STUDY PROTOCOL

VS-0145-130

Protocol Title: A Phase 1b/2 Study of Duvelisib in Combination with Pembrolizumab in Subjects with Recurrent or Metastatic Head and Neck Squamous Cell Cancer

Protocol Number: VS-0145-130

Version: 2.0

Compound: Duvelisib

Study Phase: Phase 1b/2

Short Title: A Phase 1b/2 Study of Duvelisib in Combination with Pembrolizumab in Head and Neck Cancer

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Regulatory Agency Identifier Number(s)

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Sponsor Signatory:

I have read this protocol for Study VS-0145-130, Version 2.0, and I approve the design of this study:

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Date

Verastem, Inc.

Medical Monitor Contact Information:

Medical Monitor contact information will be provided separately in a study contact list.

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1.1. Synopsis

Study Title: A Phase 1b/2 Study of Duvelisib in Combination with Pembrolizumab in Subjects with Recurrent or Metastatic Head and Neck Squamous Cell Cancer

Protocol Number: VS-0145-130

Phase: 1b/2

Investigational Product: duvelisib

Combination Product: pembrolizumab

Rationale:

Head and neck squamous cell carcinoma (HNSCC) represents over 90% of head and neck malignancies. Although the majority of patients present with locoregionally advanced disease, the clinical course is characterized by a high recurrence rate approaching 50%, as well as the development of distal metastases. Despite the recent approval of agents (e.g., pembrolizumab [Keytruda®] and nivolumab [Opdivo®]) that inhibit the interaction of programmed cell death protein 1 (PD-1) with its ligand (PD-L1), only a small subset of patients appears to derive benefit from these therapies. Although the efficacy of anti-PD-1 therapy may vary by PD-L1 expression or human papillomavirus (HPV) status, as well as the number of prior therapies, typically the overall response rate (ORR) is approximately 15% in the second-line or greater setting and somewhat higher in the first-line setting. The majority of responses in either setting are partial responses (PRs). The effectiveness of PD-1 inhibitors can be limited by infiltration of immunosuppressive myeloid cells (MDSCs) into the tumor microenvironment. Thus, there remains a large unmet medical need for better therapy options in patients with recurrent or metastatic (R/M) disease.

Phosphoinositide 3-kinase (PI3K) activity supports the growth and maintenance of cancer cells by contributing to the establishment and maintenance of the tumor microenvironment through cell proliferation, survival, differentiation, migration, and activation of non-tumor cells.

Duvelisib is a dual PI3K-δ/-γ inhibitor that reduces the cancer-promoting effects of PI3K on the tumor microenvironment and has an established clinical safety and efficacy profile in patients with hematologic malignancies (United States [US] approval in relapsed or refractory [R/R] chronic lymphocytic leukemia/small lymphocytic leukemia and accelerated approval in R/R follicular lymphoma) (COPIKTRA 2018). In in vivo nonclinical studies in solid tumor models (including HNSCC), duvelisib induced tumor growth delay. In addition, strong antitumor synergy (i.e., inhibition of tumor growth and increased survival) was observed for the combination of duvelisib and a PD-1 inhibitor vs either monotherapy in a mouse model of B-cell lymphoma (mimicking a solid tumor setting). Mechanistically, duvelisib was found to reduce regulatory T-cells (Tregs), M2 tumor-associated macrophages, and MDSCs in the context of combination with a PD-1 inhibitor. The nonclinical data suggest that reduction of Tregs and MDSCs by duvelisib in the tumor microenvironment may enhance sensitivity of the tumor to PD-1 inhibitors like pembrolizumab in this tumor setting.

Based on the hypothesis, which is supported by nonclinical data, that duvelisib can enhance the activity of PD-1 inhibitors, this study is designed to assess the safety and preliminary efficacy of duvelisib in combination with pembrolizumab in subjects with R/M HNSCC who are eligible for pembrolizumab monotherapy based on the current pembrolizumab prescribing information.

Objectives and Endpoints:	
Objectives	***Endpoints***
Stage 1 - Unique Objectives/Endpoints	
Primary	
Evaluate the safety and tolerability of duvelisib in combination with pembrolizumab in subjects with R/M HNSCC	Safety and tolerability of study interventions based on dose-limiting toxicities (DLTs), adverse events (AEs), serious AEs (SAEs), vital signs, physical examinations, and clinical laboratory measurements
Secondary	
Characterize the ORR of duvelisib in combination with pembrolizumab in subjects with R/M HNSCC	ORR, which includes PR and complete response (CR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 (Eisenhauer 2009)
Stage 1 and Stage 2- Combined Objectives/Endpoints	
Primary	
Characterize the ORR of duvelisib in combination with pembrolizumab	ORR, which includes PR and CR, according to RECIST v 1.1 (Eisenhauer 2009)
Secondary	
Characterize other efficacy parameters of duvelisib in combination with pembrolizumab	• Duration of response (DOR), defined as time from response ≥ PR to documented disease progression according to RECIST v 1.1 (Eisenhauer 2009) • Progression-free survival (PFS), defined as the time from start of treatment to documented disease progression according to RECIST v 1.1 (Eisenhauer 2009), or death due to any cause • Overall survival (OS), defined as the time from start of treatment to the date of death
Characterize the pharmacokinetics (PK) of duvelisib (and metabolite IPI-656) monotherapy and of duvelisib in combination with pembrolizumab	PK parameters for duvelisib (and metabolite IPI-656)
Evaluate the safety and tolerability of duvelisib in combination with pembrolizumab	Safety and tolerability parameters including AEs, SAEs, vital signs, physical examinations, and clinical laboratory measurements

Exploratory	
Evaluate potential biomarkers for possible associations with clinical efficacy and/or safety outcomes of duvelisib in combination with pembrolizumab	• Blood assessments of immune cell populations, chemokines, cytokines and circulating tumor DNA • Fecal assessments of protein, DNA, and/or RNA • Tumor biopsy evaluation of biomarkers such as gene and copy number variation, RNA expression, protein expression, and/or immune cell content (Required biopsies in Stage 1 and optional biopsy in Stage 2) • ORR and its relationship to tumor and/or immune cell PD-L1 levels and to tumor HPV status

Overall Design and Intervention Groups:

This is a multicenter, non-randomized, open-label Phase 1b/2 study of duvelisib in combination with pembrolizumab in subjects with R/M HNSCC who are eligible for pembrolizumab monotherapy based on the current pembrolizumab prescribing information (Keytruda 2019).

The study will follow a Simon two-stage design (Simon 1989).

Subjects will receive duvelisib 25 mg twice daily (BID) orally (PO) in combination with pembrolizumab 200 mg every 3 weeks (q3w) intravenously (IV).

In **Stage 1**, subjects will have a 1-week lead-in with duvelisib before the initiation of combination therapy with duvelisib and pembrolizumab. Approximately 13 subjects are planned to be accrued in this stage. The first 6 subjects will be assessed for DLTs. The DLT evaluation period will be Cycle 1 (4 weeks or 28 days): the 1-week duvelisib monotherapy lead-in period followed by 1 dose of pembrolizumab in combination with 3 additional weeks of continuous dosing of duvelisib. Every effort will be made to administer the first dose of pembrolizumab on Day 8 of Cycle 1 (C1D8). If the first dose of pembrolizumab on C1D8 is delayed, every effort should be made to delay the subsequent dosing of the next cycle (within the protocol-allowed window of 3 days) to achieve as close to a 3-week interval between pembrolizumab doses as possible. The Medical Monitor needs to be consulted for such adjustments to ensure uniformity of approach and to account for subject-specific circumstances. For example, if the third day of the C2D1 window falls on a weekend, an additional adjustment would need to be made on a case-by-case basis. In the event of a delay of the start of pembrolizumab therapy, DLTs will be evaluated at the end of the third week of combination therapy.

The DLT evaluation period will be used to assess DLTs in the first 6 subjects.

- If there is ≤ 1 DLT in the 6 DLT-evaluable subjects, additional subjects will be enrolled to bring the total dosed in Stage 1 to approximately 13 subjects.
- If there are ≥ 2 DLTs in the first 6 subjects, enrollment at duvelisib 25 mg BID will stop. Enrollment would restart at a reduced duvelisib dose (15 mg BID) to assess DLTs at the lower dose.

A formal analysis of available safety data will be conducted when the first 10 subjects treated have received at least 1 cycle of study treatment. This will enable assessment of toxicities of later onset, particularly outside of the DLT-window.

If an excessive rate of Grade 3 or higher overlapping SAEs (defined as any rate for each SAE that is above the highest reported in warnings and precautions of the prescribing information for either duvelisib [COPIKTRA 2018] or pembrolizumab [Keytruda 2019], respectively) such as pneumonitis, colitis, cutaneous skin reactions, and elevations of AST/ALT, is observed outside of the DLT window, a decision for stopping or modifying the study may be made. However, recognizing that the observed rate of such events can be highly sensitive due to the small sample size, the totality of safety data will be reviewed and carefully considered prior to making a formal decision.

An interim analysis of ORR will occur after all of the planned 13 subjects in Stage 1 are enrolled, dosed, and have been followed through at least the first disease response assessment.

- If there are ≤ 2 responses (CR or PR) in the 13 subjects in Stage 1, further accrual in the study may be stopped. However, all available data, including the relative proportion of CRs, will be analyzed before a final decision is made.
- If > 2 responses are observed in Stage 1, enrollment will continue in Stage 2.

In **Stage 2**, 17 additional subjects will be accrued for a total of 30 subjects in the final analysis. Subjects enrolled in Stage 2 will only receive combination therapy with duvelisib and pembrolizumab. Enrollment into Stage 2 may proceed prior to completion of the interim analysis as long as at least 2 of the 13 subjects enrolled in Stage 1 have a confirmed response.

Subjects will be monitored continuously for safety while on study treatment. Adverse events will be classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 or higher.

Higher doses of duvelisib may be explored in additional subjects via a protocol amendment, if warranted by observed data.

Subjects will be treated until documented progressive disease (PD), unacceptable toxicity, discontinuation criteria are met, withdrawal, or death. The total duration of treatment will not exceed 24 months. After treatment discontinuation, subjects will be followed for safety for an additional 30 days. All subjects with treatment-related AEs/SAEs should be observed until resolution or stabilization.

It is anticipated that the study accrual will occur over approximately 18 months. All subjects will be followed for survival for 1 year after the last subject is enrolled and dosed.

Study Population:

Inclusion Criteria

Subjects may be eligible for inclusion in the study if they meet the following criteria:

1. Must be a male or female subject ≥ 18 years of age
2. Must have histologically or cytologically-confirmed R/M HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx that is considered incurable by local therapies.

3. Must be eligible for pembrolizumab monotherapy based on the current prescribing information for pembrolizumab (Keytruda 2019): (a) for first-line treatment, subjects with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 1) as determined by a Food and Drug Administration [FDA]-approved test; (b) subjects with R/M HNSCC with disease progression on or after platinum-containing chemotherapy, regardless of PD-L1 expression.
4. Must have had 0 to 2 prior therapies for R/M HNSCC. Therapy for locally or regionally advanced HNSCC with or without radiation therapy is not counted as a line of therapy unless recurrence and/or metastasis was demonstrated < 6 months from the end of such therapy.
5. Must have at least 1 measurable lesion (which has not been previously irradiated) according to RECIST v 1.1 (Eisenhauer 2009)
6. For Stage 1 only: Must have at least 1 other lesion that can be biopsied
7. For Stage 1 only: Must be willing to undergo a pretreatment and on-treatment biopsy of the available tumor lesion (described in inclusion criterion #6). Archival tissue (up to 6 months before the first dose of duvelisib) may be considered in place of the required pretreatment biopsy after consultation with the Sponsor, as long as no intervening systemic regimen had been taken during that time frame.
8. Must provide prior data on PD-L1 expression and HPV status, if available
9. Must have adequate organ function defined by the following laboratory parameters:
    a. Adequate bone marrow reserve as evidenced by:
        - Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
        - Platelet count ≥ 100×10^9/L
        - Hemoglobin level ≥ 9.0 g/dL
    b. Adequate renal function as evidenced by:
        - a serum creatinine level < 1.5 mg/dL, or
        - estimated creatinine clearance value ≥ 60 mL/min (as determined by the Cockcroft-Gault method) for subjects with creatinine levels > 1.5 × institutional upper limit of normal (ULN)
    c. Adequate hepatic function as evidenced by:
        - Total bilirubin level ≤ 1.5 × ULN (exception: subjects with Gilbert's Syndrome may have a bilirubin level > 1.5 × ULN)
        - Aspartate aminotransaminase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/serum pyruvic transaminase (SGPT) levels ≤ 2.5 × ULN or ≤ 5 × ULN in subjects with liver metastases
10. Must have an international normalized ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN, unless subject is receiving anticoagulant therapy in which case PT or aPTT must be within therapeutic range of intended use of anticoagulants

11. Must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
12. For male and female subjects of reproductive potential (i.e., not surgically sterile or female subjects who are not postmenopausal), must be willing to use a highly effective method of contraception (see Section 10.4) for the duration of the study interventions and for at least 4 months after the last dose of study interventions
13. Must have a negative serum human chorionic gonadotropin (hCG) pregnancy test result within 7 days before the first dose of duvelisib if the subject is a woman of childbearing potential (WCBP)
14. Must provide signed and dated institutional review board (IRB)/independent ethics committee (IEC) -approved informed consent form (ICF) before any study-specific screening procedures are performed

Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Have disease that is suitable for local therapy administered with curative intent
2. Have been previously treated with 3 or more systemic regimens given for recurrent and/or metastatic disease
3. Have received anticancer treatment, major surgery, or any investigational drug within 30 days or 5 half-lives, whichever is shorter, before the first dose of duvelisib
4. Have received radiation therapy within 14 days before the first dose of duvelisib in this study, including, in addition (if necessary), the timeframe for resolution of any actual or anticipated toxicities from such radiation. Palliative radiation therapy is allowed if > 7 days before the first dose of duvelisib and any toxicity is ≤ Grade 1.
5. Have received prior radiation therapy to > 25% of bone marrow-bearing areas
6. Have co-existing head-and-neck carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary, salivary gland tumors, or any other non-squamous primary tumors involving the head and neck
7. Have received previous treatment with a PI3K inhibitor
8. Have received previous treatment with a PD-1 or PD-L1 inhibitor
9. Have received organ or allogenic bone marrow or peripheral blood stem cell transplant
10. Have a history or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function
11. Have a prior history of drug-induced colitis or drug-induced pneumonitis
12. Have active cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection (subjects with detectable viral load)
13. Have an infection with hepatitis B or hepatitis C:
    - Subjects with a positive hepatitis B surface antigen (HBsAg) or hepatitis C antibody (HCVAb) will be excluded

- Subjects with a positive hepatitis B core antibody (HBcAb) must have negative hepatitis B virus (HBV) DNA to be eligible and must be periodically monitored for HBV reactivation by institutional guidelines
- Investigators who strongly believe that a positive HBcAb is false-positive due to passive immunization from previous immunoglobulin infusion therapy should discuss the potential to defer HBV prophylaxis with the Medical Monitor

14. Have a history of or known human immunodeficiency virus (HIV) infection
15. Have a history of tuberculosis treatment within the 2 years before the first dose of duvelisib
16. Have a history of chronic liver disease or veno-occlusive disease/sinusoidal obstruction syndrome
17. Have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study
18. Are receiving ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids > 20 mg of prednisone (or equivalent) per day
19. Have an active infection or are receiving ongoing systemic treatment for a clinically significant bacterial, fungal, or viral infection at Screening

    NOTE: Subjects on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met
20. Have received a live or live attenuated vaccine within 6 weeks of first dose of duvelisib
21. Have received medications or consumed foods that are strong inhibitors or inducers of cytochrome P450 3A (CYP3A) (Section 10.2) within 2 weeks prior to the first dose of duvelisib or concurrent with duvelisib treatment
22. Are unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV), or herpes zoster (VZV) at screening
23. Have had prior surgery (e.g., gastric bypass surgery, gastrectomy) or gastrointestinal dysfunction that may affect drug absorption
24. Have any active gastrointestinal dysfunction interfering with the subject's ability to be administered oral medications
25. Is a female subject who is pregnant or breastfeeding
26. Have a baseline QT interval corrected using the Fridericia correction method (QTcF) > 500 ms (average of triplicate readings). NOTE: This criterion does not apply to subjects with a right or left bundle branch block.
27. Have New York Heart Association Class III or IV congestive heart failure
28. Have a history of another active malignancy that is progressing or requires active treatment. Exceptions include adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumors curatively treated with no evidence of disease for > 3 years.

29. Have known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of duvelisib and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to the first dose of duvelisib. The exception does not include carcinomatous meningitis.
30. Have an active autoimmune disease requiring systemic treatment within the last 3 months prior to first dose of study intervention, documented history of clinically severe autoimmune disease, or a syndrome that requires systemic or immunosuppressive agents except vitiligo, Type 1 diabetes mellitus, hypothyroidism stable on hormone-replacement therapy, Sjogren's syndrome, and resolved childhood asthma/atopy. Subjects who require intermittent use of bronchodilators, inhaled steroids, or local steroid injections may participate in this study.
31. Have a history of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months prior to first dose of duvelisib
32. Have unstable or severe uncontrolled medical condition or any important medical illness or abnormal laboratory finding that would, in the Investigator's judgment, increase the subject's risk to participating in this study

Number of Subjects (planned):

It is anticipated that the study will include approximately 13 subjects in Stage 1 and 17 subjects in Stage 2 at multiple sites in the US, for a total of 30 subjects.

Duration of Treatment and Follow-up:

Subjects will be treated until documented PD, unacceptable toxicity, discontinuation criteria are met, withdrawal, or death. The total duration of treatment will not exceed 24 months.

All subjects will be followed for survival for 1 year after the last subject is enrolled and dosed.

Statistical Methods:

This study will test the null hypothesis that the ORR in subjects is $\leq 16\%$ against the alternative that ORR is $\geq 44\%$.

The evaluation of the primary endpoint will be conducted at the highest dose that is tolerated during the DLT evaluation. Therefore, if the initial dose of 25 mg BID is not tolerated but the reduced dose of 15 mg BID is tolerated, the primary endpoint will be evaluated in all subjects starting at the tolerated dose.

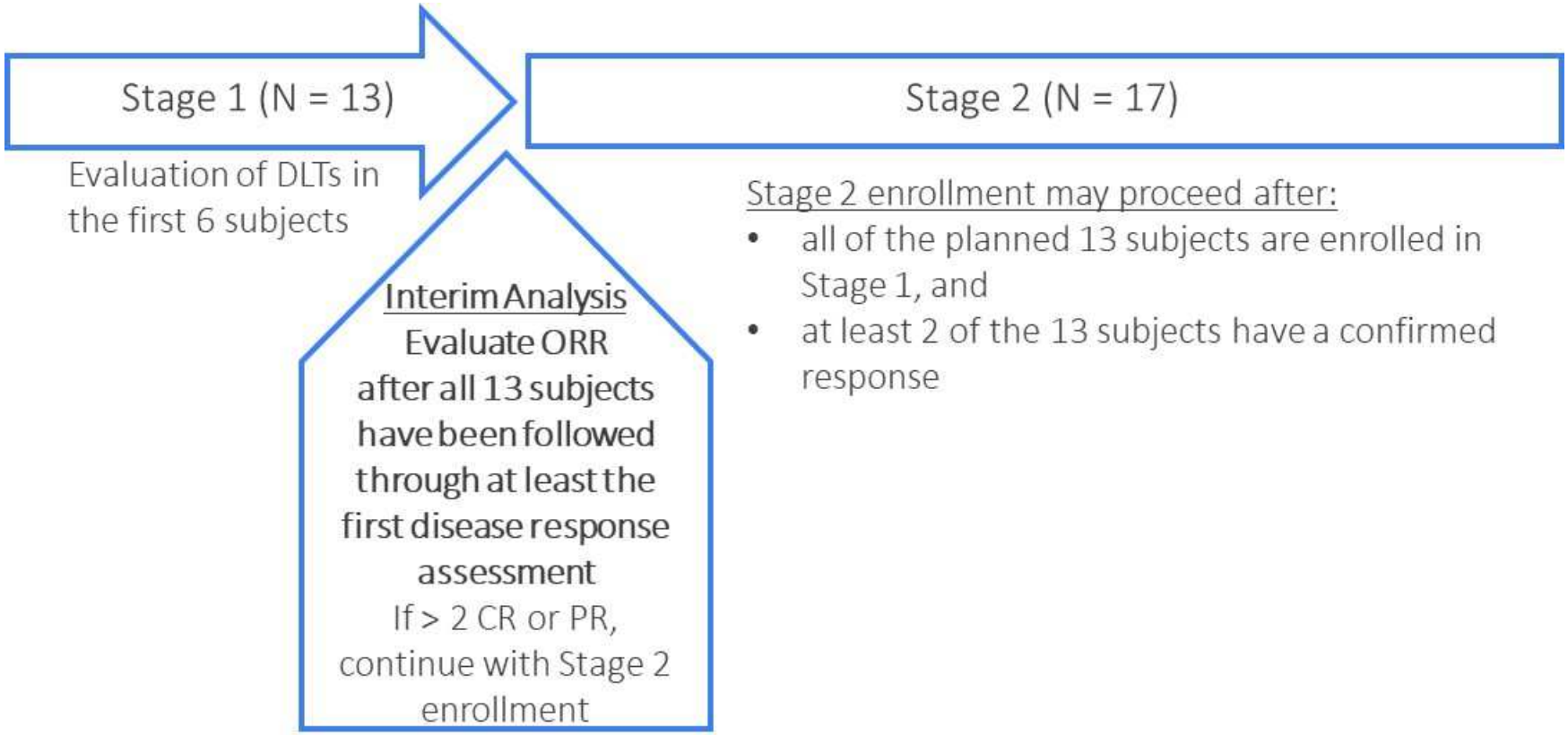
The ORR (proportion of subjects achieving CR or PR) according to RECIST v 1.1 (Eisenhauer 2009) will be estimated on the modified Intent-to-Treat (mITT) population (i.e., all subjects who receive at least 1 dose of duvelisib in combination with at least 1 dose of pembrolizumab). A 2-sided exact 95% confidence interval (CI) will be calculated.

