Title: A phase II study of duvelisib plus docetaxel in PD-1 inhibitor experienced patients with incurable head and neck squamous cell carcinoma

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SCHEMA

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1. OBJECTIVES

1.1 Study Design

This multicenter, phase II open-label, single-arm trial will enroll patients with recurrent or metastatic (R/M), incurable squamous cell carcinoma of the head and neck (SCCHN) who have failed or discontinued PD-1 blockade in the first-line (1L) advanced disease setting, regardless of human papillomavirus (HPV) and smoking status, or PI3K pathway alteration status. Participants with or without a prior response to immune checkpoint blockade are permitted, to include individuals with both inherent and acquired immune resistance. Prior taxane (paclitaxel only) exposure as part of 1L chemoimmunotherapy is permitted, but not required. Patients will receive duvelisib 25 mg by mouth twice daily continuously (days 1-21 of a 21-day cycle) with a 7-day lead-in planned prior to the start of taxane therapy. Docetaxel at 75 mg/m2 IV will be delivered on day 1 of each 21-day cycle. Treatment will continue for 24-months or until unacceptable toxicity, progression, or death.

1.2 Primary Objectives

To evaluate the anti-tumor activity of duvelisib plus docetaxel chemotherapy by evaluating the best overall response rate using RECIST v1.1 in participants with R/M SCCHN who have received prior (chemo)immunotherapy.

1.3 Secondary Objectives

- To estimate progression-free survival (PFS) and overall survival (OS)
- To estimate duration of therapeutic response
- To evaluate safety and tolerability of the combination
- To characterize patient-reported outcome (PRO) qualify of life metrics
- To correlate tumor genomic/molecular and immunologic phenotype (*TP53*, PI3K pathway alteration status; PD-L1 score) with response

2. BACKGROUND

2.1 Study Disease(s)

Squamous cell carcinoma of the head and neck (SCCHN) represents over 90% of all head and neck malignancies. Although the majority of patients present with locoregionally advanced disease, the clinical course is characterized by a high rate of recurrence approaching 50%, as well as the development of distal metastases [1-3]. The median survival in most series ranges from 6 to 15 months depending on patient-related and disease-related factors. Immune checkpoint inhibitors targeting PD-1 have redefined the treatment of advanced or recurrent or metastatic (R/M), incurable SCCHN [4-7] where outcomes are generally poor. However, objective response rates remain around 30-40% even in the first-line (1L) advanced disease setting with chemotherapy (carboplatin plus 5-fluorouracil, PF) combined with PD-1 blockade (pembrolizumab) [7]. Pembrolizumab (PD-1 inhibitor) is also approved as a single agent for 1L treatment of patients with metastatic or with unresectable, recurrent SCCHN whose tumors overexpress the tumor immune marker PD-L1

(combined positive score [CPS] ≥1) and was approved in combination with PF for all patients. In subjects with CPS ≥1, overall survival (OS) was significantly longer with pembrolizumab monotherapy vs. standard of care PF-cetuximab therapy (12.3 vs. 10.3 months, HR 0.78, p=0.01) in the recent landmark KEYNOTE-048 study. Objective response rate and median duration of response (DOR) were 19% and 20.9 months in the pembrolizumab monotherapy group vs. 35% and 4.5 months in the standard chemotherapy group, respectively. In addition, both pembrolizumab and nivolumab are approved in the platinum-refractory setting for advanced SCCHN [8, 9].

Since 1L (chemo)immunotherapy was approved in 2019 for SCCHN, available second-line (2L) treatment options consist of pre-immunotherapy era cytotoxic agents and epidermal growth factor receptor (EGFR) antibody therapy with limited response rates (frequently <15%) and unfavorable toxicity profiles as summarized in **Table 1** below.

Table 1. Efficacy and survival data with the use of systemic therapy after platinum-based chemotherapy in advanced, recurrent SCCHN

Trial	Agent(s)	Line of Therapy	*N*	ORR	PFS	OS	Grade 3-4+ toxicity
Specenier P, et al. 2011	Weekly docetaxel	2L+	30	6.7% (2/30)	7.4 weeks	17.9 weeks	no grade 4
Catimel G, et al. 1994	Gemcitabine	1-2L+	61	13% (7/61)	--	--	< 10%
Vermorken JB, et al. 2007	Cetuximab	2L+	103	13%	--	178 days	dermatitis
Machiels JP, et al. 2015	Afatinib Methotrexate	2L+	322 161	10% 6%	2.6 months 1.7 months	6.8 months 6 months	rash, diarrhea
Stewart JS, et al. 2009	Gefitinib Methotrexate	1L+	167 161	2.7-7.6% 3.9%	--	5.6-6 months 6.7 months	rash, diarrhea

ORR = overall response rate, PFS = progression-free survival, OS = overall survival

2.2 IND Agent: Duvelisib

2.2.1 Duvelisib

2.2.1.1 Mechanism of action

Duvelisib (VS-0145) is a synthetic, orally-active, small molecule dual inhibitor of phosphoinositide 3-kinase (PI3K)-δ and PI3K-γ isoforms that reduces the cancer-promoting effects of both isoforms through effects on the tumor microenvironment (TME) and has an established clinical safety and efficacy profile in patients with hematologic malignancies. Duvelisib is approved for the treatment of adult patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) after at least two prior systemic therapies and was granted accelerated approval in adult patients with follicular lymphoma (FL) after at least two prior systemic therapies [10]. Duvelisib is being developed by Secura Bio, Inc. (Secura Bio).

While the tumor-suppressing effect of duvelisib in hematologic malignancies is well established [11, 12], a direct effect of duvelisib and PI3K signaling on tumor cell proliferation and survival has not been well characterized in solid tumors. However, because of the significant presence of immune

cells in the TME, a cell-based target for duvelisib is thought to be the immunomodulating TME consisting of T cell, B cell, and myeloid lineage cells, in particular.

2.2.1.2 Clinical pharmacology and safety

A phase I trial of duvelisib in preclinical models and patients with T-cell lymphoma (TCL) was conducted among 35 patients along with in vitro and in vivo models with a primary endpoint of overall response rate [14]. The most frequent reported observed grade 3-4 adverse events were transaminase increases (40% alanine aminotransferase, 17% aspartate aminotransferase), maculopapular rash (17%), and neutropenia (17%).

In a large, randomized (1:1), multicenter, open-label trial (NCT02004522; DUO trial) comparing duvelisib to ofatumumab in 319 patients with relapsed or refractory CLL, duvelisib was dosed 25 mg orally twice daily [15]. The prescribing information contains boxed warnings for fatal and/or serious infections in the hematologic malignancy population, diarrhea or colitis, cutaneous reactions, and pneumonitis; and warnings for neutropenia and hepatotoxicity. Of a total of 442 patients with hematologic malignancies treated with duvelisib at the approved dose, 65% had serious adverse reactions, with the most frequent being infection, diarrhea or colitis, and pneumonia. The most common adverse reactions (incidence ≥20%) were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia. Adverse reactions resulted in permanent discontinuation of duvelisib in 35% of patients. Dose reduction occurred in 24% of those receiving duvelisib.

To assess possible direct effects of duvelisib on solid tumor cells, the growth inhibitory activity of duvelisib has been evaluated across 7 melanoma and 3 SCCHN cell lines expressing high levels of PI3K-δ and/or PI3K-γ [16]. Cell viability was measured after 72-hour treatment with duvelisib (0.5nM-10μM) and reported as growth inhibition (GI) at 1μM. Duvelisib showed strong anti-proliferative activity (50-100% GI) in 3 out of 7 melanoma cell lines and 1 out of 3 SCCHN cell lines, and moderate activity (15-50% GI) in 3 melanoma cell lines and an additional SCCHN cell line. Duvelisib inhibited PI3K pathway activity, as measured by p-AKT and c-myc, in all the cell lines in which strong anti-proliferative activity was observed. Taken together, these findings indicate that in addition to the established effects of duvelisib on malignant B cells and non-malignant immune cells of the TME, duvelisib can also directly inhibit signaling and proliferation of solid tumor cells expressing PI3K-δ and/or PI3K-γ, providing further rationale for clinical investigation of duvelisib for the treatment of solid tumors.

2.2.1.3 Clinical efficacy

The CLL indication is based on the randomized, multicenter, open-label DUO trial, which compared duvelisib with ofatumumab (Arzerra) in patients with relapsed or refractory CLL (NCT02004522) [13]. The trial randomized patients (1:1) to receive either duvelisib at 25 mg orally twice daily (the recommended dose) or ofatumumab. Among 196 patients receiving at least 2 prior therapies, the estimated median progression-free survival (PFS) as assessed by an independent review committee was 16.4 months with duvelisib and 9.1 months with ofatumumab. The overall response rate per independent review committee was 78% and 39% for the duvelisib and ofatumumab arms, respectively.

In the DYNAMO trial, 129 patients with any refractory, indolent non-Hodgkin lymphoma (NHL) (FL, CLL, or marginal zone B-cell lymphoma) were treated with duvelisib 25 mg orally twice daily in 28-day cycles showing an ORR of 47.3% with a median DOR of 10 months; and the median PFS was 9.5 months [17].

The follicular lymphoma (FL) indication is based on the single-arm multicenter DYNAMO + R trial of duvelisib, which enrolled 83 patients with FL whose disease was refractory to rituximab (Rituxan) and either chemotherapy or radioimmunotherapy (NCT02204982) [18]. The overall response rate, determined by an independent review committee, was 42%, with 41% of patients experiencing partial responses. Of the 35 responding patients, 15 (43%) maintained responses for at least 6 months, and 6 (17%) maintained responses for at least 12 months.

Beyond hematologic malignancies, the anti-tumor activity of duvelisib is now being assessed in solid tumors.

2.3 Other Agent: Docetaxel

2.3.1 Docetaxel

2.3.1.1 Mechanism of action

Docetaxel promotes the assembly of microtubules from tubulin dimers, and inhibits the depolymerization of tubulin which stabilizes microtubules in the cell. This results in inhibition of DNA, RNA, and protein synthesis. Most activity occurs during the M phase of the cell cycle.

