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A Multi-Center open label single arm phase II trial evaluating the efficacy of palbociclib in combination with carboplatin for the treatment of unresectable recurrent or metastatic head and neck squamous cell carcinoma
(Short Title: CarPal Head and Neck)

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Study Drug: Palbociclib (Ibrance®)
Carboplatin

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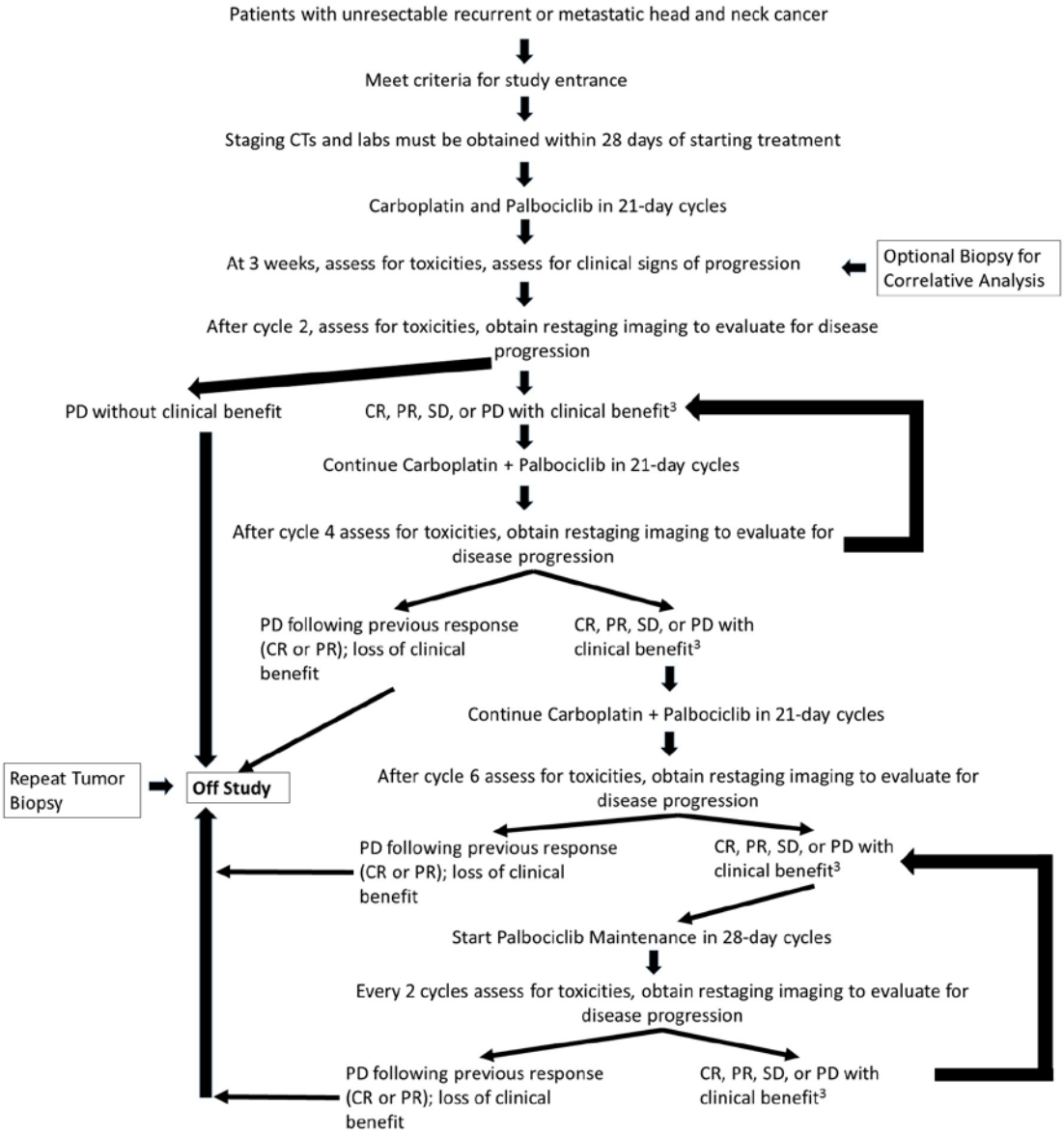
ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSU	Clinical Trials Support Unit
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IND	Investigational New Drug
IRB	Institutional Review Board
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
p.o.	per os/by mouth/orally
PR	Partial Response
PRC	Protocol Review Committee
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
UaP	Unanticipated Problem
WBC	White Blood Cells

STUDY SCHEMA



STUDY SYNOPSIS

Title	A Multi-Center open label single arm phase II trial evaluating the efficacy of palbociclib in combination with carboplatin for the treatment of unresectable recurrent or metastatic head and neck squamous cell carcinoma (Short Title: CarPal Head and Neck)
Phase	Phase II
Methodology	Open label, single arm trial
Study Duration	36 months
Study Center(s)	Multicenter - up to 3 sites including the lead site University of Michigan
Objectives	Primary Objective 1. To assess evidence of anti-tumor activity by assessment of disease control rate (CR + PR + SD) at 12 weeks in patients with metastatic head and neck squamous cell cancer treated with carboplatin and palbociclib Secondary Objectives 1. To assess survival in patients with metastatic head and neck squamous cell cancer treated with carboplatin and palbociclib 2. To describe the adverse events associated with use of carboplatin and palbociclib Exploratory Objectives 1. Explore the response to therapy based on CDK4, CDK6, Cyclin D1, CDKN2A and HPV genetic status 2. Evaluate whether molecular and biochemical markers are predictive of tumor response including: - Correlate genetic subtype with response via targeted DNA and RNA-sequencing of pre-treatment biopsy. - Assess the expression of CDK4, CDK6, Cyclin D1, CDKN2A in tumors as well as level of vascularization (CD31+ cells), apoptosis (TUNEL), proliferation (Ki67), and tumor infiltrating lymphocyte content (CD4/CD8, etc.). 3. Assess whether the dynamics of circulating tumor DNA (ctDNA) are associated with clinical and radiographic responses to therapy as well as monitor for the presence and quantity of HPV DNA or DNA containing somatic mutations identified in the targeted sequencing of the biopsy specimen.
Number of Subjects	40 evaluable patients

Inclusion Criteria	1. Histologically documented progressive squamous cell head and neck cancer with or without metastases, not amenable to curative treatment; or the patient has documented refusal of curative treatment. 2. ECOG performance status of 0-2 3. Presence of measurable disease by CT scan by RECIST v1.1. 4. Adequate bone marrow, hepatic, and renal function (including WBC≥ $3x10^9$ cells/ml, ANC ≥ $1.5x10^9$ cell/ml, platelets ≥75,000 cells/mm^3, hemoglobin ≥ 9.0 g/dL, concentrations of total serum bilirubin within 1.5 x upper limit of normal (ULN), AST, ALT within 2.5x institutional upper limits of normal unless there are liver metastases in which case AST and ALT within 5.0 x ULN, serum creatinine clearance ≥ 30 ml/min). 5. Age ≥18 years. 6. Life expectancy of ≥12 weeks. 7. Women of childbearing potential must have a negative serum or urine pregnancy test at time of screening and confirmed within 3 days prior to treatment. Women not of child-bearing potential will be defined as all women older than age 50 and anovulatory for 12 months. 8. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrollment. 9. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
Exclusion Criteria	1. Previous treatment with cytotoxic chemotherapy therapy in the recurrent/metastatic setting. Previous treatment with non-cytotoxic agents and/or concurrent chemoradiation in the recurrent/metastatic setting is permitted. 2. Gastrointestinal abnormalities causing impaired absorption precluding administration of medications by mouth or feeding tube. 3. Evidence of untreated or progressive brain metastases, spinal cord compression, or carcinomatous meningitis. 4. A serious uncontrolled medical disorder or active infection that would impair their ability to receive study treatment. 5. Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol. 6. Patients (male and female) having procreative potential who are not willing or not able to use 2 adequate methods of contraception or practicing abstinence during the study and for 90 days following their last dose of treatment. 7. Women who are pregnant or breast-feeding. 8. Patients residing in prison. 9. Prior experimental therapy within 30 days of enrollment. 10. Availability of curative treatment option for the patient's cancer, whether surgery, chemotherapy, radiation, or combination thereof, unless the patient has documented refusal of curative treatment. 11. Patients with a history of severe allergic reaction to cisplatin or carboplatin

Study Product(s), Dose, Route, Regimen	Carboplatin + Palbociclib Cohort Palbociclib (Ibrance), dose= 125 mg daily, days=1-14, cycle length: 21 days Carboplatin (IV), dose= AUC 5, day= 1, cycle length: 21 days Maintenance Palbociclib Palbociclib (Ibrance) 125 mg daily, days 1-21, cycle length: 28 days
Duration of Administration	Study drugs will be administered in an open label fashion until progression, intolerance, or patient preference.
Reference Therapy	A historical control will be utilized
Statistical Methodology	This is an open-label multi-institution single arm Phase II study with a two-stage design

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Head and neck squamous cell cancer (HNSCC) is the sixth most common cancer worldwide. Despite the prevalence of this disease, a significant proportion of patients progress despite appropriate therapy in which case treatment is palliative in intent. Unresectable recurrent or metastatic (R/M) HNSCC has a dismal survival and development of novel therapeutics has been met with little success.

Platinum compounds historically are the backbone of first line therapy however documented response rates to cytotoxic chemotherapy range between 10-30% with single agent regimens and 20-40% for multi-drug regimens. Although increased response rates are seen with doublet regimens, progression free survival (4.2-5.1 months) and overall survival (5.7-6.6 months) have not been significantly increased with the addition of further cytotoxic agents[2-4]. To date, the regimen associated with the best survival outcomes in the first line setting are seen with the use of a triplet consisting of cetuximab, a platinum, and 5-flurouracil (the 'EXTREME' regimen'). In a sentinel publication when compared to platinum plus 5-flurouracil, the EXTREME regimen resulted in improved overall survival (10.1 vs 7.4 months) and response rate (36 vs 20%). However this aggressive regimen is accompanied by significant rates of serious toxicities significantly limiting its use[5]. Given issues with toxicities and the baseline mediocre performance status at diagnosis, many patients with R/M HNSCC are not candidates for the EXTREME triplet regimen. Therefore, novel therapeutic approaches are necessary.

Now with a greater understanding of aberrant cellular signaling and function in carcinogenesis, there has been a shift in modern chemotherapeutics towards targeted therapies specific to the molecular drivers of each distinct malignancy. Commonly altered genes include cell cycle regulatory genes CDKN2A and CCND1[7]. These cell cycle regulatory genes encode a complex group of proteins including cyclin dependent kinases and cyclin D which regulate progression through the cell cycle. Sustained CDK 4/6 activation is believed to be present in the majority of tumors as a mechanism to continually allow transition from G1 to S phase[12]. In R/M HNSCC, alterations in CCND1 or CDKN2A are two genomic events which lead to loss of checkpoint control. In patients with R/M HNSCC CDKN2A alterations include homozygous deletions in 30%, additional gene mutations in 10-20%, and epigenetic alterations leading to inactivation in up to 80%. CCND1 has been noted to be amplified in 20%[7-10]. Between the two, genomic alterations in either CCND1 or CDKN2A have been identified in between 60-94% of R/M HNSCC making these potential targets of interest[7,10,11].