The study will follow a Simon two-stage design (Simon 1989). In the first stage, approximately 13 subjects will be accrued. If there are ≤ 2 responses (CR or PR) in these 13 subjects, further accrual in the study may be stopped. However, all available data will be considered before termination. In Stage 2, 17 additional subjects will be accrued for a total of 30 subjects in the final analysis. The null

hypothesis will be rejected if 10 or more responses (CR or PR) are observed in 30 subjects. This design yields an overall type I error rate of 5% and power of 90% when the true response rate is 44%. Evaluation of ORR in Stage 1 will occur after the last subject enrolled and dosed in Stage 1, has been followed through at least the first disease response assessment. Final analysis of the ORR endpoint (combined Stage 1 and Stage 2 ORR) will occur after the last subject enrolled and dosed in Stage 2 has been followed for 6 months. Safety analyses will be performed on the ITT population, and safety endpoints will be tabulated and presented.
Data Monitoring Committee: None.
Disclosure Statement: This is an open-label single-arm treatment study.

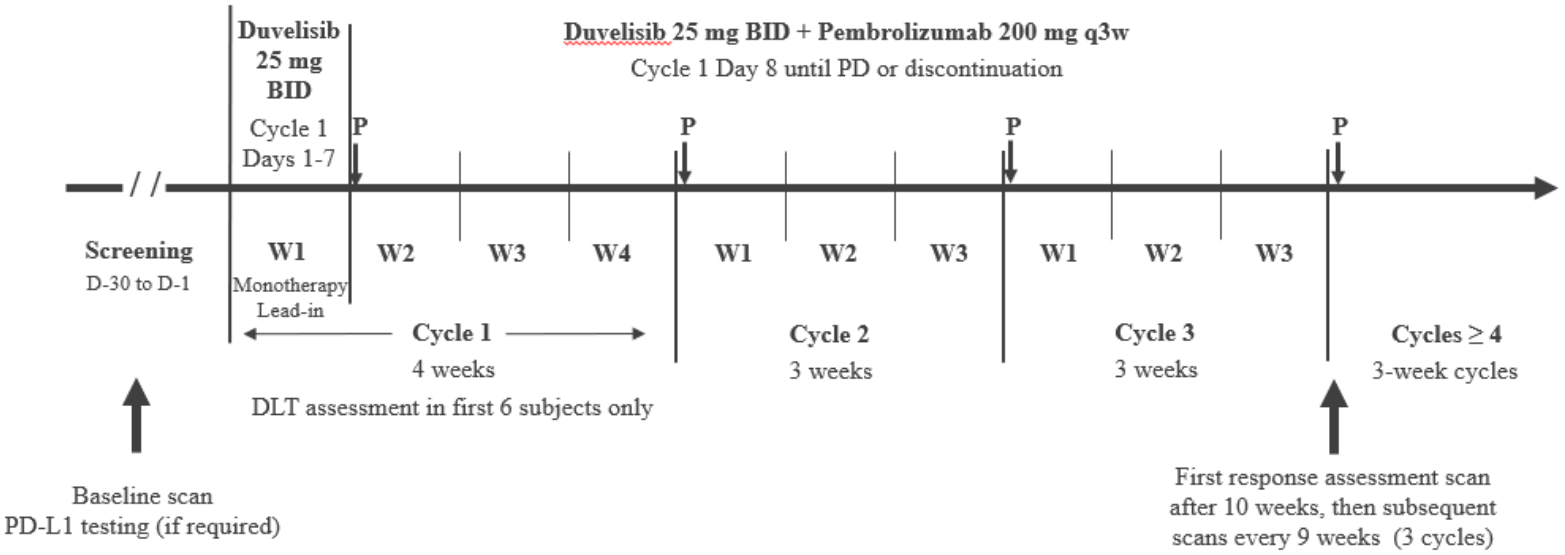
1.2. Schema

Figure 1: Study Stages



Abbreviations: CR: complete response; DLT: dose-limiting toxicity; PR: partial response; ORR: overall response rate.

Figure 2: Treatment/Imaging Scheme in Stage 1



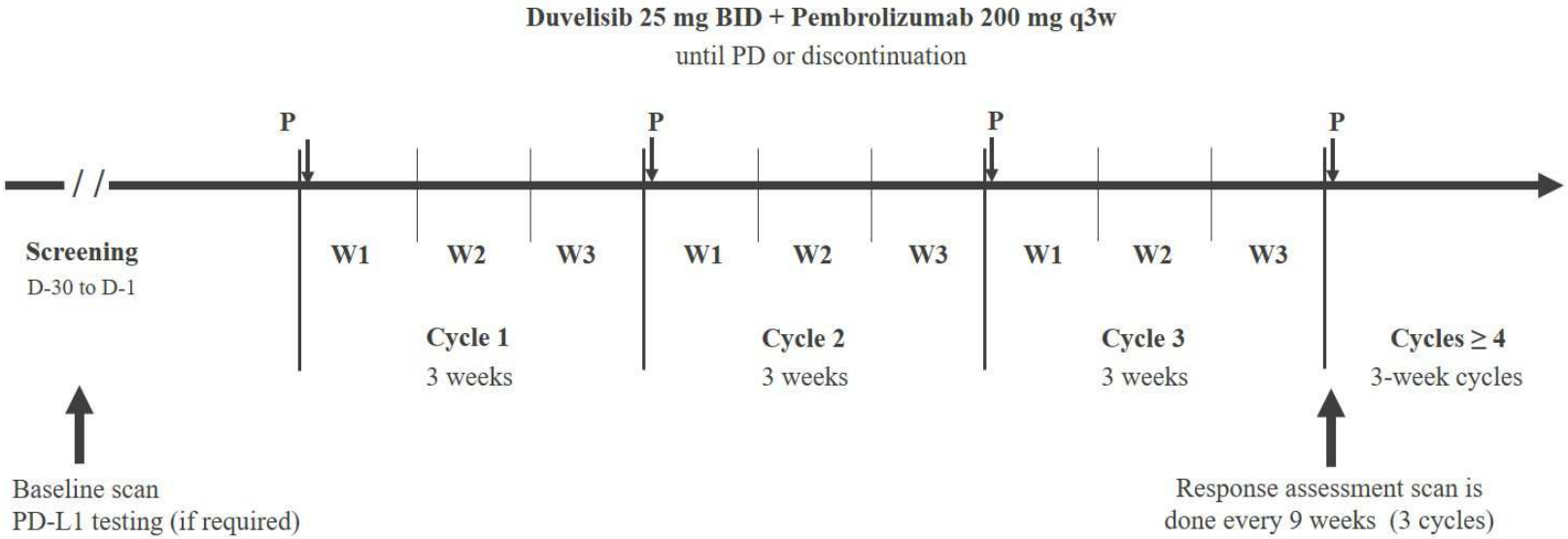
Abbreviations: BID: twice daily; D: day; DLT: dose-limiting toxicity; q3w: every 3 weeks; P: pembrolizumab; PD: progressive disease; PD-L1: programmed cell death ligand 1; W: week.

Notes:

The total duration of treatment will not exceed 24 months.

In the case of a CR or PR, a confirmatory scan must be performed per RECIST v 1.1 (Eisenhauer 2009). It is recommended that this scan be performed at 4 (+1) weeks after the initial response.

Figure 3: Treatment/Imaging Scheme in Stage 2



Abbreviations: BID: twice daily; D: day; q3w: every 3 weeks; P: pembrolizumab; PD: progressive disease; PD-L1: programmed cell death ligand 1; W: week.
Notes:
The total duration of treatment will not exceed 24 months.
In the case of a CR or PR, a confirmatory scan must be performed per RECIST v 1.1 (Eisenhauer 2009). It is recommended that this scan be performed at 4 (+1) weeks after the initial response.

1.3. Schedule of Activities (SoA) for Stage 1

Table 1: Study Activities for Stage 1: Duvelisib Monotherapy Lead-in and in Combination with Pembrolizumab

		Duvelisib Lead-in	Duvelisib in Combination with Pembrolizumab[a]				End of Treatment and Follow-up			
Activity[b]	**Screening (D-30 to D -1)**	**Cycle 1 (4 weeks)**			**Cycle 2 and Cycle 3 (3 weeks)**	**Cycles ≥ 4 (3 weeks)**	**EoT[c]**	**Safety F/U 30 D (+7) postdose)[d]**	**Survival F/U Every 3 months until End of Study**	**Notes**
		W1	**W2**	**W3**	**W1**	**W1**				
		D1	**D8 ±5**	**D15±3**	**D1 ±3**	**D1 ±3**				
Informed Consent	X									Potentially eligible subjects must sign an ICF before initiating any study specific procedures. SOC assessments that fulfill study eligibility requirements may be performed before the subjects signs the ICF.
Inclusion/Exclusion Criteria	X									Reconfirm eligibility before first dose.
Medical and Disease History, Demographics	X									Medical and Disease History includes histologic or cytologic diagnosis of HNSCC; HPV status; prior PD-L1 expression; and prior treatment information.
Archival Tumor Tissue	X									Archived tumor tissue is not required for enrollment, but should be submitted from all enrolled subjects, if available.
Physical Examination	X	X	X		X	X	X			See Section 8.2.1. Full examination (including height) at Screening and symptom-directed at subsequent time points. Screening results can be used for C1D1 if assessments are performed within 7 days of first dose.
Vital Signs and Weight	X	X	X	X	X	X	X	X		See Section 8.2.1. Vital signs measured with subject in a semi-supine position after 5 minutes rest. Includes temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.
ECOG Performance Status	X	X	X	X	X	X	X	X		See Section 8.3.1. Screening ECOG results can be used for C1D1 if test is performed within 7 days of first dose.

		Duvelisib Lead-in	Duvelisib in Combination with Pembrolizumab[a]				End of Treatment and Follow-up			
Activity[b]	**Screening (D-30 to D -1)**	**Cycle 1 (4 weeks)**			**Cycle 2 and Cycle 3 (3 weeks)**	**Cycles ≥ 4 (3 weeks)**	**EoT[c]**	**Safety F/U 30 D (+7) postdose)[d]**	**Survival F/U Every 3 months until End of Study**	**Notes**
		W1	**W2**	**W3**	**W1**	**W1**				
		D1	**D8 ±5**	**D15±3**	**D1 ±3**	**D1 ±3**				
ECG (12-lead)	X									See Section 8.2.2. ECG at Screening will be performed in triplicate. QTc measurements will use the Fridericia correction method. Additional on-treatment ECGs should be performed per the Investigator's discretion as clinically indicated.
Concomitant Medications and Procedures	Ongoing									See Section 6.5.1 for required and recommended prophylaxis. Concomitant medications and procedures occurring within 30 days before first dose will be recorded at Screening.
AE/SAE Assessment	Ongoing									See Section 8.4 for AE management. See Section 8.4.3 for reporting requirements.
Coagulation tests	X									PT, aPTT, and INR. See Table 23.
Viral Screening	X									Hepatitis serology: HCVAb, HBsAg, HBcAb. HPV testing (if status not available at Screening). CMV/EBV serology or viral load. HIV test is not required if a prior negative test within 9 months is available. See Table 23.
CMV Reactivation Monitoring (if applicable)			X		X	X				Subjects with a history of CMV infection should be monitored for reactivation by PCR at least monthly. See Section 6.5.1.
C-Reactive Protein	X	Obtain when Grade ≥ 2 diarrhea, any grade colitis, or any grade immune-mediated toxicity (e.g., pneumonitis, colitis, hepatitis, endocrinopathies, nephritis/renal dysfunction, cutaneous adverse reactions, encephalitis) occurs								See Table 23.
T3, FT4, and TSH	X				X	X		X		Every other cycle starting at C2D1.
Serum or Urine hCG Pregnancy Test for Women of	X	X[e]			X	X		X		A serum pregnancy test must be performed within 7 days of first duvelisib dose. At subsequent time points, serum testing is preferred but urine testing is allowed if a

		Duvelisib Lead-in	Duvelisib in Combination with Pembrolizumab[a]				End of Treatment and Follow-up			
Activity[b]	**Screening (D-30 to D -1)**	**Cycle 1 (4 weeks)**			**Cycle 2 and Cycle 3 (3 weeks)**	**Cycles ≥ 4 (3 weeks)**	**EoT[c]**	**Safety F/U 30 D (+7) postdose)[d]**	**Survival F/U Every 3 months until End of Study**	**Notes**
		W1	**W2**	**W3**	**W1**	**W1**				
		D1	**D8 ±5**	**D15±3**	**D1 ±3**	**D1 ±3**				
Childbearing Potential										blood draw for other assessments is not performed. A positive urine test result must be confirmed by a serum test. See Table 23.
Clinical Chemistry with Liver Function Tests	X	X	X	X	X	X	X	X		BUN, potassium, creatinine, sodium, total protein, glucose (fasting), calcium, LDH, ALT, AST, total and direct bilirubin, and ALP. Screening test results can be used for C1D1 if tests are performed within 7 days of first dose. See Table 23.
Hematology	X	X	X	X	X	X	X	X		Hematology panel plus a 5-part differential. Screening test results can be used for C1D1 if tests are performed within 7 days of first dose. See Table 23.
Urinalysis	X		X		X	X		X		See Table 23.
Imaging and Disease Response Assessment via RECIST v 1.1 (Eisenhauer 2009)	X					X	X[f]			See Section 8.1. After Screening disease assessment, response will be assessed at C4D1 (10 weeks after first dose of duvelisib) and then D1 of every third cycle thereafter (approximately every 9 weeks). The same method of assessment used at Screening should be used throughout the study. In the case of a CR or PR, a confirmatory scan must be performed per RECIST v 1.1. It is recommended that this scan be performed at 4 (+1) weeks after the initial response.
FDA-approved PD-L1 Testing (if required)	X									Perform if specified in the current pembrolizumab prescribing information (Keytruda 2019), if results are not already available. Information on FDA-approved tests is available at: http://www.fda.gov/CompanionDiagnostics.

		Duvelisib Lead-in	Duvelisib in Combination with Pembrolizumab[a]				End of Treatment and Follow-up			
Activity[b]	**Screening (D-30 to D -1)**	**Cycle 1 (4 weeks)**			**Cycle 2 and Cycle 3 (3 weeks)**	**Cycles ≥ 4 (3 weeks)**	**EoT[c]**	**Safety F/U 30 D (+7) postdose)[d]**	**Survival F/U Every 3 months until End of Study**	**Notes**
		W1	**W2**	**W3**	**W1**	**W1**				
		D1	**D8 ±5**	**D15±3**	**D1 ±3**	**D1 ±3**				
PK, PDn, and Biomarker Assessments (See details in Table 2)	X[g]		X	X	X	X[h]	X			Details for these assessments are in Table 2. Also obtain stool sample if subject has colitis or Grade ≥ 3 diarrhea.
Tumor Biopsy (See details in Table 2)	X[g]		X							See details for tumor biopsies in Table 2. Tumor biopsies at Screening/C1D1and C1D8 are mandatory; however, archival tissue at Screening/C1D1 may be acceptable (See Section 8.8.1).
Review of Duvelisib Self-Administration Diaries		X	X	X	X	X				Subjects are required to log each self-administration of duvelisib in a diary during first year on treatment only
Duvelisib Administration		Continuous duvelisib BID until PD or discontinuation								On study visit days, instruct the subject not to take the AM duvelisib dose. Duvelisib will be administered in the clinic (and before the pembrolizumab infusion is started, if applicable). See Section 6.1.1 and Table 2 for specific timing. Please see required and recommended prophylaxis in Section 6.5.1.
Pembrolizumab Administration			X[i]		X	X				Pembrolizumab should be administered as an IV infusion over 30 minutes See Section 6.1.2 and Table 2 for dosing on C1D8 and C2D1. On days when postdose PK samples are not collected, the infusion should be started within 10 minutes after the dose of duvelisib is administered.

		Duvelisib Lead-in	Duvelisib in Combination with Pembrolizumab[a]				End of Treatment and Follow-up			
Activity[b]	**Screening (D-30 to D -1)**	**Cycle 1 (4 weeks)**			**Cycle 2 and Cycle 3 (3 weeks)**	**Cycles ≥ 4 (3 weeks)**	**EoT[c]**	**Safety F/U** **30 D (+7) postdose)[d]**	**Survival F/U** **Every 3 months until End of Study**	**Notes**
		W1	**W2**	**W3**	**W1**	**W1**				
		D1	**D8 ±5**	**D15±3**	**D1 ±3**	**D1 ±3**				
Survival									X	Survival Follow-up will occur every 3 months (± 2 weeks) from the Safety F/U Visit for up to 1 year after the last subject starts duvelisib (Section 4.3). Information on survival status and anticancer therapy will be collected (Section 8.1.3). This assessment will be conducted by telephone interview and records review (if available).

Abbreviations: AE/SAE: adverse event/serious adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BID: twice daily; BUN: blood urea nitrogen; CMV: cytomegalovirus; CR: complete response; CxDx: Cycle x, Day x; CxWx: Cycle x, Week x; D: Day; EBV: Epstein-Barr virus; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; FDA: Food and Drug Administration; FT4: free thyroxine; F/U: follow-up; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCVAb: hepatitis C antibody; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; HNSCC: head and neck squamous cell carcinoma; HPV: human papillomavirus; ICF: informed consent form; INR: international normalized ratio; LDH: lactate dehydrogenase; PCR: polymerase chain reaction; PD: progressive disease; PD-L1: programmed cell death ligand 1; PDn: pharmacodynamic; PK: pharmacokinetic; PR: partial response; PT: prothrombin time; RECIST: Response Evaluation Criteria in Solid Tumors; SOC: standard of care; T3: triiodothyronine; TSH: thyroid-stimulating hormone; W: week.

[a] Day 1 of each cycle (except Cycle 1) of combination therapy is the day of pembrolizumab administration.

[b] The tests detailed in Table 23 will be performed by the local laboratory. See Section 8.2.4 for guidance on repeating/recording laboratory tests with values that are considered clinically significant or that require a change in subject management. The PK, PDn, and biomarker assessments detailed in Table 2 will be performed by a laboratory selected by the Sponsor, as specified in the Laboratory Manual.

[c] For all subjects who permanently discontinue the study interventions (i.e., duvelisib and pembrolizumab), an EoT Visit will be performed within 7 days after the decision to discontinue study interventions. EoT assessments need not be repeated if performed within the previous 14 days, or 30 days for imaging.

[d] A Safety Follow-up Visit is to be performed 30 + 7 days from last dose. If possible, this visit should occur before the initiation of any subsequent anticancer therapy.

[e] If the pregnancy test at Screening was performed within 7 days of C1D1, the test does not need to be repeated on C1D1.

[f] A scan will be performed at the EoT if one was not previously performed within 30 days of the EoT Visit.

[g] Blood for biomarker assessments and tumor biopsy may be obtained either at Screening or at first dose of duvelisib on C1D1 (preferred).

[h] Please refer to Table 2 for assessments and timing for C4D1 and beyond.

[i] Every effort will be made to administer the first dose of pembrolizumab on Day 8 of Cycle 1 (C1D8). If the first dose of pembrolizumab on C1D8 is delayed, every effort should be made to delay the subsequent dosing of the next cycle (within the protocol-allowed window of 3 days) to achieve as close to a 3-week interval between pembrolizumab doses as possible. The Medical Monitor needs to be consulted for such adjustments to ensure uniformity of approach and to account for subject-specific circumstances. For example, if the third day of the C2D1 window falls on a weekend, an additional adjustment would need to be

made on a case-by-case basis. In the event of a delay of the start of pembrolizumab therapy, DLTs will be evaluated at the end of the third week of combination therapy.

Table 2: Pharmacokinetic, Pharmacodynamic, and Biomarker Sampling in Stage 1

Cycle	Day	Sampling Time Points[a]	PK Samples	Whole Blood for PDn Analysis	Serum and Plasma for Biomarkers	Whole Blood for Immune Cell Analysis	Stool Sample for Biomarker Analysis[b]	Swab for Genomic Analysis	Tumor Biopsies[c]
Screening or C1D1					X[d]	X[d]	X[e]	X[d]	X[d, f]
1	8	Pre-duvelisib dose[g]	X[g]	X	X	X			
1	8	1 hour (± 10 min) after duvelisib dose	X[g]	X					
1	8	2 hours (± 10 min) after duvelisib dose	X[g]						
1	8	Approximately 2 to 4 hours after duvelisib dose	X[g]						X[f, g]
1	8	0 hours (± 5 min) after the end of pembrolizumab infusion	X						
1	15	Predose	X						
2	1	Predose[h]	X	X	X	X			
2	1	0 hours (± 5 min) after the end of pembrolizumab infusion	X						
2	1	1 hour (± 10 min) after the end of pembrolizumab infusion	X						
2	1	2 hours (± 10 min) after the end of pembrolizumab infusion	X						
3	1	Predose[i]	X						
4	1	Predose[i]	X		X	X	X[j]		
5	1	Predose[i]	X						

Cycle	Day	Sampling Time Points[a]	PK Samples	Whole Blood for PDn Analysis	Serum and Plasma for Biomarkers	Whole Blood for Immune Cell Analysis	Stool Sample for Biomarker Analysis[b]	Swab for Genomic Analysis	Tumor Biopsies[c]
≥ 7[k]	1	Predose[i]			X	X			
End of treatment					X	X			

Abbreviations: CxDx: Cycle x Day x; min: minutes; PDn: pharmacodynamic; PK: pharmacokinetic; SOC: standard of care.