2.3.1.2 Clinical pharmacology and safety

Docetaxel (*Taxotere*®) was first approved for use by the US Food and Drug Administration in 1996 for locally advanced or metastatic breast cancer after failure of prior chemotherapy, with a dose of 60 to 100 mg/m^2 administered intravenously over 1 hour every 3 weeks. Thereafter, additional indications were approved at a dose of 75 mg/m^2 [19]. In a phase I trial, the PK of docetaxel was linear, determined by 23 patients receiving 20–115 mg/m^2. At high doses of docetaxel (85–115 mg/m^2), a three-compartment model was found to provide a better fit than a two-compartment model with a terminal half-life of 13.5 ± 7.5 h (mean ± SD), a plasma clearance of 21.1 ± 5.3 L/h/m^2 and a distribution volume of 72 ± 40 L/m [20]. Docetaxel exposure as measured by the area under the plasma concentration time curve (AUC) was the only significant predictor of severe toxicity during the first course of chemotherapy. It was also reported that docetaxel PK were similar for weekly and 3-weekly regimens [21]. Short-lasting neutropenia is the dose-limiting toxicity. Other common but non-dose-limiting toxicities are mucositis, alopecia, fatigue, sensory peripheral neuropathy, fluid retention, rash, and acute hypersensitivity reactions. Studies have confirmed that dexamethasone as prophylaxis against hypersensitivity reactions and fluid retention is both warranted and effective with docetaxel use.

2.3.1.3 Clinical efficacy

Several groups first reported on the activity of docetaxel as a single agent in SCCHN in the late 1990s. Two published trials, conducted by the Dana-Farber Cancer Institute in Boston and the early

trials of the European Organization for Research and Treatment of Cancer (EORTC), treated a total of 75 patients with docetaxel monotherapy at 100 mg/m^2 every 21 days [22, 23]. Patients enrolled on these trials were of good performance status and had not been previously treated with palliative chemotherapy, although approximately one third of the patients had previously received induction chemotherapy. Of 68 assessable patients, six (9%) achieved a complete response and 21 (31%) a partial response.

After cetuximab with platinum-based 5-fluorouracil (5-FU) containing chemotherapy was established as the former 1L standard combination (EXTREME regimen) for R/M SCCHN [24] prior to the era of immunotherapy, the taxane docetaxel was later exchanged for 5-FU in the TPEx regimen [25] and among 539 patients randomized 1:1 showed comparable OS between groups (HR=0.87, p=0.15) with 2-year OS rates that were similar (28.6 vs. 21% favoring the docetaxel-containing combination) with overall less toxicity. A number of other docetaxel-platinum core combination regimens have shown encouraging activity in advanced SCCHN [26] (**Table 2**).

Table 2. Efficacy and survival data with the use of docetaxel-containing chemotherapy regimens in advanced, recurrent SCCHN

Trial	Agent(s)	*N*	ORR	2-year OS	Median OS
Gedlicka, et al. 2002	D (75 mg/m^2) + C (75 mg/m^2) q21d	38	52.5%	9%	11.0 (1-30)
Yabuuchi, et al. 2003	D (60 mg/m^2) + C (70 mg/m^2)	17	71%	--	--
Hehr, et al. 2005	D (50 mg/m^2) + C (15 mg/m^2 days 2-5) q21d + 2Gy RT daily	39	80%	20%	10.0
Baghi, et al. 2006	D (75 mg/m^2) + C (100 mg/m^2) + 5-fluorourail (1 g/m^2 d1-4) q21d	24	42%	--	13.0
Peyrade, et al. 2006	D (75 mg/m^2) + C (75 mg/m^2) + 5-fluorourail (750 mg/m^2 d2-5) q21d	40	63%	--	13.0

ORR = overall response rate, OS = overall survival, D = docetaxel, C = cisplatin, d = day

2.4 Rationale

Phosphatidylinositol 3-kinase (PI3K) pathway activation contributes to both tumor resistance and disease progression in SCCHN [27] and is among the most frequently altered pathways in SCCHN tumors [28]. Moreover, pre-clinical data suggests that PI3K-γ/δ inhibition (avoiding direct cytotoxicity to normal B cells [29] can reduce regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) in the TME which may enhance sensitivity of the tumor in the context of prior PD-1 inhibitor exposure [30]. In addition, inhibition of the PI3K pathway has been shown to lead to increased efficacy of the taxane microtubule inhibitor paclitaxel in ovarian cancer and malignant glioma cell lines [31] – supporting the rationale for combining PI3K targeted therapy with a taxane after immunotherapy exposure.

Prior to the approval of 1L (chemo)immunotherapy in R/M SCCHN in 2019, the phase II BERIL-1 study showed that median PFS and OS was superior (4.6 vs. 3.5, p=0.01; 10.4 vs. 6.5), and tolerability reasonable, with the use of the pan-PI3K inhibitor buparlisib vs. placebo when combined with paclitaxel among 2L, platinum-refractory patients [32]. The overall response rate was 39% vs. 14% (p<0.01) favoring the buparlisib plus paclitaxel combination. Follow-up analyses showed that patients with *TP53* alterations, HPV negative disease, and immune cell infiltration in their tumors had improved outcomes with the combination [33], the latter providing further support that exposure

after PD-1 blockade may be beneficial.

We propose a novel clinical trial to evaluate the combination of the PI3K-γ/δ inhibitor duvelisib in combination with taxane therapy (docetaxel) for the treatment of R/M, incurable SCCHN patients who previously received PD-1 inhibitor-based therapy in the 1L. We hypothesize that utilizing 2L PI3K pathway inhibition with taxane therapy after immunotherapy exposure will yield an overall response rate approaching 30%.

2.5 Correlative Studies Background

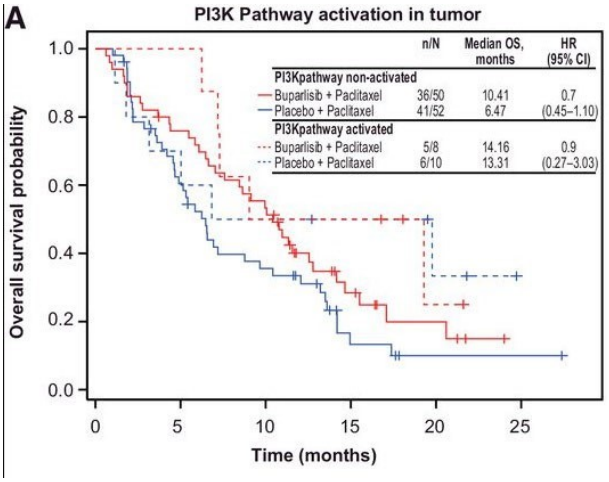
Alterations leading to activation of the PI3K pathway include gain-of-function mutations and amplifications in PIK3CA, PTEN alterations (such as loss of heterozygosity, inactivating mutations, or loss of expression), as well as overexpression or activation of downstream or upstream signaling molecules. While *PIK3CA* mutations (15%–20%) and reduced PTEN activity (identified in 6% to 82% of patients) are the most frequently reported molecular alterations of the PI3K pathway in SCCHN, overexpression of the upstream EGFR (occurring in about 90% of patients) is also expected to lead to PI3K pathway activation [34]. Additionally, activation of the PI3K pathway is likely to affect the response of SCCHN to taxanes such as paclitaxel, as PI3K activation was shown to contribute to paclitaxel resistance in other tumor types [35-37]. Further, inhibition of the PI3K pathway led to an increased efficacy of paclitaxel (a taxane) in ovarian cancer and malignant glioma cell lines [31]. These observations, together with the reported activity of the PI3K inhibitor buparlisib in SCCHN further support the key role of PI3K pathway in SCCHN.

Several other molecular alterations are frequently reported in SCCHN, including TP53 mutation (40%–75%), or amplification (10%–30%), and CDKN2A (p14/ARF) inactivation (75%). TP53 mutations are known to be associated with a poor prognosis, as patients with TP53-altered tumors have decreased postsurgical survival [38]. Various publications have also reported an association between TP53 mutational status and response to platinum-based therapy in SCCHN. While some have reported that TP53 mutations may predict improved SCCHN cell response to cisplatin, or that TP53-mutant ovarian tumors were sensitive to taxane-platinum–based chemotherapy, other publications showed that functional or high-risk TP53 mutations were associated with resistance to cisplatin-based therapies [39, 40]. These observations highlight the importance of understanding the p53 cellular networks and their relation to responses to therapy.

Infection with the human papillomavirus (HPV), occurring in up to approximately 44% of cases, has been shown to contribute to SCCHN etiology and to influence outcomes [41]. HPV-negative SCCHN tumors differ markedly from HPV-positive SCCHN in their clinical, immunological, and molecular characteristics – and have an overall worse prognosis. In addition, a strong association has been reported between TP53 alterations and HPV-negative SCCHN [34, 42].

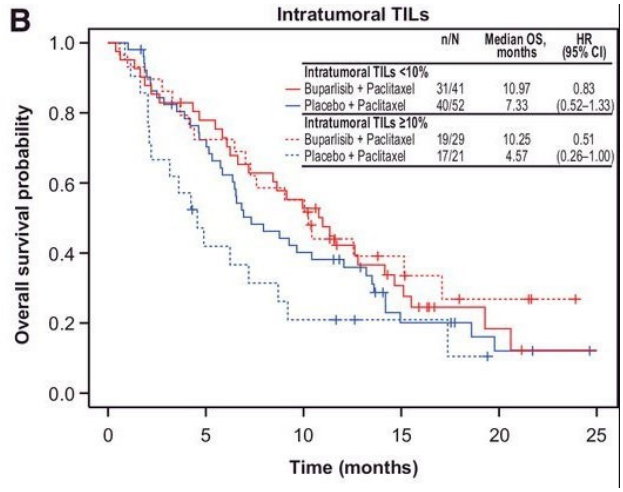
The importance of immune markers in predicting outcome in SCCHN has been highlighted in recent studies. Infiltration of immune cells, especially CD8+ cells, was previously shown to be associated with an improved response to chemoradiotherapy [43]. In addition, data suggest that expression of the programmed cell death ligand-1 (PD-L1) correlates with an improved clinical outcome under treatment with programmed cell death receptor-1 (PD-1) inhibitors [44]. Mutational load, identified by the total number of mutations present in a tumor specimen, is a potential biomarker for response

to immunotherapy, as highly mutated tumors are more likely to harbor neoantigens, which make them targets of activated immune cells [45]. These data highlight the potential of immune markers and mutational load as prognostic and predictive markers in SCCHN and warrant further exploration.



