Essai Clinique

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Titre	The BURAN Study of Buparlisib (AN2025) In Combination With Paclitaxel Compared to Paclitaxel Alone, in Patients With Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma
Protocole ID	BURAN (AN2025H0301)
ClinicalTrials.gov ID	NCT04338399
Type(s) de cancer	ORL
Phase	Phase III
Type étude	Clinique
Médicament	Buparlisib + paclitaxel versus paclitaxel seul
Institution	CENTRE HOSPITALIER DE L'UNIVERSITE DE MONTREAL
Ville	
Investigateur principal	Dr Denis Soulières
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Statut	Fermé
But étude	The BURAN study is a randomized, open-label phase III study to assess the treatment effect of once-daily buparlisib in combination with weekly paclitaxel compared to weekly paclitaxel alone in patients with refractory, recurrent, or metastatic head and neck squamous cell carcinoma (HNSCC) that have progressed after prior anti PD 1/anti PD L1 monotherapy; prior anti PD 1/anti PD L1 therapy in combination with platinum-based therapy; or after sequential treatment of anti PD 1/anti PD L1 therapy, either prior to or post, platinum-based therapy.

Critères d'éligibilité	• Aged ≥18 years old.
	• Able to provide informed consent obtained before any trial related activities and according to local guidelines.
	• Patient has histologically and/or cytologically-confirmed HNSCC.
	• Patient has archival or new tumor tissue for the analysis of biomarkers and confirmation of HPV status (if unknown). One tumor block (preferred) or a recommended minimum of 5 unstained slides for patients with known HPV status (for tumor DNA characterization) or a recommended minimum of 10 slides for patients whose HPV status is unknown (5 slides for HPV testing plus 5 slides needed for biomarker testing). Enrollment in the study is contingent on confirmation of the availability of an adequate amount of tumor tissue, except in rare special circumstances, which must be reviewed and approved by the sponsor.
	• Patient has either progressive or recurrent disease after treatment with PDL1/PD1 based therapy for recurrent or metastatic disease:
	  • PDLl/PD1 therapy alone for metastatic (monotherapy) disease
	  • PDL1/PD1 in combination with chemotherapy for metastatic and recurrent disease
	  • PDL1/PD1 used for metastatic disease, after or prior to receiving a platinum agent for locally advanced or metastatic disease.
	• 6. Patient has received no more than two prior lines of systemic treatment for HNSCC (single agent chemotherapy used as a radiosensitizer is not counted as a prior line of therapy).
	• Patient has measurable disease as determined per RECIST version 1.1. If the only site of measurable disease is a previously irradiated lesion, documented progression of disease and a four-week period since radiotherapy completion is required.
	• Patient has adequate bone marrow function and organ function as shown by the following:
	  • Absolute neutrophil count (ANC) ≥1.5 x 109/L.
	  • Hemoglobin ≥9 g/dL (which may be reached by transfusion).
	  • Platelets ≥100 x 109/L (which may be reached by transfusion).
	  • International normalized ratio (INR) ≤1.5.

	• Calcium (corrected for serum albumin) within normal limits (WNL) or ≤ grade 1 severity according to NCI-CTCAE version 5.0 if judged clinically not significant by the Investigator. Patients concomitantly taking bisphosphonates or denosumab for calcium correction are eligible. • Normal potassium and magnesium levels. • Alanine aminotransferase (AST) and aspartate aminotransferase (ALT) ≤ 1.5 x upper limit of normal (ULN) or < 3.0 x ULN if liver metastases are present. • Total serum bilirubin ≤ ULN or ≤ 1.5 x ULN if liver metastases are present; or total bilirubin ≤ 3.0 x ULN with direct bilirubin below or within normal range in patients with well documented Gilbert's Syndrome. Gilbert's syndrome is defined as presence of episodes of unconjugated hyperbilirubinemia with normal results from cells blood count (including normal reticulocyte count and blood smear), normal liver function test results, and absence of other contributing disease processes at the time of diagnosis. • Serum creatinine ≤ 1.5 x ULN or calculated and directly measured creatinine clearance (CrCL) > 30 mL/min. • Haemoglobin A1c (glycosylated hemoglobin; HbA1c) ≤8%. • Patient has Eastern Cooperative Oncology Group (ECOG) performance status ≤1. • Patient is able to swallow and retain oral medication. Patients able to swallow oral medication but mostly self-nourished through gastric or jejunal feeding tube are eligible. • Patients must apply highly effective contraception during and throughout the study, as well after the final dose of study treatment