[a] Sample collections may be reduced, or limited to certain sites/countries, based on emerging data or feasibility. Reductions/limitations may be implemented before amendment of the protocol. Specific collection and processing details (e.g., serum or plasma) will be described in the Laboratory Manual. Any increase in the number or type of samples collected will require a protocol amendment.

[b] Stool samples may be collected either predose or postdose. Obtain additional stool sample if subject has colitis or Grade ≥ 3 diarrhea.

[c] See Section 8.8.1. Request aliquot of colon biopsies if taken due to colitis or Grade ≥ 3 diarrhea or as SOC for any immune-mediated adverse events.

[d] The following samples can be obtained either at Screening or before the first dose of duvelisib on C1D1: serum and plasma for biomarkers, whole blood for immune cell analysis, swab for genomic analysis, and tumor biopsy. C1D1 is preferred for samples other than the swab.

[e] The Screening/C1D1 stool sample may be collected up to 7 days before first dose.

[f] See Section 8.8.1. Tumor biopsies at Screening/C1D1 and C1D8 are mandatory. However, archival tissue beyond the 30-day Screening window and up to 6 months before C1D1 may be considered in place of the required Screening/C1D1 biopsy after consultation with the Sponsor, as long as no intervening systemic regimen had been taken during that time frame. Collection procedures and amounts are according to the Laboratory Manual. Please note that the same set of tumor biopsies are included in both Table 1 and Table 2.

[g] On C1D8, duvelisib will be administered at the start of the visit after the predose PK, PDn, and blood sample collection. Blood samples to evaluate the PK of duvelisib and metabolite IPI-656 will be collected at 1 and 2 hours after duvelisib administration. Pembrolizumab will not be administered until the biopsy for biomarkers has been collected; the optimal timing for collection of the biopsy is approximately 2 to 4 hours after duvelisib administration, however, a tumor biopsy at a later time during this clinic visit on C1D8 is acceptable. The fourth PK sample should be collected at approximately 2 to 4 hours after duvelisib dose, as soon as possible after the biopsy, and prior to pembrolizumab administration.

[h] Predose sample is to be taken before either study intervention (i.e., duvelisib or pembrolizumab) is administered. On C2D1, duvelisib will be administered 30 minutes before the start of the pembrolizumab infusion

[i] Predose sample is to be taken before either study intervention (i.e., duvelisib or pembrolizumab) is administered. The pembrolizumab infusion should be started within 10 minutes after the dose of duvelisib is administered.

[j] The C4D1 stool sample may be collected up to 3 days before C4D1.

[k] Samples will be collected on C7D1 and D1 of every third cycle thereafter (approximately every 9 weeks) or until the Sponsor terminates the collection.

1.4. Schedule of Activities (SoA) for Stage 2

Table 3: Study Activities for Stage 2: Duvelisib in Combination with Pembrolizumab

		Duvelisib in Combination with Pembrolizumab[a]			End of Treatment and Follow-up			
Activity[b]	**Screening (D-30 to D -1)**	**Cycle 1 (3 weeks)**	**Cycle 2 and Cycle 3 (3 weeks)**	**Cycles ≥ 4 (3 weeks)**	**EoT[c]**	**Safety F/U 30 D (+7) postdose)[d]**	**Survival F/U Every 3 months until End of Study**	**Notes**
		W1	**W1**	**W1**				
		D1±3	**D1 ±3**	**D1 ±3**				
Informed Consent	X							Potentially eligible subjects must sign an ICF before initiating any study specific procedures. SOC assessments that fulfill study eligibility requirements may be performed before the subjects signs the ICF.
Inclusion/Exclusion Criteria	X							Reconfirm eligibility before first dose.
Medical and Disease History, Demographics	X							Medical and Disease History includes histologic or cytologic diagnosis of HNSCC; HPV status; prior PD-L1 expression; and prior treatment information.
Archival Tumor Tissue	X							Archived tumor tissue should be submitted from all enrolled subjects, if available.
Physical Examination	X	X	X	X	X			See Section 8.2.1. Full examination (including height) at Screening and symptom-directed at subsequent time points. Screening results can be used for C1D1 if assessments are performed within 7 days of first dose.
Vital Signs and Weight	X	X	X	X	X	X		See Section 8.2.1. Vital signs measured with subject in a semi-supine position after 5 minutes rest. Includes temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.
ECOG Performance Status	X	X	X	X	X	X		See Section 8.3.1. Screening ECOG results can be used for C1D1 if test is performed within 7 days of first dose.
ECG (12-lead)	X							See Section 8.2.2. ECG at Screening will be performed in triplicate. QTc measurements will use the Fridericia correction method. Additional on-treatment ECGs should be performed per the Investigator's discretion as clinically indicated.

		Duvelisib in Combination with Pembrolizumab[a]			End of Treatment and Follow-up			
Activity[b]	**Screening (D-30 to D -1)**	**Cycle 1 (3 weeks)**	**Cycle 2 and Cycle 3 (3 weeks)**	**Cycles ≥ 4 (3 weeks)**	**EoT[c]**	**Safety F/U 30 D (+7) postdose)[d]**	**Survival F/U Every 3 months until End of Study**	**Notes**
		W1	**W1**	**W1**				
		D1±3	**D1 ±3**	**D1 ±3**				
Concomitant Medications and Procedures	Ongoing							See Section 6.5.1 for required and recommended prophylaxis. Concomitant medications and procedures occurring within 30 days before first dose will be recorded at Screening.
AE/SAE Assessment	Ongoing							See Section 8.4 for AE management. See Section 8.4.3 for reporting requirements.
Coagulation tests	X							PT, aPTT, and INR. See Table 23.
Viral Screening	X							Hepatitis serology: HCVAb, HBsAg, HBcAb. HPV testing (if status not available at Screening). CMV/EBV serology or viral load. HIV test is not required if a prior negative test within 9 months is available. See Table 23.
CMV Reactivation Monitoring (if applicable)		X	X	X				Subjects with a history of CMV infection should be monitored for reactivation by PCR at least monthly. See Section 6.5.1.
C-Reactive Protein	X	Obtain when Grade ≥ 2 diarrhea, any grade colitis, or any grade immune-mediated toxicity (e.g., pneumonitis, colitis, hepatitis, endocrinopathies, nephritis/renal dysfunction, cutaneous adverse reactions, encephalitis) occurs						See Table 23.
T3, FT4, and TSH	X		X	X		X		Every other cycle starting at C2D1.
Serum or Urine hCG Pregnancy Test for Women of Childbearing Potential	X	X[e]	X	X		X		A serum pregnancy test must be performed within 7 days of first duvelisib dose. At subsequent time points, serum testing is preferred but urine testing is allowed if a blood draw for other assessments is not performed. A positive urine test result must be confirmed by a serum test. See Table 23.
Clinical Chemistry with Liver Function Tests	X	X	X	X	X	X		BUN, potassium, creatinine, sodium, total protein, glucose (fasting), calcium, LDH, ALT, AST, total and direct bilirubin, and ALP. Screening test results can be used for C1D1 if tests are performed within 7 days of first dose. See Table 23.

		Duvelisib in Combination with Pembrolizumab[a]			End of Treatment and Follow-up			
Activity[b]	**Screening (D-30 to D -1)**	**Cycle 1 (3 weeks)**	**Cycle 2 and Cycle 3 (3 weeks)**	**Cycles ≥ 4 (3 weeks)**	**EoT[c]**	**Safety F/U 30 D (+7) postdose)[d]**	**Survival F/U Every 3 months until End of Study**	**Notes**
		W1	**W1**	**W1**				
		D1±3	**D1 ±3**	**D1 ±3**				
Hematology	X	X	X	X	X	X		Hematology panel plus a 5-part differential. Screening test results can be used C1D1 if tests are performed within 7 days of first dose. See Table 23.
Urinalysis	X		X	X		X		See Table 23.
Imaging and Disease Response Assessment via RECIST v 1.1 (Eisenhauer 2009)	X			X	X[f]			See Section 8.1. After Screening disease assessment, response will be assessed at approximately every 9 weeks after first dose of duvelisib plus pembrolizumab (e.g., at C4D1 and then D1 of every third cycle thereafter). The same method of assessment used at Screening should be used throughout the study. In the case of a CR or PR, a confirmatory scan must be performed per RECIST v 1.1. It is recommended that this scan be performed at 4 (+1) weeks after the initial response.
FDA-approved PD-L1 Testing (if required)	X							Perform if specified in the current pembrolizumab prescribing information (Keytruda 2019), if results are not already available. Information on FDA-approved tests is available at: http://www.fda.gov/CompanionDiagnostics.
PK and Biomarker Assessments (See details in Table 4)	X[g]	X	X	X[h]	X			Details for these assessments are in Table 4. Also obtain stool sample if subject has colitis or Grade ≥ 3 diarrhea.
Tumor Biopsy (optional) (See details in Table 4)			X					An optional tumor biopsy may be collected after the first cycle (on C2D1) for an exploratory analysis of biomarkers. If collection of the biopsy is not feasible on C2D1, a biopsy collected after the second cycle (on C3D1) would also be acceptable.
Review of Duvelisib Self-Administration Diaries		X	X	X				Subjects are required to log each self-administration of duvelisib in a diary during first year on treatment only
Duvelisib Administration		Continuous duvelisib BID until PD or discontinuation						On study visit days, instruct the subject not to take the AM duvelisib dose. Duvelisib will be administered in the clinic before the pembrolizumab infusion is started. See Table 4 and Section 6.1.1 for specific timing.

		Duvelisib in Combination with Pembrolizumab[a]			End of Treatment and Follow-up			
Activity[b]	**Screening (D-30 to D -1)**	**Cycle 1 (3 weeks)**	**Cycle 2 and Cycle 3 (3 weeks)**	**Cycles ≥ 4 (3 weeks)**	**EoT[c]**	**Safety F/U 30 D (+7) postdose)[d]**	**Survival F/U Every 3 months until End of Study**	**Notes**
		W1	**W1**	**W1**				
		D1±3	**D1 ±3**	**D1 ±3**				
								Please see required and recommended prophylaxis in Section 6.5.1.
Pembrolizumab Administration		X	X	X				Pembrolizumab should be administered as an IV infusion over 30 minutes. See Section 6.1.2 and Table 4 for dosing on C1D1 and C2D1.
Survival							X	Survival Follow-up will occur every 3 months (± 2 weeks) from the Safety F/U Visit for up to 1 year after the last subject starts duvelisib (Section 4.3). Information on survival status and anticancer therapy will be collected (Section 8.1.3). This assessment will be conducted by telephone interview and records review (if available).

Abbreviations: AE/SAE: adverse event/serious adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BID: twice daily; BUN: blood urea nitrogen; CMV: cytomegalovirus; CR: complete response; CxDx: Cycle x, Day x; CxWx: Cycle x, Week x; D: Day; EBV: Epstein-Barr virus; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: end of treatment; FDA: Food and Drug Administration; FT4: free thyroxine; F/U: follow-up; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCVAb: hepatitis C antibody; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; HNSCC: head and neck squamous cell carcinoma; HPV: human papillomavirus; ICF: informed consent form; INR: international normalized ratio; LDH: lactate dehydrogenase; QTc: corrected QT interval PCR: polymerase chain reaction; PD: progressive disease; PD-L1: programmed cell death ligand 1; PDn: pharmacodynamic; PK: pharmacokinetic; PR: partial response; PT: prothrombin time; RECIST: Response Evaluation Criteria in Solid Tumors; SOC: standard of care; T3: triiodothyronine; TSH: thyroid-stimulating hormone; W: week.

[a] Day 1 of each cycle of combination therapy is the day of pembrolizumab administration.

[b] The tests detailed in Table 23 will be performed by the local laboratory. See Section 8.2.4 for guidance on repeating/recording laboratory tests with values that are considered clinically significant or that require a change in subject management. The PDn, and biomarker assessments detailed in Table 4 will be performed by a laboratory selected by the Sponsor, as specified in the Laboratory Manual.

[c] For all subjects who permanently discontinue the study interventions (i.e., duvelisib and pembrolizumab), an EoT Visit will be performed within 7 days after the decision to discontinue study interventions. EoT assessments need not be repeated if performed within the previous 14 days, or 30 days for imaging.

[d] A Safety Follow-up Visit is to be performed 30 + 7 days from last dose. If possible, this visit should occur before the initiation of any subsequent anticancer therapy.

[e] If pregnancy test at Screening was performed within 7 days of C1D1, the test does not need to be repeated on C1D1

[f] A scan will be performed at the EoT if one was not previously performed within 30 days of the EoT Visit.

[g] Biomarker assessments may be obtained either at Screening or at first dose of duvelisib on C1D1 (preferred).

[h] Please refer to Table 4 for assessments and timing for C4D1 and beyond.

Table 4: Pharmacokinetic and Biomarker Sampling in Stage 2

Cycle	Day	Sampling Time Points[a]	PK Samples	Serum and Plasma for Biomarkers	Whole Blood for Immune Cell Analysis	Stool Sample for Biomarker Analysis[b]	Swab for Genomic Analysis	Tumor Biopsy (optional)[c]
Screening or C1D1				X[d]	X[d]	X[e]	X[d]	
1	1	Pre-duvelisib dose[f]	X[f]					
1	1	1 hour (± 10 min) after duvelisib dose	X[f]					
1	1	2 hours (± 10 min) after duvelisib dose	X[f]					
1	1	0 hours (± 5 min) after the end of pembrolizumab infusion	X					
2	1	Predose[g]	X	X	X			X[h]
3	1	Predose[i]	X					X[h]
4	1	Predose[i]		X	X	X[j]		
≥ 7[k]	1	Predose[i]		X	X			
End of treatment				X	X			

Abbreviations: CxDx: Cycle x Day x; min: minutes; PK: pharmacokinetic; SOC: standard of care.

[a] Sample collections may be reduced, or limited to certain sites/countries, based on emerging data or feasibility. Reductions/limitations may be implemented before amendment of the protocol. Specific collection and processing details (e.g., serum or plasma) will be described in the Laboratory Manual. Any increase in the number or type of samples collected will require a protocol amendment.

[b] Stool samples may be collected either predose or postdose. Obtain additional stool sample if subject has colitis or Grade ≥ 3 diarrhea.

[c] See Section 8.8.1. Request aliquot of colon biopsies if taken due to colitis or Grade ≥ 3 diarrhea or as SOC for any immune-mediated adverse events.

[d] The following samples can be obtained either at Screening or before the first dose of duvelisib on C1D1: serum and plasma for biomarkers, whole blood for immune cell analysis, and swab for genomic analysis. C1D1 is preferred for samples other than the swab.

[e] The Screening/C1D1 stool sample may be collected up to 7 days before first dose.

[f] On C1D1, duvelisib will be administered at the start of the visit after the predose PK and blood sample collection. Pembrolizumab will be administered 30 minutes after collection of the 2-hour postdose duvelisib PK sample.

[g] Predose sample is to be taken before either study intervention (i.e., duvelisib or pembrolizumab) is administered.

[h] An optional tumor biopsy may be collected after the first cycle (on C2D1) for an exploratory analysis of biomarkers. If collection of the biopsy is not feasible on C2D1, a biopsy collected after the second cycle (on C3D1) would also be acceptable.
[i] Predose sample is to be taken before either study intervention (i.e., duvelisib or pembrolizumab) is administered. The pembrolizumab infusion should be started within 10 minutes after the dose of duvelisib is administered.
[j] The C4D1 stool sample may be collected up to 3 days before C4D1.
[k] Samples will be collected on C7D1 and D1 of every third cycle thereafter (approximately every 9 weeks) or until the Sponsor terminates the collection.

2. INTRODUCTION

2.1. Duvelisib

Duvelisib (VS-0145) is a synthetic, orally-active, small molecule dual inhibitor of phosphoinositide 3-kinase (PI3K)-δ and PI3K-γ isoforms that 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 2 prior systemic therapies and has received accelerated approval in adult patients with follicular lymphoma (FL) after at least 2 prior systemic therapies (COPIKTRA 2018). Duvelisib is being developed by Verastem, Inc. (Verastem; study Sponsor) for the treatment of other hematologic malignancies and solid tumors.

2.2. Study Rationale

Despite the recent approval of agents (e.g., pembrolizumab [Keytruda®] and nivolumab [Opdivo®]) that inhibit the interaction of programmed cell death protein 1 (PD-1) with its ligand (PD-L1), only a small subset of patients appears to derive benefit from these therapies. Although the efficacy of anti-PD-1 therapy may vary by PD-L1 expression or human papillomavirus (HPV) status as well as the number of prior therapies, typically the overall response rate (ORR) is approximately 15% in the second-line or greater setting and somewhat higher in the first-line setting (Ferris 2016, Keytruda 2019). The majority of responses in either setting are partial responses (PRs). The effectiveness of PD-1 inhibitors can be limited by infiltration of immunosuppressive myeloid cells (MDSCs) into the tumor microenvironment (De Henau 2016, Diaz-Montero 2014, Gebhardt 2015). Thus, there remains a large unmet medical need for better therapy options in patients with recurrent or metastatic (R/M) disease.

Duvelisib, a dual PI3K-δ and PI3K-γ inhibitor, was found to reduce regulatory T cells (Tregs), M2 tumor-associated macrophages (i.e., macrophages that are alternatively activated by exposure to certain cytokines), and MDSCs when combined with a PD-1 inhibitor in a mouse model mimicking a solid tumor setting (Pachter 2018). In a study in a head and neck squamous cell carcinoma (HNSCC; i.e., murine oral cancer [MOC1]) model, the combination of duvelisib and a mouse PD-L1 monoclonal antibody (mAb) resulted in significantly enhanced control of primary tumor growth and survival of MOC1 tumor-bearing mice over either monotherapy (Davis 2017). These nonclinical data suggest that reduction of Tregs and MDSCs by duvelisib in the tumor microenvironment may enhance sensitivity of the tumor to PD-1 inhibitors like pembrolizumab in this tumor setting.

This is the first clinical study of duvelisib in subjects with R/M HNSCC and of duvelisib in combination with a PD-1 inhibitor. Based on the hypothesis, which is supported by nonclinical data, that duvelisib can enhance the activity of PD-1 inhibitors, this study is designed to assess the safety and preliminary efficacy of duvelisib in combination with pembrolizumab in subjects with R/M HNSCC who are eligible for pembrolizumab monotherapy based on the current pembrolizumab prescribing information (Keytruda 2019).

2.3. Background

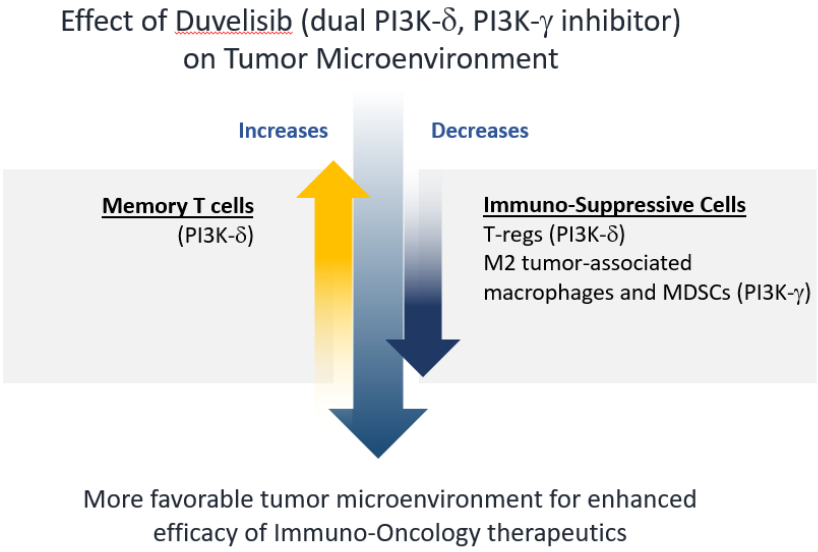
The PI3K/mammalian target of rapamycin (mTOR) intracellular signaling pathway is known to play a critical role in tumorigenesis (Janku 2017). There are 4 PI3K isoforms: alpha (α), beta (β), gamma (γ), and delta (δ). PI3K-δ and PI3K-γ activity supports the growth and maintenance of cancer cells by contributing to the establishment and maintenance of the tumor microenvironment through cell proliferation, survival, differentiation, migration, and activation of non-tumor cells. Both isoforms have been shown to suppress antitumor immune responses and support solid tumor growth in in vivo studies (Ali 2014, De Henau 2016, Kaneda 2016).

PI3K-γ inhibition decreases the number of MDSCs and M2 tumor-associated macrophages (Kaneda 2016, De Henau 2016), while PI3K-δ inhibition in Tregs may induce tumor regression through activation of CD8+ cytotoxic T cells (Ali 2014). Mice lacking functional PI3K-γ showed significantly reduced growth of implanted HNSCC, lung carcinoma, and breast carcinoma cells (Kaneda 2016). Mice bearing an inactivating mutation in PI3K-δ were resistant to tumor growth after inoculation with melanoma, lung carcinoma, or thymoma cell lines, supporting the hypothesis that PI3K-δ inhibition decreases immunosuppressive Tregs in the tumor microenvironment (Ali 2014, Ahmad 2017).