Follow-up analyses from the BERIL-1 study comparing either buparlisib or placebo with paclitaxel in R/M SCCHN has provided some insight in regards to meaningful biomarker findings in this setting [33]. They characterized frequencies of molecular alterations and found PI3K pathway activation in 13.8-16.1% of patients; with 76-85% of their study population being HPV-negative. TP53 was altered in 58-67% of HPV-negative paricipants compared with 34-42% among the HPV-positive subgroup. A higher frequency of TP53 alterations and a lower frequency of PIK3CA alterations was noted in the HPV-negative group. When accounting for differences in survival based on PI3K pathway activation status in the BERIL-1 study, there was no difference between the buparlisib and placebo arms. A trend towards improved PFS and ORR was noted with buparlisib use, however (**Figure** *panel A*). Of interest, patients with tumors having HPV-negative status, TP53 alterations or low mutational load derived clinical benefit with the combination of buparlisib and paclitaxel.

A potential relationship between PD-L1 expression and treatment benefit was explored, using the 1% expression cutoff previously described in the literature. An improved OS benefit with the combination of buparlisib and paclitaxel was observed in patients showing immune cell infiltration, regardless of the compartment where this infiltration occurred. OS benefit with this combination was increased in patients with the presence of intratumoral tumor infiltrating lymphocytes (TILs) ≥10% [HR = 0.51 (95% CI, 0.26–1.00)] (**Figure** *panel B*), stromal TILs ≥15% [HR = 0.53, (95% CI, 0.33–0.85)], intratumoral CD8-positive cells ≥5% [HR = 0.45 (95% CI, 0.23–0.86)], stromal CD8-positive cells ≥10% [HR = 0.47, (95% CI, 0.28–0.79)] or CD8-positive cells in invasive margins >25% [HR = 0.37 (95% CI, 0.14–0.94)]. There was, however, no clear relationship between the molecular alterations noted above and the markers of immune infiltration – understanding samples sizes in some subgroups were limited.



While these preliminary biomarker findings are important, further investigation is warranted to understand how prior anti-PD-1 therapy impacts these molecular associations and immunologic parameters, which will be an important part of the exploratory correlative analysis of the present study.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

1. Participants must have histologically confirmed squamous cell carcinoma of the head and neck (SCCHN) with evidence of recurrent, metastatic (R/M) or advanced, incurable disease from any mucosal subsite including oral cavity, oropharynx, larynx, hypopharynx, nasal cavity, and the paranasal sinuses.
2. Participants must have at least one RECIST v1.1 measurable lesion, as defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) ≥1 cm with CT scans or MR imaging.
3. Must have had at least 1, but no more than 2, prior lines of prior systemic therapy for R/M SCCHN; one of these lines should have included PD-1/L1 blockade
    a. Platinum-based therapy as part of definitive/adjuvant or curative-intent treatment *can* count as 1 prior line of therapy if the subject progressed within 6 months of receiving therapy.
    b. At least 2 weeks must have elapsed since the end of prior chemotherapy, biological agents (3 weeks for anti-cancer monoclonal antibody containing regimens) or any investigational drug product, with adequate recovery of treatment-related toxicity to NCI CTCAE Version 5.0 grade ≤1 (or tolerable grade 2) or back to baseline (except for alopecia or peripheral neuropathy).
4. Be ≥18 years of age on the day of signing informed consent.
5. Must provide prior data on tumor PD-L1 expression status and HPV status, if available
6. Have a performance status of 0 or 1 on the ECOG Performance Scale (see *Appendix A*).
7. Participants must have adequate organ and marrow function as defined below (within 14 days prior to study registration):

- absolute neutrophil count ≥ 1,000/mcL
- hemoglobin ≥ 9 g/dL
- platelets ≥ 100,000/mcL
- total bilirubin ≤ upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) ≤ 2.5x institutional ULN (or ≤ 1.5x institutional ULN if concomitant with alkaline phosphatase >2.5x institutional ULN) or ≤ 5x ULN for those with liver metastases
- serum creatinine ≤ 1.5x ULN
  OR
- creatinine clearance ≥ 60 mL/min/1.73 m^2 for participants with creatinine levels above 1.5x ULN

- coagulation profile — INR ≤ 1.5x ULN unless the participant is receiving an anticoagulant

8. Baseline tumor measurements must be documented from imaging within 28 days prior to study registration.
9. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 7 days of study registration. Female subjects of childbearing potential should have a negative urine or serum pregnancy test repeated within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
10. Female and male subjects of childbearing potential must agree to use an adequate method of contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and 4 months after completion of stud drug administration. Contraception is required before starting the first dose of study medication through 120 days after the last dose of study medication. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
11. Be willing and able to provide written informed consent for the trial.

3.2 Exclusion Criteria

Participants who exhibit *any* of the following conditions at screening will not be eligible for admission into the study.

1. Have been previously treated with 3 or more lines of systemic therapy for R/M SCCHN.
    a. Have received treatment with a prior PI3K pathway inhibitor
2. Have received radiation therapy (RT) within 14 days of the first dose of duvelisib on study.
3. Participant has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging *and* off systemic steroids for at least 4 weeks prior to the first dose of study treatment), and have no evidence of new or enlarging brain metastases. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability, because of the poor prognosis and progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
4. Concurrent administration of other cancer specific therapy or investigational agents during the course of this study.
5. Uncontrolled intercurrent illness including but not limited to ongoing or active infection; evidence of symptomatic congestive heart failure, unstable angina pectoris, stroke, or ventricular arrhythmia within 6 months of enrollment.
6. Have received a live or live attenuated vaccine within 4 weeks of the first dose of duvelisib.
7. Have received medications or consumed foods that are strong inhibitors or inducers of cytochrome P450 (CYP3A) within 2 weeks of, or while on, duvelisib.

8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions might include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
9. Known human immunodeficiency virus (HIV) carrier. Any known positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, e.g., hepatitis B surface antigen (HBsAg, Australia antigen) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).
10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
11. Subjects who are pregnant, or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment. Breastfeeding should be discontinued if the mother is treated on this protocol. Women who could potentially become pregnant while undergoing treatment on this protocol must be willing to use 2 methods of contraception.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. Women, minorities and other underrepresented populations are all at risk to develop head and neck cancers.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP#: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the DFCI by the Study Coordinator. All sites should call the Study Coordinator to verify registration. Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Sponsor-Investigator. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the participating site and faxed or e-mailed to the Study Coordinator:

- Signed participant consent form
- HIPAA authorization form
- Completed eligibility checklist

The participating site will then call or e-mail the Study Coordinator to verify eligibility. The Study Coordinator will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The Study Coordinator will fax or e-mail the participant study number to the participating site. The Study Coordinator will also contact the participating site and verbally confirm registration.

5. TREATMENT PLAN

5.1 Treatment Regimen

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in *Section 7*. Appropriate dose modifications are described in *Section 6*.

Safety Run-In: The first N=3 subjects to enroll to the study will be part of a safety run-in to ensure adequate safety in combining duvelisib with docetaxel and monitor for drug interactions between the two study agents -- given the potential for overlapping toxicities. Those participants in the safety run-in will receive the lead-in phase of duvelisib as outlined below (25 mg orally twice daily for 7 ± 2 days) prior to initiation of docetaxel. Following the lead-in phase, in cycle 1 of duvelisib they will receive docetaxel at 56 mg/m^2 intravenously (IV) (prespecified dose level -1) on a 21-day cycle and continue that dose in subsequent cycles (there is no escalation of the docetaxel dose on study for these patients). Toxicity management should follow guidelines in *Section 6.1*. If >1 subject in the safety run-in has an unacceptable toxicity (see *Section 6.4*) then study accrual will pause for review by the overall PI and drug sponsor; otherwise, enrollment may proceed using the 75 mg/m^2 of docetaxel outlined below for all subsequent patients.

Lead-In Phase: For the first cycle only, patients will receive duvelisib 25 mg orally twice daily for 7 ± 2 days (1 week) prior to the initiation of docetaxel chemotherapy. Duvelisib may be administered

without regard to meals; however, subjects should avoid grapefruit and grapefruit juice while on duvelisib. Duvelisib capsules should be swallowed whole with a glass of water. Patients are advised not to open, break, or chew the capsules.

Following the lead-in phase, patients will continue onto cycle 1 of duvelisib at the same dose of 25 mg orally twice daily on days 1 through 21. Docetaxel will be administered intravenously (IV) at a dose of 75 mg/m^2 on day 1 of a 21-day cycle (in all remaining participants after the N=3 patients start the safety run-in) until disease progression or unacceptable toxicity. Treatment duration is planned for 24 months (or longer if patient exhibits good tolerance and clinical benefit), unless unacceptable toxicity, disease progression, or withdrawl of consent occurs. Following the first 21-day cycle of therapy, both duvelisib and docetaxel are to be continued concurrently in 21-day subsequent cycles.

Duvelisib compliance will be monitored as part of the study. Each participant will be required to maintain a medication diary of each dose of medication. The medication diary will be returned to the clinic study staff at the end of each 21-day cycle.

With docetaxel chemotherapy, granulocyte-colony stimulating factor (GCSF) support can be administered (at the treating physician's discretion). For pegfilgrastim, 6 mg subcutaneosly should be administered once, at least 24 hours and no later than 72 hours after completion of the docetaxel infusion. Alternatively, tbo-filgrastim can be administered once per day at a dose of 300 or 480 mcg(based on patient weight) at least 24 hours after the completion of the docetaxel infusion and no later than 72 hours after completion of the docetaxel infusion. Tbo-filgastrim should be administered dailyfor at least 5 days and continued for a maximum of 14 days, or until the ANC is $\geq$1000. Tbo-filgrastim should not be administered with 24 hours of the start of the next cycle of docetaxel.

Standard pre-medications including dexamethasone, palonosetron or ondansetron, and (fos)aprepitant are permitted for anti-emetic effect. Pre-medication with dexamethasone prior to taxane exposure is strongly encouraged for all participants.