1.2 Palbociclib- Background and Associated Known Toxicities

- Palbociclib is a reversible, oral, highly selective inhibitor of CDK 4 and 6 (CDK 4/6)[13] approved in combination with either fulvestrant or letrozole as first line treatment for hormone receptor positive metastatic breast cancer.
- The predominance of the clinical experience with palbociclib comes from the PALOMA trials (-1,-2, and -3) evaluating its efficacy in the first line treatment of hormone receptor positive metastatic breast cancer. When considered together, over 870 patients have been treated with palbociclib in combination with hormone therapy (letrozole or anastrozole) on these trials[14-16]. These trials demonstrated significant improvement in median progression free survival with the addition of palbociclib (14.5 to 24.8 months with the addition to Letrozole, 4.6 to 9.5 months with the addition to Fulvestrant). Response information from these trials are summarized in Table 1. Interestingly, although the rate of objective response was somewhat increased with the addition of palbociclib, the biggest impact with the addition of palbociclib was

increase in the rate of stable disease and clinical benefit (defined as percentage of patients who had a confirmed complete response, partial response, or stable disease for 24 weeks or more). Given the mechanism of CDK4/6 inhibition, response has been evaluated by biomarker status (CCND1 amplification, p16 loss, PIK3CA mutant) in PALOMA -1 and -3. These trials have demonstrated responses and improvement in survival in both biomarker positive negative populations[14,16]. Based on the results of these studies, palbociclib has been approved in combination with either fulvestrant or letrozole as first line treatment for hormone receptor positive metastatic breast cancer.

Table 1: Summary of Response Rates from PALOMA Trials

PALOMA 1: Phase 2 Trial of Palbociclib + Letrozole vs Letrozole

	Palbociclib + Letrozole (n=83)	Letrozole (n=77)
Complete Response	1%	1%
Partial Response	42%	32%
Stable Disease ≥24 weeks	44% 38%	37% 25%
Clinical Benefit	68%	47%
Progressive Disease	4%	22%
Indeterminate	10%	7%

PALOMA 2: Phase 3 Trial of Palbociclib + Letrozole vs Letrozole + Placebo

	Palbociclib + Letrozole (n=444)	Placebo + Letrozole (n=222)	P value
Objective Response*	42.1%	34.7%	0.06
Clinical Benefit Response**	84.9%	70.3%	<0.001
Median Duration of Response	22.5 mo	16.8 mo	

*Objective response defined as percentage of patients who had a confirmed complete response or a partial response

**Clinical benefit response defined as percentage of patients who had a confirmed complete response, partial response, or stable disease for 24 weeks or more

PALOMA 3: Phase 3 Trial of Palbociclib + Fulvestrant vs Fulvestrant + Placebo

	Intention to treat					*PIK3CA* positive					*PIK3CA* negative				
	Fulvestrant plus palbociclib		Fulvestrant plus placebo		p value	Fulvestrant plus palbociclib		Fulvestrant plus placebo		p value	Fulvestrant plus palbociclib		Fulvestrant plus placebo		p value
	n	% (95% CI)*	n	% (95% CI)*		n	% (95% CI)*	n	% (95% CI)*		n	% (95% CI)*	n	% (95% CI)*	
Intention to treat															
Population	347	..	174	..	..	85	..	44	..	..	180	..	86	..	..
Complete response†	0	0	4	2%	..	0	0	0	0	..	0	0	4	5%	..
Partial response†	66	19%	11	6%	..	13	15%	7	16%	..	53	29%	12	14%	..
Stable disease	213	61%	94	54%	..	54	64%	21	48%	..	91	51%	38	44%	..
Progressive disease	58	17%	57	33%	..	16	19%	15	34%	..	32	18%	28	33%	..
Indeterminate	10	3%	8	5%	..	2	2%	1	2%	..	4	2%	4	5%	..
Objective tumour response	66	19% (15·0–23·6)	15	9% (4·9–13·8)	..	13	15% (8·4–24·7)	7	16% (6·6–30·1)	..	53	29% (22·9–36·7)	16	19% (11·0–28·4)	..
Odds ratio		2·47 (1·36–4·91)	..	..	0·0019	..	1·16 (0·38–3·95)	..	..	0·98	..	1·78 (0·92–3·66)	..	..	0·090
Clinical benefit	231	67% (61·3–71·5)	69	40% (32·3–47·3)		51	60% (48·8–70·5)	16	36% (22·4–52·2)		129	72% (64·5–78·1)	34	40% (29·2–50·7)	
Odds ratio		3·05 (2·07–4·61)	..	..	<0·0001	..	2·17 (0·93–5·04)	..	..	0·078	..	4·21 (2·35–7·76)	..	..	0·00010

*Clinical benefit defined as percentage of patients who had a confirmed complete response, partial response, or stable disease for 24 weeks or more

- There is a significant amount of safety information available surrounding the use of palbociclib, most comprehensively documented through the PALOMA trials. The most common SAEs are hematologic including neutropenia, leukopenia, and anemia as summarized below in Table 2. Interestingly, despite the rate of neutropenia, febrile neutropenia and discontinuation due to adverse events has repeatedly been noted to be extremely low[14-16]. A complete description of the safety information can be found in the current Investigator's Brochure or Study Agent Prescribing Information.

Table 2: Summary of Adverse Events from PALOMA Trials

PALOMA 1: Phase 2 Trial of Palbociclib + Letrozole vs Letrozole

	Palbociclib + Letrozole		Letrozole	
	Grade 3	Grade 4	Grade 3	Grade 4
Any AE	59%	17%	21%	0%
Neutropenia*	48%	6%	1%	1%
Anemia	5%	1%	5%	1%
Leukopenia	19%	0%	0%	0%
Fatigue	2%	2%	1%	0%

*No cases of neutropenic fever were reported in the Palbociclib + Letrozole group despite high rate of Grade 3/4 neutropenia

PALOMA 2: Phase 3 Trial of Palbociclib + Letrozole vs Letrozole + Placebo

	Palbociclib + Letrozole		Placebo + Letrozole	
	Grade 3	Grade 4	Grade 3	Grade 4
Any AE	62%	13.5%	22.1%	2.3%
Neutropenia*	56.1%	10.4%	0.9%	0.5%
Anemia	5.2%	0.2%	1.8%	0%
Leukopenia	24.1%	0.7%	0%	0%
Fatigue	1.8%	0%	0.5%	0%

*Febrile neutropenia was reported as serious in 1.6% the Palbociclib + Letrozole group

PALOMA 3: Phase 3 Trial of Palbociclib + Fulvestrant vs Fulvestrant + Placebo

	Palbociclib + Fulvestrant		Fulvestrant + Placebo	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	55%	10%	0%	1%
Anemia	3%	0%	2%	0%
Leukopenia	27%	1%	1%	1%
Infections	2%	1%	3%	0%
Fatigue	2%	0%	1%	0%

- Recognizing the potential as a targeted therapy in other cancers with CDK abnormalities, palbociclib has been evaluated in advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. The study met its primary end point with a 12 week PFS of 66% (historical PFS for a second line agent 20-40%). Treatment was reasonably well tolerated with predominantly hematologic adverse events. Grade 3 to 4 hematologic toxicities included anemia (17%), neutropenia (50%), and thrombocytopenia (30%). Only one episode of grade 3 febrile neutropenia was noted[17]. This study acts not only to demonstrate a signal of response in CDK4-amplified well-differentiated or dedifferentiated liposarcoma but also demonstrates the promise of this agent for the treatment of diverse malignancies with cyclin-dependent kinase dysregulation.
- Palbociclib is a novel therapeutic in R/M HNSCC. Only one small phase I trial utilizing a doublet of palbocicilb and cetuximab (an IgG1 anti-EGFR monoclonal antibody) has been conducted in R/M HNSCC. This phase 1 study, presented at ASCO 2015, demonstrated suggestion of activity in both p16 negative and positive patients[18]. Nine patients were enrolled in this Phase 1 study; 5 of whom were both platinum and cetuximab resistant, 1 of whom was cetuximab resistant. Of the nine patients, 5 patients were p16- and 4 p16+. No dose limiting toxicities or AE related treatment discontinuations were encountered hence the maximum tolerated dose (MTD) was not reached. Tumor assessment after cycle 2 demonstrated partial response (PR) in 2 patients, stable disease (SD) in 5 patients, progressive disease (PD) in 1 patient, and one patient was non-evaluable. Responses were seen in patients who were cetuximab resistant as well as those resistant to platinum and cetuximab. Based on the results of this trial, a Phase II utilizing cetuximab with palbociclib in HPV- patients is ongoing (NCT02101034). Therefore, the early results of this trial support further exploration of palbociclib in R/M HNSCC.

1.3 Carboplatin- Background and Rationale for Synergy

1.3.1 Background

Carboplatin is a commercially available cytotoxic chemotherapeutic which is a standard first line agent for the management of R/M HNSCC[19]. Please see detailed information on adverse events and potential risks in Section 9.0.

1.3.2 Rationale for Synergy

Two preclinical studies have explored the role of combining cytotoxic chemotherapy with CDK4/6 inhibitors. Matranga et al examined demonstrated exquisite sensitization to the pan-CDK flavopiridol following chemotherapeutic exposure. This effect was seen with numerous agents including cisplatin and

gemcitabine. This was demonstrated to be due to chemotherapy induced tumor S-Phase recruitment/synchronization resulting in a greater degree of cell cycle arrest and apoptosis with flavopiridol. Interesting, the increased apoptotic effect was observed only in immortalized cells[20]. Similar synergistic lethality was observed in a study examining other chemotherapeutics in a xenograft model[21].

Preclinical and phase II studies have previously demonstrated potentiation of doxorubicin efficacy by flavopiridol. In the Phase II study by Jones et al, the doublet of doxorubicin and flavopiridol in well and de-differentiated liposarcoma resulted in improved response rates compared to historical controls without encountering a MTD[22].