2.3.1. Duvelisib Mechanism of Action

Duvelisib is a dual PI3K-δ/-γ inhibitor that reduces the cancer-promoting effects of both isoforms through effects on the tumor microenvironment (Figure 4) and has an established clinical safety and efficacy profile in patients with hematologic malignancies (United States [US] approval in R/R CLL/SLL and accelerated approval in R/R FL) (COPIKTRA 2018).

Figure 4: Effect of Duvelisib on Tumor Microenvironment

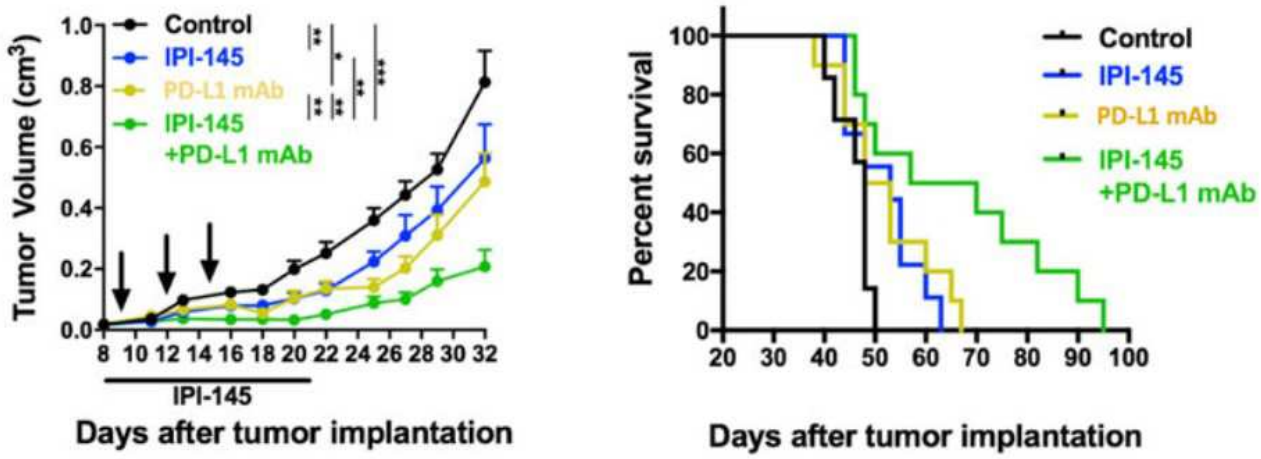


Abbreviations: MDSCs: immunosuppressive myeloid cells; PI3K: phosphoinositide 3-kinase; Tregs: regulatory T-cells.

While the tumor-suppressing effect of duvelisib in hematologic malignancies is well established (Dong 2014, Faia 2015), 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 tumor, a cell-based target for duvelisib is thought to be the immune-modulating tumor microenvironment consisting of T-, B-, and myeloid lineage cells, in particular.

Data from a study by Davis (Davis 2017) in an HNSCC (i.e., MOC1) model suggest that reduction of Tregs and MDSCs in the tumor microenvironment may contribute to the activity of duvelisib in combination with PD-1 inhibitors. The combination of duvelisib and PD-L1 mAb resulted in significantly enhanced control of primary tumor growth and survival of MOC1 tumor-bearing mice over either monotherapy (Figure 5) (Davis 2017). In this tumor model, which, like human HNSCC, lacks significant responses to PD-1-based inhibition, combination therapy induced CD8+ T lymphocyte-dependent primary tumor growth delay and prolonged survival. Dual PI3Kδ/γ inhibition with 15 mg/kg duvelisib sensitized T-cell inflamed MOC1 oral cavity cancers to PD-L1 inhibition through at least modulation of granulocytic MDSC arginine and inducible nitric oxide synthetase expression and T-lymphocyte suppressive capacity. These results offer a nonclinical proof of concept for the use of duvelisib to suppress MDSCs to enhance responses to immune PD-1 blockade (Davis 2017).

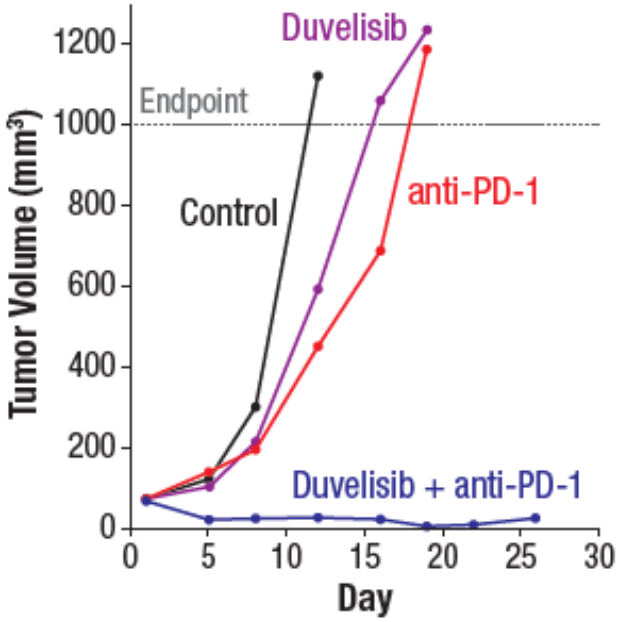
Figure 5: Combination of Duvelisib and a PD-L1 mAb Resulted in Significantly Enhanced Control of Primary Tumor Growth and Survival in a MOC1 Model



Source: Davis 2017.
Abbreviations: mAb: monoclonal antibody; IPI-145: duvelisib; MOC1: murine oral cancer; PD-L1:. programmed cell death ligand 1.

In a nonclinical study in a mouse model of B-cell lymphoma (mimicking a solid tumor setting), duvelisib and PD-1 inhibitor treatments each induced tumor growth delay (Pachter 2018). In addition, strong antitumor synergy (i.e., inhibition of tumor growth and increased survival) was observed when duvelisib and a PD-1 inhibitor were combined (Figure 6).

Figure 6: Combination of Duvelisib and a PD-1 Inhibitor (anti-PD-1) Is Synergistic in Inhibition of Tumor Growth in A20 B-Cell Model



Source: Pachter 2018.
Abbreviations: PD-1: programmed cell death protein 1.

Mechanistically, duvelisib was found to reduce Tregs, M2 tumor-associated macrophages, and MDSCs in the context of combination with a PD-1 inhibitor, and duvelisib (dual PI3K-δ/γ inhibition) was found to inhibit all 3 immunosuppressive cell populations more effectively than idelalisib (PI3K-δ only) or IPI-549 (PI3K-γ only) (Pachter 2018).

2.3.2. Recurrent or Metastatic HNSCC Therapeutic Landscape

HNSCC represents over 90% of head and neck malignancies. Although the majority of patients present with locoregionally advanced disease, the clinical course is characterized by a high recurrence rate approaching 50%, as well as the development of distal metastases (Forster 2018, Vigneswaran 2014, Rothschild 2018). The current standard of care (SOC) in patients with R/M HNSCC in a first-line setting includes platinum-based chemotherapy regimens, which have ORRs of 30 to 40% with median overall survival (OS) of 6 to 9 months (NCCN 2019).

On 10 June 2019, pembrolizumab was approved as a single agent for first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-LI (combined positive score [CPS] ≥ 1) as determined by a Food and Drug Administration (FDA)-approved test and was approved in combination with platinum and 5 fluorouracil (5-FU) for all patients with R/M HNSCC (Keytruda 2019). In subjects with CPS ≥ 1, OS was significantly longer with pembrolizumab monotherapy vs SOC (12.3 months vs10.3 months, HR 0.78, p = 0.0171, respectively). ORR and median DOR were 19% and 20.9 months in the pembrolizumab monotherapy group vs 35% and 4.5 months in the SOC group. There was no difference in PFS between groups (HR 1.15, 95% CI 0.95 to 1.38).

In a second-line setting, PD-1 inhibitors (pembrolizumab and nivolumab) are a current SOC after progression on or during platinum-based therapy (NCCN 2019). Pembrolizumab is approved for the treatment of adult subjects with R/M HNSCC whose disease progressed on or after platinum-based chemotherapy (Keytruda 2019). The results of the Phase 3 KEYNOTE-040 confirmatory study in subjects with R/M HNSCC whose disease progressed during or after platinum-containing treatment showed a longer OS in subjects who received pembrolizumab monotherapy vs SOC (8.4 vs 6.9 months, HR 0.80, p <0.01, respectively). ORR and median DOR were 14.6% and 8.4 months in the pembrolizumab monotherapy group vs 10.1% and 5.0 months in the SOC group, respectively (Cohen 2019).

Although duvelisib has not yet been evaluated in subjects with solid tumors, several other PI3K inhibitors, such as a class 1 pan-isoform PI3K inhibitor (PX-866), a specific oral pan-class 1 PI3K inhibitor (buparlisib), and a specific α isoform inhibitor of PI3K (alpelisib), are being tested in combination with SOC in Phase 1 and Phase 2 studies in subjects with HNSCC (De Felice 2017). Preliminary safety and efficacy results for the combination of buparlisib and paclitaxel were promising, with increases in PFS, ORR, and OS observed with the buparlisib-paclitaxel combination vs placebo + paclitaxel, with a manageable safety profile (Soulieres 2017). Pan-isoform PI3K inhibitors are proposed to have antitumor activity by targeting the tumor cell PIKα isoform expression.

Despite the recent approval of agents (e.g., pembrolizumab [Keytruda® and nivolumab [Opdivo®]) that inhibit the interaction of PD-1 with its ligand (PD-L1), only a small subset of patients appears to derive benefit from these therapies. Although the efficacy of anti-PD-1 therapy may vary by PD-L1 expression or HPV status, as well as the number of prior therapies, typically the ORR is approximately 15% in the second-line or greater setting and somewhat higher in the first-line setting (Ferris 2016, Keytruda 2019). The majority of responses in either setting are PRs. The effectiveness of PD-1 inhibitors can be limited by infiltration of MDSCs into the tumor microenvironment (De Henau 2016, Diaz-Montero 2014, Gebhardt 2015). Thus, there remains a large unmet medical need for better therapy options in patients with R/M disease.

This Phase 1b/2 study will assess the safety and tolerability of duvelisib in combination with pembrolizumab in subjects with R/M HNSCC and determine if the addition of duvelisib to pembrolizumab will result in increased antitumor responses in subjects with R/M HNSCC.

2.4. Benefit/Risk Assessment

This is the first clinical study of duvelisib in subjects with R/M HNSCC and of duvelisib in combination with a PD-1 inhibitor.

As there are no clinical data for duvelisib in subjects with R/M HNSCC to date, the benefit/risk assessment for duvelisib reflects extensive clinical experience in subjects with hematologic malignancies who were treated with duvelisib (COPIKTRA 2018). The approved dose of each agent (duvelisib 25 mg BID PO; pembrolizumab 200 mg q3w IV) will be used for assessment of initial safety. As the maximal tolerated dose of duvelisib monotherapy is 75 mg twice daily (BID) in subjects with hematologic malignancies, which may suggest a relatively wide therapeutic window for duvelisib, such an approach is considered reasonable.

2.4.1. Risk Assessment

As the effect of duvelisib in subjects with R/M HNSCC is unknown, Stage 1 of the study includes a 1-week lead-in with duvelisib monotherapy to monitor for safety and biomarker sampling before the initiation of combination therapy with duvelisib and pembrolizumab.

For subjects with hematologic malignancies, clinical study results to date support a favorable benefit-risk assessment of duvelisib. The risks of duvelisib for subjects with hematologic malignancies are consistent with the adverse event (AE) profile for the PI3K inhibitor drug class and AEs experienced by patients undergoing treatment for advanced cancers. Important identified risks of duvelisib include infections, diarrhea/colitis, cutaneous reactions, pneumonitis, neutropenia, and alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevation. Potential risks include hepatotoxicity, drug-drug interaction (DDI), and reproductive toxicity. These toxicities are managed using a combination of prophylaxis, supportive care, and dose modifications. Guidance on management of these AEs, including duvelisib dose interruptions and modifications, is provided in Section 6.6 and Section 6.7. Detailed information about the known and expected risks and reasonably expected AEs of duvelisib may be found in the Investigator's Brochure (IB).

The identified risks of pembrolizumab (Keytruda 2019) are infusion reactions and the following immune-mediated conditions: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, and cutaneous adverse reactions (including rash). Refer to the pembrolizumab prescribing information for guidance on management of these AEs (Keytruda 2019).

Based on the monotherapy safety profiles for each drug, potential overlapping toxicities for duvelisib in combination with pembrolizumab include non-infectious diarrhea or colitis, cutaneous reactions, pneumonitis without suspected infectious cause, and elevations in ALT and AST levels (Section 6.6.1). These events will be closely monitored during the study.

Although duvelisib has not yet been evaluated in subjects with solid tumors, initial safety results for an ongoing first-in-human study of the oral selective inhibitor of PI3K-γ (IPI-549) in combination with nivolumab in patients with melanoma, non-small cell lung cancer (NSCLC), or HNSCC demonstrated favorable tolerability (Sullivan 2018).

2.4.2. Benefit Assessment

Subjects may derive benefit due to improvements in symptoms and tumor control. Duvelisib treatment produced clinical activity in subjects with hematologic malignancies, including CLL/SLL (approval), FL (accelerated approval), and peripheral T-cell lymphoma. More detailed information about the clinical efficacy observed in duvelisib studies can be found in the IB and the duvelisib prescribing information (COPIKTRA 2018).

Pembrolizumab has shown benefit in multiple solid tumor indications. Pembrolizumab is approved as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-LI (CPS ≥ 1) as determined by an FDA-approved test and is approved in combination with platinum and 5-FU for all patients with R/M HNSCC (Keytruda 2019). As presented in the pembrolizumab prescribing information (Keytruda 2019), results for the pre-specified interim analysis in the KEYNOTE-048 study of pembrolizumab as first-line treatment for patients with R/M HNSCC showed that compared with standard first-line treatment (i.e., EXTREME, consisting of cetuximab plus carboplatin or

cisplatin), pembrolizumab monotherapy had superior OS among patients whose tumors had PD L1 CPS of ≥ 20 or ≥ 1, and noninferior OS in the total population with favorable safety. Pembrolizumab is approved as a second-line treatment in patients with R/M HNSCC with disease progression on or after platinum-containing chemotherapy based on the ORR of 16% (complete response [CR] = 5%) and the DOR (2.41 months to 27.71 months; 23 of 28 responding patients [82%] had response durations of ≥ 6 months) in the KEYNOTE-012 study (Keytruda 2019).

In vivo data from nonclinical studies in solid tumor models, including an HNSCC (i.e., MOC1) model, support the hypothesis that the addition of duvelisib may improve the activity of PD-1 inhibitors in solid tumors (Section 2.3.1).

Although duvelisib has not yet been evaluated in subjects with solid tumors, initial efficacy results from an ongoing study of an oral selective inhibitor of PI3K-γ (IPI-549) in combination with nivolumab in patients with melanoma, NSCLC, or HNSCC demonstrated early signs of clinical activity and evidence of immune modulation (Sullivan 2018). In this study, 2 patients had PR at first assessment (8 weeks) and 40% of patients (n = 12) remained on study ≥ 12 weeks.

It is anticipated that analysis of safety, tolerability, pharmacokinetics (PK), biomarker and preliminary efficacy data will help guide future development of duvelisib in combination with pembrolizumab in HNSCC.

2.4.3. Overall Benefit/Risk Conclusion

As early phase clinical studies are designed to provide information about the safety and efficacy of an investigational drug, subjects enrolled in the study cannot expect to receive a direct benefit from an experimental treatment.

Although pembrolizumab is approved for the treatment of patients with HNSCC, the ORR (19% for first-line treatment in patients with CPS ≥ 1 and 16% for second-line treatment) was relatively low (Keytruda 2019). Based on the strong antitumor synergy (i.e., inhibition of tumor growth and prolonged survival) for duvelisib in combination with a PD-1 inhibitor observed in the nonclinical in vivo studies and the manageable AE profile for duvelisib in patients with hematologic malignancies, subjects with R/M HNSCC could potentially benefit from improved response rates.

3. OBJECTIVES AND ENDPOINTS

Table 5: Objectives and Endpoints

Objectives	***Endpoints*** (See Section 9.4 for definitions)
Stage 1 - Unique Objectives/Endpoints	
Primary	
Evaluate the safety and tolerability of duvelisib in combination with pembrolizumab in subjects with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC)	Safety and tolerability of study interventions based on dose-limiting toxicities (DLTs), adverse events (AEs), serious AEs (SAEs), vital signs, physical examinations, and clinical laboratory measurements
Secondary	
Characterize the overall response rate (ORR) of duvelisib in combination with pembrolizumab in subjects with R/M HNSCC	ORR, which includes partial response (PR) and complete response (CR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 (Eisenhauer 2009)
Stage 1 and Stage 2 – Combined Objectives/Endpoints	
Primary	
Characterize the ORR of duvelisib in combination with pembrolizumab	ORR, which includes PR and CR, according to RECIST v 1.1 (Eisenhauer 2009)
Secondary	
Characterize other efficacy parameters of duvelisib in combination with pembrolizumab	• Duration of response (DOR), defined as time from response ≥ PR to documented disease progression according to RECIST v 1.1 (Eisenhauer 2009) • Progression-free survival (PFS), defined as the time from start of treatment to documented disease progression according to RECIST v 1.1 (Eisenhauer 2009), or death due to any cause • Overall survival (OS), defined as the time from start of treatment to the date of death
Characterize the pharmacokinetics (PK) of duvelisib (and metabolite IPI-656) monotherapy and of duvelisib in combination with pembrolizumab	PK parameters for duvelisib (and metabolite IPI-656)
Evaluate the safety and tolerability of duvelisib in combination with pembrolizumab	Safety and tolerability parameters including AEs, SAEs, vital signs, physical examinations, and clinical laboratory measurements

Objectives	***Endpoints*** (See Section 9.4 for definitions)
Exploratory	
Evaluate potential biomarkers for possible associations with clinical efficacy and/or safety outcomes of duvelisib in combination with pembrolizumab	• Blood assessments of immune cell populations, chemokines, cytokines and circulating tumor DNA • Fecal assessments of protein, DNA, and/or RNA • Tumor biopsy evaluation of biomarkers such as gene and copy number variation, RNA expression, protein expression, and/or immune cell content (Required biopsies in Stage 1 and optional biopsy in Stage 2) • ORR and its relationship to tumor and/or immune cell programmed cell death ligand 1 (PD-L1) levels and to tumor human papillomavirus (HPV) status

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, non-randomized, open-label, Phase 1b/2 study of duvelisib in combination with pembrolizumab in subjects with R/M HNSCC who are eligible for pembrolizumab monotherapy based on the current pembrolizumab prescribing information (Keytruda 2019). This study will be conducted at multiple sites in the US and will include approximately 13 subjects in Stage 1 and 17 additional subjects in Stage 2, for a total of 30 subjects in the final analysis.

The study will follow a Simon two-stage design (Simon 1989).

The study stages are depicted in Figure 1 and the treatment/imaging schemes for Stage 1 and Stage 2 are depicted in Figure 2 and Figure 3, respectively.

Subjects will receive duvelisib 25 mg BID orally (PO) in combination with pembrolizumab 200 mg every 3 weeks (q3w) intravenously (IV).

In **Stage 1**, subjects will have a 1-week lead-in with duvelisib before the initiation of combination therapy with duvelisib and pembrolizumab. Approximately 13 subjects are planned to be accrued in this stage. The first 6 subjects will be assessed for dose-limiting toxicities (DLTs). The DLT evaluation period will be Cycle 1 (4 weeks or 28 days): the 1-week duvelisib monotherapy lead-in period followed by 1 dose of pembrolizumab in combination with 3 additional weeks of continuous dosing of duvelisib. Every effort will be made to administer the first dose of pembrolizumab on Day 8 of Cycle 1 (C1D8). If the first dose of pembrolizumab on C1D8 is delayed, every effort should be made to delay the subsequent dosing of the next cycle (within the protocol-allowed window of 3 days) to achieve as close to a 3-week interval between pembrolizumab doses as possible. The Medical Monitor needs to be consulted for such adjustments to ensure uniformity of approach and to account for subject-specific circumstances. For example, if the third day of the C2D1 window falls on a weekend, an additional adjustment would need to be made on a case-by-case basis. In the event of a delay of the start of pembrolizumab therapy, DLTs will be evaluated at the end of the third week of combination therapy.

The DLT evaluation period will be used to assess DLTs in the first 6 subjects.

- If there is ≤ 1 DLT in the 6 DLT-evaluable subjects, additional subjects will be enrolled to bring the total dosed in Stage 1 to approximately 13 subjects.
- If there are ≥ 2 DLTs in the first 6 subjects, enrollment at duvelisib 25 mg BID will stop. Enrollment would restart at a reduced duvelisib dose (15 mg BID) to assess DLTs at the lower dose (dose level -1; see Table 6).

Table 6: Duvelisib Dose Levels

Dose Level	Duvelisib, mg BID PO
Starting Dose	25
-1	15

Abbreviations: BID: twice daily; PO: oral.

A formal analysis of available safety data will be conducted when the first 10 subjects treated have received at least 1 cycle of study treatment. This will enable assessment of toxicities of later onset, particularly outside of the DLT window.