In addition to the continuous routine toxicity monitoring by the study team throughout the duration of the trial, the following stopping rule will be used to monitor excessive protocol treatment related toxicity/delays (as noted in *Sectio 6.4*): if 3 or more of the first 10 patients (which includes the 3 patients treated as part of the safety run-in) who begin protocol treatment experience treatment related toxicities, accrual to the trial will be suspended to further evaluate the events and decisions made regarding the overall status of the trial. Adverse events will be continuously monitored throughout the trial by the study team with decisions made accordingly regarding the study status and patient entry throughout the duration of the trial.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

Eligibility and exclusion criteria are provided in *Section 3*. These criteria will be assessed within 28 days of the first day of study treatment to establish eligibility and baseline values. Informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments. If screening assessments occur within 3 days before start of study treatment, then they may serve as the baseline Cycle 1 Day 1 visit, and Cycle 1 Day 1 labs do not need to be performed. Cycle 1 Day 1 labs do not need to re-meet eligibility criteria.

Demographic information and baseline characteristics will be collected at the Screening Visit. Standard demographic parameters include age, sex, and race/ethnicity (recorded in accordance with prevailing regulations). Baseline characteristics will include ECOG performance status (*Appendix A*), disease status, medical histories, and prior and concomitant medications.

Additional testing required, as per *Section 10*, includes: hematology panel (see **Table 2**), chemistry panel, coagulation panel, urine or serum HCG (in women of childbearing potential; see *Section 3* for when serum HCG testing is required), and an ECG.

Table 2. *Clinical Laboratory Testing*

Category	Test
Hematology panel	Hematocrit, hemoglobin, platelet count, white cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), absolute neutrophil count
Chemistry panel	Chloride, potassium, sodium, BUN, serum creatinine, phosphorus, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, total bilirubin (Note: the frequency of checking magnesium levels is at the discretion of the treating provider)
Coagulation profile	PT/INR and aPTT
Thyroid function tests	TSH and free T4 if indicated with prior head and neck radiation exposure
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; PT = prothrombin time/INR = international normalized ratio; aPTT = partial thromboplastin time; TSH = thyroid stimulating hormone	

A fresh tumor biopsy sample is preferred but *not* required prior to the start of duvelisib and docetaxel, so as to garner the most recent possible information about PD-L1 status and other biomarkers. If obtaining a fresh biopsy is unfeasible or carries an unacceptable risk/benefit profile, an archival tissue sample must be available for histologic confirmation of SCCHN.

5.2.2 Subsequent Cycles

Reasonable effort should be made to conduct study visits on the day scheduled (± 3 days).

Any changes from screening clinical evaluation findings that meet the definition of an adverse event (AE) will be recorded on the AE page of the eCRF.

The participants ECOG performance status, weight (in kilograms), vital signs, interval history since the last visit, and physical examination are performed at each study visit. Concomitant medications

should also be reviewed at each study visit. In addition, the adverse event (AE) grid should be completed at each study visit. All laboratory values should be reviewed before proceeding with an additional cycle of treatment. Participants will undergo every-21 day or every 3-week assessments while on study (which coincides with the start of each cycle of therapy). The drug diary for the prior cycle should be reviewed at each study visit by the clinical staff.

5.2.3 Additional On-treatment Assessments

Tumor Assessments:

Tumor assessments will be performed according to RECIST v1.1 (see *Section 11*), at baseline and with response evaluations performed every 9 weeks (every 3 cycles), or as clinically indicated. In the case of response, confirmatory scans are recommended at least 4 weeks after initial response and every 9 weeks after the scan that documented the initial response. In the case of progressive disease, confirmatory scans are not required and are at the discretion of the treating investigator.

Continued treatment after initial progression is permitted, provided the patient is thought to be deriving clinical benefit and is counseled regarding the risks and benefits of continued treatment. This decision should be made in discussion with the overall study PI. If progression is confirmed, the date of progression is dated as the time of the original scans for study monitoring purposes.

On-Treatment Tumor Biopsy Collections:

An on-treatment tumor tissue biopsy will be offered at the end of cycle 2 (around week 6) but before cycle 3 (around week 9) in a subset of patients who are willing and able to undergo tissue sampling. Details about collection and handling of the tumor biopsy specimen can be found in *Sections 9* and *10*.

5.2.4 End-of-treatment Procedures

All subjects will be asked to return to the site for a final, end-of-treatment visit (EOT). This visit must be performed within 30 days of final administration of study treatment. EOT assessments will not have to be repeated if the same assessments were performed within 7 days of this planned visit. The subject will be followed for 30 days after the last study intervention (duvelisib or docetaxel) for adverse events.

The reason for the study participant coming off therapy should be clearly documented. For any reason other than for progression of disease, tumor assessments should be performed every 8-12 weeks if a patient comes off the study drug within 1 year of enrollment (but ultimately at the discretion of the treating investigator).

The participants ECOG performance status, weight (in kilograms), vital signs, interval history since the last visit, and physical examination are performed at the end-of-treatment visit. Concomitant medications should also be reviewed at this visit. In addition, the adverse event (AE) grid should be completed at this visit.

5.3 Chemotherapy and Targeted Therapy Administration

5.3.1 Docetaxel

On the day of docetaxel administration, the drug will be administered per standard institutional guidelines followed by a 30 minute wait period at the end of the infusion, to evaluate for an infusion reaction. On the day of docetaxel administration, the morning dose of duvelisib should be given at least 30 minutes prior to starting the docetaxel, and the evening dose of duvelisib should occur at least 1 hour after the completion of the infusion of docetaxel. For docetaxel, standard operating procedure should be applied when recalculating weight-based dosing at the beginning of each cycle. Additional intravenous hydration is not required at study visits, but is at the discretion of the treating investigator. Pre-medication with dexamethasone prior to taxane exposure is strongly encouraged for all participants.

5.3.2 Duvelisib

Duvelisib capsules should be swallowed whole with a glass of water (approximately 8 ounces). Advise patients not to open, break, or chew the capsules. Duvelisib may be administered without regard to meals; however, subjects should avoid grapefruit and grapefruit juice while on duvelisib.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Concomitant Medication Guidelines

The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids with the exception of pre-medication and anti-emetic purposes
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents)

Prohibited Concomitant Therapy	Guidance
Use of Vaccines	For all subjects, the use of live or live attenuated vaccines is prohibited during the treatment with either study intervention. The use of inactivated (or killed) vaccines (such as pneumococcal pneumonia vaccine) is allowed during the study.
Immunosuppressants	Subjects are not to receive ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids for >1 week at doses higher than the equivalent of 20 mg prednisone once daily.
Medications or Foods that Strongly Inhibit or Induce CYP3A4	Use of a strong CYP3A inhibitor or inducer during treatment with duvelisib is prohibited. Co-administration with a strong CYP3A inhibitor increases duvelisib exposure, which may increase the risk of duvelisib toxicities. Co-administration with a strong CYP3A inducer decreases duvelisib exposure, which may reduce duvelisib

	efficacy. *See* **Table** *below.*
Medications that are Substrates of CYP3A	Co-administration with duvelisib decreases AUC of a sensitive CYP3A4 substrate which may decrease the efficacy of these drugs. Consider finding an alternative drug that is not a substrate of CYP3A4. *See* **Table** *below.*

Strong Inhibitors[1]	**Moderate inhibitors[2]**	**Weak inhibitors[3]**
Boceprevir, clarithromycin, conivaptan, grapefruit juice[4], indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil[5] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice[4], imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo[6], goldenseal[6], isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

Abbreviations: AUC: area under the curve; CL: clearance; CYP: Cytochrome P450; US: United States.

1. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by ≥ 5-fold or > 80% decrease in CL.
2. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by < 5-fold but ≥ 2-fold or 50 to 80% decrease in CL.
3. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by < 2-fold but ≥ 5-fold or 20 to 50% decrease in CL.
4. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
5. Withdrawn from the US market because of safety reasons.
6. Herbal product.

5.4.2 Recommended Prophylaxis

Based on the duvelisib clinical experience to date, the following are *recommended*:

- Subjects are <u>required</u> to receive pneumocystis prophylaxis concomitant with duvelisib treatment per institutional guidelines. After completion/discontinuation of duvelisib treatment, continue prophylaxis until the absolute CD4+ T-cell count is greater than 200 cells/μL.
- HSV and VZV infections have been observed with duvelisib; therefore, herpes (HSV/VZV) prophylaxis concomitant with treatment is <u>recommended</u>, per treating investigator discretion according to institutional guidelines.
- Subjects with a history of CMV infection/reactivation or viremia should be monitored for reactivation by polymerase chain reaction (PCR) or antigen test at least monthly. Prophylactic treatment per institutional guidelines is <u>recommended</u> for subjects considered by Investigators to be at high risk for CMV reactivation.
- Antimicrobial prophylaxis and pneumococcal pneumonia vaccine are <u>recommended</u> for subjects with history of or considered at high risk for infections and during periods of severe

neutropenia. Choice of antimicrobial agent (antifungal, antibiotic, antiviral) is per treating investigator discretion, but the restrictions on the use of CYP3A inducers, inhibitors, and substrates should be considered.

5.4.3 Supportive Care Guidelines

The following treatments are permitted throughout the duration of the study treatment phase and during follow-up:

- Standard therapies for pre-existing medical conditions unless listed as prohibited therapy below. Any medication intended solely for supportive care (e.g., analgesics, anti-diarrheal, anti-depressants) may be used at the investigator's discretion. At the discretion of the investigator, prophylactic antiemetic and anti-diarrheal medication(s) may be used as per standard clinical practice before subsequent doses of study drugs.
- Anticoagulants: anticoagulation with heparin, heparin derivatives, and/or warfarin may be given at the discretion of the treating physician. Coagulation parameters should be checked at each cycle, or more frequently at the discretion of the treating physician.
- Pain medications administered per standard clinical practice are acceptable while the patient is enrolled in the study.

Patients who experience toxicities should be treated symptomatically as clinically indicated. Medications that are considered necessary for the subject's welfare and that are not expected to interfere with the evaluation of study treatment or be restricted may be given at the discretion of the investigator. Ancillary treatments will be given as medically indicated.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), see *Section 6.0*
- Participant demonstrates an inability or unwillingness to comply with study requirements and/or activities, including the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Pregnancy

Participants will be removed from the protocol therapy when any of these criteria apply (discussion with the PI is encouraged in this scenario). The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1. .

