blood Cell (PRBC) transfusion for symptomatic anemia is allowed, at the discretion of the investigator. However, any PRBC transfusion must be accompanied by dose reduction by one dose level. For any patient who requires PRBC transfusion, repeat complete cell count should be obtain within 1 week after completion of the transfusion to provide a new baseline hemoglobin level for consideration of subsequent hemoglobin levels.

Absolute Neutrophil Count (ANC) and Platelets

ANC (K/mcL) and Platelet Count (K/mcL)
ANC ≥ 1.0 and Plts ≥ 100: Treat without dose reduction.
ANC < 1.0 and/or Platelets <100: Hold. If repeat ANC the next week ≥ 1.0 and repeat Plts next week ≥ 100, resume treatment. Dose reduction by one dose level is not mandatory, but is allowed at the discretion of the investigator.
*Febrile Neutropenia**: Hold until resolution. When ANC ≥ 1.5 and afebrile and Plts ≥ 100, may proceed but reduce by 1 dose level

Dose delays and dose reductions are not required for uncomplicated leukopenia, uncomplicated lymphopenia, or other abnormal values in the complete blood cell count (other than hemoglobin ANC, and platelets) without clinical consequence.

11.3 Hepatic Toxicity Management

11.3.1 Alkaline Phosphatase, ALT, AST

If AST and ALT are both elevated, the more abnormal of the two values (AST or ALT) should be used in determining the dose.

	AST or ALT:			
ALK PHOS:	**≤ ULN**	**>1X but ≤1.5X ULN**	**>1.5X but ≤5X ULN**	**>5X ULN**
≤ 1.5 X ULN	Full Dose	Full Dose	Treat at Full Dose, Or Treat at Reduced Dose, Or Hold, at discretion of investigator*	Hold*, [2]
>1.5 X but ≤ 2.5X ULN	Full Dose	Full Dose	Hold or Treat at Reduced Dose, at discretion of investigator*	Hold*, [2]
>2.5X but ≤ 5X	Full Dose	Hold*	Hold*, [1]	Hold*, [2]
>5X ULN	Hold*	Hold*	Hold*, [2]	Hold*, [2]

*****If treatment is held, treatment should not resume until liver function tests have "recovered", maximum 21 days. "Recovered" is defined as meeting requirements for treatment according to this table.

[1] Upon recovery, resume treatment at full dose or reduce by 1 dose level, at the discretion of the investigator.
[2]Upon recovery, resume treatment at next lower dose level

11.3.2 Bilirubin

Total bilirubin > ULN but ≤ 1.5 X ULN: May hold treatment, treat at full dose, or treat at reduced dose, at the discretion of the investigator

Total bilirubin > 1.5 X ULN: Hold treatment until serum total bilirubin is ≤ 1.5 X ULN (maximum 21 days), then re-treat at next lower dose level

11.4 Renal Toxicity

If serum creatinine is ≥ 1.5 on planned treatment date, estimate the creatinine clearance (CrCl) by the Cockcroft and Gault Equation.

Calculated Creatinine Clearance (CrCl)	Management
≥ 45 ml/min	Hydrate as clinically indicated. May treat at full dose, treat at next lower dose level of ribavirin, or hold treatment, at the discretion of the investigator.
< 45 ml/min	Hold treatment for the week and hydrate as clinically indicated. If repeat CrCl ≥ 45 ml/min, may resume treatment at the next lower dose level of ribavirin

11.5 Diarrhea

Grade 1 or Grade 2 Diarrhea:
Ribavirin treatment may be continued at full dose, continued at the next lower dose level, or held. Antidiarrheals may be used as needed. Dose reduction is at the discretion of the investigator.

Grade 3 Diarrhea:
In the event of diarrhea requiring hospitalization (ie, Grade 3), supportive measures may include hydration, octreotide, and antidiarrheals.

Ribavirin treatment will be held until diarrhea has improved to ≤ Grade 1, with dose reductions as follows:

If Grade 3 diarrhea duration is ≤ 48 hours, the next treatment may be given at full dose or at the next lower dose level, at the discretion of the investigator.

If Grade 3 diarrhea duration is > 48 hours, subsequent ribavirin should be given at the next lower dose level

Grade 4 Diarrhea:
Off Study (if felt to be treatment related)

11.6 Nausea/Vomiting

Prophylactic anti-emetics are not planned. However, for any patient experiencing nausea, use of anti-emetics is at the discretion of the investigator.

For any patient experiencing ≥ Grade 3 nausea > 72h and/or ≥ Grade 3 vomiting > 24h during a cycle, if felt to be possibly related to ribavirin, then upon resolution of these toxicity(ies) to ≤ Grade 1, ribavirin may be resumed at the next lower dose level of ribavirin. Anti-emetics may be incorporated at the discretion of the investigator.