If an excessive rate of Grade 3 or higher overlapping SAEs (defined as any rate for each SAE that is above the highest reported in warnings and precautions of the prescribing information for either duvelisib [COPIKTRA 2018] or pembrolizumab [Keytruda 2019], respectively), such as pneumonitis, colitis, cutaneous skin reactions, and elevations of AST/ALT, is observed outside of the DLT window, a decision for stopping or modifying the study may be made. However, recognizing that the observed rate of such events can be highly sensitive due to the small sample size, the totality of safety data will be reviewed and carefully considered prior to making a formal decision.

An interim analysis of ORR will occur after all of the planned 13 subjects in Stage 1 are enrolled, dosed, and have been followed through at least the first disease response assessment.

- If there are ≤ 2 responses (CR or PR) in the 13 subjects in Stage 1, further accrual in the study may be stopped. However, all available data, including the relative proportion of CRs, will be analyzed before a final decision is made.
- If > 2 responses are observed in Stage 1, enrollment will continue in Stage 2.

In **Stage 2**, 17 additional subjects will be accrued for a total of 30 subjects in the final analysis. Subjects enrolled in Stage 2 will only receive combination therapy with duvelisib and pembrolizumab. Enrollment into Stage 2 may proceed prior to completion of the interim analysis as long as at least 2 of the 13 subjects enrolled in Stage 1 have a confirmed response.

The ORR and PFS will be assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 (Eisenhauer 2009).

Subjects will be monitored continuously for safety while on study treatment. Adverse events will be classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 or higher.

Higher doses of duvelisib may be explored in additional subjects via a protocol amendment, if warranted by observed data.

Subjects will be treated until documented progressive disease (PD) (Section 8.1.2), unacceptable toxicity (Section 6.6), discontinuation criteria are met (Section 7.1), withdrawal (Section 7.2), or death. The total duration of treatment will not exceed 24 months. After treatment discontinuation, subjects will complete an End of Treatment visit and will be followed for safety

for an additional 30 days. All subjects with treatment-related AEs/serious adverse events (SAEs) should be observed until resolution or stabilization.

It is anticipated that the study accrual will occur over approximately 18 months. All subjects will be followed for survival for 1 year after the last subject is enrolled and dosed.

4.2. Scientific Rationale for Study Design

The purpose of the study is to evaluate the safety and tolerability of duvelisib in combination with pembrolizumab in subjects with R/M HNSCC and determine if the addition of duvelisib to pembrolizumab may improve treatment responses.

Pembrolizumab was selected for combination with duvelisib in this study for the following reasons:

1. Strong antitumor synergy (i.e., inhibition of tumor growth and increase in survival) was observed for the combination of duvelisib and a PD-1 inhibitor vs either monotherapy in vivo (Pachter 2018, Davis 2017)
2. Pembrolizumab (Keytruda®) is approved for R/M HNSCC (Keytruda 2019)

As this is the first clinical study of duvelisib in subjects with R/M HNSCC, the first 6 subjects in Stage 1 will be evaluated for DLTs. Furthermore, a 1-week duvelisib monotherapy lead-in has been included so that subjects can be monitored on monotherapy and a steady-state duvelisib PK sample and biomarker samples can be obtained before the treatment with pembrolizumab is started. The lead-in design with duvelisib is expected to provide scientific and safety information for the potential contribution of duvelisib in this combination setting.

The efficacy endpoints will be assessed using the standard RECIST v 1.1 (Eisenhauer 2009), which were also used in the registrational study for pembrolizumab in HNSCC (Keytruda 2019). Justification for Dose of Study Interventions

The combination of the 25 mg BID dosage of duvelisib and the 200 mg q3w dosage of pembrolizumab was selected based on the approved dosage for duvelisib in patients with hematologic malignancies (COPIKTRA 2018) and the approved dosage for pembrolizumab in patients with R/M HNSCC (Keytruda 2019).

4.3. End of Study Definition

A subject is considered to have completed the study if he/she has completed the last scheduled procedure shown in the Schedule of Activities (SoA) (Section 1.3 and Section 1.4), including the Survival Follow-up of up to 1 year after the last subject is enrolled and dosed.

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (Section 1.3 and Section 1.4) for the last subject in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Subjects may be eligible for inclusion in the study if they meet the following criteria:

1. Must be a male or female subject ≥ 18 years of age
2. Must have histologically or cytologically-confirmed R/M HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx that is considered incurable by local therapies.
3. Must be eligible for pembrolizumab monotherapy based on the current prescribing information for pembrolizumab (Keytruda 2019): (a) for first-line treatment, subjects with metastatic or with unresectable, recurrent HNSCC whose tumors express PD L1 (CPS ≥ 1) as determined by an FDA-approved test; (b) subjects with R/M HNSCC with disease progression on or after platinum-containing chemotherapy, regardless of PD-L1 expression.
4. Must have had 0 to 2 prior therapies for R/M HNSCC. Therapy for locally or regionally advanced HNSCC with or without radiation therapy is not counted as a line of therapy unless recurrence and/or metastasis was demonstrated < 6 months from the end of such therapy.
5. Must have at least 1 measurable lesion (which has not been previously irradiated) according to RECIST v 1.1 (Eisenhauer 2009).
6. For Stage 1 only: Must have at least 1 other lesion that can be biopsied
7. For Stage 1 only: Must be willing to undergo a pretreatment and on-treatment biopsy of the available tumor lesion (described in inclusion criterion #6). Archival tissue (up to 6 months before the first dose of duvelisib) may be considered in place of the required pretreatment biopsy after consultation with the Sponsor, as long as no intervening systemic regimen had been taken during that time frame.
8. Must provide prior data on PD-L1 expression and HPV status, if available
9. Must have adequate organ function defined by the following laboratory parameters:
   a. Adequate bone marrow reserve as evidenced by:
      – Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
      – Platelet count ≥ 100×10^9/L
      – Hemoglobin level ≥ 9.0 g/dL
   b. Adequate renal function as evidenced by:
      – a serum creatinine level < 1.5 mg/dL, or
      – estimated creatinine clearance value of ≥ 60 mL/min (as determined by the Cockcroft-Gault method) for subjects with creatinine levels > 1.5 × institutional upper limit of normal (ULN)

c. Adequate hepatic function as evidenced by:

- Total bilirubin level ≤ 1.5 × ULN (exception: subjects with Gilbert's Syndrome may have a bilirubin level > 1.5 × ULN)
- AST/serum glutamic-oxaloacetic transaminase (SGOT) and ALT/serum pyruvic transaminase (SGPT) levels ≤ 2.5 × ULN or ≤ 5 × ULN in subjects with liver metastases

10. Must have international ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN, unless subject is receiving anticoagulant therapy in which case PT or aPTT must be within therapeutic range of intended use of anticoagulants
11. Must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
12. For male and female subjects of reproductive potential (i.e., not surgically sterile or female subjects who are not postmenopausal), must be willing to use a highly effective method of contraception (see Section 10.4) for the duration of the study interventions and for at least 4 months after the last dose of study interventions
13. Must have a negative serum human chorionic gonadotropin (hCG) pregnancy test result within 7 days before first dose of duvelisib if the subject is a woman of childbearing potential (WCBP) (defined in Section 10.4)
14. Must provide signed and dated institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form (ICF) before any study-specific screening procedures are performed

5.2. Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Have disease that is suitable for local therapy administered with curative intent
2. Have been previously treated with 3 or more systemic regimens given for recurrent and/or metastatic disease
3. Have received anticancer treatment, major surgery, or any investigational drug within 30 days or 5 half-lives, whichever is shorter, before the start of study intervention
4. Have received radiation therapy within 14 days prior to the first dose of duvelisib in this study, including, in addition (if necessary), the timeframe for resolution of any actual or anticipated toxicities from such radiation. Palliative radiation therapy is allowed if > 7 days before first dose of duvelisib and any toxicity is ≤ Grade 1.
5. Have received prior radiation therapy to > 25% of bone marrow-bearing areas
6. Have co-existing head-and-neck carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary, salivary gland tumors, or any other non-squamous primary tumors involving the head and neck
7. Have received previous treatment with a PI3K inhibitor
8. Have received previous treatment with a PD-1 or PD-L1 inhibitor

9. Have received organ or allogenic bone marrow or peripheral blood stem cell transplant
10. Have a history or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function
11. Have a prior history of drug-induced colitis or drug-induced pneumonitis
12. Have active cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection (subjects with detectable viral load)
13. Have an infection with hepatitis B or hepatitis C:
    - Subjects with a positive hepatitis B surface antigen (HBsAg) or hepatitis C antibody (HCVAb) will be excluded
    - Subjects with a positive hepatitis B core antibody (HBcAb) must have negative hepatitis B virus (HBV) DNA to be eligible and must be periodically monitored for HBV reactivation by institutional guidelines
    - Investigators who strongly believe that a positive HBcAb is false-positive due to passive immunization from previous immunoglobulin infusion therapy should discuss the potential to defer HBV prophylaxis with the Medical Monitor
14. Have a history of or known human immunodeficiency virus (HIV) infection
15. Have a history of tuberculosis treatment within the 2 years prior to first dose of duvelisib
16. Have a history of chronic liver disease or veno-occlusive disease/sinusoidal obstruction syndrome
17. Have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study
18. Are receiving ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids > 20 mg of prednisone (or equivalent) per day
19. Have an active infection or are receiving ongoing systemic treatment for a clinically significant bacterial, fungal, or viral infection at Screening

    NOTE: Subjects on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met
20. Have received a live or live attenuated vaccine within 6 weeks of first dose of duvelisib
21. Have received medications or consumed foods that are strong inhibitors or inducers of cytochrome P450 3A (CYP3A) (Section 10.2) within 2 weeks prior to the first dose of duvelisib or concurrent with duvelisib treatment
22. Are unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV), or herpes zoster (VZV) at screening
23. Have had prior surgery (e.g., gastric bypass surgery, gastrectomy) or gastrointestinal dysfunction that may affect drug absorption
24. Have any active gastrointestinal dysfunction interfering with the subject's ability to be administered oral medications
25. Is a female subject who is pregnant or breastfeeding

26. Have a baseline QT interval corrected using the Fridericia correction method (QTcF) > 500 ms (average of triplicate readings). NOTE: This criterion does not apply to subjects with a right or left bundle branch block.
27. Have New York Heart Association Class III or IV congestive heart failure
28. Have a history of another active malignancy that is progressing or requires active treatment. Exceptions include adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumors curatively treated with no evidence of disease for > 3 years.
29. Have known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of duvelisib and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to the first dose of duvelisib. The exception does not include carcinomatous meningitis.
30. Have an active autoimmune disease requiring systemic treatment within the last 3 months prior to first dose of study intervention, documented history of clinically severe autoimmune disease, or a syndrome that requires systemic or immunosuppressive agents except vitiligo, Type 1 diabetes mellitus, hypothyroidism stable on hormone-replacement therapy, Sjogren's syndrome, and resolved childhood asthma/atopy. Subjects who require intermittent use of bronchodilators, inhaled steroids, or local steroid injections may participate in this study.
31. Have a history of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months prior to first dose of duvelisib
32. Have an unstable or severe uncontrolled medical condition or any important medical illness or abnormal laboratory finding that would, in the Investigator's judgment, increase the subject's risk to participating in this study

5.3. Lifestyle Considerations

Male and female subjects of reproductive potential (i.e., not surgically sterile or female subjects who are not postmenopausal) must use highly effective contraception for the duration of the study interventions and for at least 4 months after the last dose of study interventions. Please see Section 10.4 for detailed contraceptive requirements.

Subjects should be advised to use appropriate protective measures to minimize exposure to direct sunlight or UV light sources during the treatment period and for at least 30 days after the last dose of duvelisib. Please see the duvelisib IB for additional details on the potential for phototoxicity.

Subjects should refrain from consumption of grapefruit juice and St. John's Wort, and other foods and herbal products that are strong inhibitors or inducers of CYP3A during treatment with duvelisib. Please see Section 6.5.2 for additional information on restrictions on the use of CYP 3A inhibitors, inducers, and substrates, and Section 10.2 for lists of CYP3A inhibitors, inducers, and substrates. The duvelisib IB contains additional details on potential interactions with foods.

5.4. Definition of Enrolled

"Enrolled" means a subject's, or their legally acceptable representative's, agreement to participate in a clinical study after completion of the informed consent process. Potential subjects who are pre-screened for the purpose of determining eligibility for the study but do not sign an ICF are not considered enrolled.

5.5. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs that occur after the ICF is signed.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date. Please note that repeating of clinical laboratory assessments during screening does not constitute rescreening.

5.6. Replacement of Subjects

During the DLT evaluation period in Stage 1, subjects who discontinue duvelisib before the end of Cycle 1, for reasons other than a DLT, or who receive < 75% of the scheduled duvelisib doses during Cycle 1 may be replaced.

Any other subjects who withdraw from the study for reasons other than PD or treatment-related toxicity before receiving at least 1 cycle of study intervention may be replaced.

6. STUDY INTERVENTIONS

Study intervention(s) is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

6.1. Study Interventions Administered

Table 7: Study Interventions

Intervention Name	Duvelisib	Pembrolizumab
Type	Investigational Drug	Biologic
Drug Substance Description	White to off-white crystalline solid	Sterile, preservative-free, non-pyrogenic, clear to slightly opalescent, colorless to slightly yellow solution
Dose Formulation	Capsule	Vial
Unit Dose Strength(s)	15 mg, 25 mg	100 mg/4 mL
Formulation Excipients	Excipients (diluent, glidant, disintegrant, and lubricant) that are listed in the US FDA Inactive Ingredients Database for approved drug products and/or GRAS	L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP
Dosage Level(s) and Frequency[a]	25 mg PO BID	200 mg IV q3w
Route of Administration	Oral	IV
Use	Experimental	Experimental
IMP or NIMP	IMP	NIMP
Sourcing	Provided by the Sponsor	Site Pharmacy
Packaging and Labeling	Prepared to meet all regulatory requirements	As described in Keytruda® US prescribing information
Current/Former Name(s) or Alias(es)	VS-0145, IPI-145, Copiktra®	Keytruda®

Abbreviations: BID: twice daily; FDA: Food and Drug Administration; GRAS: Generally Regarded as Safe; IMP: Investigational Medicinal Product; IV: intravenous; NIMP: Non-Investigational Medicinal Product; PO: oral; q3w: every 3 weeks; US: United States; USP: United States Pharmacopeia.

[a] Subjects will be treated until documented PD (Section 8.1.2), unacceptable toxicity (Section 6.7), discontinuation criteria are met, withdrawal (Section 7.2), or death. The total duration of treatment will not exceed 24 months.

6.1.1. Duvelisib

Duvelisib should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL). Advise subjects not to open, break, or chew the capsules.

Duvelisib 25 mg will be administered BID PO. Duvelisib may be administered without regard to meals; however, subjects must avoid grapefruit and grapefruit juice while on duvelisib (COPIKTRA 2018).

On days of pembrolizumab dosing, duvelisib will be administered in the clinic before the pembrolizumab infusion is started.

On the days when postdose PK samples are collected, specific timing for the administration of duvelisib is required (see Table 2 and Table 4), as follows:

- Stage 1: On C1D8, duvelisib will be administered at the start of the visit after the predose PK, pharmacodynamic, and blood sample collection
- Stage 1: On C2D1, duvelisib will be administered 30 minutes before the start of the pembrolizumab infusion
- Stage 2: On C1D1, duvelisib will be administered at the start of the visit after the predose PK and blood sample collection

Refer to the Pharmacy Manual for additional instructions regarding duvelisib administration.

6.1.2. Pembrolizumab

Pembrolizumab will only be administered by qualified site personnel during clinic visits in accordance with the prescribing information for pembrolizumab (Keytruda 2019).

Pembrolizumab 200 mg should be administered q3w as an IV infusion over 30 minutes.

On the days when postdose PK samples are collected, specific timing for the administration of pembrolizumab is required (see Table 2 and Table 4) as follows:

- Stage 1: On C1D8, pembrolizumab will not be administered until the biopsy for biomarkers has been collected; the optimal timing for collection of the biopsy is approximately 2 to 4 hours after duvelisib administration, however, a tumor biopsy at a later time during this clinic visit on C1D8 is acceptable. The fourth PK sample should be collected at approximately 2 to 4 hours after duvelisib dose, as soon as possible after the biopsy, and prior to pembrolizumab administration.
- Stage 1: On C2D1, the pembrolizumab infusion will be started 30 minutes after administration of duvelisib
- Stage 2: On C1D1, pembrolizumab will be administered 30 minutes after collection of the 2-hour postdose duvelisib PK sample

With the exception of the days when postdose PK samples are collected (i.e., C1D8 and C2D1 in Stage 1 and C1D1 in Stage 2), the pembrolizumab infusion should be started within 10 minutes after the dose of duvelisib is administered.

Please refer to the prescribing information for current detailed instructions on administration of pembrolizumab (Keytruda 2019).

6.2. Preparation/Handling/Storage

6.2.1. Duvelisib

Dispensing and storage instructions for duvelisib will be provided in the Pharmacy Manual. 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 Pharmacy Manual. Expired drug is not to be dispensed (COPIKTRA 2018).

6.2.2. Pembrolizumab

Please refer to the prescribing information for current instructions on preparation, handling, and storage of pembrolizumab (Keytruda 2019).

Pembrolizumab to be used in combination with duvelisib in this study will be obtained by the study sites from commercially available sources.

6.2.3. Accountability

Only subjects enrolled in the study may receive study interventions (i.e., duvelisib in combination with pembrolizumab) and only authorized site staff may supply or administer study interventions.

All study interventions stored at the site must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention(s) accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused duvelisib are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias

This is an open-label study with a single treatment arm.

Subjects will be assigned a unique number in ascending numerical order at each study site.

6.4. Study Intervention Compliance

When subjects are dosed at the site, they will receive study interventions (i.e., duvelisib and pembrolizumab) directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the case report form (CRF). The dose of study interventions and study subject identification will be confirmed at the time of dosing by a member of the study site staff.

When subjects administer duvelisib at home, compliance with duvelisib will be assessed by the study site at each visit. Compliance of duvelisib dosing will be assessed by reviewing subject diaries (first year on treatment only) and counting returned capsules during the site visits and will

be documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of duvelisib capsules dispensed to and taken by each subject must be maintained and reconciled with duvelisib and compliance records. Pembrolizumab infusion start and stop times and duvelisib start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5. Concomitant Therapy

Any other medication (e.g., supportive care) that is considered necessary for the subject's welfare and that is not expected to interfere with the evaluation of duvelisib may be given at the discretion of the Investigator.

Any medication that the subject received within 30 days prior to the first dose or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and stop dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Required and Recommended Prophylaxis

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

- Subjects are required 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 recommended, per 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 recommended for subjects considered by Investigators to be at high risk for CMV reactivation.
- 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 Investigator discretion, but the restrictions on the use of CYP3A inducers, inhibitors, and substrates should be considered (see Section 6.5.2).

6.5.2. Concomitant Therapies Restrictions

Table 8: Prohibited Concomitant Therapies

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; however, subjects and their physicians should be aware that the effectiveness of any vaccine administered concomitantly with duvelisib may be diminished. The ability to generate an immune response to any vaccine after the administration of duvelisib has not been studied and data for pembrolizumab are preliminary (Läubli 2018).
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 QD. Note: Acute treatment for underlying autoimmune disorders (e.g., reactive airway disease, rheumatoid arthritis) with corticosteroid doses > 20 mg prednisone or equivalent QD for ≤ 1 week is permitted during the study. Corticosteroid doses of ≤ 20 mg prednisone or equivalent QD are permitted during the study for physiologic replacement or chronic treatment for underlying autoimmune disorders (e.g., reactive airway disease, rheumatoid arthritis). See Table 10 and Table 13 for use of systemic steroids for study intervention toxicity when study intervention(s) is withheld or discontinued.
Other Anticancer Therapy or Investigational Agents	During the study intervention period, subjects are not to receive any additional anticancer therapy or other investigational agents not outlined in the protocol.
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. Section 10.2 provides a list of medications and foods known to inhibit (Table 20) or induce (Table 21) CYP3A. Please note that these tables do not provide a comprehensive list of all medications that may modulate CYP3A activity. No formal PK drug-drug interaction studies have been conducted with pembrolizumab (Keytruda 2019).

Abbreviations: CYP3A: cytochrome P450 3A; QD: once daily; PK: pharmacokinetic.

Table 9: Concomitant Therapies: Use with Caution During Treatment with Duvelisib

Concomitant Therapy: Use with Caution	Guidance
Medications or Foods that Weakly or Moderately Inhibit or Induce CYP3A4	Please discuss use of weak or moderate CYP3A inhibitors and inducers with the Medical Monitor. Section 10.2 provides a list of medications and foods known to inhibit (Table 20) or induce (Table 21) CYP3A. Please note that these tables do not provide a comprehensive list of all medications that may modulate CYP3A activity.
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. Table 22 in Section 10.2 provides a list of medications known to be substrates of CYP3A. Please note that Table 22 is not a comprehensive list of all medications that may be substrates of CYP3A. The Sponsor should be contacted with any questions regarding concomitant use of medications that are CYP3A substrates.

Abbreviations: AUC: area under the curve; CYP3A: cytochrome P450 3A; QD: once daily.

6.5.3. Contraception and Pregnancy

The effects of duvelisib on conception, pregnancy, and lactation are unknown.

Refer to the prescribing information for pembrolizumab for the effects of pembrolizumab on conception, pregnancy, and lactation (Keytruda 2019).