5.6 Duration of Follow-Up

Participants will be followed for best overall response and development and documentation of first disease progression and for survival throughout the course of the trial for 3 years from the time of study registration. Participants removed from protocol therapy for unacceptable adverse event(s) who have not developed first disease progression at the time of discontinuation of protocol therapy, will continue to be followed for disease progression. All participants enrolled will be followed for survival (until death or 3 years from study registration,whichever occurs first). All adverse events leading to treatment discontinuation will be followed as appropriate until resolution or stabilization.

5.7 Criteria for Taking a Participant Off Study

Participants will also be removed from study when any of the following criteria apply:

- Patient completed required follow-up
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant. In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Glenn J. Hanna, MD, at DFCI/Partners pager 46231.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated below. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed prophylactically and/or supportively. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and within 30 days of the last study intervention. Participants continuing to experience toxicity at the last scheduled study visit may be kept on the study until the toxicity has resolved, or until the toxicity is deemed irreversible.

If one of the study two drugs is delayed due to drug related toxicities during a treatment cycle, the other study drugs in the regimen may be administered at the discretion of the investigator; when dosing is resumed, dose reduction should only be applied to the study drug that was withheld. Missed days or cycles of either drug can be made up, at the discretion of the treating investigator.

6.1 Duvelisib

The dose level of duvelisib may be modified to manage duvelisib toxicities or overlapping toxicities in combination with docetaxel. Non-hematologic and hematologic adverse events (AEs) for duvelisib for non-overlapping toxicities in combination with docetaxel should be managed with supportive care, treatment hold, dose reduction, or discontinuation of duvelisib as described below. Additional information regarding management of duvelisib toxicities can be found in the Summary of Data and Guidance to the Investigator section of the duvelisib investigator brochure (IB).

Refer to **Table 3** for dose level modifications recommended for duvelisib (this applies to patients in the safety run-in). Subjects who have a duvelisib dose reduction due to a toxicity will not be eligible for a dose re-escalation. Any subject who develops an unacceptable toxicity at the 15 mg BID dosage of duvelisib should discontinue duvelisib but can continue docetaxel on study at the discretion of the treating investigator.

If a dose is missed or vomited up by fewer than 6 hours, the patient should take the missed dose right away and take the next dose as usual. If a dose is missed or vomited up by more than 6 hours, advise patients to wait and take the next dose at the usual time.

Provide prophylaxis for Pneumocystis jirovecii (PJP) during treatment with duvelisib. Following completion of treatment, continue PJP prophylaxis until the absolute CD4+ T cell count is greater than 200 cells/μL. Withhold duvelisib in patients with suspected PJP of any grade, and discontinue if PJP is confirmed. Consider prophylactic antivirals during duvelisib treatment to prevent cytomegalovirus (CMV) infection including CMV reactivation.

Duvelisib may be held up to 42 days due to toxicity. While duvelisib is being held, the subject may continue to receive docetaxel at the discretion of the treating investigator. Doses held for >42 days due to treatment-related toxicity will result in *permanent discontinuation* of duvelisib.

Table 3. Duvelisib Dose Level Modifications for Toxicity

Dose Level	Duvelisib
Starting Dose	25 mg by mouth twice daily
Dose Level -1	15 mg by mouth twice daily
Subsequent Dose Modification	Discontinue duvelisib if patient is unable to tolerate 15 mg twice daily

Table 4. Recommended Duvelisib Dose Modifications for the Management of Duvelisib Toxicities

Toxicity	Adverse Reaction Grade	Dose Modification and Recommended Management
Non-hematologic AEs		
Infections	Grade 3 or higher	Withhold duvelisib until resolved. Resume at the same or reduced dose
	Clinical CMV infection or viremia (positive PCR or antigen test)	Withhold duvelisib until resolved. Resume at the same or reduced dose. If duvelisib is

		resumed, monitor subjects for CMV reactivation (by PCR or antigen test) at least monthly
	PJP	For suspected PJP, withhold duvelisib until evaluated. For confirmed PJP, discontinue duvelisib
Non-infectious diarrhea or colitis	Mild/moderate diarrhea (Grade 1-2, up to 6 stools per day over baseline) and responsive to antidiarrheal agents, OR Asymptomatic (Grade 1) colitis	No change in dose • Initiate supportive therapy with antidiarrheal agents as appropriate • Monitor at least weekly until resolved
	Mild/moderate diarrhea (Grade 1-2, up to 6 stools per day over baseline) and unresponsive to antidiarrheal agents	Withhold duvelisib until resolved • Initiate supportive therapy with enteric acting steroids (e.g., budesonide) • Monitor at least weekly until resolved • Resume at a reduced dose (see Table 3)
	Abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs, OR Severe diarrhea (Grade 3, >6 stools per day over baseline)	Withhold duvelisib until resolved • Initiate supportive therapy with enteric acting steroids (e.g., budesonide) or systemic steroids • Monitor at least weekly until resolved • Resume at a reduced dose (see Table 3) • For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue duvelisib
	Life-threatening	Discontinue duvelisib
Cutaneous reactions	Grade 1-2	No change in dose • Initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids • Monitor closely
	Grade 3	Withhold duvelisib until resolved • Initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids • Monitor at least weekly until resolved • Resume at reduced dose (see Table 3) • If severe cutaneous reaction does not improve, worsens, or recurs, discontinue duvelisib
	Life-threatening	Discontinue duvelisib
	SJS, TEN, DRESS (any grade)	Discontinue duvelisib
Pneumonitis without suspected infectious cause	Moderate (Grade 2) symptomatic pneumonitis	Withhold duvelisib • Treat with systemic steroid therapy • If pneumonitis recovers to Grade 0 or 1, duvelisib may be resumed at reduced dose (see Table 3) • If non-infectious pneumonitis recurs or patient does not respond to steroid therapy, discontinue duvelisib

	Severe (Grade 3) or lifethreatening pneumonitis	Discontinue duvelisib • Treat with systemic steroid therapy
ALT/AST elevation	3 to 5 × upper limit of normal (ULN) (Grade 2); >3 to 5x baseline if baseline was abnormal	Maintain duvelisib dose • Monitor at least weekly until return to < 3 × ULN
	> 5 to 20 × ULN (Grade 3); >5 to 20x baseline if baseline was abnormal	• Withhold duvelisib and monitor at least weekly until return to < 3 × ULN • Resume duvelisib at same dose (first occurrence) or at a reduced dose for subsequent occurrence (see Table 3)
	> 20 × ULN (Grade 4); >20x if baseline was abnormal	Discontinue duvelisib
Other Grade 3 Toxicities Attributed to Duvelisib		Withhold duvelisib until resolved • Resume at a reduced dose (see Table 3)
Hematologic AEs		
Febrile neutropenia	Grade 3-4	Interrupt duvelisib until afebrile and resolution of Grade 3 or Grade 4 neutropenia to Grade ≤2 (ANC >1.0 Gi/L). Monitor ANC at least weekly until >1.0 Gi/L. Resume at same dose (first occurrence) or at a reduced dose for subsequent occurrence
Neutropenia	ANC 0.5-1.0 Gi/L	Maintain duvelisib dose. Monitor ANC at least weekly
	ANC <0.5 Gi/L	Withhold duvelisib. Monitor ANC until >0.5 Gi/L. Resume duvelisib at same dose (first occurrence) or at a reduced dose for subsequent occurrence
Thrombocytopenia	Platelet count 25 to <50 Gi/L (grade 3) with grade 1 bleeding	No change in dose. Monitor platelet counts at least weekly
	Platelet count 25 to <50 Gi/L (grade 3) with grade 2 bleeding or platelet count <25 Gi/L (grade 4)	Withhold duvelisib. Monitor platelet counts until ≥25 Gi/L and resolution of bleeding (if applicable). Resume duvelisib at same dose (first occurrence) or resume at a reduced dose for subsequent occurrence

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CMV = cytomegalovirus; DRESS = drug reaction with eosinophilia and systemic systems; PCR = polymerase chain reaction; PJP = Pneumocystis jirovecii; pneumonia; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal.

6.2 Docetaxel

Dose modifications for the docetaxel component of the combined regimen are permitted and should follow institutional standards based on toxicity, with the following suggested modifications:

A maximum of two dose reductions are permitted (or one dose reduction for patients in the safety run-in): if additional reductions are required, the docetaxel component of the regimen should be discontinued. Once a dose has been decreased, it should remain reduced for all subsequent dosing unless dose is further reduced. No dose (re-) escalations will be allowed.

Docetaxel may be held up to 60 days due to toxicity. While docetaxel is being held, the subject may continue to receive duvelisib at the discretion of the treating investigator. Doses held for >60 days

due to treatment-related toxicity will result in *permanent discontinuation* of docetaxel unless discussed with the Sponsor-investigator.

Recommended Dose Levels:

Dose Level	Docetaxel dose
Starting dose*	75 mg/m^2
Dose Level -1	56 mg/m^2
Dose Level -2	37 mg/m^2

* except for N=3 initial participants in the safety run-in (starting dose is at dose level -1)

Recommended Dose Modifications for Toxicity:

Toxicity	Docetaxel
Neutrophils (ANC) <500/mm^3 lasting ≥5 days	Decreased by -1 dose level
Febrile neutropenia (body temperature ≥38.5C and ANC <1000/mm^3)	Decreased by -1 dose level
Platelets <25,000/mm^3	Decreased by -1 dose level
Platelets <50,000/mm^3 with significant bleeding or requiring transfusion	Decreased by -1 dose level
Grade 4 hemoglobin (<6.5 g/100 mL)	Decreased by -1 dose level
Nausea or emesis ≥grade 3 despite optimal medical management	Decreased by -1 dose level
Stomatitis ≥grade 3	Decreased by -1 dose level
Diarrhea ≥grade 3 despite optimal medical management	Decreased by -1 dose level
Neuropathy (sensory or motor) grade 2 lasting >7 days or grade 3 lasting 7 days or less	Decreased by -1 dose level
Nephrotoxicity (creatinine clearance 50-59 mL/min or grade 3 creatinine elevation)	No modification
Total bilirubin >1.5x ULN	No modification
Total bilirubin >2.5x ULN	75% of previous dose
Total bilirubin >4x ULN	50% of previous dose
Other grade ≥3 toxicities (except fatigue or transient arthralgias, myalgias)	Decreased by -1 dose level

6.3 Recommended Dose Modifications for the Management of Overlapping Toxicities for Duvelisib in Combination with Docetaxel

Hematologic issues, non-infectious diarrhea or colitis, and hepatotoxicity are potential overlapping toxicities for duvelisib with docetaxel. In the event of overlapping toxicity while on combination therapy, the treating investigator may opt to hold one, or both, agents depending on the clinical suspicion for attribution to one or both agents. However, we recommend following the guidelines outined in *Sections 6.1-6.2* for each respective agent in determing when to hold, for how long, and at what dose (if any) to resume.