Within our institution, combination of CDK4/6 inhibitors and platinum chemotherapy has been of significant interest. Unpublished research from our colleagues (Coffman, Buchanovich, et al) has explored the role for combining cisplatin with CDK 4/6 inhibition in ovarian cancer cell lines and xenografts. Publication of this work is expected in the near future but they clearly demonstrated a synergistic effect with concurrent cisplatin and CDK 4/6 inhibition using Ribociclib. Interestingly, they demonstrated reduction in stem-like cells in both Rb mutant and wild type cell lines. This treatment was found to lead to complete and more permanent cell arrest (Personal Communications, Unpublished Data). Similarly, Baldassarre et al presented data at the 2015 AACR Ovarian Cancer Meeting demonstrating CDK 6 inhibition inhibited ART and led to platinum sensitization. Based on this compelling data, a clinical trial evaluating the efficacy of concurrent carboplatin and Ribociclib in platinum sensitive ovarian cancer is underway.

Preclinical work in head and neck squamous cell lines has similarly demonstrated suggested synergistic potential of palbociclib and platinum therapy. Two HNSCC cell lines, UMSCC-59 and UMSCC-103 HNSCC, have been examined both of which were derived from stage IV oral cavity carcinomas. Cells were plated and allowed to expand into logarithmic growth phase, then treated with either vehicle (DMSO), cisplatin alone, palbociclib alone, or cisplatin and palbociclib in combination. Cell response was analyzed with cell proliferation with resazurin assays and clonogenic cell survival assays. Enhanced response was seen with the combination of cisplatin and palbociclib in comparison to either agent alone. For UMSCC-59, survival fractions were 33% for combination therapy, 71% for cisplatin alone, and 88% for palbociclib alone. For UMSCC-103, survival fractions were 34% for combination therapy, 40% for cisplatin alone, and 80% for palbociclib alone. There was suggestion of increased sensitivity with the presence of a CDKN2A mutation (UMSCC-59) compared to wildtype CDKN2A (UMSCC-103) (Brenner, Unpublished Data- Manuscript in progress).

1.3.3 Dosing Rationale

Dosing of carboplatin and palbociclib for this trial is adapted from the results of the PALOMA trials as well as standard of care dosing for carboplatin. We will utilize a dose of Carboplatin AUC 5, day 1, and Palbociclib 125 mg daily, 2 weeks on and one week off. Cycle length will be 21 days. Support of this doublet is supported by an ongoing phase I Trial “Palbociclib with Cisplatin or Carboplatin in Advanced Solid Tumors” (NCT02897375) which has demonstrated non-overlapping toxicities or dose limiting toxicities (Unpublished Personal Communication). We will be performing frequent interim analysis to evaluate toxicities of this dosing regimen and adjust if necessary.

1.4 Rationale in Head and Neck Cancer

Given the molecular alterations (CDKN2A, CCND1) seen in R/M HNSCC and signal of efficacy with the use of palbociclib in patients in other malignancies with these alterations, exploration in R/M HNSCC is warranted. Based on preclinical evidence, the combination of a CDK 4/6 inhibitor with cytotoxic chemotherapy in the first line setting is a rational therapeutic approach and holds promise as an effective doublet in head and neck cancer.

We propose a phase II trial to evaluate the combination of palbociclib and carboplatin for the first-line cytotoxic treatment of R/M HNSCC. This will be a single arm, non-randomized, non-blinded phase II trial. Patients with unresectable recurrent or metastatic HNSCC with no previous cytotoxic chemotherapy therapy in the recurrent/metastatic setting will be included. Previous treatment with immunotherapeutics in the recurrent/metastatic setting will be permitted.

Based on pre-clinical data, we hypothesize that this doublet will have activity in eliciting a greater antitumor response and hence improved disease control rate. Much of the benefit seen in previous palbociclib trials was SD and clinical benefit (CR + PR + SD at 24 weeks) rather than improvement in ORR, CR, or PR. As the increase in SD was associated with improved PFS compared to placebo in these trials, we believe this represents drug effect rather than disease biology. Therefore, we believe disease control rate (DCR) at 12 weeks is an appropriate primary end point for this phase II trial.

1.5 Correlative Studies

Recently published results from Palbociclib clinical trials and our internal in vitro studies described above have shown a correlation between response to therapy and molecular genetics for genetic networks centers on *RB1* amplification and/or *CDKN2A* loss. Some studies have used RB1 phosphorylation as a marker for enrollment, others have retrospectively assessed molecular profiles. Thus, to assess the potential of using molecular genetics to enrich for responsive populations in future studies of head and neck cancer, we propose to determine correlations of the molecular networks with Palbociclib-based therapy. According to our recent and published NGS data (including with the TCGA network) patients with R/M HNSCC have *CDKN2A* alterations (30% homozygous deletion, 10-20% mutations, and epigenetic alterations) leading to loss of RNA expression. Likewise, *CCND1* as a gene within the 11q13 ampicon has been noted to be amplified and overexpressed in 20% of cases[7-10]. With low rates of alterations also seen in *RB1* and *CDK4/6* at the DNA level, the role of these genes as prognostic biomarkers may be more informative at RNA or protein expression levels. However, in primary untreated disease, potentially activating *CDK4* and *CDK6* mutations are rare and have only been reported in 0.5% of the population and it will be important to identify patients with these alterations. Given the overall alteration frequency of the genes as well as the potential to define a companion molecular diagnostic for this therapy, we propose the following hypothesis: *Specific genetic networks will correlate with response to Palbociclib-based therapy including patients with alterations in CDKN2A, CyclinD1, CDK4/6, RB and/or human papilloma virus.*

In addition to advancing studies of pre-enrollment companion diagnostics, we also propose to leverage our experience with analyzing ctDNA in the saliva and serum to assess ctDNA for its ability to identify response to therapy. In other cancers, ctDNA is routinely monitored as a potential biomarker to assess response to therapy as well as to provide early identification of obvious mutations that drive resistance to targeted inhibitors[23-26]. With the recent advances in the utility of molecular barcoding for next generation sequencing, quantification of low yield DNA samples has become a pivotal method for the detection of ctDNA in patients and is a technology that we propose to

leverage in this proposal. Thus, we also propose the following hypothesis: *Cancer response to therapy can be detected in saliva and serum biospecimens collected at routine interval time points and will identify tumor recurrence earlier than interim imaging.*

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To assess evidence of anti-tumor activity by assessment of disease control rate at 12 weeks in patients with metastatic head and neck squamous cell cancer treated with carboplatin and palbociclib

2.2 Secondary Objectives

2.2.1 To describe the adverse events associated with use of carboplatin and palbociclib

2.2.2 To assess survival in patients with metastatic head and neck squamous cell cancer treated with carboplatin and palbociclib

2.3 Exploratory Objectives

2.3.1 Explore the response to therapy based on CDK4, CDK6, Cyclin D1, CDKN2A and HPV genetic status.

2.3.2 Evaluate whether molecular and biochemical markers are predictive of tumor response.

2.3.2.1 Correlate genetic subtype with response via targeted DNA and RNA-sequencing of pre-treatment biopsy.

2.3.2.2 Assess the expression of CDK4, CDK6, Cyclin D1, CDKN2A in tumors as well as level of vascularization (CD31+ cells), apoptosis (TUNEL), proliferation (Ki67), and tumor infiltrating lymphocyte content (CD4/CD8, etc.).

2.3.3 Assess whether the dynamics of circulating tumor DNA (ctDNA) are associated with clinical and radiographic responses to therapy as well as monitor for the presence and quantity of HPV DNA or DNA containing somatic mutations identified in the targeted sequencing of the biopsy specimen.

2.4 Endpoints

2.3.1 Primary Endpoint

2.3.1.1 Disease control rate will be defined as the proportion of patients achieving either complete response (CR), partial response (PR), or stable disease (SD) at 12 weeks. Response will be assessed via RECIST v1.1.

2.3.2 Secondary Endpoints

2.3.2.1 Adverse events will be evaluated by clinical evaluation as well as routine lab work. Toxicities will be assessed via CTCAE v 4.03.

2.3.2.2 Survival endpoints to be assessed will include both overall survival and progression free survival time

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a subject is enrolled.

3.1 Inclusion Criteria

3.1.1 Histologically documented progressive squamous cell head and neck cancer with or without metastases, not amenable to curative treatment; or the patient has documented refusal of curative treatment.

3.1.2 ECOG performance status of 0-2

3.1.3 Presence of measurable disease by CT scan per RECIST v1.1.

3.1.4 Age ≥18 years.

3.1.5 Life expectancy of ≥12 weeks.

3.1.6 Women of childbearing potential must have a negative serum or urine pregnancy test at time of screening and confirmed within 3 days prior to treatment. Women not of child-bearing potential will be defined as all women older than age 50 and anovulatory for 12 months.

3.1.7 Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrollment.

3.1.8 Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

3.1.9 Adequate organ and marrow function as defined below:

WBC	≥ 3 x 10^9 cells/mL
ANC	≥ 1.5 x 10^9 cells/mL
Hemoglobin	≥ 9 g/dL
Platelets	≥ 75,000 cells/mm^3
Total Serum Bilirubin	Within 1.5 x upper limit of normal (ULN)
AST	Within 2.5 x ULN unless there are liver metastases in which case, AST within 5 x ULN
ALT	Within 2.5 x ULN unless there are liver metastases in which case, ALT within 5 x ULN
Serum Creatinine Clearance	≥ 30 mL/min

3.2 Exclusion Criteria

3.2.1 Previous treatment with cytotoxic chemotherapy therapy in the recurrent/metastatic setting. Previous treatment with non-cytotoxic agents and/or concurrent chemoradiation in the recurrent/metastatic setting is permitted.

3.2.2 Gastrointestinal abnormalities causing impaired absorption precluding administration of medications by mouth or feeding tube.

3.2.3 Evidence of untreated or progressive brain metastases, spinal cord compression, or carcinomatous meningitis.

3.2.4 A serious uncontrolled medical disorder or active infection that would impair their ability to receive study treatment.

3.2.5 Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol.

3.2.6 Patients (male and female) having procreative potential who are not willing or not able to use 2 adequate methods of contraception during the study and for 90 days following their last dose of treatment. Adequate contraception is defined as:

a. Total abstinence or
b. Male or female sterilization or
c. Combination of any two of the following (i+ii or i+iii, or ii+iii):
   i. Use of oral, injected or implanted hormonal methods of contraception
   ii. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
   iii. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

3.2.7 Women who are pregnant or breast-feeding.

3.2.8 Patients residing in prison.

3.2.9 Prior experimental therapy within 30 days of enrollment.

3.2.10 Availability of curative treatment option for the patient's cancer, whether surgery, chemotherapy, radiation, or combination thereof, unless the patient has documented refusal of curative treatment.

3.2.11 Patients with a history of severe allergic reaction to cisplatin or carboplatin

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

Patient registration for this trial will be centrally managed by the Coordinating Center of The University of Michigan Rogel Cancer Center as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on the Screening and Enrollment Log provided by the Coordinating Center.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient registration request to the Coordinating Center. After patient eligibility has been determined, a copy of the completed Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the Coordinating Center, by email to CTSU-Oncology-Multisite@med.umich.edu.