At Screening, all male and female subjects of reproductive potential (i.e., not surgically sterile or female subjects who are not postmenopausal) must agree to use a highly effective method of contraception for the duration of the study interventions and for at least 4 months after the last dose of study interventions. See Section 10.4 for Contraceptive Guidance including examples of highly effective contraceptive methods. Pregnancy testing will be performed throughout the study as shown in the SoA (Table 1 and Table 3).

6.6. Supportive Care, Dose Modifications, and Management of Toxicities

Supportive care should be provided as clinically indicated. Granulocyte colony stimulating factor may be used according to the American Society of Clinical Oncology (ASCO) guidelines (Smith 2015). Transfusions may be used at any time as clinically indicated and according to ASCO guidelines. Subjects on a stable dose of erythropoietin to treat baseline anemia may continue this therapy at this dose.

General recommendations for the management of overlapping toxicities for duvelisib in combination with pembrolizumab (Section 6.6.1), toxicities for duvelisib (non-overlapping toxicities or as monotherapy) (Section 6.6.2), and toxicities for pembrolizumab (non-overlapping toxicities) (Section 6.6.3) are provided below.

Please refer to the pembrolizumab prescribing information (Keytruda 2019) for additional information regarding management of pembrolizumab toxicities.

Additional information regarding management of duvelisib toxicities can be found in the Summary of Data and Guidance to the Investigator section of the duvelisib IB.

In the event that all study interventions are discontinued, subjects should be followed for AEs (for 30 days after the last dose of last study intervention) and survival as outlined in the SoA (Table 1 and Table 3).

6.6.1. Recommended Dose Modifications for the Management of Overlapping Toxicities for Duvelisib in Combination with Pembrolizumab

Non-infectious diarrhea or colitis, cutaneous reactions, pneumonitis without suspected infectious cause), and elevations in ALT and AST levels are potential overlapping toxicities for duvelisib with pembrolizumab. Refer to Table 10 for recommended management of these events in subjects being treated with duvelisib in combination with pembrolizumab.

If, during the management of an AE for an individual subject receiving both duvelisib and pembrolizumab, the Investigator suspects that pembrolizumab may be the cause of that event, the Investigator should discuss the case with the Medical Monitor. If an excessive rate of Grade 3 or higher overlapping SAEs is observed, the totality of safety data will be evaluated by the Medical Monitor and the Investigators, and a decision to hold enrollment of subjects may be made (see Section 4.1).

For additional information, please refer to the prescribing information for pembrolizumab (Keytruda 2019) and the Summary of Data and Guidance to the Investigator section of the duvelisib IB.

Table 10: Recommended Dose Modifications for the Management of Overlapping Toxicities for Duvelisib in Combination with Pembrolizumab

Toxicity	Adverse Reaction Grade	During Treatment with Duvelisib in Combination with Pembrolizumab	
		Dose Modification	**Recommended Management**
Non-infectious Diarrhea or colitis	Grade 1 diarrhea (up to 3 stools per day over baseline) and responsive to antidiarrheal agents, OR Asymptomatic (Grade 1) colitis	• No change in pembrolizumab dose • No change in duvelisib dose	• Initiate supportive therapy with antidiarrheal agents as appropriate • Monitor at least weekly until resolved or Grade 0
	Grade 1 diarrhea (up to 3 stools per day over baseline) and unresponsive to antidiarrheal agents	• Withhold duvelisib dose • No change in pembrolizumab dose	• Treat with enteric acting steroids (e.g., budesonide) • Monitor at least weekly until resolved • Resume duvelisib at a reduced dose when event resolves (see Table 11)
	Grade 2 diarrhea or colitis	• Withhold pembrolizumab and duvelisib	• Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) • Resume in subjects with complete or partial resolution (Grades 0 to 1) after corticosteroid taper
	Abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs OR Severe diarrhea or colitis (Grade 3, > 6 stools per day over baseline)	• Withhold pembrolizumab and duvelisib	• For Grade 2/Grade 3 colitis, initiate supportive therapy with enteric acting steroids (e.g., budesonide) or systemic steroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) • Monitor at least weekly until resolved • Resume pembrolizumab treatment when event resolves • Resume duvelisib at a reduced dose when event resolves (see Table 11) • For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue pembrolizumab and duvelisib
	Life-threatening	• Discontinue pembrolizumab and duvelisib	

Toxicity	Adverse Reaction Grade	During Treatment with Duvelisib in Combination with Pembrolizumab	
		Dose Modification	**Recommended Management**
Cutaneous reactions	Grade 1-2	• No change in dose for pembrolizumab or duvelisib	• Initiate supportive care with emollients, anti-histamines (for pruritus), or topical steroids • Monitor closely
	Grade 3	• Withhold duvelisib dose • Based on the severity of the adverse reaction, withhold or permanently discontinue pembrolizumab	• Initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids • Monitor at least weekly until resolved • Resume duvelisib at reduced dose when event resolves (see Table 11) • If severe cutaneous reaction does not improve, worsens, or recurs, discontinue duvelisib
	Life-threatening	• Discontinue pembrolizumab and duvelisib	
	SJS, TEN, DRESS (any grade)	• Discontinue pembrolizumab and duvelisib	
Pneumonitis without suspected infectious cause	Moderate (Grade 2) symptomatic pneumonitis	• Withhold pembrolizumab and duvelisib	• Treat with corticosteroids (1 to 2 mg/kg/day prednisone or equivalent, followed by corticosteroid taper) • If pneumonitis recovers to Grade 0 or 1 , pembrolizumab may be resumed and duvelisib may be resumed at reduced dose (see Table 11) • If non-infectious pneumonitis recurs or subject does not respond to steroid therapy, discontinue duvelisib and pembrolizumab
	Recurrent Grade 2 pneumonitis, severe (Grade 3), or life-threatening pneumonitis	• Discontinue pembrolizumab and duvelisib	

Toxicity	Adverse Reaction Grade	During Treatment with Duvelisib in Combination with Pembrolizumab	
		Dose Modification	**Recommended Management**
Hepatotoxicity	AST or ALT > 3 and up to 5 × ULN or total bilirubin > 1.5 and up to 3 × the ULN	• Withhold pembrolizumab and duvelisib	• Treat with corticosteroids (0.5 to 1 mg/kg/day prednisone or equivalent followed by corticosteroid taper • Monitor at least weekly until ALT or AST returns to < 3 × ULN • Resume treatment when adverse reaction improves to Grade 0 or 1 after corticosteroid taper
	In subjects without liver metastases, AST or ALT > 5 × ULN or total bilirubin > 3 × ULN	• Discontinue pembrolizumab and duvelisib	
	In subjects with liver metastasis and Grade 2 AST or ALT at baseline, with an increase in AST or ALT of 50% or more relative to baseline that persists for at least 1 week	• Discontinue pembrolizumab and duvelisib	

Abbreviations: ALT: alanine aminotransferase; AST: aspartate transaminase; DRESS: drug reaction with eosinophilia and systemic symptoms; SJS: Stevens Johnson syndrome; TEN: toxic epidermal necrolysis; ULN: upper limit of normal.

6.6.2. Recommended Duvelisib Dose Modifications for the Management of Duvelisib Toxicities

The dose level of duvelisib may be modified to manage duvelisib toxicities (Table 12) or overlapping toxicities in combination with pembrolizumab (Table 10).

Non-hematologic and hematologic AEs for duvelisib for non-overlapping toxicities in combination with pembrolizumab should be managed with supportive care, treatment hold, dose reduction, or discontinuation of duvelisib as described in Table 12. Additional information regarding management of duvelisib toxicities can be found in the Summary of Data and Guidance to the Investigator section of the duvelisib IB.

Refer to Table 11 for dose level modifications recommended for duvelisib. 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 the study interventions.

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

If duvelisib is discontinued, the subject will also discontinue pembrolizumab and proceed with their End of Treatment (EoT) Visit.

Table 11: Duvelisib Dose Level Modifications for Toxicities

Dose Level	Duvelisib
Starting Dose	25 mg BID PO
-1	15 mg BID PO[a]

Abbreviations: BID: twice daily; PO: oral.
[a] Discontinue duvelisib if subject is unable to tolerate duvelisib 15 mg BID.

Table 12: Recommended Duvelisib Dose Modifications for the Management of Duvelisib Toxicities

Toxicity	Adverse Reaction Grade	Dose Modification and Recommended Management
Non-hematologic Adverse Reactions		
Infections	Grade 3 or higher infection	• Withhold duvelisib until resolved • Resume at the same or reduced dose (see Table 11)
	Clinical CMV infection or viremia (positive PCR or antigen test)	• Withhold duvelisib until resolved • Resume at the same or reduced dose (see Table 11) • 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

Toxicity	Adverse Reaction Grade	Dose Modification and Recommended Management
		• For confirmed PJP, discontinue duvelisib
Hematologic Adverse Reactions		
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 to 1.0 Gi/L	• Maintain duvelisib dose • Monitor ANC at least weekly
	ANC less than 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 (see Table 11)
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 (see Table 11)

Toxicity	Adverse Reaction Grade	Dose Modification and Recommended Management
Non-hematologic Adverse Reactions During the Duvelisib Monotherapy Lead-in Only[a]		
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 11)
	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 11) • 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, anti-histamines (for pruritus), or topical steroids • Monitor closely
	Grade 3	• Withhold duvelisib until resolved • Initiate supportive care with emollients, anti-histamines (for pruritus), or topical steroids • Monitor at least weekly until resolved • Resume at a reduced dose (see Table 11) • 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 11) • If non-infectious pneumonitis recurs or subject does not respond to steroid therapy, discontinue duvelisib
	Severe (Grade 3) or life-threatening pneumonitis	• Discontinue duvelisib • Treat with systemic steroid therapy

Toxicity	Adverse Reaction Grade	Dose Modification and Recommended Management
ALT/AST elevation	3 to 5 × ULN (Grade 2)	• Maintain duvelisib dose • Monitor at least weekly until return to < 3 × ULN
	> 5 to 20 × ULN (Grade 3)	• 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 11)
	> 20 × ULN (Grade 4)	• Discontinue duvelisib

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

[a] See Table 10 for recommended dose modifications for the management of overlapping toxicities for duvelisib in combination with pembrolizumab.

6.6.3. Recommended Pembrolizumab Dose Modifications for the Management of Pembrolizumab Toxicities

Non-hematologic and hematologic AEs for pembrolizumab for non-overlapping toxicities in combination with duvelisib should be managed as described in the current pembrolizumab prescribing information (Keytruda 2019). The general recommendations cited in the June 2019 pembrolizumab prescribing information are summarized in Table 13.

Table 13: Recommended Pembrolizumab Dose Modifications for the Management of Pembrolizumab Toxicities

Adverse Reaction	Severity[a]	Dose Modification	Recommended Management
Immune-mediated hypophysitis (including hypopituitarism and adrenal insufficiency)	Grade 2 hypophysitis	Withhold dose until clinically stable	Treat with corticosteroids and hormone replacement as clinically indicated
	Grade 3 or 4 hypophysitis	Withhold dose until clinically stable or permanently discontinue	
Immune-mediated thyroid disorders	Grade 2 thyroid disorders	No change in dose	Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate
	Grade 3 or 4 thyroid disorders	Withhold dose until clinically stable or permanently discontinue	

Adverse Reaction	**Severity**[a]	**Dose Modification**	**Recommended Management**
Immune-mediated type 1 diabetes mellitus	Grade 3 or 4 hyperglycemia	Withhold dose until clinically stable	Administer insulin for type 1 diabetes and administer anti-hyperglycemics in subjects with severe hyperglycemia
Immune-mediated nephritis and renal dysfunction	Grade 2	Withhold dose	Treat with corticosteroids (1 to 2 mg/kg/day prednisone or equivalents followed by a taper)
	Grade 3 or 4	Permanently discontinue	
Other immune-mediated adverse reactions	Grade 2 or 3 based on the severity and type of reaction	Withhold dose	Administer corticosteroids[b] Based on limited data from clinical studies in subjects whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.
	Grade 3 based on the severity and type of reaction or Grade 4	Permanently discontinue	
Recurrent immune-mediated adverse reactions	Recurrent Grades 3 or 4	Permanently discontinue	
Inability to taper corticosteroid dosage	Requirement for ≥ 10 mg per day prednisone or equivalent for > 12 weeks after last dose of pembrolizumab	Permanently discontinue	

Adverse Reaction	Severity[a]	Dose Modification	Recommended Management
Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathy)	Persistent Grade 2 or 3 adverse reactions lasting ≥12 weeks after last dose of pembrolizumab	Permanently discontinue	

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; ULN: upper limit of normal.
[a] Severity was graded per NCI CTCAE v4.
[b] Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month.

6.6.4. Management of Infusion-related Reactions

Infusion reactions (or suspected hypersensitivity infusion reaction and/or anaphylaxis) are defined below (Table 14).

Table 14: NCI CTCAE Grading for Infusion Reactions

Grade	Description
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.
3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae
4	Life-threatening consequences; urgent intervention indicated
5	Death

Abbreviations: IV: intravenous; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID: nonsteroidal anti-inflammatory drug.

Study site policies shall be used for the management of infusion reactions.

Treatment should be permanently discontinued for severe and life-threatening infusion reactions. The rate of infusion should be slowed or interrupted in subjects with mild or moderate infusion reactions (Keytruda 2019).

6.7. DLT Evaluation

In Stage 1, the DLT evaluation period is Cycle 1 (4 weeks or 28 days): 1 week of duvelisib monotherapy lead-in followed by 3 additional weeks of duvelisib in combination with pembrolizumab. Every effort will be made to administer the first dose of pembrolizumab on Day 8 of Cycle 1 (C1D8). If the first dose of pembrolizumab on C1D8 is delayed, every effort should be made to delay the subsequent dosing of the next cycle (within the protocol allowed

window of 3 days) to achieve as close to a 3-week interval between pembrolizumab doses as possible. The Medical Monitor needs to be consulted for such adjustments to ensure uniformity of approach and to account for subject-specific circumstances. For example, if the third day of the C2D1 window falls on a weekend, an additional adjustment would need to be made on a case-by-case basis. In the event of a delay of the start of pembrolizumab therapy, DLTs will be evaluated at the end of the third week of combination therapy.

The DLT evaluation period will be used to assess DLTs in the first 6 subjects.

- If there is ≤ 1 DLT in the 6 DLT-evaluable subjects, additional subjects will be enrolled to bring the total dosed in Stage 1 to approximately 13 subjects
- If there are ≥ 2 DLTs in the first 6 subjects, enrollment at duvelisib 25 mg BID will stop. Enrollment would restart at a reduced duvelisib dose (15 mg BID) to assess DLTs at the lower dose (dose level -1; see Table 6)

6.7.1. Definition of Dose-limiting Toxicity

Dose-limiting toxicity is defined as an AE that occurs during the initial 4-week period (DLT evaluation period, Cycle 1), is at least possibly related to duvelisib, and fulfills at least 1 of the following criteria:

- Grade 3 or higher febrile neutropenia or Grade ≥ 3 neutropenia with infection or Grade 4 neutropenia lasting more than 7 days
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 3 or Grade 4 treatment-related non-hematologic toxicity, except nausea, vomiting, diarrhea and elevations in ALT or AST, which will be considered dose-limiting only if the subject develops:
  - Grade 3 nausea, vomiting, or diarrhea lasting more than 48 hours despite use of appropriate therapy or Grade 4 vomiting or diarrhea
  - Grade 3 elevations in ALT or AST lasting longer than 1 week, Grade 4 elevation in ALT or AST, or any ALT or AST elevations that require permanent discontinuation of study treatment
  - Grade 3 elevations in bilirubin elevation > 2 × ULN (> 2 × baseline for subjects with Gilbert's syndrome) lasting longer than 1 week, Grade 4 elevation in bilirubin, or any elevations in bilirubin that require permanent discontinuation of study treatment
  - Alkaline phosphatase (ALP) elevations will be evaluated on a case-by-case basis by the study team in assessing whether there is a DLT
- Grade 3 hypersensitivity reaction lasting longer than 24 hours or Grade 4 hypersensitivity regardless of duration
- A DLT for cardiac dysfunction will include any heart failure that is Grade ≥ 2 NCI CTCAE (Version 5.0 or higher). The AE must be clinically significant and at least possibly related to the study drug in order to be considered a DLT
- Any other toxicity that does not meet the definition of a DLT but requires permanent discontinuation of study treatment or is of concern to the Investigator and Sponsor may be considered to be a DLT

In rare instances, an event may fall within the definition of a DLT, as defined above, but the event may not be considered a DLT (e.g., not clinically meaningful). If this occurs, the Investigator and Sponsor will review the event and supporting data, and the reasons for not considering the event to be a DLT will be clearly documented with supporting rationale. Toxicities will be graded and documented according to the NCI CTCAE (Version 5.0 or higher).

6.7.2. Subjects With a DLT

In general, a subject who experiences a DLT should discontinue the study interventions. However, if there is evidence that a subject who experiences a DLT has also derived clinical benefit from the study interventions, the Medical Monitor and Investigator will review the specifics of the case, and the subject may be allowed to continue on study at the same dose or at a lower dose level of duvelisib if the consensus judgment is that continued treatment is in the subject's best interest. Subjects should have recovered from toxicity to baseline or Grade 1 (except alopecia) before re-treatment. For a DLT due to low hemoglobin or thrombocytopenia, the subject's hemoglobin concentrations should have returned to baseline grade before re-treatment; transfusions of packed red blood cells to treat anemia are permitted.

6.8. Intervention after the End of the Study

Subjects receiving clinical benefit from duvelisib in combination with pembrolizumab therapy may continue receiving treatment until either the final analysis of the ORR endpoint has been completed or all active subjects have been followed for 1 year after entry of the last subject, whichever is later. If the study is ended before all subjects discontinue treatment, any subject continuing to receive benefit will be provided the opportunity to continue to receive study intervention. However, in any case, the total duration of therapy will not exceed 24 months.

7. DISCONTINUATION OF STUDY INTERVENTION(S) AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Interventions

Study interventions will be discontinued for any of the following reasons:

- Subject withdrawal of informed consent
- Protocol-specified disease progression
- Clinical deterioration (at the discretion of the Investigator)
- Duvelisib interruption for > 42 days due to duvelisib-related toxicity, unless approved by study Medical Monitor
- Unacceptable toxicity (as defined by the Investigator)
- Pregnancy
- Termination of the study by the Sponsor
- Death
- Maximum treatment duration of 24 months is reached
- Other reasons, including major protocol violation or noncompliance

The Investigator must determine the primary reason for discontinuation of study intervention(s) and record this information in the CRF.

Subjects who discontinue the study interventions (i.e., duvelisib and pembrolizumab) will complete an EoT Visit and should continue in the study so that follow-up information on survival status may be obtained (See Section 8.1.3). See the SoA (Table 1 and Table 3) for data to be collected at the time of discontinuation of study interventions and during follow-up and for any further evaluations that need to be completed.

Discontinuation of specific sites or of the study as a whole are described in Section 10.6.8.

7.2. Subject Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If a subject withdraws during the treatment phase, an EoT Visit should be conducted, if possible, as described in the SoA (Table 1 and Table 3).
- Additional visits may be conducted as necessary for any abnormal findings that require medical follow-up.
- The subject will be permanently discontinued from the study interventions and withdrawn from the study at that time.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible. If contact with the subject is made, the site should counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject. These contact attempts (e.g., 3 phone calls followed by a certified letter) should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1, Table 2, Table 3, and Table 4). Protocol waivers or exemptions are not allowed.
- Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention(s).
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. Screening activities will be performed within 30 days before the first dose (C1D1). Repeat laboratory assessments during the Screening Period do not constitute rescreening. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screen failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will be described in the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Assessment of disease response and progression status in all subjects will be evaluated by the Investigator according to RECIST v 1.1 (Eisenhauer 2009). Response and progression will be evaluated using imaging scans (see Section 8.1.1), as indicated in the SoA (Table 1 and Table 3).

8.1.1. Imaging Scans

Computed tomography (CT) or magnetic resonance imaging (MRI) scans may be used, but CT is preferred. The same method must be used throughout the study. Imaging will occur at fixed calendar intervals (i.e., first scan in Stage 1 after 10 weeks [± 3 days], then every 9 weeks [± 3 days]; scans every 9 weeks [± 3 days] in Stage 2) regardless of any changes to visit or cycle schedules. In the case of a CR or PR, a confirmatory scan must be performed per RECIST v1.1 (Eisenhauer 2009). It is recommended that this scan be performed at 4 (+1) weeks after the initial response.

8.1.2. Investigator Assessment of Response and Progression Status

Assessment of response and progression status will be evaluated by the Investigator at each scheduled disease response assessment as outlined in the SoA (Table 1 and Table 3). Assessment of response and progression status in all subjects will be evaluated according to RECIST v 1.1

(Eisenhauer 2009) for clinical decision-making and assessment of response. Please see Section 10.1 for detailed descriptions of these response criteria.

8.1.3. Survival Follow-up

Subjects who discontinue both study interventions will participate in the Survival Follow-up which will occur every 3 months (± 2 weeks) after the Safety Follow-up Visit for up to 1 year after the last subject is enrolled and dosed. This assessment will be conducted by telephone interview and records review (if available). Information on survival status and initiation of other anticancer therapy (including start date, stop date [if appropriate]; therapy type; and response on treatment) will be collected.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1 and Table 3). Additional visits may be conducted as necessary for any abnormal findings that require medical follow-up.