6.4 Unacceptable Toxicity

Unacceptable Toxicity Warranting Duvelisib and Docetaxel *Discontinuation*:

- Any grade 4 adverse event will require *permanent discontinuation* with the following exceptions:
  - Grade 4 electrolyte abnormalities that are <72 hours in duration
  - Grade 4 neutropenia or lymphopenia which are <5 days in duration
  - For confirmed *Pneumocystis jiroveci* pneumonia (duvelisib discontinuation only)

The consideration to re-initiate study therapy under these exceptions will be made on a case by case basis after considering the overall benefit/risk profile and in consultation with the PI.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting in addition to routine reporting.

7.1 Expected Toxicities

Virtually all patients treated with duvelisib and/or docetaxel experience some drug-related toxicity, especially fatigue, some degree of cytopenias, limiting gastrointestinal toxicity (diarrhea or nausea and/or emesis). These adverse effects are seldom permanent or irreversible nor do they usually require interruption of therapy.

Duvelisib	**Docetaxel**
>10% Edema Fatigue, headache Skin rash Hypophosphatemia, hyponatremia, hyperkalemia, hypoalbuminemia, hypocalcemia, weight loss Diarrhea, colitis, elevated serum lipase or amylase, nausea, abdominal pain, constipation, vomiting, mucositis, low appetite Neutropenia, anemia, thrombocytopenia, lymphocytosis Increased serum ALT or AST or alkaline phosphatase Sepsis, serious infection Musculoskeletal pain Renal insufficiency, increased creatinine Upper respiratory infection, pneumonia, dyspnea Fever	>10% Skin reaction Fluid retention Diarrhea, nausea, stomatitis, vomiting Anemia, leukopenia, neutropenia, thrombocytopenia Increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) Infection Dysesthesia or paresthesia Asthenia, generalized weakness, myalgias Pulmonary disease Fever
1-10% Skin reaction Cytolomegalovirus disease Arthralgias Pneumonitis or *Pneumocystis jiroveci* pneumonia	1-10% Hypotension Dysgeusia Increased alkaline phosphatase, serum bilirubin Infusion site reaction Peripheral motor neuropathy Arthralgias
	<1% Onycholysis

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

- **Attribution** of the AE should be documented with respect to each study treatment as follows:
  - 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.

7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the PI.

7.3.2 Investigators must report to the PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form. .

7.3.3 Serious Adverse Events

7.3.3.1 Definition

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g. medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g. death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

7.3.3.2 Reporting SAEs

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of discontinuation of dosing. All SAEs should be followed to resolution or stabilization.

Investigators will be notified of all suspected, unexpected serious adverse reactions (SUSARs; 7-/15-Day Safety Reports) that occur during any clinical studies that are using duvelisib. Each site is responsible for notifying their IRB/IEC/Central Ethics Committee of these additional SUSARs in accordance with local regulations.

7.3.3.3 Overdose of Duvelisib

For this study, overdose is defined as a daily dose of a study intervention higher than the prescribed daily dose. In the case of overdose, clinic staff should be notified immediately, and supportive care is to be given as indicated. Subjects should be informed to contact their doctor immediately if they have taken an overdose and should stop taking study interventions. Overdoses will **not** be considered SAEs unless the outcome of the overdose meets seriousness criteria as defined in Section 7.3.31. In the event of an overdose, the Sponsor should be notified within 24-hours. The subject should be carefully monitored for potential adverse reactions and symptomatic treatment instituted as per institutional practices. The study investigator will determine if and when dosing should resume.

7.4 DF/HCC Adverse Event Reporting Guidelines

All participating sites will report AEs to the Sponsor-Investigator per DF/HCC requirements, and the IRB of record for each site as applicable per IRB policies. The table below indicates which events must be reported to the DF/HCC Sponsor-Investigator.

Attribution	DF/HCC Reportable Adverse Events(AEs)				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					

* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, events must be reported within 1 business day of learning of the event.

7.5 Reporting to the Food and Drug Administration (FDA)

The Sponsor-Investigator will be responsible for all communications with the FDA. The Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 Reporting to Hospital Risk Management

Participating co-investigators will report to local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy. Secura Bio will be copied on all such reports in a timely fashion.

7.7 Reporting to the Secura Bio

The Medical Monitors for this study may be contacted for advice or assistance. Contact details will be provided separately in a study contact list. Report SAEs to Secura Bio

7.8 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions to the PI on the toxicity case report forms. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions. Secura Bio will be copied on all such reports in a timely fashion.

8. PHARMACEUTICAL INFORMATION

8.1 Study Agent: Duvelisib

Devulisib; brand name: *Copiktra*®

8.1.1 Description

Duvelisib is an oral PI3K inhibitor with dual inhibitory activity primarily against PI3K-δ and PI3K-γ which are expressed in hematologic malignancies. Inhibition of PI3K-δ reduced tumor cell proliferation while allowing survival of normal cells. Distribution: V_d: 28.5 L. Protein binding: >98%. Metabolism: Hepatic; primarily via CYP3A4. Bioavailability: 42%. Half-life elimination: 4.7 hours. Time to peak: 1 to 2 hours. Excretion in feces: 79% (11% as unchanged drug) and urine: 14% (<1% as unchanged drug).

8.1.2 Form

Duvelisib is available as a capsule in 15 and 25 mg doses.

8.1.3 Storage and Stability

On receipt at the investigative site, duvelisib should remain in the packaging as provided until use or dispensation. The packaged product should be stored at the investigative site at 20 to 25°C (68 to 77°F), with excursions permitted at 15 to 30°C (59 to 86°F). Temperature excursion procedures are provided in the IB (Section 4.6 or page 26). Expired drug is not to be dispensed.

8.1.4 Availability

Duvelisib is commercially available (*Copkitra*), but will provided as investigational supply.

8.1.5 Administration

Duvelisib will be administered by trained medical personnel at the investigational site. Treatment compliance will be monitored through documentation of study treatment administration in the subject's medical record and via drug diary. Oral: administer with or without food. Swallow capsules whole; do not open, break or chew capsules. Provide PJP prophylaxis during treatment and continue until the absolute CD4+ T cell count is >200 cells/mL; consider prophylactic antivirals during treatment to prevent CMV infection and reactivation. It is acceptable for the on-site pharmacy to dispense the needed quantity of duvelisib in an amber prescription bottle.

8.1.6 Ordering

8.1.7 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the duvelisib, using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

8.1.8 Destruction and Return

Unused and expired supplies of duvelisib will be destroyed on site per institutional standard practice.

8.2 Docetaxel

Docetaxel will be commercially supplied. Docetaxel will be stored, prepared, and administered per standard of care/institutional standards.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Background information on the pre-clinical and clinical rationale for these investigations is discussed in *Section 2.5* above.

As study participants carry a diagnosis of R/M SCCHN it is expected that most, if not all, will have undergone prior tumor biopsy sampling with tissue available for assessment of tumor PD-L1 CPS testing, tumor genomic sequencing with an available targeted in-house platform or commercially available assay (Foundation Medicine CDx, Guardiant360 CDx, Caris, etc.). If not previously completed prior to study enrollment, all subjects should have a biopsy of tumor tissue obtained subsequent to most recent prior anti-neoplastic therapy sent for tumor next-generation genomic sequencing and PD-L1 tumor testing (reported as CPS), if feasible. If this is not feasible or constitutes significant risk, tissue from archival reserves may be submitted. This would be considered standard of care for molecular and immune profiling in advanced head and neck cancer. The results of tumor molecular or gene and immune profiling will be used to determine PD-L1 status, *TP53* and PI3K pathway activation status, as well as HPV testing (if needed) for correlative analyses planned as part of the study.

An on-treatment tumor tissue biopsy will be offered (as optional) to all participants on study with the expectation that roughly 50% of participants (N=15 subjects) would be willing and able to undergo re-biopsy. This will be offered at the end of cycle 2 (6 weeks) but before cycle 3 (9 weeks) if safe and feasible. Tumor tissue will be stored for later use to evaluate changes in gene and protein expression while on PI3K plus taxane therapy, and to assess changes in immunoprofiling metrics perhaps through digital spatial profiling (DSP) or multiplexed immunofluorescence (MIF) on FFPE tissue blocks or slides.

9.1.1 Collection and Handling of Specimens

Ideally **two** core biopsies will be obtained at the time of all biopsy collections: cores should be placed in 10% neutral buffered formalin tube supplied by the study team.

After being obtained, processing of the cores is as follows: all samples should be de-identified and labeled with the participant initials, participant study ID number and date of procedure.

Individual participanting sites will obtain and store their on-treatment biopsy samples in local labs with the expectation that samples will later be shipped to the central study site (DFHCC) for analysis. Tumor specimens obtained at DFHCC will be delivered to:

9.1.2 Specimen Processing and Analysis

Beyond targeted tumor genomic sequencing and PD-L1 tumor testing, tumor samples obtained on-

study will be stored for future gene and protein expression analyses, along with tumor immune profiling to be determined in the future.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within **28 days** prior to study registration (except for pregnancy test and baseline tumor biopsy, as detailed below). If these screening assessments occur 3 days before start of study treatment, then they may serve as the baseline Cycle 1 Day 1 values. Scans must be done within **28 days** prior to study registration.

As detailed in the *Study Calendar*, a negative pregnancy test in women of child-bearing potential must be documented within 72 hours before the first dose of study medication.