The Multi-Site Coordinator, who acts as the registrar, will review the submitted documents and process the registration. Sites should inform the Multi-Site Coordinator of a potential registration by 5 p.m. on the day prior to registration. Same day registrations cannot be guaranteed.

An email will be sent by the registrar to the requesting site registrar to confirm patient registration and to provide the study identification number that has been assigned to the patient. In addition, a copy of the Eligibility Worksheet signed and dated by the registrar, will be sent back to the requesting site registrar.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Protocol treatment must start within 5 business days of enrollment to the study.

5.1.1 This study will be a non-randomized phase II trial. We will enroll 40 patients with R/M HNSCC. Patients will be treated with Carboplatin (AUC=5, IV, day 1) as well as Palbociclib (125 mg,daily, days 1-14). Cycle length will be 21 days. Patients will be monitored closely for toxicity and undergo imaging to evaluate efficacy once every 2 cycles. After 6 cycles of Carboplatin + Palbociclib, if patients continue to garner a response to therapy, they will be transitioned to maintenance single agent palbociclib at a dose of 125 mg daily, days 1-21, cycle length: 28 days

5.1.2 Carboplatin + Palbociclib Regimen

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Carboplatin	Premedications per discretion of prescribing physician	AUC=5	IV	Days 1, week 1	3 weeks (21 days)
Palbociclib	Capules -Swallow capsules whole. Do not cut, chew, or crush -Should be taken with food at approximately the same time each day Solution -Should be taken at approximately the same time each day. Does not need to be taken with food.	125 mg daily	Capsule or Solution	Days 1-14	

5.1.2.1 Carboplatin Administration
5.1.2.1.1 Carboplatin is an IV drug which will be administered as an outpatient
5.1.2.1.2 Premedications per discretion of prescribing physician

5.1.2.2 Palbociclib Administration
5.1.2.2.1 Palbociclib will be self-administered and may be taken by mouth or via feeding tube.
5.1.2.2.1.1 If patients can swallow pills, Palbociclib will be administered as a capsule formulation
5.1.2.2.1.1.1 Swallow palbociclib capsules whole. Do not cut, chew, or crush capsules
5.1.2.2.1.1.2 Palbociclib capsules should be taken with food at approximately the same time each day
5.1.2.2.1.2 If patients are unable to swallow pills, or rely on feeding tube for administration of medications (ie PEG, NG tubes) then solution formulation Palbociclib will be utilized
5.1.2.2.1.2.1 Palbociclib solution should be taken at approximately the same time each day. It does not need to be taken with food.
5.1.2.2.1.2.2 Patient administration directions using syringe are detailed in Pfizer Approved 'Administration Instruction' Handouts (Appendix C- Administration Instructions for Oral Dose Using Syringe and Appendix D- Administration Instructions for Each Dose via NG Tubes)
5.1.2.2.2 Palbociclib solution will be available by late January/ early February 2018 for patients who cannot swallow the Palbociclib capsules.
5.1.2.2.2.1 Patients who begin the study receiving the oral solution will remain on the solution for the duration of their time on treatment in the study.
5.1.2.2.2.2 Patients, who begin the study receiving capsules but develop difficulty swallowing the capsules and did not have disease progression, will be allowed to switch to the Palbociclib oral solution. These patients will then remain on the oral solution for the duration of their time on treatment in the study.
5.1.2.2.3 Patients should be instructed that if they vomit any time after taking a dose of Palbociclib, that they must not "make it up" with an extra dose, but instead resume subsequent doses as prescribed. Missed doses may be taken late, up to 6 hours after the scheduled dose, otherwise should be skipped and reported to the investigators.

5.1.3 Maintenance Single Agent Palbociclib

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Palbociclib	Capsules -Swallow capsules whole. Do not cut, chew, or crush	125 mg daily	Capsule or Solution	Days 1-21	4 weeks (28 days)

	-Should be taken with food at approximately the same time each day <u>Solution</u> - Should be taken at approximately the same time each day. Does not need to be taken with food				

5.1.3.1 Single agent palbociclib will be administered in a matter identical to that described in Section 5.1.2.2

5.1.4 Compliance and Monitoring

5.1.4.1 The patients will be asked to bring medication bottles to each follow-up visit, and remaining pills in bottle will be counted at each visit to document compliance. This information will be recorded in each patient's data file.

5.1.4.1.1 If patients are being treated with oral solution, they will be asked to return the bottles in clear Ziplock bag. For drug accountability, research staff may use a best approximation (in units of milliliters) as to the remaining solution as they may be unable to open HDPE bottles

5.1.4.2 Drug Administration will be provided to record compliance with drug administration, route of administration (by mouth or feeding tube) as well as document dose adjustments.

5.2 Toxicities and Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.1). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

5.2.1 Dosing Interruptions

Patients experiencing any of the following adverse events should have their treatment interrupted/delayed

- Uncomplicated Grade 3 neutropenia (ANC<1000/mm^3)
- Grade 3 neutropenia (ANC <1000/mm^3) associated with a documented infection of fever ≥ 38.5° C
- Grade 4 neutropenia (ANC <500/mm^3)
- Grade 4 thrombocytopenia (platelet count < 25,000/mm^3)
- Grade ≥ 3 non-hematologic toxicity (including nausea, vomiting, diarrhea, fatigue, and hypertension only if persisting despite optimal medical treatment)

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in Section 5.2.2.

Doses of palbociclib ± carboplatin infusions may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even delay the initiation of the subsequent cycle. If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria in Section 5.2.3.

In the event of a treatment interruption for reasons other than treatment-related toxicity (ie non-cancer related surgery) lasting >2 weeks, treatment resumption will be decided in consultation with the co-principal investigators.

5.2.2 Dose Delay

Retreatment following treatment interruption for treatment-related toxicity or at the start of a new cycle may not occur until all of the following parameters have been met:

- Platelet count ≥ 50,000/mm^3
- ANC ≥ 1000/mm^3 and no fever
- Grade 3 or higher treatment-related non-hematologic AEs (including nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment), with the exception of alopecia, have recovered to Grade ≤ 1 or baseline (or, at the investigator's discretion, Grade ≤ 2 if not considered a safety risk for the patient)

If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be increased as clinically indicated. G-CSF (Filgrastim or Peg-filgrastim) may be given for neutropenia at the investigator's discretion.

If these parameters are met within 2 weeks of treatment interruption or cycle delay, treatment may be resumed. Please see Section 5.2.3 for dose reductions at the time of treatment resumption.

If these parameters have not been met after 2 weeks of dosing interruption (including the scheduled 1 week off Palbociclib treatment) or 2 weeks of cycle delay, permanent treatment discontinuation should be considered. Treatment resumption for patients recovering from toxicity after > 2 weeks of treatment interruption of cycle delay but deemed to be deriving obvious clinical benefit per the investigator's best medical judgement is left at the investigator's discretion.

A new cycle only starts when the criteria listed above are met and treatment with palbociclib ± carboplatin may be administered. Otherwise, initiation of the new cycle must be delayed until such criteria are met. In the event that the start of a new cycle is delayed due to treatment related toxicity, procedures required on Day 1 of the given cycle will be performed when palbociclib ± carboplatin is resumed. New Day 1 procedures that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated 1) if not required to

determine whether study drugs may be resumed and 2) if performed within 7 days prior to study drug resumption.

5.2.3 Dose Reductions

Following dosing interruption or cycle delay, the dose of the study drugs may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity.

Dose reduction of palbociclib and carboplatin by 2 dose levels will be allowed depending on the type and severity of toxicity encountered (Table 3 and 4). Patients requiring more than 2 dose reductions will be discontinued from the study and entered into the follow-up phase.

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed.

Table 3: Study Drug Dose Levels

Palbociclib Dose Levels

Dose Level	Dose	Dispensed as
0 (starting dose)	125 mg daily, days 1-14	125 mg capsules OR 5 mL solution
-1	100 mg daily, days 1-14	100 mg capsules OR 4 mL solution
-2	75 mg daily, days 1-14	75 mg capsules OR 3 mL solution

Carboplatin Dose Levels

Dose Level	Dose
0 (starting dose)	AUC= 5, day 1
-1	AUC= 4, day 1
-2	AUC= 3, day 1

Table 4: Dose Modifications for Treatment Related Toxicities Requiring Treatment Interruption/Delay or Persisting Despite Optimal Medical Treatment

Toxicity	**Restart Palbociclib Treatment at:**	**Restart Carboplatin Treatment at:**
Uncomplicated Grade 3 neutropenia *(ANC <1000 mm/mm^3)*	Same dose level	Same dose level
Grade 3 neutropenia *(ANC <1000/mm^3)* associated with a documented infection or fever ≥ 38.5° C	↓ 1 dose level	↓ 1 dose level

Grade 4 neutropenia *(ANC<500/mm^3)*	↓ 1 dose level	↓ 1 dose level
Grade 4 thrombocytopenia *(platelet count <25,000/mm^3)*	↓ 1 dose level	↓ 1 dose level
Grade ≥3 non-hematologic toxicity *(including nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)*	↓ 1 dose level	↓ 1 dose level
Note: G-CSF (Filgrastim or Peg-filgrastim) may be added for low ANC at treating physician's discretion.		

5.3 Concomitant Medications

5.3.1 Patients will be allowed to take supportive medications as needed. Anti-emetic medications should be used to treat nausea/vomiting at physicians' discretion.

5.3.4 G-CSF (Filgrastim and Neulasta) may be added for low ANC at treating physician's discretion.

5.3.5 Other concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed at the discretion of the treating physician.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria apply:

- Disease progression as defined in Section 7.0 unless evidence of clinical benefit per the judgement of the treating clinician as per Section 5.5
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient voluntarily withdraws from treatment **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.5 Treatment Beyond Disease Progression

Subjects will be permitted to continue on treatment beyond RECIST v1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and do not have rapid disease progression
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (i.e. CNS metastases)

- Subject provides written informed consent prior to receiving any additional treatment with Carboplatin and Palbociclib, using an informed consent describing any reasonably foreseeable risk or discomforts, or other alternative treatment options.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

All decisions to continue treatment beyond initial progression must be documented in the study records. Subjects will be re-consented with an informed consent describing any reasonably foreseeable risks or discomforts.

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

For statistical analysis that include the investigator-assessed progression date, subjects who continue treatment beyond investigator-assessed, response defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

5.6 Off Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.4 apply. Document in the source the reason for ending protocol therapy and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.6. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.7 Duration of Follow-Up

Patients will be followed for survival until death. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. End of treatment visit will be conducted within 30 days (+/- 5 days) of treatment discontinuation, however if patient refuses to present for a clinic visit, phone contact will be made within 30 days after study discontinuation of study treatment. Survival assessment can be done by phone and will be performed once every three months (+/- 1 month) until death.