8.2.1. Physical Examinations and Vital Signs

A full physical examination (PE) will be conducted at Screening. The full PE should include measurements of height and weight, vital signs, general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, neurological examination, clinical assessment of tumor masses (if evaluable by PE), and review of disease-related constitutional symptoms.

Symptom-directed PEs should include body systems as appropriate and will be conducted at subsequent time points per the SoA (Table 1 and Table 3).

Any pre-existing PE abnormality deemed clinically significant by the Investigator during Screening will be reported as medical history. Any PE abnormality that emerges or has worsened after signing of the ICF and that is assessed as clinically significant by the Investigator will be reported as an AE.

Vital signs will be measured with the subject in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate. Vital sign abnormalities will be assessed for clinical significance.

8.2.2. Electrocardiogram

A standard 12-lead electrocardiogram (ECG), including a description of the cardiac rate, rhythm, interval durations, and an overall impression, will be conducted at Screening, after an approximate 10-minute rest period, per the SoA (Table 1 and Table 3). Corrected QT interval (QTc) will be calculated using the Fridericia correction method (QTcF). The ECG will be performed in triplicate to rule out clinically significant abnormalities. Additional on-treatment ECGs should be performed per the Investigator's discretion as clinically indicated.

8.2.3. Concomitant Medication and Procedures

Concomitant medications and procedures will be assessed and recorded in the CRF during Screening (including those occurring within 30 days before first dose) and at each visit.

8.2.4. Clinical Safety Laboratory Assessments

- See Table 23 for the list of clinical laboratory tests to be performed and the SoA (Table 1 and Table 3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant* abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subjects condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study interventions should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or the Medical Monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
    - All protocol-required laboratory assessments, as defined in Table 23, must be conducted in accordance with the Laboratory Manual and the SoA (Table 1 and Table 3).
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or requiring dose modification), then the results must be recorded in the CRF.

*Note: Clinically significant findings are findings that are directly responsible for discontinuation from the study, require treatment or other therapeutic intervention, require further monitoring and/or require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality). A result outside of the normal range or different from what is expected may be determined to be not clinically significant based on the clinical situation and investigator judgment (i.e., laboratory finding just below or above the normal limit).

8.3. Other Assessments

8.3.1. ECOG Performance Status

ECOG performance status will be assessed at the time points as shown in the SoA (Table 1 and Table 3). If the ECOG performance status assessed at Screening is performed within 7 days of the first dose, the Screening assessment can be used and does not need to be repeated at C1D1.

8.4. Adverse Event Management

8.4.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the study (investigational) product. This includes an exacerbation of pre-existing conditions or events, concurrent illnesses, drug interaction, or the significant worsening of the indication under investigation. Anticipated fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening, need not be considered AEs.

Symptoms of the disease under study/lack of efficacy/disease progression should not be classified as an AE if they are within the normal day-to-day fluctuation or expected progression of the disease.

It is the responsibility of the Investigator to document all AEs that occur during the study. AEs should be reported on the appropriate CRF.

8.4.2. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence at any dose (including those occurring after the ICF is signed and before dosing) that:

- Results in death
- Is life-threatening (subject is at immediate risk of death from the event as it occurred)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, are not immediately life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For SAE reporting purposes, hospitalization is defined as inpatient hospital stay. Hospitalizations for elective surgery or other medical procedures that are not related to a treatment-emergent AE (TEAE) are not considered SAEs. Hospitalization, which in the opinion of the Investigator, is unrelated to the study intervention, and due to purely non-medical circumstances (e.g., respite care, lack of a caretaker at home, lack of transportation home) is also not considered to be an SAE. SAEs resulting from PD during the study (including signs and symptoms of progression) if documented by use of appropriate methods, should ONLY be reported as an SAE if the outcome of the PD is fatal during the study or within the safety reporting period (see Section 8.4.3). If the

malignancy has a fatal outcome during the study or within the safety reporting period, then the event should be reported using the term "disease progression" with a CTCAE severity of Grade 5.

Death should not be reported as an SAE. The primary reason for a subject's death should be reported as the SAE, with death reported as the outcome.

8.4.3. Reporting of Adverse Events and Serious Adverse Events

The AE reporting period begins from the time that the subject signs the ICF through and including 30 calendar days after the last study intervention dose. All subjects with treatment-related AEs/SAEs should be observed until resolution or stabilization of the event. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to the study intervention(s) is suspected. If the subject begins a new anticancer therapy, the safety reporting period ends at the time the new treatment is started, however, death must always be reported if it occurs during the AE reporting period irrespective of intervening treatment.

Elective or previously scheduled hospitalizations for pre-existing conditions that have not worsened after initiation of treatment should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE.

All AEs should be recorded individually unless, in the opinion of the Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be reported rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE, as appropriate, on the relevant form(s) (SAE Report Form and/or AE CRF). If a diagnosis is subsequently established, it should be reported as follow-up information becomes available. If a diagnosis is determined after the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Each AE will be evaluated for duration, severity, seriousness, and causal relationship to each study intervention. The action taken with each study intervention and the outcome must also be recorded.

All SAEs, regardless of relationship to each study intervention, must be reported immediately (within 24 hours of awareness of event by Investigator) to the Sponsor and contract research organization pharmacovigilance group. Initial SAE notification should be made by e-mailing or faxing the SAE report form to the e-mail or fax number provided on the SAE report form.

An initial SAE Report may be sent without the Investigator's signature but must be followed by a report signed by the Investigator within 48 hours of becoming aware of the event. Follow-up SAE reports must be submitted by the Investigator as new information becomes available.

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

8.4.4. Severity of Adverse Events

The severity of the AE will be graded according to the NCI CTCAE, Version 5.0 or higher (see web page https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 for details). Only AEs not listed in the CTCAE should be graded as summarized in Table 15.

Table 15: CTCAE (Version 5.0 or higher) AE Grading

CTCAE Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated, although this could improve the overall well-being or symptoms of the subject
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk
Grade 4	Life-threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical condition that prevents work or performing normal daily activities; treatment or medical intervention is required to maintain survival
Grade 5	Death	AE resulting in death

Abbreviations: AE: adverse event, CTCAE: Common Terminology Criteria for Adverse Events.

8.4.5. Relationship of Adverse Events to Study Intervention

The Investigator will make a judgment regarding whether or not the AE was related to each study intervention, as outlined below:

- **Definitely related:** This category applies when, after careful medical consideration, there is almost no consideration of other causation.
- **Probably related:** There is a clinically plausible time sequence between onset of the AE and study intervention administration. The AE is unlikely to be caused by a concurrent or underlying illness, other drugs, or procedures. If applicable, the AE follows a clinically consistent resolution pattern upon withdrawal of study intervention.
- **Possibly related:** There is a clinically plausible time sequence between onset of the AE and study intervention administration, but the AE could also have been caused by the concurrent or underlying illness, other drugs, or procedures. Information regarding study intervention withdrawal may be lacking or unclear. “Possible” should be used when study intervention administration is one of several biologically plausible causes of the AE.

- **Unlikely related:** The AE is most likely due to a cause not related to study intervention administration. However, association with the study intervention cannot be completely ruled out.
- **Unrelated:** Another cause of the AE is most plausible, and a clinically plausible temporal sequence is inconsistent with the onset of the AE and study intervention administration and/or a causal relationship is considered biologically implausible.

For the purpose of regulatory reporting requirements, causal relationships of definite, probable, and possible will be considered treatment-related, while unlikely and unrelated will be considered not treatment-related.

8.4.6. Clinical Laboratory Adverse Events

A clinical laboratory AE is any laboratory value that is deemed clinically significant by the Investigator and is accompanied by one of the following:

- requires a medical intervention
- requires a modification or interruption of study intervention
- is accompanied by clinical symptoms

Laboratory abnormalities that do not require medical intervention should not be recorded as AEs and will be captured and reported in the laboratory section of the clinical study report (CSR). If a medical intervention occurs, it should be recorded as a treatment with the abnormal laboratory finding as the AE (e.g., anemia with treatment required and blood transfusion recorded as a procedure, hyperglycemia with treatment required and change in insulin dose recorded on the concomitant medications CRF).

The Investigator should decide, based upon the AE criteria and the clinical condition of the subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

If, at the end of the treatment phase with the study intervention, there are pathological laboratory values that were not present at Baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (i.e., concomitant disease) is found for the pathologic laboratory values.

8.4.7. Regulatory Aspects of Adverse Event Reporting

The Sponsor is responsible for submitting reports of SAEs associated with the use of the study interventions to the appropriate Regulatory Authority (e.g., the US FDA), Investigators, and IRB/IEC/Central Ethics Committee in accordance with all applicable regulations and guidelines.

It is the responsibility of the Investigator to notify the IRB of SAEs that occur at his or her site per IRB requirements. 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.

8.4.8. Overdose

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 if needed and 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 8.4.2. In the event of an overdose that causes an SAE, 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 SOC. The Investigator will determine if and when dosing should resume.

8.4.9. Pregnancy

Any pregnancy must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the pregnancy using a Pregnancy Report Form.

Pregnancy per se is not considered an AE unless there is cause to believe that the study interventions may have interfered with the effectiveness of a contraceptive medication or if the outcome of the pregnancy meets SAE criteria (miscarriage or congenital anomaly/birth defect, etc.), in which case it should be reported in the same manner and timelines as an SAE. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to the in-utero exposure to the study interventions should also be reported as an SAE. Hospitalization for normal delivery of a healthy newborn is not an SAE.

Since duvelisib and pembrolizumab have not been evaluated in pregnant or nursing women, the treatment of pregnant women or WCBP who are not using highly effective contraception is contraindicated (see Table 23 and Section 10.4 for instructions on pregnancy testing and contraception).

Pregnancies occurring in subjects or partners of male subjects during the study intervention period and until 30 days after the subject's last dose of study interventions are considered immediately reportable events. If a pregnancy occurs in a subject, study interventions must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. The Investigator will observe the pregnant woman until completion of the pregnancy and must notify the Sponsor of the outcome within 24 hours of the Investigator's knowledge of the pregnancy outcome using a Pregnancy Outcome Form. This notification includes pregnancies resulting in live, "normal" births.

8.5. Pharmacokinetics

PK samples will be collected during the study.

- Blood samples will be collected to evaluate the PK of duvelisib and metabolite IPI-656 at the visits and time points defined in the SoA (Table 2 and Table 4)

- On the days when postdose PK samples are collected, specific timing for the administration of duvelisib and pembrolizumab is required (see Table 2 and Table 4), as follows:
  - Stage 1: On C1D8, duvelisib will be administered at the start of the visit after the predose PK, pharmacodynamic, and blood sample collection. Blood samples to evaluate the PK of duvelisib and metabolite IPI-656 will be collected at 1 and 2 hours after duvelisib administration. Pembrolizumab will not be administered until the biopsy for biomarkers has been collected; the optimal timing for collection of the biopsy is approximately 2 to 4 hours after duvelisib administration, however, a tumor biopsy at a later time during this clinic visit on C1D8 is acceptable. The fourth PK sample should be collected at approximately 2 to 4 hours after duvelisib dose, as soon as possible after the biopsy, and prior to pembrolizumab administration.
  - Stage 1: On C2D1, duvelisib will be administered 30 minutes before the start of the pembrolizumab infusion.
  - Stage 2: On C1D1, duvelisib will be administered at the start of the visit after the predose PK and blood sample collection. Pembrolizumab will be administered 30 minutes after the collection of the 2-hour postdose duvelisib PK sample.
- Predose samples are preferred, therefore on the days that include PK assessments the morning dose of duvelisib should be administered in the clinic to facilitate collection of samples before dosing. However, the sample should still be collected even if the morning dose of duvelisib has already been taken. The date and time of the sample collection and date and time of the previous duvelisib dose must be recorded for all collected samples.
- Additional PK samples beyond those listed in the SoA (Table 2 and Table 4) may be requested (when feasible) for any unusual safety event. (i.e., an AE different in type and severity from that which is expected in the setting of duvelisib use).
- Specific instructions on sample collection and handling will be provided in a separate Laboratory Manual.
- Retained duplicate PK samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these PK samples.
- Subject confidentiality will be maintained.

8.6. Pharmacodynamics

Pharmacodynamic biomarkers are described in Section 8.8.

8.7. Genetics

Normal germline genetic studies are not evaluated in this study. Tumor genomic studies may be conducted as part of exploratory biomarker research (Section 8.8). A swab of non-tumor tissue (genomics control) will be collected to compare polymorphisms in the subject's non-tumor cells vs the tumor cells.

8.8. Biomarkers

Blood and tissue specimens are to be collected according to the SoA (Table 2 and Table 4) and assessments will be conducted to evaluate potential biomarkers. Each of the specimens listed may be analyzed at a central laboratory or at a specialized laboratory vendor as determined by the Sponsor, for the various biomarkers outlined below:

1. Pharmacodynamic markers of target inhibition in HNSCC
2. Immunophenotypes and functional tests of major immune populations in the blood and/or feces
3. Cytokines and other circulating biomarkers
4. Prognostic markers assessed by DNA, RNA, and protein analysis from tissue and blood specimens

In addition, C-reactive protein levels in blood (a clinical safety laboratory assessment) will be evaluated as a potential biomarker (Table 23).

Sample collections may be reduced, or limited to certain sites/countries, based on emerging data or feasibility. Reductions/limitations may be implemented before amendment of the protocol. Specific collection and processing details (e.g., serum or plasma) will be described in the Laboratory Manual. Any increase in the number or type of samples collected will require a protocol amendment.

8.8.1. Tumor Biopsy and Colon Biopsy

In Stage 1 of the study, 2 tumor biopsies (Screening/C1D1 and C1D8) are mandatory, as specified in the SoA (see Table 2). The 2 biopsies do not need to be done on the same lesion.

- Screening/C1D1 biopsy: Archival tissue beyond the 30-day Screening window and up to 6 months before C1D1 may be considered in place of the required Screening/C1D1 biopsy after consultation with the Sponsor, as long as no intervening systemic regimen had been taken during that time frame.
- C1D8 biopsy: The optimal timing for collection is approximately 2 to 4 hours after duvelisib administration but before pembrolizumab administration. However, a tumor biopsy at a later time during this clinic visit on C1D8 is acceptable.

In Stage 2, an optional tumor biopsy may be collected after the first cycle (on C2D1) for an exploratory analysis of biomarkers (Table 4). If collection of the biopsy is not feasible on C2D1, a biopsy collected after the second cycle (on C3D1) would also be acceptable.

Collection procedures and amounts are described in the Laboratory Manual.

If available, aliquots of any colon biopsies taken due to colitis or Grade ≥ 3 diarrhea or as SOC for any immune-mediated AEs should also be provided.

8.9. Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL METHODOLOGY

A detailed description of the statistical methodology for this study can be found in the Statistical Analysis Plan (SAP). Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final CSR.

9.1. Statistical Hypotheses

This study will test the null hypothesis that the ORR is ≤ 16% against the alternative that ORR is ≥ 44%. The ORR (proportion of subjects achieving CR or PR) according to RECIST v 1.1 (Eisenhauer 2009) will be estimated on the modified Intent-to-Treat (mITT) population (i.e., all subjects who receive at least 1 dose of duvelisib in combination with at least 1 dose of pembrolizumab). For this study "response" is defined as a confirmed response, per RECIST v 1.1 (Eisenhauer 2009), unless otherwise specified. Details for determination of confirmation of response will be provided in the SAP. A 2-sided exact 95% CI will be calculated.

The ORR of 16% being used for the null hypothesis is based on multiple sources. The pembrolizumab prescribing information (Keytruda 2019) reports an ORR for pembrolizumab monotherapy of 16% in subjects previously treated with a platinum-containing therapy in the KEYNOTE-012 study. An ORR of 16% is also reported for subjects naïve to anti-PD-L1 therapy in the KEYNOTE-055 study (Bauml 2017). Further, the ORR for pembrolizumab monotherapy is reported in the USPI as 19%. Therefore, an uninteresting response rate of 16% will be used for all subjects in this study.

The evaluation of the primary endpoint will be conducted at the highest dose that is tolerated during the DLT evaluation. Therefore, if the initial dose of 25 mg BID is not tolerated but the reduced dose of 15 mg BID is tolerated, the primary endpoint will be evaluated in all subjects starting at the tolerated dose.

9.2. Sample Size Determination

The study will follow a Simon two-stage design (Simon 1989). In the first stage, approximately 13 subjects will be accrued. If there are 2 or fewer responses (CR or PR) in these 13 subjects, further accrual in the study may be stopped. However, all available data will be considered before termination.

In Stage 2, 17 additional subjects will be accrued for a total of 30 subjects in the final analysis. The null hypothesis will be rejected if 10 or more responses (CR or PR) are observed in 30 subjects. This design yields an overall type I error rate of 5% and power of 90% when the true response rate is 44%.

9.3. Populations for Analyses

The populations for the analyses are described in Table 16.

Table 16: Populations for Analyses

Population	Description
Enrolled[a]	All subjects who sign the ICF
DLT Evaluable	The first 6 subjects in Stage 1 who complete Cycle 1 and who receive ≥ 75% of the scheduled duvelisib doses during Cycle 1 or who have a DLT during Cycle 1
ITT	All subjects who receive at least 1 dose of duvelisib. The ITT analysis set will serve as the primary analysis set for all safety endpoints and baseline parameters.
mITT	All subjects who receive at least 1 dose of duvelisib in combination with at least 1 dose of pembrolizumab. The mITT analysis set will serve as the primary analysis set for all efficacy endpoints.

Abbreviations: DLT: dose-limiting toxicity; ICF: informed consent form; ITT: intent-to-treat; mITT: modified intent-to-treat.

[a] "Enrolled" means a subject's, or their legally acceptable representative's, agreement to participate in a clinical study after completion of the informed consent process. Potential subjects who are pre-screened for the purpose of determining eligibility for the study but do not sign an ICF are not considered enrolled.

9.4. Statistical Analyses

The SAP will be finalized before database lock and it will include a more technical and detailed description of the statistical analyses summarized in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints.

9.4.1. General Considerations

Hypothesis testing will be used for the interim (Stage 1) and final (Stage 1 + Stage 2) analyses of the efficacy endpoint of ORR. No formal hypothesis testing will be used for any other endpoints or other study data, such as demographics and safety data.

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented, as well as 2-sided 95% CIs, unless stated otherwise. For continuous variables, the number of subjects, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as number and percentage of censored observations.

The Investigator's assessments of disease response will be used as the basis for the evaluation of the primary and secondary efficacy endpoints.

9.4.1.1. Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures. Details of procedures for handling missing, unused, or spurious data can be found in the SAP.

9.4.2. Primary Endpoint Efficacy Analysis

ORR will be assessed according to RECIST v 1.1 (Eisenhauer 2009). Final analysis of the combined Stage 1 and Stage 2 ORR will occur after the last subject enrolled and dosed in Stage 2 has been followed for 6 months.

9.4.3. Secondary Efficacy Endpoints Analyses

- ORR will be assessed according to RECIST v 1.1 (Eisenhauer 2009). Evaluation of ORR in Stage 1 will occur after the last subject enrolled and dosed in Stage 1 has been followed through at least the first disease response assessment.
- DOR will be calculated for those subjects with a CR or PR from the time of first response to PD using KM methods
- PFS will be assessed using KM methods from time of first treatment to PD or death
- OS will be assessed using KM methods from time of first treatment to death

9.4.4. Primary Safety Endpoint Analysis: Stage 1

- Safety analyses will be performed on the ITT population, and safety endpoints will be tabulated and presented.
- AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or higher for purposes of summarization. All AEs occurring during the study will be included in by-subject data listings and tabulated by MedDRA system organ class and preferred term. Adverse events will be summarized overall, by relationship to each study intervention, and by severity. Events leading to death, SAEs, and events resulting in discontinuation of study interventions will be listed and, if warranted by the data, tabulated.
- AEs of special interest (AESI) will be defined for analysis purposes in the SAP and will be summarized using the methods as described in the above bullet.
- Exposure to duvelisib and pembrolizumab, including the proportion of expected doses received, will be tabulated.
- Changes from baseline over time for vital sign measurements (including diastolic and systolic blood pressure) will be summarized.
- Individual subject laboratory parameter values and changes from baseline over time will be summarized using descriptive statistics. Severity of select clinical laboratory measures will be determined using NCI CTCAE criteria and Grade 3 or 4 laboratory values will be presented in a separate table.

- The use of concomitant medications, coded using the World Health Organization Drug Dictionary, will be tabulated and included in a by-subject listing.

9.4.5. Secondary Safety Endpoint Analysis

Safety analyses, as described in Section 9.4.4, will be performed on the ITT population for Stage 1 and Stage 2 combined, and safety endpoints will be tabulated and presented.

9.4.6. Secondary PK Endpoints Analyses

- PK analyses will be conducted on the ITT population.
- Blood samples will be taken for the analyses of duvelisib and metabolite IPI-656 in plasma at the time points defined in the SoA (Table 2 and Table 4). PK exposure parameters (maximum observed concentration [C_{max}] and area under the curve [AUC]) will be determined using the bioanalytical data and Population PK (POPPK) modeling. The PK data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form.
- Based on the exposure parameters determined from POPPK model, the relationship between duvelisib exposure and response and AEs will be analyzed.

9.4.7. Exploratory Endpoints Analyses

- Changes from baseline over time for ECOG performance status will be summarized. A by-subject listing of ECOG performance status data will be prepared.
- Pharmacodynamic analyses will be conducted on the ITT population for Stage 1.
- Pharmacodynamic and prognostic markers will be evaluated relative to baseline levels and change from baseline levels.
- Biomarker effects will be summarized using descriptive statistics; associations of biomarkers, including tumor and/or immune cell PD-L1 levels and HPV status, with clinical efficacy and/or safety outcomes may be explored.