Critères d'exclusion	Patients meeting any of the following criteria will not be eligible for participation in the study:
	• Patient has received previous treatment with any protein kinase B (PKB/AKT), mammalian target of rapamycin (mTOR) inhibitors, or phosphatidylinositol 3 kinase (PI3K) pathway inhibitors.
	• Patient received treatment with a taxane as part of prior treatment for metastatic disease.
	• Patient has symptomatic central nervous system (CNS) metastases. Patients with asymptomatic CNS metastases may participate in this study. Patient must have completed any prior local treatment for CNS metastases ≥ 28 days prior to the start of study treatment (including radiotherapy) and must be on a stable low dose of corticosteroid therapy. Radiosurgery must have been completed at least 14 days prior to start of study treatment.
	• Patient has received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study treatment or who have adverse events which have not recovered to grade 1 or better from previous chemotherapy treatment (except alopecia, autoimmune endocrine events must be stable and controlled).
	• Patient has grade ≥ 2 neuropathy, colitis, pneumonitis, , and uncontrolled endocrinopathies (e.g., hypothyroidism, diabetes with hemoglobin A1c > 8%) from previous treatment
	• Patient has had major surgery within 14 days prior to starting study treatment or has not recovered from major side effects.
	• Patient is currently receiving increasing or chronic treatment (>5 days) with corticosteroids or another immunosuppressive agent. The following uses of corticosteroids are permitted: single doses; standard premedication for paclitaxel, topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops, or local injections (e.g., intra-articular), or < 10 mg prednisolone or equivalent.
	• Patient is being treated at start of study treatment with any of the following drugs:
	  • Drugs known to be strong or moderate inhibitors or inducers of isoenzyme cytochrome P450 3A4 (CYP3A4) including herbal medications (see Table 16).
	  • Drugs with a known risk of inducing Torsades de Pointes. Note: The patient must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the treatment is initiated. Switching to a different medication prior to starting study treatment is allowed.
	• Patient is currently receiving warfarin or other coumarin-derived anti-coagulant, for treatment, prophylaxis, or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), fondaparinux or new oral anticoagulants (NOACs) is allowed.
	• Patient has a known hypersensitivity and/or contraindication to paclitaxel, standard premedication for paclitaxel, or other products containing Cremophor®.
	• Patient has other concurrent severe and/or uncontrolled medical conditions that would, in the Investigator's judgment, contraindicate patient participation in the clinical study (e.g., active or uncontrolled severe infection, chronic active hepatitis, immunocompromised, acute or chronic pancreatitis, uncontrolled high blood pressure, interstitial lung disease, etc).
	• Patient has a known history of human immunodeficiency virus (HIV) infection (testing not mandatory).
	• Patient has any of the following cardiac abnormalities:
	  • Symptomatic congestive heart failure within 12 months of the screening period.
	  • History of documented congestive heart failure (New York Heart Association functional classification III-IV) or documented cardiomyopathy and left ventricular ejection fraction (LVEF) <50% as determined by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO).
	  • Myocardial infarction ≤six months prior to enrollment.
	  • Unstable angina pectoris.
	  • Serious uncontrolled cardiac arrhythmia.
	  • Symptomatic pericarditis.
	  • QT interval corrected according to the formula of Fridericia (QTcF) > 450 msec for males and > 470 msec for females, on the screening electrocardiogram (ECG).
	  • Currently receiving treatment with medication that has a known risk to prolong the QT

interval or inducing Torsades de Pointes, and the treatment cannot be discontinued or switched to a different medication prior to starting study treatment.

- Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study treatment (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
- Patient has a medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (e.g., risk of doing harm to self or others), or active severe personality disorders (defined according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition [DSM-V]) are not eligible. Note: For patients with psychotropic treatments ongoing at baseline, the dose and the schedule should not be modified within the previous six weeks prior to start of study treatment.
- Patient has other prior or concurrent malignancy except for the following: adequately treated basal cell or squamous cell skin cancer, or other adequately treated in situ cancer, early gastric or GI cancer resected completely by endoscopy procedures or any other cancer from which the patient has been disease free for ≥ 3years.
- Patient has a history of non-compliance to any medical regimen or inability to grant consent.
- Patient is concurrently using or has used another approved or investigational cancer agent within 4 weeks of randomization.
- Patient is pregnant or nursing (lactating). Patients with elevated human chorionic gonadotrophin (hCG) at baseline that is judged to be related to the tumor are eligible if hCG levels do not show the expected doubling when repeated five to seven days later, or pregnancy has been ruled out by vaginal ultrasound.
- Patient has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed. Non-live COVID vaccinations or boosters should not occur within 30 days of study start.