11.7 Non-hematologic toxicity not otherwise specified

Dose delay and/or dose reduction is optional at the discretion of the investigator as regards the following ≥ grade 3 adverse events: dental adverse events, hearing-related adverse events, INR or aPTT elevation, insomnia, weight gain or weight loss, SIADH, low bicarbonate, low albumin, hypophosphatemia. Similarly, the decision regarding whether to institute dose modifications for grade 2 or 3 fatigue will be at the discretion of the investigator.

For non-hematologic toxicity not otherwise specified:

≥ Grade 3: Interrupt until resolved to ≤ grade 1, then:
If resolution to grade ≤1 in ≤ 7 days, resume ribavirin at the current dose level or at next lower dose level, at investigator discretion
If resolution to grade ≤1 in > 7 days, resume ribavirin at one lower dose level

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Response and progression will be evaluated in this study using modified international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [38]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. The schedule for scan assessments is provided in Section 10.

12.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on study.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be discussed with the principle investigator.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks prior to registration.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

12.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).
The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.
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13.0 CRITERIA FOR REMOVAL FROM STUDY

Any patient who experiences toxicity requiring ribavirin dose reduction below "dose level minus 3" (See Section 11.1) will be removed from study.

Any subject who requires treatment delay of more than 21 days in a given cycle will be removed from study.

If at any time the patient develops progressive disease, he/she will be taken off study.

Patients may be removed from the study for protocol non-compliance.

If at any time the patient develops unacceptable toxicity, he/she will be removed from study.

Participants can be removed from the study at any time if the study doctor feels that it is in their best interest to do so.

14.0 BIOSTATISTICS

A sample size of 12 patients will be accrued and followed until progression of disease (or until removal of study for other medical/logistical reasons), in this pilot study with the objective to obtain preliminary evidence of efficacy in the selected patient population of R/M HPV related malignancies. Radiographic responses, determined by RECIST 1.1 criteria, will be tabulated by adding partial responses and complete responses (CR + PR). The best response for each patient during the study will be used.

Efficacy considerations for the statistical design of this study are informed by historical data regarding second-line or greater systemic therapy for patients with recurrent/metastatic (R/M) head and neck cancer, cervical cancer, or anal cancer. Among patients with R/M head and neck cancer, the historical estimate for objective response rate with palliative chemotherapy after first line is 15% [39, 40]. Similarly, the response rate of palliative single agent chemotherapy for advanced cervical cancer is approximately 15-20% [41, 42]. For R/M anal cancer, no regimen has been shown to be effective after first line platinum + 5-fluorouracil [43].

The regimen would be considered worthy of further study if radiographic responses are observed in at least 2 of 12 subjects. The probability of missing an effect (observing 0 or 1 responses out of 12 patients if the true response rate is 30%), is 0.09. Overall Survival and Progression-Free Survival will be estimated with the Kaplan-Meier method.

Tissue correlative studies will be for purposes of hypothesis generation. We will explore if the anti-Gli-1 IHC score (scale 0-3 dichotomized to low/high) is related to response (CR+PR) using Chi-square or Fisher's exact test. The following provisional scoring system will be used (% refers to percentage of tumor cells that stain positively [cytoplasm and/or nucleus] for Gli 1):
IHC score 0: <=5%
IHC score 1: >5 and <=30%
IHC score 2: >30% and <=50%
IHC score 3: >50%

Additionally, baseline and post-progression Gli-1 expression will be reported (using this provisional scoring system) among the patients who have an initial radiographic response and a post-progression biopsy.

The number and grade of toxicities will be tabulated using NCI CTCAE version 4, as well as the number of dose reductions in all cycles.

The projected accrual rate is 1 to 2 patients per month.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

Not applicable. There is no randomization in this study.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb5.mskcc.org/intranet/_assets/_tables/content/359709/DSMPlans07.pdf*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for

Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol is assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Potential risks to human subjects include drug related toxicity, pain and discomfort associated with ribavirin side effects (Section 11), phlebotomy, and possible psychological discomfort from the stresses associated with obtaining imaging studies (eg, CT scan), and possible risks associated with research biopsy. All efforts will be made to avoid any complication by completely reviewing patients' symptoms, providing appropriate management, and monitoring blood tests.

If an adverse medical event occurs, the patient will first contact his/her study doctor, a research nurse, or the Principal Investigator. At nights and on weekends, there is an oncology physician on call at all times. Patients may either call or come directly to the Urgent Care Center at Memorial Hospital (or to their local emergency room) to be seen. Patients suffering serious adverse reactions must be carefully followed and all follow-up information also recorded.

Participation in this trial is voluntary. All patients who participate in the study must provide written informed consent.

The patient will be responsible for all costs related to treatment and complications of treatment. Costs to the patient (third party insurer) will include the costs hospitalizations, routine blood tests and diagnostic studies, office visits, baseline EKG, and doctor's fees. Patients will not be charged for ribavirin or any research tests performed on research specimens (research biopsy, immunohistochemistry).

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

17.2.1

Not applicable.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

20.0 APPENDICES

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20.0 APPENDICES

Appendix A. Pill Diary