9.5. Interim Analyses

An interim analysis of the primary endpoint will be conducted at the end of Stage 1 as part of the Simon two-stage design (Simon 1989).

9.6. Data Monitoring Committee

This study will not use a data monitoring committee.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS: APPENDICES

Table 17: Appendices

Appendix	Title	Section
1	RECIST Version 1.1	10.1
2	CYP3A Inhibitors, Inducers, and Substrates	10.2
3	Clinical Laboratory Tests	10.3
4	Contraceptive Guidance	10.4
5	ECOG Performance Status	10.5
6	Regulatory, Ethical, and Study Oversight Considerations	10.6
7	Abbreviations	10.7

10.1. Appendix 1: RECIST Version 1.1

(Modified from Eisenhauer 2009)

All subjects will have their BEST RESPONSE on study classified as outlined below (Table 18 and Table 19):

Complete Response (CR)

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

Partial Response (PR)

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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.

Progressive Disease (PD)

At least a 20% increase in the sum of 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. The appearance of one or more new lesions will also be considered PD.

Response Duration

Response duration will be measured from the time that the measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference for PD the smallest measurements recorded on study.

Stable Disease Duration

Stable disease duration will be measured from the time of start of the intervention until the criteria for progression are met, taking as reference the smallest sum of diameters recorded on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

Table 18: Evaluation of Best Overall Response – Subject with Target (± Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD/or not all evaluated	No	PR
SD	Non-PD/or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR: complete response; NE: inevaluable; PD: progressive disease; PR: partial response; SD: stable disease.

Table 19: Evaluation of Best Overall Response – Subject with Non-target Disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR: complete response; NE: inevaluable; PD: progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease because SD is increasingly used as an endpoint for assessment of efficacy in some studies; therefore, to assign this category when no lesions can be measured is not advised.

Note: Subjects with a global deterioration of health status requiring discontinuation of intervention without objective evidence of PD at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of study interventions.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical Lesions

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

Chest X-ray

A chest CT scan is preferred over a chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-rays may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT (preferred) or MRI Scans

CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is defined based on the assumption that the CT slice thickness is 5 mm or less. When CT scans have a slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. An MRI scan is also acceptable in certain situations (e.g., for body scans).

Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure with CT, MRI may be used instead of CT in selected instances.

Cytology, Histology

These techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain) from PD.

10.2. Appendix 2: CYP3A Inhibitors, Inducers, and Substrates

10.2.1. Medications or Foods Known to Inhibit CYP3A

The following list provides medications or foods known to induce or inhibit CYP3A activity. Note that this is not a comprehensive list of all medications or foods which may modulate CYP3A activity. Additional information can be found at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Note: Subjects receiving duvelisib are prohibited from concomitant use of medications or foods that are known to be strong inhibitors or inducers of CYP3A.

Table 20: Classification of In Vivo Inhibitors of CYP3A

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.

10.2.2. Medications Known to Induce CYP3A

Please discuss use of weak or moderate CYP3A inhibitors and inducers with the Medical Monitor.

Table 21: Classification of In Vivo Inducers of CYP3A

Strong Inducers ≥ 80% decrease in AUC	**Moderate Inducers 50-80% decrease in AUC**	**Weak Inducers 20-50% decrease in AUC**
Avasimibe[1], arbamazepine, phenytoin, rifampin, St. John's Wort[2,3]	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, Echinacea[3] pioglitazone, prednisone, rufinamide

Abbreviations: AUC: area under the curve; CYP3A: cytochrome P450 3A.

1. Not a marketed drug.
2. The effect of St. John's Wort varies widely and is preparation-dependent.
3. Herbal product.

10.2.3. Medications Known to Be CYP3A Substrates

Known sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic range are listed in Table 22. Consider finding an alternative drug that is not a substrate of CYP3A4.

Additional information can be found at:

https://drug-interactions.medicine.iu.edu/main-table.aspx

http://www.pharmacytimes.com/issue/pharmacy/2008/2008-09/2008-09-8687

Table 22: Cytochrome P450 3A (CYP3A) Substrates

Sensitive CYP3A Substrates	
budesonide	midazolam
buspirone	saquinavir
eplerenone	sildenafil
eletriptan	simvastatin
felodipine	triazolam
fluticasone	vardenafil
lovastatin	
CYP3A Substrates with a Narrow Therapeutic Range	
alfentanil	fentanyl
astemizole	pimozide
cisapride	quinidine
cyclosporine	sirolimus
diergotamine	tacrolimus
ergotamine	terfenadine

10.3. Appendix 3: Clinical Laboratory Tests

- The tests detailed in Table 23 will be performed by the local laboratory. The timing and frequency are detailed in the SoA Table 1 and Table 3.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.
- The results of each test must be entered in the CRF.

Table 23: Protocol-required Safety Laboratory Assessments

Laboratory Assessments[a]	**Parameters**			
Hematology	Platelet Count		RBC Indices: Mean corpuscular volume Mean corpuscular hemoglobin %Reticulocytes	White blood cell count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry[1]	Blood urea nitrogen	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase (ALP)	Lactate dehydrogenase (LDH)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick. If positive, quantitative analysis is needed if not previously noted as part of medical history. • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments[a]	**Parameters**
Pregnancy	• Highly sensitive serum/urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]
Other Screening Tests	• Viral screening: serology (hepatitis B surface antigen [HBsAg], hepatitis B core antibody [HBcAb], hepatitis C virus antibody [HVCAb], Epstein-Barr virus [EBV] antibody, human immunodeficiency virus [HIV] antibody); HPV testing (if status not available at Screening), cytomegalovirus (CMV) via serology, or viral load detection via polymerase chain reaction (PCR). Subjects with a negative HBsAg and positive HBcAb require an undetectable/negative hepatitis B DNA test (e.g., PCR test) to be dosed. ○ HIV testing is required for subjects without documentation of a prior negative test result from within the last 9 months. Results will be analyzed locally and will not be captured in the study database. Only subjects with negative results will be eligible to begin study intervention. • Coagulation tests: prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) • C-reactive protein[b] • Triiodothyronine (T3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) • Food and Drug Administration (FDA)-approved PD-L1 testing is required for indications specified in the current pembrolizumab prescribing information (Keytruda 2019), unless results are already available. Information on FDA-approved tests is available at: http://www.fda.gov/CcompanionDiagnostics.
NOTES: 1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are provided in Table 12 for duvelisib and in Table 13 for pembrolizumab. All liver-related SAEs must be reported as described in Section 8.4.3. 2. A serum pregnancy test must be performed within 7 days of the first dose. At subsequent time points, serum testing is preferred but urine testing is allowed if a blood draw for other assessments is not performed. A positive urine test result must be confirmed by a serum test.	

[a] See Section 8.2.4 for guidance on repeating/recording laboratory tests with values that are considered clinically significant or that require a change in subject management.
[b] Also obtain when Grade ≥ 2 diarrhea, any grade colitis, or any grade immune-mediated toxicity (e.g., pneumonitis, colitis, hepatitis, endocrinopathies, nephritis/renal dysfunction, cutaneous adverse reactions, encephalitis) occurs.

10.4. Appendix 4: Contraception Guidance

The effects of duvelisib on conception, pregnancy, and lactation are unknown. Every woman of childbearing potential (WCBP) and male subjects with a partner who is a WCBP must use contraception as described below. A woman is considered to be a WCBP after menarche and until becoming postmenopausal (i.e., > 55 years and postmenopausal for at least 1 year), unless permanently sterile.

At Screening, all male and female subjects of reproductive potential (i.e., not surgically sterile or female subjects who are not postmenopausal) must agree to use a highly effective method of contraception (see Section 10.4.1) for the duration of the study interventions, and for at least 4 months after the last dose of study interventions. Male subjects must also refrain from donating sperm during their participation in the study and for at least 4 months after the last dose of study interventions.

The use of contraceptive methods is not required if the male subject or the male partner (of the female subject) has a documented history of a vasectomy or if the female subject or the female partner (of the male subject) has a documented history of bilateral oophorectomy, hysterectomy, or tubal ligation, or if she is > 55 years of age and postmenopausal for at least 1 year.

See Section 8.4.9 for requirements for pregnancy reporting.

10.4.1. Highly Effective Methods of Contraception

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[a]:
  - oral
  - injectable
  - implantable[b]
- intrauterine device (IUD)[b]
- intrauterine hormone-releasing system (IUS)[b]
- bilateral tubal occlusion[b]
- vasectomized partner[b,c]
- sexual abstinence[d]

[a] Hormonal contraception may be susceptible to interaction with the Investigational Medicinal Product (IMP), which may reduce the efficacy of the contraception method.

[b]This method of contraception should preferably be used, in particular when contraception is introduced as a result of participation in the clinical study.

[c]Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

10.5. Appendix 5: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken 1982.

10.6. Appendix 6: Regulatory, Ethical, and Study Oversight Considerations

10.6.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.6.2. Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.6.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements (where applicable), and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent was obtained when the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects will be re-consented to the most current version of the ICF(s) during their participation in the study as necessary.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

Note: The subject must sign the ICF before initiating any study specific procedures. SOC assessments that fulfill study eligibility requirements may be performed before the subject signs the ICF.

10.6.4. Subject Data Protection

- Subjects will be assigned a unique identifier during Screening. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.6.5. Dissemination of Clinical Study Data

The Sponsor will comply with current regulatory requirements for disclosure and submission of study results. The Sponsor's policy on publication of study results is described in Section 10.6.9.

10.6.6. Data Quality Assurance

- All subject data relating to the study will be recorded in the electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements (including handling of noncompliance issues and monitoring techniques [central, remote, or on-site monitoring]) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion, for a period of 2 years after a marketing application is approved for duvelisib in the study population, until 2 years after shipment and delivery of the drug for investigational use is discontinued, or as long as required by local regulations, whichever is longer. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.6.7. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported in the CRF or entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in ICH guidance for industry E6 Good Clinical Practice: Consolidated Guidance.

10.6.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor or designee reserves the right to close a study site or terminate the study at any time for any reason (e.g., as necessary for subject safety) at the sole discretion of the Sponsor. Study

sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.6.9. Publication Policy

- The results of this study may be published or presented at scientific meetings with prior approval of the Sponsor. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-site studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement between the Sponsor and the Investigators.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.7. Appendix 7: Abbreviations

Table 24: List of Abbreviations

Abbreviation	Definition
5-FU	5-fluorouracil
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice daily
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum observed concentration
CMV	Cytomegalovirus
CPS	Combined positive score
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CxDx	Cycle x Day x
CYP3A	Cytochrome P450 3A
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DRESS	Drug reaction with eosinophilia and systemic symptoms
EBV	Epstein-Barr virus

Abbreviation	Definition
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EoT	End of treatment
FDA	Food and Drug Administration
FL	Follicular lymphoma
FT4	Free thyroxine
F/U	Follow-up
hCG	Human chorionic gonadotropin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C antibody
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HR	Hazard ratio
HSV	Herpes simplex virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	international normalized ratio
IPI-145	Duvelisib
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
KM	Kaplan-Meier
L	Liter
LDH	Lactate dehydrogenase
MDSCs	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
mg	Milligram
mITT	Modified intent-to treat
MOC1	Murine oral cancer
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
p	P-value
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PDn	Pharmacodynamic
PE	Physical examination
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PJP	*Pneumocystis jiroveci* pneumonia
PK	Pharmacokinetic
PO	Orally/oral
POPPK	Population PK
PR	Partial response
PT	Prothrombin time
q3w	Every 3 weeks
QD	Once daily
QTcF	QT interval corrected with Fridericia's method
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid

Abbreviation	Definition
R/M	Recurrent or metastatic
R/R	Relapsed or refractory
SAE	Serious adverse event
SAP	Statistical analysis plan
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum pyruvic transaminase
SJS	Stevens Johnson syndrome
SLL	Small lymphocytic lymphoma
SoA	Schedule of Activities
SOC	Standard of care
T3	Triiodothyronine
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
Tregs	Regulatory T-cells
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
vs	Versus
VZV	Varicella zoster virus
WCBP	Woman of childbearing potential

10.8. Appendix 8: Protocol Amendment History

10.8.1. Protocol Version 2.0 (Amendment 1), 17 September 2019

10.8.1.1. Amendment Rationale

The primary purpose for this amendment is to provide updated safety guidance.

The revised protocol, Version 2.0, dated 17 September 2019 will be submitted by the Investigator(s) to all applicable IRBs, IECs, or CECs, and by Verastem, Inc. to all applicable Regulatory Authorities.

A summary of key changes that were made to protocol Version 1.0, including the rationales for these changes, is provided in Table 25.

Table 25: Summary of Changes for Version 2.0

Section(s)	Description of Change	Rationale for the Change
Global	Updated the version number and date of protocol from Version 1.0 dated 18 June 2019 to Version 2.0 dated 17 September 2019	Administrative change
Global	Minor corrections to grammar/spelling	Administrative changes
Title Page	Updated the IND number to the IND number for duvelisib in solid tumors	The IND number for duvelisib in hematologic cancers was used for Version 1 because the IND number for duvelisib in solid tumors was not available until after Version 1 was finalized
Signature Page	Updated the Sponsor signatory	Administrative change
Synopsis Figure 1 Figure 2 Figure 3 Table 1 Table 3 Section 4.1 Section 8.1.1 Section 9.1	• Deleted the following from the Synopsis and Section 4.1: "During the evaluation of available efficacy and safety data at the end of Stage 1, enrollment is anticipated to remain open for Stage 2 in the absence of safety or other concerns that may affect further development." • Clarified that enrollment in Stage 2 will not begin until all of the planned 13 subjects are enrolled in Stage 1 and at least 2 of 13 subjects have a confirmed response. • In Figures 2 and 3, Tables 1 and 3, and Section 8.1.1: Clarified that in the case of a CR or PR, a confirmatory scan must be performed per RECIST v1.1 and added the recommendation that this scan be performed at 4 (+1) weeks after the initial response. • In Section 9.1, clarified that "response" is defined as a confirmed response, per RECIST v 1.1, unless otherwise specified, and that details for determination of	To clarify that enrollment in Stage 2 will not begin until all of the planned 13 subjects are enrolled in Stage 1 and at least 2 of 13 subjects have a confirmed response and add specific criteria related to confirmation of response.

Section(s)	Description of Change	Rationale for the Change
	confirmation of response will be provided in the SAP.	
Synopsis Figure 2 Figure 3 Section 4.1 Table 7, footnote "a" Section 6.8 Section 7.1	Limited administration of study treatment to a maximum of 24 months	To align the duration of pembrolizumab treatment with the prescribing information for Keytruda
Synopsis Table 1, footnote "i" Section 4.1 Section 6.7	• Clarified that in cases for which the first dose of pembrolizumab on C1D8 is delayed, every effort should made to delay the subsequent dosing of the next cycle (within the protocol-allowed window of 3 days) to achieve as close to a 3-week interval between pembrolizumab doses as possible. • Specified that the Medical Monitor needs to be consulted for such adjustments to ensure uniformity of approach and to account for subject-specific circumstances. For example, if the third day of the C2D1 window falls on a weekend, an additional adjustment would need to be made on a case-by-case basis.	• To provide details regarding the management of subsequent dosing of pembrolizumab in cases where the first dose is delayed • To ensure uniformity of approach and to account for subject-specific circumstances
Synopsis Table 2, footnote "g" Table 5 Section 5 Section 8.5 Section 9.4.6	Specified the metabolite of duvelisib as IPI-656	To clarify PK data analysis
Synopsis Section 4.1 Section 4.2 Table 5 Table 7 Section 8.1.2.1 (removed) Table 15 (removed) Section 10.7 Section 11	Removed all references to immune Response Evaluation Criteria in Solid Tumors (iRECIST) and specified that subjects will not be permitted to continue study treatment after RECIST-defined progressive disease	Pseudo-progression does not need to be included in the protocol because it is rarely seen in subjects with HNSCC who receive therapy with immune checkpoint inhibitors
Synopsis Section 4.1 Section 6.6.1	Added the following to the Synopsis and Section 4.1: • A formal analysis of available safety data when the first 10 subjects treated have received at least 1 cycle of study treatment.	To enable assessment of toxicities of later onset, particularly outside of the DLT window and clarify the approach of assessing the serious Grade 3 or higher overlapping toxicities (i.e., pneumonitis, colitis,

Section(s)	Description of Change	Rationale for the Change
	• Definition and stopping rule for excessive rate of Grade 3 or higher overlapping SAEs In Section 6.6.1, added that an evaluation of the totality of safety data will be performed by the Medical Monitor and the Investigators if an excessive rate of Grade 3 or higher overlapping SAEs is observed and that a decision to hold enrollment of subjects may be made.	cutaneous skin reactions, elevations of AST/ALT)
Synopsis Section 5.2	Revised exclusion criterion 14 to remove history of human T cell lymphotropic virus 1 infection as an exclusion criterion	HTLV-1 screening is not relevant to this study
Table 1 Table 3	• Simplified the duvelisib administration note in Table 1 and Table 3 to state "on study visit days" • Added "if applicable" to the duvelisib administration note in Table 1 indicating that duvelisib will be administered before the pembrolizumab infusion is started	• Details are not needed because all clinic visits are either C1D1, PK assessment days, or pembrolizumab dosing days • There is no pembrolizumab infusion for Stage 1 on C1D1 or C1D15
Table 1 Table 3 Table 23	Added HPV testing if HPV status is not available at Screening	HPV status is needed for the exploratory analysis of the relationship of ORR to tumor HPV status
Table 2, footnote "g" Section 6.1.2 Section 8.5	Revised to state that the PK blood draw after biopsy collection should be collected as soon as possible after the biopsy and prior to pembrolizumab administration	To clarify the timing for collection of the post-biopsy PK blood draw
Section 2.4.1 Section 6.6.1 Section 6.7.1 Table 10	In Sections 2.4.1, 6,6,1, and 6.7.1, clarified that elevations in ALT and AST levels are potential overlapping toxicities. Modified Table 10 as follows: a. Separated recommendations for Grade 2 diarrhea or colitis from those for Grade 1; specified that duvelisib and pembrolizumab be withheld for Grade 2 diarrhea or colitis and added recommendations for management. b. Modified to contain only 1 set (i.e., the more conservative recommendations for immune-related hepatitis) of recommendations for elevations in AST and ALT (e.g., hepatoxicity/hepatitis).	To align with prescribing information and use the more conservative dose modification/management recommendations (e.g., those for immune-related hepatitis) for AST and ALT elevations because it is generally not possible to distinguish immune-related elevations in AST and ALT from non-immune-related elevations (without a biopsy)
Section 5.5	Deleted text stating that rescreened subjects should be assigned the same subject number as for the initial screening.	To align with current practice
Table 10 Table 12	Moved the guidance for duvelisib monotherapy adverse reactions from the overlapping toxicities table (Table 10) to the monotherapy toxicities table (Table 12)	To streamline the guidance for managing duvelisib toxicities during the monotherapy lead-in
Section 6.7.1	Modified the DLT criteria as follows:	To tighten the DLT criteria

Section(s)	Description of Change	Rationale for the Change
	a. Removed "or higher" from the DLT criterion related to nausea, vomiting or diarrhea and added "or Grade 4 vomiting or diarrhea" b. Modified the DLT criterion for elevations in ALT or AST to include any elevations in AST or ALT requiring permanent discontinuation of study treatment c. Modified the DLT criterion for elevations in bilirubin to include any elevations in bilirubin requiring permanent discontinuation of study treatment d. Modified the DLT criterion for any other toxicity to include any toxicity requiring permanent discontinuation of study treatment	
Table 13	Removed the row for "immune-mediated hepatitis in subjects with hepatocellular carcinoma"	Subjects with hepatocellular carcinoma will not be enrolled in this study
Section 8.4.8	Clarified that only cases of overdose that cause an SAE are required to be reported within 24 hours	Reporting of overdose within 24 hours is only required if it causes an SAE
Section 9.4.6	Specified that a Population PK model will be developed to analyze the relationship between duvelisib exposure and response and AEs	To clarify PK data analysis
Table 23	Removed the CD4+ T-cell count as a post-treatment test	Although pneumocystis prophylaxis concomitant with duvelisib treatment must be done per institutional guidelines, collection of a post-treatment CD4+ T-cell count result is not required in this study
Table 24	Updated list of abbreviations	Administrative change
Section 10.8.1	Added Summary of Changes made for Version 2.0	Administrative change
Section 10.8.2	Added version history	Administrative change

10.8.2. Version History

Table 26: Primary Reason for Each Version

Version	Primary Reason for Version
2.0	To provide updated safety guidance
1.0	Original version

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Verastem Oncology

05 June, 2020

Clinical Study Protocol: VS-0145-130 Version 2.0 dated 17 September 2019 entitled "A Phase 1b/2 Study of Duvelisib in Combination with Pembrolizumab in Subjects with Recurrent or Metastatic Head and Neck Squamous Cell Cancer"

Memorandum re: Clarification regarding Stage 1 PK draw at Cycle 5 Day 1 (pre-dose)

Section 1.3 Schedule of Activities for Stage 1 - Table 2 notes that PK samples should be drawn at Cycle 5 Day 1, pre-dose. This PK draw is not required and should not be performed. The PK draw will be deleted from the Protocol's Schedule of Events when/if the protocol is amended in the future.

[redacted]

[redacted]