Baseline laboratory evaluations must be completed **within 14 days** prior to study registration. In the event that the participant's clinical condition is deteriorating, laboratory evaluations should be repeated within 48 hours of treatment initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

Table of Events

	Screening[A]	Lead-In[B]	C1-3 Day 1	C4 Day 1 and beyond	End of treatment[C]	Follow-up[D]	EDC timepoints
Duvelisib		X	X	X			Lead-in, day 1 of each cycle
Docetaxel			X	X			Day 1 of each cycle
Informed consent	X						N/A
Demographics	X						Baseline
Medical history	X	X	X	X	X	X	Baseline
Concurrent medications[E]	X	X	X	X	X		N/A
Vital signs	X	X	X	X	X		N/A
Physical exam	X	X	X	X	X		N/A
Height	X		X	X			Baseline
Weight[F]	X		X	X	X		Baseline
Performance status[G]	X	X	X	X	X	X	Baseline, EOT
Hematology labs	X		X	X	X		Baseline
Chemistries[H]	X		X	X	X		Baseline
Coagulation profile[I]	X						N/A
Pregnancy testing[J]	X		X[J]				Baseline
Thyroid function testing[K]	X						Baseline, EOT
Hepatitis testing[L]	X						Baseline
CMV Testing[M]	X						Baseline
ECG	X						Baseline
Molecular and immune testing[N]							Baseline
Tumor biopsy[O]	X		X[O]				Baseline, on-treatment
Adverse event evaluation		X	X	X	X		All visits
Tumor measurements[P]	X			X		X	Baseline, every 3 cycles, EOT
Patient reported surveys[Q]	X	X	X	X	X		Baseline, lead-in, every 3 cycles, EOT

A Baseline evaluations are to be conducted within 28 days prior to study registration (except for pregnancy test and baseline tumor biopsy) If these screening assessments occur 3 days before start of study treatment, then they may serve as the baseline Cycle 1 Day 1 values

B Participants will receive duvelisib 25 mg orally twice daily for 7 ± 2 days (1 week) prior to the initiation of the first cycle of docetaxel chemotherapy

C All subjects will be asked to return to the site for a final, end-of-treatment visit (EOT), if possible This visit must be performed within 30 days of final administration of study treatment EOT assessments will not have to be repeated if the same assessments were performed within 7 days of this planned visit

D Participants will be followed for best overall response and development and documentation of first disease progression and for survival throughout the course of the trial for 3 years from the time of study registration Participants removed from protocol therapy for unacceptable adverse event and if they have not developed first disease progression at time of discontinuation of protocol therapy, will continue to be followed until first disease progression and survival until death or 3 years from study registration (whichever occurs first)

E See Section 5 4 for details about concurrent medication administration (specifically CYP3A4 interactions), supportive care medication guidelines, and the use of recommended viral and infectious prophylaxis while on duvelisib Antimicrobial prophylaxis and pneumococcal pneumonia vaccine are recommended for subjects with history of or considered at high risk for infections and during periods of severe neutropenia Choice of antimicrobial agent (antifungal, antibiotic, antiviral) is per treating investigator discretion, but the restrictions on the use of CYP3A inducers, inhibitors, and substrates should be considered

F Weight in kilograms (kg) should be used for docetaxel dosing per standard institutional practice

G As per ECOG performance status scale (see *Appendix A*)

H Routine chemistry labs include: a comprehensive metabolic panel with liver function tests; magnesium levels are discretionary per the investigator

I Includes PT/INR and aPTT testing

J Only required on day 1 of cycle 1 Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 7 days of study registration Female subjects of childbearing potential should have a negative urine or serum pregnancy test repeated within 72 hours prior to receiving the first dose of study medication If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required

K TSH and free T4 if indicated with prior head and neck exposure

L Hepatitis B virus and hepatitis C virus testing required Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HbsAb), hepatitis B core antibody (HbcAb), and hepatitis C antibody (HCV antibody with reflex HCV PCR viral testing if HCV antibody positive) testing required

M Subjects with a history of CMV infection/reactivation or viremia should be monitored for reactivation by polymerase chain reaction (PCR) or antigen test at least monthly Prophylactic treatment per institutional guidelines is recommended for subjects considered by investigators to be at high risk for CMV reactivation

N The results of tumor molecular (targeted nex-generation gene sequencing) and immune profiling (PD-L1 CPS) will be used to determine PD-L1 status, *TP53* and PI3K pathway activation status These reports should be available at baseline prior to enrollment

O A fresh tumor biopsy sample is not required prior to the start of duvelisib and docetaxel if an archival tissue sample is available for histologic confirmation of SCCHN An on-treatment tumor tissue biopsy will be offered at the end of cycle 2 (around week 6) but before cycle 3 (around week 9) in a subset of patients who are willing and able to undergo tissue sampling Details about collection and handling of the tumor biopsy specimen can be found in *Section 9*

P Tumor assessment scans (contrast-enhanced CT or MRI of the neck; CT chest, abdomen, and pelvis or PET-CT) will be performed at screening/baseline After starting protocol, following the completion of 3 cycles of therapy, imaging will be repeated with a neck CT or MRI and chest CT (abdomen and pelvis CT are discretionary based on disease sites) or PET-CT at 9 week intervals (every 3 cycles) Post end of protocol treatment, if first local, locoregional, or distant recurrence has not been confirmed, imaging should continue every 2-3 months (including a survival status update) until first disease progression is confirmed After documentation of first disease recurrence, only survival status will continue to be updated until death or 3 years post study registration (whichever occurs first)

Q Quality of life surveys will be completed at screening, after completion of the lead-in phase, every 3 cycles, and at 30-day follow-up Patients will complete the EORTC QOL Module for Head and Neck Cancer (QLQ-C30 and HN35)

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 9 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

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

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

11.1.2 Disease Parameters

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

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

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are

considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

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

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

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

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

11.1.3 Methods for Evaluation of Disease

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

To the greatest extent possible the same method of assessment and the same techniques should be used to characterize each identified and reported lesion at baseline and during each follow-up, however exceptions may be made for the development of contrast alleriges and/or other extenuating circumstances, at the discretion of the treating investigator. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

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

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

11.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response

assignment will depend on the achievement of both measurement and confirmation criteria.

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

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

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

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

11.1.6 Survival and Clinical Parameters

Overall Survival: Overall Survival (OS) is defined as the time from registration to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from registration to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from registration to progression, or censored at date of last disease evaluation for those without progression reported.

Clinical benefit rate: defined as CR, PR and stable disease (SD) ≥24 weeks.

11.1.7 Response Review

For trials where the response rate is the primary endpoint, it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the participants' files and radiological images is the best approach.

11.1.8 Quality of life measurements

Quality of Life Assessment: The EORTC QOL Module for Head and Neck Cancer (QLQ-C30 and HN35) will be used to assess the effect of cancer treatment on physical, social and emotional well-being and function. The survey consists of 30 and 35 items, respectively.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in *Section 7.0* (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Sponsor-Investigator and study team.

The DSMC generally reviews each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported across all sites; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multi-Center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the overall study PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in *Appendix B*.

The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required. Secura Bio will be copied on all such reports in a timely fashion.

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- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

A Simon optimal two-stage design will be utilized. The primary hypothesis is that the combination of duvelisib and docetaxel will increase the overall response rate (ORR) in this PD-1 inhibitor refractory patient population. Under the standard-of-care, we expect an ORR less than 10% [**Table 1** above] for this population. We anticipate that an ORR of 30% would represent a clinically important advance.

Thirteen evaluable patients (eligible and begin protocol treatment) are to be entered into the first stage including those in lead-in stage. If there are ≤ 1 patients with disease in response, accrual to this trial will be closed with the expectation that there is little evidence that the response rate will

reach 30%. The probability that the trial will close early is 62% if the true response rate is 10%. If there are >1 evaluable patients with disease in response, accrual will continue until a total of 26 evaluable patients are registered to the trial. If there are >4 evaluable patients with disease in response among 26 evaluable patients, further testing of this regimen will be considered. If the true response rate is 30%, the probability of concluding the regimen is effective is 89.2%, if the true response rate is 10%, the probability of concluding the regimen is effective is 9.8%.

13.2 Sample Size and Accrual Rate

To account for patients who are registered to the trial but do not begin protocol treatment an additional 4 patients could be enrolled, for a total of up to N=30 patients registered.

With **three planned sites** throughout the U.S. at academic centers in major cities, we anticipate accruing 1-2 patients per month for a **total enrollment period** of 12 months for 26 planned subjects. Due to possible delays in initiation of approval at other sites and/or initiation of accrual itself, the accrual period could take longer. As is customary with two-stage designs, accrual will be suspended after the first stage in order to assess outcome; however, this suspension is also dependent on the actual observed accrual rate and the number of patients with confirmation of disease response status while the first stage of the trial is accruing.

13.3 Stratification Factors

There are no stratification factors in this trial.

13.4 Interim Monitoring Plan

Interim analysis will be conducted after the first stage which has 13 evaluable patients enrolled (refer to Section 13.1).

Safety run-in: An initial safety run-in cohort of 3 patients is planned prior to enrolling the remainder of the study cohort with a safety pause to ensure tolerability of the regimen.

The following stopping rule will be used to monitor excessive protocol treatment related toxicity/delays (as noted in *Sectio 6.4*): if 3 or more of the first 10 patients (which includes the 3 patients treated as part of the safety run-in) who begin protocol treatment experience treatment related toxicities, accrual to the trial will be suspended to further evaluate the events and decisions made regarding the overall status of the trial. If the true rate due to toxicity is 10% then the probability of suspending accrual is 7%; if the true rate is 20%, then the probability of suspending accrual is 32.2%; if the true rate due to toxicity is 30% then the probability of suspending accrual is 62%.

13.5 Analysis of Primary Endpoint

The primary efficacy population includes all eligible patients who begin protocol treatment. Best overall response will be summarized as a proportion with a corresponding exact 95% confidence interval (CI) (if the trial closes to accrual after the first stage), or a corresponding 95% two-stage CI if the trial closes to accrual after the second stage.

13.6 Analysis of Secondary Endpoints

For the secondary endpoints, the Kaplan-Meier method will be used to estimate time-to-event endpoints with corresponding 95% confidence intervals for the median or time-specific event time.

Another endpoint is to assess patient-reported quality of life (QOL). QOL will be assessed via self-report questionnaires at the timepoints outlined in the Study Calendar (*Section 10*). Descriptive statistics from the questionnaires will be summarized across timepoints of assessment. Rates of drop-out/non-response to QOL assessments and corresponding reason will also be summarized across timepoints of assessment.