5.8 Discontinuation Criteria

5.8.1 Disease progression with lack of investigator-assessed clinical benefit

5.8.2 Patient withdraws consent (termination of treatment and follow-up);

5.8.3 Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;

5.8.4 Patient is unable to comply with protocol requirements;

5.8.5 Treating physician judges continuation on the study would not be in the patients best interest;

5.8.6 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.8.7 Lost to Follow-up. If a research subject cannot be located to document survival after a period of 1 year, the subject may be considered “lost to follow-up.” All attempts to contact the subject during the one year must be documented;

5.8.8 Termination of the study by The University of Michigan or any other regulatory body

5.9 Patient Replacement

Patients enrolled but who do not receive protocol treatment will be replaced. Protocol treatment is defined as at least one dose of each drug.

6.0 STUDY PROCEDURES

6.1 Time and Events Table

6.1.1 Calendar

	Screening[1]	Treatment									Maintenance			End of Treatment	Survival
		Cycle 1			Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8+	Every 8 weeks from Cycle 7, Day 1		
Day of Cycle		**1**	**8**	**14**	**1**	**14**	**1**	**1**	**1**	**1**	**1**	**1**		**EOT[9]**	**Survival[10]**
Informed Consent	X														
Demographics	X														
Inclusion/Exclusion Criteria	X														
Tumor Biopsy for Correlative Analysis[14]	X														
Interim Biopsy for Correlative Analysis[12,16]					X[3]										
Tumor Biopsy to confirm progression[15,16]														X	
H&P, Relevant Medical History	X														
Pregnancy Test	X	X													
Clinic Visit[4]	X	X			X[2,13]		X[2,13]	X[2,13]	X[2,13]	X[2,13]	X[2,13]	X[2,13]		X	
Performance Status	X	X			X[2,13]		X[2,13]	X[2,13]	X[2,13]	X[2,13]	X[2,13]	X[2,13]			
Physical Exam[4]	X	X			X[2,13]		X[2,13]	X[2,13]	X[2,13]	X[2,13]	X[2,13]	X[2,13]			
QOL Survey[4]		X			X[2,13]		X[2,13]	X[2,13]	X[2,13]	X[2,13]	X[2,13]	X[2,13]			
Adverse Effects Assessment[5]		X			X[2,13]		X[2,13]	X[2,13]	X[2,13]	X[2,13]	X[2,13]	X[2,13]		X	

	Screening[1]	Treatment									Maintenance			End of Treatment	Survival
		Cycle 1			Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8+	Every 8 weeks from Cycle 7, Day 1		
Day of Cycle		1	8	14	1	14	1	1	1	1	1	1		EOT[9]	Survival
CBC[6]	X	X		X^{2}	$X^{2,13}$	X^{2}	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$		X	
CMP[6]	X	X			$X^{2,13}$		$X^{2,13}$	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$		X	
Correlative: Salivary Rinse[7]		X	X^{2}		$X^{2,13}$		$X^{2,13}$	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$			
Correlative: 2 Serum Tubes[7]		X	X^{2}		$X^{2,13}$		$X^{2,13}$	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$	$X^{2,13}$			
Correlative: 1 Serum Tube[7]		x													
CT Imaging[8]	X						X^{3}		X^{3}		X^{3}		X^{3}		
Palbociclib Dosing[11]		125 mg daily, days 1-14. Cycle Length: 21 Days									125 mg daily, days 1-21. Cycle Length: 28 Days				
Carboplatin Infusion		X			X		X	X	X	X					
Survival Assessment															X^{10}

1= May be performed within 28 days of Cycle 1, Day 1 unless otherwise specified

2= May be performed +/- 4 days

3= May be performed +/- 7 days

4= Vital signs, physical exam, ECOG performance status will be checked at each visit as well administration of FACT H&N questionnaire (see Appendices B and C)

5= Toxicities will be evaluated using CTCAE version 4.03

6= Labs will be obtained pre-dose. CMP includes Basic Metabolic Profile (Na, K, Cl, CO2, BUN, Cr, Glu), AST/SGOT, ALT/SGPT, Alk Phos, T Bili, Albumin, Ca, and Total Protein

7= Collection tubes (see lab manual) will be drawn and sent to the Brenner lab for DNA isolation and long term storage. May be performed +/- 4 days

8= CT Neck and Chest will be obtained in all patients. Further imaging (ie CT Abdomen/Pelvis, Bone Scan) will be performed as deemed appropriate by the treating physician. Initial staging imaging may be performed within 28 days prior to treatment

9= Will be performed within 30 days after discontinuation of study treatment. If the patient refuses to present for a clinic visit, phone contact will be made within 30 days after discontinuation of study treatment

10= Survival assessment can be done by phone and will be performed once every three months (+/- 1 month)

11= Will be administered orally on a daily basis, dose as defined per protocol

12=Biopsy at Cycle 2 will be offered if clinically safe and feasible. Patients may refuse repeat biopsy

13= In the event that the start of a new cycle is delayed due to treatment related toxicity, procedures required on Day 1 of the given cycle will be performed when palbociclib ± carboplatin is resumed. New Day 1 procedures that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated 1) if not required to determine whether study drugs may be resumed and 2) if performed within 7 days prior to study drug resumption.

14= A biopsy demonstrating metastatic disease must be obtained within the 56 days prior to study treatment. FFPE core biopsy is preferred, however, if not clinically feasible or safe to obtain a core biopsy a block made from several FNA passes is acceptable. No systemic therapy (i.e. immunotherapy) may have been administered since obtaining the biopsy, if so, a new biopsy is needed.

15= If treating physician deems biopsy to be either unsafe or not clinically feasible, this must be documented and patient may forego repeat biopsy

16= FFPE core biopsy is preferred, However, if not clinically feasible or safe to obtain a core biopsy, contact coordinating site PIs (P.S. and F.W.) as a block made from several FNA passes is acceptable after PI approval.

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*EJC* 45 (2009) 228-247]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

7.1.1 Definitions

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

7.1.2 Evaluable for response. Only those patients who have measurable disease present at baseline and have at least one dose of each drug will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. In the case of death or disease progression before response classification, the outcome will be considered PD for calculation of disease control rate. Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) for studies with a slice thickness of ≤5mm or twice the slice thickness or MRI
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm 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.

Tumor lesions in previously irradiated areas are considered measurable if there has been progression in the lesion since completion of radiotherapy

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total 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 organ,

but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered nonpathological and should not be recorded or followed. 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 as noted above, 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 pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

7.1.3 Guidelines for Evaluation of Measurable Disease

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 should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions (with a minimum absolute increase of 5 mm), taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR (taking as reference the baseline sum LD) nor sufficient increase to qualify for PD (taking as reference the smallest sum LD since the treatment started).

7.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): 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.

7.1.4.3 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.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/SD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	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	

* 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.

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

7.1.5 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 recurrent 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.

7.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

7.2 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 for reporting of non-hematologic adverse events.

8.0 ADVERSE EVENTS

8.1 Experimental Therapy with Carboplatin

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

8.1.1 Contraindications

8.1.1.1 Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum containing compounds

8.1.1.2 Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding

8.1.2 Special Warnings and Precautions for Use

8.1.2.1 Needles or intravenous administration sets containing aluminum parts that may come in contact with carboplatin should not be used for the preparation or administration of the drug as aluminum can react with carboplatin causing precipitate formation and loss of potency

8.1.2.2 Bone marrow suppression is dose dependent and is the dose limiting toxicity. Peripheral blood

counts should be monitored frequently during treatment and until recovery is achieved

8.1.2.3 Carboplatin can induce emesis which can be more severe in patients previously receiving emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with antiemetics

8.1.2.4 Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin

8.1.2.5 Allergic reactions to carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is increased risk of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy

8.1.2.6 Carboplatin injection may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant

8.1.3 Interaction with other medications

8.1.3.1 The renal effects of nephrotoxic compounds may be potentiated by carboplatin

8.1.4 Adverse Reactions

8.1.4.1 The most common adverse reactions (incidence ≥ 10%) are bone marrow suppression (anemia, thrombocytopenia, and/or neutropenia), nausea, vomiting, mild elevations in alkaline phosphatase, and mild decreases in serum electrolyte values

8.1.4.2 Hypersensitivity to carboplatin has been reported in 2% of patients. These allergic reactions have been similar in nature and severity to those reported with other platinum containing compounds and have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy

8.2 Experimental Therapy with Palbociclib

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

8.2.1 Contraindications

8.2.1.1 There are no known contraindications

8.2.2 Special Warnings and Precautions for Use

8.2.2.1 Neutropenia- Monitor CBC prior to start of palbociclib therapy and at the beginning of each cycle, and as clinically indicated

8.2.2.2 Pulmonary embolism- Monitor patients for signs and symptoms of pulmonary embolism and treat as medically appropriate

8.2.2.3 Embryo-Fetal toxicity- Can Cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception

8.2.3 Adverse Reactions

8.2.4.1 The most common adverse reactions (incidence ≥ 10%) are neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, headache, diarrhea, thrombocytopenia, constipation, alopecia, vomiting, rash, and decreased appetite

8.2 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment administration through 30 days after the last dose of study treatment. Any serious adverse event that occurs more than 30 days after the last study treatment and is considered related to the study treatment must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.3, occurring from the initial study treatment administration through 30 days following the last dose of the study treatment must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment. All serious adverse events (SAEs) and unanticipated problems (UPs), regardless of causality to study drug, will be reported to the Principal Investigator and also to the Coordinating Center. In addition, SAEs should be submitted to the Coordinating Center and PI any time after the administration of the last dose of palbociclib if the Investigator suspects a causal relationship between the palbociclib and the SAE.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment is also considered an adverse event.

8.3 Definitions

8.3.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- *Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.*

- *Abnormal laboratory values or test results constitute adverse events if they induce clinical signs or symptoms or require therapy. They are to be captured under the signs, symptoms or diagnoses associated with them.*

8.3.2 Serious Adverse Event

An adverse event is considered “serious” if, in the view of either the investigator or sponsor-investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- A life-threatening adverse event
  An adverse even is considered ‘life-threatening’ if, in the view of either the investigator [or sponsor-investigator], its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for $\geq$ 24 hours.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

- Important medical event
  Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of “Serious Adverse Event”. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

8.3.3 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

8.3.4 Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

8.4 Adverse Event Characteristics

8.4.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

8.4.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.
Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

8.5 Serious Adverse Event Reporting Guidelines

All SAEs and UPs must be reported to the Coordinating Center within 24 hours of first awareness of the event. Events should be reported using the Coordinating Center SAE form. A copy of the Coordinating Center SAE form should be sent to the Coordinating Center via fax at 734-232-0744 or via email to CTSU-Oncology-Multisite@med.umich.edu within 24 hours of the site's knowledge of the event.

Contact information for Principal Investigator SAE Reporting:

Paul L. Swiecicki, M.D.
University of Michigan Rogel Cancer Center
N13A23 North Ingalls Building, 300 North Ingalls St., SPC 5419
Ann Arbor MI 48109
Phone: 734-647-1017, Fax: 734-647-9480
pswiecic@med.umich.edu

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

All SAEs and UPs will be reported to the local IRBs per current institutional standards.