Molecular and immune correlative studies are also planned for the future. Given the small sample size of this trial, these studies are exploratory. Information on markers from samples will be summarized descriptively. Within subject changes (paired) in these molecular markers will be analyzed.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration (*Section 13.0*). If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study. The overall study PI (Glenn J. Hanna, M.D.) will be responsible for reporting and publishing the data. Secura Bio shall be given the opportunity to comment on all potential publications related to the Study, and good faith efforts shall be made to incorporate such comments, as scientifically appropriate, prior to submission for publication.

15. REFERENCES

1. Rothschild U, Muller L, Lchner A, et al. Immunotherapy in head and neck cancer –scientific rationale, current treatment options and future directions, Swiss Med Wkly. 2018;148:w14625.
2. Forster MD and Devlin M-J. Immune checkpoint inhibition in head and neck cancer. Front Oncol. 2018;8(310).
3. Vigneswaran N and Williams MD. Epidemiological trends in head and neck cancer and aids in diagnosis. Oral Maxillofac Surg Clin North Am. 2014; May;26(2):123–141.
4. Chow LQ, Haddad R, Gupta S, et al. Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort. J Clin Oncol, 2016. 34(32): p. 3838-45.
5. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med, 2016. 375(19): p. 1856-67.
6. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol, 2016. 17(7): p. 956-65.
7. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr, Psyrri A, Basté N, Neupane P, Bratland Å, Fuereder T, Hughes BGM, Mesía R, Ngamphaiboon N, Rordorf T, Wan Ishak WZ, Hong RL, González Mendoza R, Roy A, Zhang Y, Gumuscu B, Cheng JD, Jin F, Rischin D; KEYNOTE-048 Investigators. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3

study. Lancet. 2019 Nov 23;394(10212):1915-1928. doi: 10.1016/S0140-6736(19)32591-7. Epub 2019 Nov 1. Erratum in: Lancet. 2020 Jan 25;395(10220):272. Erratum in: Lancet. 2020 Feb 22;395(10224):564. PMID: 31679945.

8. Cohen EEW, Soulières D, Le Tourneau C, et al. KEYNOTE-040 investigators. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet 2018;393(10167): p.156-67.
9. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016;375(19): p.1856-67.
10. COPIKTRA (duvelisib), capsules for oral use. United Prescribing Information,. 2019: http://www.verastem.com/wp-content/uploads/2018/08/prescribing-information.pdf
11. Dong S, Guinn D, Dubovsky J, et al. IPI-145 antagonizes intrinsic and extrinsic survival signals in chronic lymphocytic leukemia cells. Blood. 2014;124(24):3583-3586
12. Faia K, Proctor J, Andrade P, et al. High throughput in vitro combination sensitivity screen in hematologic malignancies with the phosphoinositide-3 kinase (PI3K)-delta,gamma Inhibitor, duvelisib. Poster Presented at ASCO Annual Meeting, 31 May 2015, Chicago, IL. 2015
13. De Felice F, Guerrero Urbano T. New drug development in head and neck squamous cell carcinoma: the PI3-K inhibitors. Oral Oncol. 2017;67:119–23
14. Horwitz SM, Porcu P, Flinn I, et al. Duvelisib (IPI-145), a Phosphoinositide-3-Kinase-delta,gamma inhibitor, shows activity in patients with relapsed/refractory T-cell lymphoma. Blood. 2014;124(21):803.
15. Flinn IW, Hillmen P, Montillo M, et al . The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood. 2018 Dec 6;132(23):2446-2455. doi: 10.1182/blood-2018-05-850461. Epub 2018 Oct 4. PMID: 30287523; PMCID: PMC6284216.
16. Coma S, Weaver DT, Pachter JA. Abstract 663: The dual PI3K-δ/PI3K-γ inhibitor duvelisib inhibits signaling and proliferation of solid tumor cells expressing PI3K-δ and/or PI3K-γ. Proceedings: AACR Annual Meeting 2020. DOI: 10.1158/1538-7445.AM2020-663 Published August 2020
17. Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: A Phase II Study of Duvelisib (IPI-145) in Patients With Refractory Indolent Non-Hodgkin Lymphoma. J Clin Oncol. 2019 Apr 10;37(11):912-922. doi: 10.1200/JCO.18.00915. Epub 2019 Feb 11.
18. https://clinicaltrials.gov/ct2/show/NCT02204982
19. Taguchi T, Furue H, Niitani H, et al. Phase I clinical trial of RP 56976 (docetaxel) a new anticancer drug. Gan To Kagaku Ryoho. 1994;21:1997–2005
20. Bruno R, Olivares R, Berille J, et al. Alpha-1-acid glycoprotein as an independent predictor for treatment effects and a prognostic factor of survival in patients with non-small cell lung cancer treated with docetaxel. Clin Cancer Res. 2003;9:1077–82
21. Baker SD, Zhao M, Lee CK, et al. Comparative pharmacokinetics of weekly and every-three-weeks docetaxel. Clin Cancer Res. 2004;10:1976–83
22. Dreyfuss A, Clark J, Norris C, et al. Docetaxel: an active drug for squamous cell carcinoma of the head and neck. J Clin Oncol 1996;14:1672-8
23. Catimel G, Verwij J, Hanauske A. Docetaxel (taxotere): an active drug for the treatment of patients with advanced squamous cell carcinoma of the head and neck. Ann Oncol 1994;5:553-37
24. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359(11):1116
25. Guigay J, Fayette J, Mesia R, et al. TPExtreme randomized trial: TPEx versus Extreme regimen in 1st line recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). DOI: 10.1200/JCO.2019.37.15_suppl.6002 Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 6002-6002
26. Rapidis A, Sarlis N, Lefebvre JL, et al. Docetaxel in the treatment of squamous cell carcinoma of the head and neck. Ther Clin Risk Manag. 2008 Oct; 4(5): 865–886. Published online 2008 Oct. doi: 10.2147/tcrm.s3133
27. Du L, Shen J, Weems A, Lu SL. Role of Phosphatidylinositol-3-Kinase Pathway in Head and Neck Squamous Cell Carcinoma, 2012. J Oncol. Article ID 450179, 12 pages, 2012. https://doi.org/10.1155/2012/450179
28. Cancer Genome Atlas N. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 2015;517:576–82.
29. Dong S, Guinn D, Dubovsky JA, Zhong Y, Lehman A, Kutok J, Woyach JA, Byrd JC, Johnson AJ. IPI-145 antagonizes intrinsic and extrinsic survival signals in chronic lymphocytic leukemia cells. Blood. 2014;124:3583–6.
30. Beck TN, Golemis EA. Genomic insights into head and neck cancer. Cancer Head Neck 2016;1:1.
31. L Hu, J Hofmann, Y Lu, GB Mills, RB Jaffe. Inhibition of phosphatidylinositol 3′-kinase increases efficacy of

paclitaxel in in vitro and in vivo ovarian cancer models. Cancer Res, 62 (2002), pp. 1087-1092.
32. Soulières D, Faivre S, Mesía R, Remenár É, Li SH, Karpenko A, Dechaphunkul A, Ochsenreither S, Kiss LA, Lin JC, Nagarkar R, Tamás L, Kim SB, Erfán J, Alyasova A, Kasper S, Barone C, Turri S, Chakravartty A, Chol M, Aimone P, Hirawat S, Licitra L. Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Oncol. 2017 Mar;18(3):323-335. doi: 10.1016/S1470-2045(17)30064-5. Epub 2017 Jan 26. PMID: 28131786.
33. Soulières D, Licitra L, Mesía R, Remenár É, Li SH, Karpenko A, Chol M, Wang YA, Solovieff N, Bourdeau L, Sellami D, Faivre S. Molecular Alterations and Buparlisib Efficacy in Patients with Squamous Cell Carcinoma of the Head and Neck: Biomarker Analysis from BERIL-1. Clin Cancer Res. 2018 Jun 1;24(11):2505-2516. doi: 10.1158/1078-0432.CCR-17-2644. Epub 2018 Feb 28. PMID: 29490986.
34. Beck TN, Golemis EA. Genomic insights into head and neck cancer. Cancer Head Neck 2016;1:1
35. Du F, Wu X, Liu Y, et al. Acquisition of paclitaxel resistance via PI3Kdependent epithelial–mesenchymal transition in A2780 human ovarian cancer cells. Oncol Rep 2013;30:1113–8.
36. Li Y, Chen K, Li L, et al. Overexpression of SOX2 is involved in paclitaxel resistance of ovarian cancer via the PI3K/Akt pathway. Tumour Biol 2015;36:9823–8
37. Liu Z, Zhu G, Getzenberg RH, et al. The Upregulation of PI3K/Akt and map kinase pathways is associated with resistance of microtubule-targeting drugs in prostate cancer. J Cell Biochem 2015;116:1341–9
38. Poeta ML, Manola J, Goldwasser MA, et al. TP53 mutations and survival in squamous-cell carcinoma of the head and neck. N Engl J Med 2007;357:2552–61
39. Bradford CR, Zhu S, Ogawa H, et al. P53 mutation correlates with cisplatin sensitivity in head and neck squamous cell carcinoma lines. Head Neck 2003;25:654–61
40. Osman AA, Neskey DM, Katsonis P, et al. Evolutionary action score of TP53 coding variants is predictive of platinum response in head and neck cancer patients. Cancer Res 2015;75:1205–15
41. Feldman R, Gatalica Z, Knezetic J, et al. Molecular profiling of head and neck squamous cell carcinoma. Head Neck 2016;38 (Suppl 1):E1625–38
42. Argiris A, Li S, Ghebremichael M, et al. Prognostic significance of human papillomavirus in recurrent or metastatic head and neck cancer: an analysis of Eastern Cooperative Oncology Group trials. Ann Oncol 2014;25:1410–6
43. Balermpas P, Michel Y, Wagenblast J, et al. Tumour-infiltrating lymphocytes predict response to definitive chemoradiotherapy in head and neck cancer. Br J Cancer 2014;110:501–9
44. Ferris RL, Blumenschein G Jr., Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016;375:1856–67
45. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124–8

16. APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.

1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.