The Coordinating Center will disseminate information regarding SAEs and UPs to the participating sites within 5 days of review of the information by the Coordinating Center's Principal Investigator (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study drug.

The Coordinating Center will be responsible for reporting to Pfizer by facsimile any Serious Adverse Event that occur during the SAE reporting period. The coordinating center will report the SAE within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening).

The Multi-site team will coordinate with the Sponsor-Investigator and the Michigan Institute for Clinical and Health Research (MICHR) IND/IDE Investigator Assistance Program (MIAP) office for the reporting of any and all IND safety reports to the FDA as per the requirements outlined in 21 CFR 312.32. A summary of all non-expedited safety reports will be submitted in the annual report.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment is also considered an adverse event.

8.6 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.7 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and

3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB according to the local IRB reporting requirements.

9.0 DRUG INFORMATION

9.1 Carboplatin

- Other names for the drug: Carboplatin (Paraplatin ®)
- Description: IV Medication. Vial sizes of 50 mg/5 mL, 150 mg/15 mL, 450 mg/45 mL, 600 mg/60 mL all in individually packaged multi-dose vials.
- Classification - type of agent: Cytotoxic/Alkylating-Like Compound
- Mode of action: Carboplatin produces interstrand DNA cross-links which in turn interfere with mitosis. DNA damage leads to attempts at DNA repair however, when repair is not possible apoptosis is activated, especially in the case of double strand DNA breaks.
- Pharmacokinetics: Carboplatin exhibits linear pharmacokinetics with Cmax and AUC increasing linearly with dose.
    - Half-life- Plasma levels of intact carboplatin decay in a biphasic manner with a half-life of 2.6-5.9 hours.
    - Elimination- The major route of elimination is renal excretion. The primary determinant of carboplatin clearance is glomerular filtration rate
    - Metabolism- Minimally hepatic to aquated and hydroxylated compounds
- Side effects:
    - The most common adverse reactions (incidence ≥ 10%) are bone marrow suppression (anemia, thrombocytopenia, and/or neutropenia), nausea, vomiting, mild elevations in alkaline phosphatase, and mild decreases in serum electrolyte values
    - Hypersensitivity to carboplatin has been reported in 2% of patients. These allergic reactions have been similar in nature and severity to those reported with other platinum containing compounds and have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy
    - Please refer to the package insert for a comprehensive list of adverse events.
- Drug Interactions:
    - Fosphenytoin/Phenytoin- Carboplatin may decrease serum concentrations of these drugs hence monitor therapy
- Storage and stability:
    - Unopened vials of carboplatin are stable to the expiration date indicated on the

package when stored at 25°C (77°F); excursions permitted from 15°C-30°C (59°-86°F). Protect from light
- Multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries
- Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration. Solutions for infusion should be discarded 8 hours after preparation

- Administration:
  - Needles or intravenous administration sets containing aluminum parts that may come in contact with carboplatin should not be used for the preparation or administration of the drug as aluminum can react with carboplatin causing precipitate formation and loss of potency

- Availability**:** Commercially available. Will be purchased from commercial sources and billed to patients or their insurers

9.2 Palbociclib

- Other names for the drug: Palbociclib (Ibrance ®)

- Description: Oral Medication. Supplied as capsules which must be swallowed or solution which may be swallowed or administered via feeding tube (ie nasogastric tube or PEG). Capsules are supplied in 125 mg, 100 mg, 75 mg doses. Bottles consist of 21 tablets. Solution is supplied at a concentration of 25 mg/mL and 112 mL are in each bottle

- Classification - type of agent: Cyclin-dependent kinase (CDK) 4 and 6 inhibitor

- Mode of action: Palbociclib is an inhibitor of CDK 4/6. Cyclin D1, CDK 4, and CKD 6 are downstream signaling pathways which lead to cellular proliferation. In vitro, palbociclib reduced cellular proliferation of estrogen receptor-positive breast cancer cee lines by blocking the progression of the cell from G1 into S phase of the cell cycle.

- Pharmacokinetics:
  - Absorption- The mean time to reach maximum concentration (Tmax) is between 6-12 hours following oral administration. The mean bioavailability of palbociclib after an oral 125 mg dose is 46% and in the dosing range of 25-225 mg the AUC and Cmax increased proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. In studies utilizing capsules, food intake reduced the intersubject variability of palbociclib exposure therefore the palociclib capsules should be taken with food. Pharmacokinetic studies of the solution demonstrate no change in the variability of palbociclib exposure with food administration. Therefore, palbociclib solution may be taken with or without food.

  - Half-life- The plasma elimination half-life is 29 (+/- 5) hours in patients with advanced breast cancer

  - Metabolism- Palbociclib undergoes hepatic metabolism in humans. The primary metabolic pathways for palbociclib involve oxidation and sulfonation. CYP3A and

SULT2A1 are mainly involved in the metabolism of palbociclib. Palbociclib is a weak time-dependent inhibitor of CYP3A following daily dosing to steady state.

- Elimination- Fecal elimination is the major route of excretion (74.1%) with an additional 17.5% recovered in urine. The majority of excreted materials were metabolites

- Side effects:
  - The most common adverse reactions (incidence ≥ 10%) are neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, headache, diarrhea, thrombocytopenia, constipation, alopecia, vomiting, rash, and decreased appetite

- Drug Interactions:
  - None applicable

- Storage and stability:
  - Store at 20° C -25° C (68° F-77° F), excursions permitted between 15° C-30° C (59° F-86° F)
  - Palbociclib must be stored in a secure, limited access area.

- Preparation and Dispensing:
  - **How Supplied:** Supplied as capsules which must be swallowed or solution which may be swallowed or administered enterally via feeding tubes (ie nasogastric tube or gastric tube).
    - Capsules are supplied in 125 mg, 100 mg, 75 mg doses. Bottles consist of 21 tablets.
    - Oral solution is supplied at a concentration of 25 mg/mL and 112 mL are in each bottle Oral solution (25 mg/mL) will be supplied in HDPE packaged bottles with a PIBA (push in bottle adapter) and a reusable oral syringe for dosing. Labeling will occur according to local regulatory requirements. Each clinical site will be provided the oral solution product manual which contains the detailed dosage and administration instructions for preparation of the oral solution. Please note the oral solution product manual is sponsor-provided and utilized for multiple studies. All references to placebo formulation do not apply for this protocol and should be disregarded.
  - **Note:** Capsules should not be repackaged after they are dispensed. Capsules should not be opened or emptied into another vehicle for oral delivery. Similarly, oral solution should not be transferred into any other container.

- Administration:
  - Palbociclib Capsules
    - Take once daily by mouth at approximately the same time each day.
    - Palbociclib should be taken orally with food
    - Patients should be instructed that if they vomit any time after taking a dose, that they must not “make it up” with an extra dose, but instead resume subsequent doses as prescribed. Missed doses may be taken late, up to 6 hours after the scheduled dose, otherwise should be skipped and reported to the investigators.
  - Palbociclib Solution
    - Will be available for patients who are unable to swallow capsules or develop

an inability to swallow capsules during the study.

- Will be administered using an oral syringe at volumes corresponding to the dose prescribed by the investigator (125 mg dose = 5mL, 100 mg dose = 4 mL, and 75 gm dose = 3 mL). Detailed instructions patient administration directions using syringe are detailed in Pfizer Approved 'Administration Instruction' Handouts (Appendix C- Administration Instructions for Oral Dose Using Syringe and Appendix D- Administration Instructions for Each Dose via NG Tubes)
- Take once daily at approximately the same time each day
- Solution does not need to be taken with food
- May be taken by mouth or by administration via feeding tube

- The patients will be asked to bring medication bottles to each follow-up visit, and remaining pills in bottle will be counted at each visit to document compliance. This information will be recorded in each patient's data file.
- If patients are being treated with oral solution, they will be asked to return the bottles in clear ziplock bag. For drug accountability research staff may use a best approximation as to the remaining solution as they may be unable to open HDPE bottles.

- Drug administration will be provided by the Coordinating Center to record compliance with study drug administration, route of administration (by mouth or feeding tube) as well as document dose adjustments.

- Availability**:** Provided by sponsor free of charge.

- Under no circumstance will the study medication palbociclib be used other than as directed by the protocol.

- Do Not Use Commercially Available Product.

- Drug Accountability:
  The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the drug, palbobciclib. The drug accountability records will capture drug receipt, drug dispensing, drug return and final disposition.

10.0 CORRELATIVES/SPECIAL STUDIES

10.1 Sample Collection Guidelines

We plan on collecting and banking serial saliva and serum samples as well as tumor tissue.

10.1.1 Serum and Saliva Samples

10.1.1.1 These samples are mandatory. They will be obtained at Day 1 Cycle 1, Day 8 (+/- 4 days) Cycle 1, and Day 1 (+/- 4 days) of each subsequent Cycle while on therapy (see section 6.1).

10.1.1.4 Sample Transportation

- Whenever as specimen has been obtained (i.e. after a procedure, blood draw, oral rinse in clinic), sample will be labeled with the subject's de-identified study number and collection date, and the

study coordinator will transport the sample directly to the Brenner laboratory.

10.1.2 Tumor Samples

10.1.2.1 We plan on obtaining tumor samples at screening, at Cycle 2 Day 1, and at progression.

- Screening biopsy sample is mandatory. This must be obtained within the 56 days prior to study treatment. No systemic therapy (i.e. immunotherapy) may have been administered since obtaining the biopsy, if so, a new biopsy is needed.
- Interim Biopsy at Cycle 2, Day 1 (+/- 7 days) is optional and will be offered if safe and clinically feasible
- Biopsy at the time of progression is mandatory however if the treating physician deems biopsy to be either unsafe or not clinically feasible, this must be documented and patient may forego repeat biopsy
- FFPE core biopsy is preferred, However, if not clinically feasible or safe to obtain a core biopsy, contact coordinating site PIs (P.S. and F.W.) as a block made from several FNA passes is acceptable.

10.1.3 Brenner lab will receive and process samples. See Lab Manual for details

10.2 Assay Methodology

Hypothesis 1. *Specific genetic networks will correlate with response to Palbociclib-based therapy including patients with alterations in CDKN2A, CyclinD1, CDK4/6, RB and/or human papilloma virus. Thus, developing genetic biomarkers that predict response to this therapy will help identify the patients that would most benefit from early advancement to precision medicine trials.*

Experimental design: We will perform integrative targeted sequencing of all available tumor specimens to identify the distribution of lesions co-incident with commonly deregulated genes (e.g. *CyclinD1* and *CDKN2A* and their modifying genes) as well as the transcriptional programs deregulated in these tumors. We will utilize the knowledge gained from existing publicly available sequencing studies[10,11,27-32] to perform targeted DNA and RNA sequencing in our cohort using our 250 gene MiOTOseq panel. We will also perform targeted RNA-Seq to assess the expression of genes used to classify tumors into immunogenic, classical, mesenchymal, basal or atypical molecular subtypes. The co-incidence of events will be correlated with immunohistochemical stains for established HNSCC biomarkers and correlations established between molecular events and clinical data.

1i. Preparation of biopsy specimens for targeted DNA and RNA sequencing. Collaborator Dr. McHugh is a board certified pathologist and will identify representative FFPE sections with >50% tumor content, he has extensive experience in tissue specimen evaluation for molecular analysis[33-45]. We will use macrodissection to enrich for tumor content as needed. At least 3x10um sections per case will be cut for simultaneous DNA/RNA extraction using the Qiagen Allprep FFPE DNA/RNA kit and protocols optimized by our group to isolate assayable DNA (median 1.5 ug) and RNA (median 5.3 ug). As little as 9x10um sections from a single needle biopsy core yield sufficient DNA and RNA for the studies proposed herein. DNA and RNA will be quantified using the Qubit fluorometer.

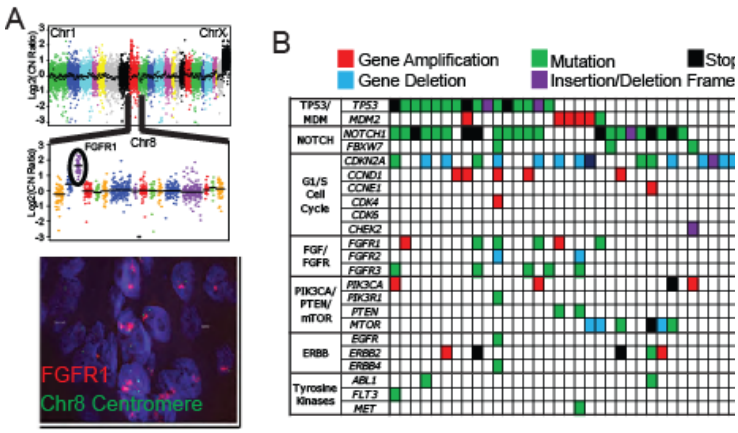


Fig 11: Targeted DNA-SEQ to molecularly characterize HPV negative H&N tumors. A) (Upper) Plot shows relative DNA copy number from AmpliSEQ analysis of an FFPE tumor sample. Top panel shows genes assessed across the genome. Chr1 shown on left and ChrX on the right. Bottom panel shows zoomed in Chr8 and *FGFR1* copy number increase. **(Below)** FISH was performed with *FGFR1* and Centromere8 probes to confirm amplification. A representative image is shown taken with a 40x objective lens. **B)** Plot shows relative aberration status from 42 FFPE isolated DNA samples from HNSCC tumors that were profiled using the Ampliseq method and the Oncomine Cancer panel (OCP). Alignment and variant calling were performed using standard plugins in the Torrent Server Suite (v3.6) and variants were filtered through a pipeline to remove low confidence calls, sequencing errors, germline variants and common polymorphisms [1]. Results were compared to known mutations in COSMIC, the

1ii. Targeted next generation sequencing (NGS). Targeted, capture based NGS will be performed as shown in our preliminary data to the left using Ion Torrent or Illumina based sequencing (as in Fig 11). Briefly, barcoded libraries will be generated from 40ng of DNA per sample using our HNSCC-gene enriched custom Ion AmpliSeq panel, and the Ion Ampliseq Library Kit 2.0 with barcode incorporation. Templates will be prepared using the PGM Template OT2 Kitv2 on the Ion One Touch2; all protocols will be performed according to the manufacturer's instructions. Sequencing of multiplexed templates will be performed on Ion 318 chips using the Ion PGM 200 Sequencing Kitv2, sequenced to an average depth >100x. We routinely generate between 400-500 million aligned bases per 318 chip, yielding ~300-500x coverage for ~4-6 Oncomine Cancer Panel prepared templates. Mutation analysis will be performed in Torrent Suite 3.6, with alignment by TMAP using default parameters, and variant calling using the Torrent Variant Caller plugin using default low-stringency somatic variant settings. Variants will be annotated using ANNOVAR[46]. Called variants will be filtered to prioritize likely candidate somatic drivers by removing the following variants: synonymous variants, those with frequencies >0.001 in ESP6500 or 1000 genomes, those with flow corrected read depths (FDP) <20, flow variant allele containing reads (FAO) <5 or variant allele fractions (FAO/FDP) <0.05. Copy number alterations will be identified as described[34,47] (24, 39) using normalized read counts per amplicon with GC content correction and comparison to distributions from multiple unrelated normal FFPE derived genomic DNA samples. Gene-level copy number estimates will be determined by taking the coverage-weighted mean of the per-probe ratios, with expected error determined by the probe-to-probe variance; genes with |Z|>2.5 with respect to both the normal pool and the internal error will be considered as gained or lost. Our team has established robust protocols for Ion Torrent sequencing, and has used the above methodology to characterize >600 tissue specimens. Alterations will be advanced for potential as HPV+ co-dependent drivers and correlated with RNA pathway alterations based on known roles in oncogenesis and H&N cancer, comparison to Oncomine (including TCGA and publicly available data) and COSMIC mutational data, and comparison to in house databases of driving lesions. Sanger sequencing, FISH, or qPCR will be performed to confirm prioritized alterations.

1iii. Targeted RNA-SEQ for molecular subtyping, gene fusion identification and pathway activity. Reverse transcription will be performed on 300ng of isolated RNA from each tissue sample using gene specific priming with subsequent targeted RNA-SEQ using FFPE optimized assays as in Fig12. Genes have been selected to assess critical HNSCC pathways including HPV signaling status (including both E6 and E7 genes), deregulated CDK4/6 pathway genes, known HNSCC cancer fusions (through 5' and 3' assays for *FGFR-TACC3*[48] and *EGFR-ADACM* (TCGA-CV-6941), R-spondin [49], potential therapeutic targets in other malignancies (ie. 5' and 3' assays for ALK and RET overexpression), and housekeeping genes. Our team has extensive experience in RNA-SEQ, transcriptome evaluations and statistical analysis and will determine the frequencies of RNA signatures with DNA lesions as described[33-40,50-58].

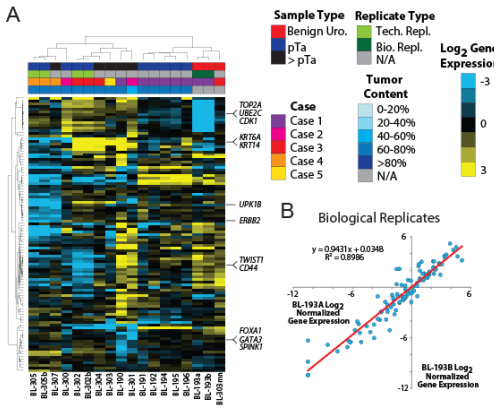


Fig 12. Example of targeted RNA-seq from FFPE isolated RNA. A) Reverse transcription and targeted multiplexed PCR (Ampliseq) was performed on 20ng FFPE isolated RNA per sample on a cohort of macrodissected benign urothelium, non-invasive urothelial carcinoma (pTa) and invasive urothelial carcinoma (>pTa). Technical and biological replicates are indicated, as well as unique components isolated from the same case. For each sample, the $\log_2$ total reads for each target gene (n=103) was normalized to the average $\log_2$ total reads for 8 housekeeping genes. Median centered normalized target gene expression and samples were clustered using centroid linkage clustering and visualized as a heatmap. **B)** Scatter plot of target gene expression (log2 normalizd gene expression) for two biological replicates of normal urothelium (BL193A and BL193B, macrodissected from separate blocks). (R^2=0.8986).

1iv. Determination of protein expression and validation of sequencing data. We will create a tissue microarray of excess FFPE tissue from samples sequenced for this Aim. Gene fusions and copy number alterations will be confirmed by fluorescence in situ hybridization (FISH) and critical targets advanced from sequencing studies will also be assessed by immunohistochemistry (IHC) if IHC grade antibodies are available. Staining and scoring will be completed as we described[59-61] with prioritization beginning with proteins found in the CDK4/6 pathway (e.g. CDK4, CDK6, RB, CyclinD1, etc.). We will leverage this data by integrating it with the sequencing data generated here to identify correlations between copy number, mutation and expression as well as HPV status using statistical methods described above.

Pitfalls, alternative strategies and future directions. We do not anticipate significant obstacles as we have extensive experience in tissue examination, NGS and integrative statistical analysis of molecular data in cancer as well as modeling of disease[34,40,41,43,44,51,62]. Additionally, Dr. Brenner is involved in several protocols that are sequencing tissue specimens as part of clinical trials or protocols, including the MiOncoseq-SU2C program[48,63]. The cohort size is based on conservative statistical estimates as noted to reach independent correlative endpoints. Targeted sequencing has been proposed to enable a focused analysis of tumors with limited DNA/RNA yields. However, we have had success sequencing whole exomes from FFPE tissues from large quantities of DNA using multiple platforms and may implement these if the technology becomes robust enough during the course of the proposal for smaller quantities of DNA. Similarly, we are currently evaluating whole transcriptome analysis as an alternative to targeted RNA-SEQ from FFPE in samples with sufficient RNA yield. Overall, we expect that completion of this Aim will identify the co-incident frequency of commonly deregulated pathways on the DNA and RNA levels that will predict response to standard therapy. Importantly, we will create a molecularly characterized TMA of specimens from this clinical trial to assess correlations between genetic and protein expression status. Taken together, this Aim will provide a wealth of data and resources for future studies

and provide a comprehensive data set correlating genetic aberrations with clinical outcome in this trial setting.

Hypothesis 2: Cancer response to therapy can be detected in saliva and serum biospecimens collected at routine interval time points and will identify tumor response earlier than interim imaging.

Correlative Justification

Less than 40% have a response (SD, PR, CR) to chemotherapy in R/M which currently only be identified by interval imaging after approximately 8-12 weeks of therapy. As patients are at risk for treatment failure, a non-invasive biomarker for detecting response earlier in therapy is of extreme importance. The measurement of serum and saliva circulating tumor ctDNA as a biomarker for recurrence may be an important, noninvasive method to detect treatment responses. Our group and others have identified HPV and mutant ctDNA in both the blood and saliva samples of patients with advance or recurrent HNSCC, suggesting this noninvasive biomarker as a way to measure disease response to therapy. Finally, using data generated from the targeted next generation sequencing on tumor specimens from above, we can prioritize evaluable somatic mutations in ctDNA from both the blood and saliva of each patient for targeted sequencing studies as well as monitor for the occurrence of mutations common in tumors that become resistant to Palbociclib treatment. Therefore, our goal is to collect longitudinal samples of saliva and serum as a part of our trial to determine if serum and saliva biomarkers can predict response to therapy and also identify emergence of resistant clones.

10.3 Specimen Banking

Patient samples collected for this study will be retained at the Brenner lab. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Specimens being stored long-term for potential use not outlined in the protocol are subject to University Policy Governing Tissue Sample Collection, Ownership, Usage, and Disposition within all UMMS Research Repositories.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints

This is an open-label multi-institution single arm Phase II study with a two-stage design. We will power this study to detect a 20% improvement in disease control rate (DCR) with the addition of palbociclib. Based on historical data, the DCR in R/M HNSCC with single agent platinum therapy is 40%[4,64]. We hypothesize that addition of Palbociclib to carboplatin will increase the DCR at 12 weeks to 60%. We anticipate no loss to followup for this endpoint. The primary clinical objective of this trial is to estimate disease control rate (DCR) at 12 weeks in patients with metastatic head and neck squamous cell cancer treated with carboplatin and palbociclib. Response will be assessed after every two cycles. DCR will be defined as either CR, PR or SD at 12 weeks. The regimen will be considered promising if the true disease control rate is 60% or better. Conversely, if the DCR is 40% or lower, there would be little interest in pursuing this therapy in further studies. In this case, we would like to terminate the trial early and consider a new therapy. The optimal two-stage accrual design has been adopted[65].

In the first stage, we will accrue 18 response-evaluable patients as defined in section 7.1.1.If 8 or less subjects are considered DCR at 12 weeks, the trial will be stopped and we will conclude that the therapy is ineffective. If we observe 9 or more with disease control (CR, PR, or SD) at 12 weeks, trial will continue to the second stage and an additional 22 response-evaluable patients will be entered. Based on all 40 subjects, if 21 or more patients have achieved disease control, the therapy will be considered promising. If fewer than 21 evaluable subjects achieve DCR at 12 weeks, we will consider the therapy to be ineffective.

Early termination or modification for toxicity

At the initial stage, after 10 patients have been evaluated, if more than 70% experienced grade 3 or 4 toxicity events, the trial will be halted for further safety review and the investigators will consider terminating the study or adjusting the doses. Throughout the study if more than 70% of patient's experience grade 4 toxicity, then the study will be halted for consideration of further adjustments to dosing.

11.2 Sample Size and Accrual

We will be using a two-stage design. This design yields a type I error rate of 0.059 and power of 0.80 when the true response rate is 0.60. The alpha level will be 0.05. The two-stage sample size calculations were carried out assuming a null DCR probability of 0.40.

11.3 Data Analyses Plans

Disease control will be defined by RECIST v1.1 criteria at 12 weeks. CR, PR or SD will be considered disease control. The initial DCR rate with 95% confidence interval (CI) will be reported to give a point estimate and precision of the estimate at the conclusion of the trial. The number and proportion of adverse events will be reported by grade according to CTCAE version 4.03 guidelines. Progression free and overall survival time will be estimated using a Kaplan-Meier analysis.

12.0 DATA AND SAFETY MONITORING

The Data and Safety Monitoring Committee (DSMC) of The University of Michigan Rogel Cancer Center is the DSMC for this study. This committee is responsible for monitoring the safety and data integrity of the trial.

At each site the study team is required to meet quarterly to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

These meetings are to be documented by the site data manager or study coordinator using the Protocol Specific Data and Safety Monitoring Report (DSMR), signed by the site principal investigator or co-investigator. Each site is required to submit the completed DSMR to the Multi-Site Coordinator at the University of Michigan Coordinating Center on a quarterly basis together with other pertinent documents.

Similarly, protocol deviations are to be documented using the Notice of Protocol Deviation Form and requires the signatures of both the sites data manager or study coordinator and the site

principal investigator or co-investigator. These reports are to be sent to the University of Michigan Coordinating Center within 7 calendar days of awareness of the event and on a quarterly basis with the Protocol Specific Data and Safety Monitoring Report.

13.0 QUALITY ASSURANCE AND AUDITS

Data and Safety Monitoring Committee can request a 'for cause' quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues. A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Coordinating Center that such a request has been made.

14.0 CLINICAL MONITORING PROCEDURES

Clinical studies coordinated by The University of Michigan Rogel Cancer Center must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be monitored by a representative of the Coordinating Center of the University of Michigan Rogel Cancer Center. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo site initiation meeting to be conducted by the Coordinating Center. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his study staff should make every effort in attending the site initiation meeting. Study–related questions or issues identified during the site initiation meeting will be followed-up by the appropriate Coordinating Center personnel until they have been answered and resolved.

Monitoring of this study will include both 'Centralized Monitoring', the review of source documents at the Coordinating Center and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes first treatment cycle. The study site will send the de-identified source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the Coordinating Center representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The Coordinating Center expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the Coordinating Center, the site will be required to ship or fax documents to be reviewed.

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit.

15.0 APPENDICES

Appendix A- ECOG Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of sedentary nature (e.g. light house work, office work)
2	Ambulatory and capable of all self care but unable to carry our any work activities; up and about more than 50% of waking hours
3	Capable of only limited self care; confined to bed or chair more than 50% of waking day
4	Completely disabled, cannot carry on any self care; totally confined to bed or chair
5	Dead

Appendix B- FACT Head and Neck Questionnaire

FACT-H&N (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

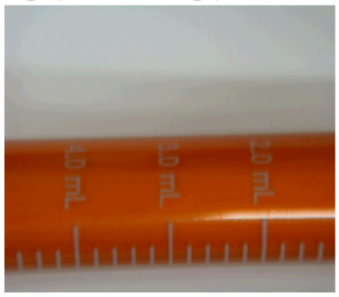
FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

Appendix C- Administration Instructions for Oral Dose Using Syringe

4.5 Administration Instruction for Each Oral Dose Using a Syringe

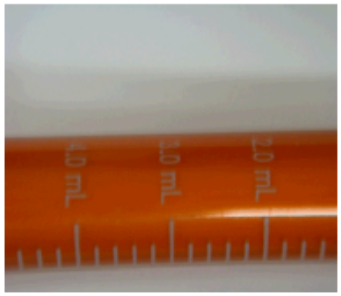
Administration Instructions for each Oral Dose using a syringe Note: A clean, dry dosing syringe must be used to deliver each dose.	
Steps	
1	Inspect the dosing syringe prior to each dose withdrawal and administration to ensure the syringe is clean and dry. Use either 1 mL syringe (0.1 mL markings) or 5 mL syringe (0.2 mL markings)  
2	Completely depress the plunger of the dosing syringe. Remove the cap from the bottle and insert the dosing syringe tip into the PIBA.
3	Invert the bottle and syringe: Pick up the bottle with one hand while holding the dosing syringe securely in the PIBA with the other hand and invert the bottle.
4	Place the thumb of the hand on the dosing syringe against the syringe barrel grip to hold the dosing syringe in place.
5	Pull back on the plunger of the oral dosing syringe to the appropriate graduation mark on the oral dosing syringe barrel, being careful not to remove the syringe from the PIBA (see picture below).  Make sure all air bubbles are expelled to ensure accurate dose withdrawal. This may be achieved by pulling small volumes into the syringe and pushing it back into the bottle. Repeat as needed to ensure bubbles are expelled. Measure the dose by aligning the rib on the plunger to the appropriate marking on the barrel (as described in step 1 above). When using the 5 mL syringe, ensure to dose using the 0.2 mL increments (if required). **Do not use** the 0.25 mL increments for dosing.
6	Return the bottle to the upright position, remove the oral dosing syringe from the PIBA and place it on a clean surface, then securely place the cap back on the bottle.

7	Deliver the dose by placing the tip of the oral dosing syringe into the mouth of the patient and pushing the plunger to expel the liquid. Be careful to not expel the dose directly into the back of the throat, to avoid choking. Drinking water after dosing is acceptable. If more than 5 mL is required to complete the dose, re-use the syringe to deliver the entire dose.
8	Clean the syringe by removing the plunger and rinsing the barrel and plunger with warm water. Allow the barrel and plunger to air dry or use a clean paper towel or clean cloth to dry. When dry, push the plunger back into the syringe barrel prior to the next dose. Syringes should be re-used for all subsequent doses with the bottle.

Appendix D- Administration Instructions for Each Dose via NG Tubes

4.6 Administration Instruction for Each Dose via NG Tubes

Administration Instructions for each dose via NG tubes Note: A clean, dry dosing syringe must be used to deliver each dose.	
Steps	
Rinsing the NG tubes	
1	Inspect the dosing syringe prior to each dose withdrawal and administration to ensure the syringe is clean and dry.
2	Using a 5 mL syringe, draw up water to the 5 mL mark. Remove the feeding tube cap, and firmly attach the syringe tightly to the feeding tube port. Dispense the entire syringe content into the feeding tube.
Preparation and Administration of Dose	
3	Inspect the dosing syringe prior to each dose withdrawal and administration to ensure the syringe is clean and dry.
4	Completely depress the plunger of the dosing syringe. Remove the cap from the bottle and insert the dosing syringe tip into the PIBA.
5	Invert the bottle and syringe: Pick up the bottle with one hand while holding the dosing syringe securely in the PIBA with the other hand and invert the bottle.
6	Place the thumb of the hand on the dosing syringe against the syringe barrel grip to hold the dosing syringe in place.

7	Pull back on the plunger of the oral dosing syringe to the appropriate graduation mark on the oral dosing syringe barrel, being careful not to remove the syringe from the PIBA (see picture below).  Make sure all air bubbles are expelled to ensure accurate dose withdrawal. This may be achieved by pulling small volumes into the syringe and pushing it back into the bottle. Repeat as needed to ensure all bubbles are sufficient expelled. Measure the dose by aligning the rib on the plunger to the appropriate marking on the barrel (see pictures below).   When using the 5 mL syringe ensure to dose using the 0.2 mL increments (if required) at volume with increment markings on the syringe barrel only. **Do not use** the 0.25 mL increments.
8	Return the bottle to the upright position, remove the oral dosing syringe from the PIBA and place it on a clean surface, then securely place the cap back on the bottle.
9	Remove the feeding tube cap, and firmly attach the syringe tightly to the feeding tube port. Administer the oral solution completely to the feeding tube to deliver the dose by pushing the plunger to expel the liquid. If a second dose is needed, use the same syringe.
10	Using a clean 5 mL syringe, pull up rinsing water until it just reaches the 5 mL mark. Then firmly attach the syringe tightly to the feeding tube port. Administer the contents of ***syringe*** to the feeding tube.
11	Remove the syringe from the syringe port and clean both syringes by removing the plunger and rinsing the barrel and plunger with warm water. Allow the barrel and plunger to air dry or use a clean paper towel or clean cloth to dry. When dry, push the plunger back into the syringe barrel prior to the next dose. Syringes should be re-used for all subsequent doses with the bottle.

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