Département d'oncologie
Plateformes du DO
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Indication	**Head and Neck**, carcinome épidermoïde, stade localisé avancé
Title	A Phase I/II randomized study to determine the maximum tolerated dose, safety, pharmacokinetics and antitumor activity of Debio 1143 combined with concurrent Chemo-Radiation Therapy in patients with locally advanced squamous cell carcinoma of the head and neck.
Protocol ID	Debio 1143-201
Phase	**Phase I/II**
Sponsor	Debiopharm SA
Local PI	Prof. Jean Bourhis
Primary Objective	**Phase I study (dose escalation)** To determine the maximum tolerated dose (MTD) of Debio 1143 in combination with concurrent CRT in patients with LA-SCCHN. **Phase II study (randomized, double-blind, placebo-controlled at Recommended Dose)** To evaluate the anti-tumour activity of Debio 1143 in comparison with placebo when added to standard concurrent CRT in patients with LA-SCCHN
Inclusion/exclusion criteria	**Inclusion Criteria** 1. Willing and able to sign a written informed consent; 2. Male or female ≥18 ≤75 years of age. 3. Histologically confirmed diagnosis of previously untreated LA-SCCHN (Stage III, IVa and IVb according to the American Joint Committee on Cancer Staging System) of one or more of the following sites: oral cavity, oropharynx, hypopharynx and larynx; 4. Tumour HPV negative status for oropharynx cancer patients, determined by p16 IHC; 5. Positive smoking history (> 10 packs/year); 6. Availability of pre-treatment tumour sample (optional for Phase I; mandatory for Phase II [10-20 tumour slides]); 7. Measurable disease by the RECIST 1.1 criteria; 8. Negative medical history of Hepatitis B and Hepatitis C; 9. Women of child-bearing potential: a. Negative serum pregnancy test at screening; b. Agreement to use appropriate contraception methods from study entry to 6 months after the last day of treatment. Agreement to use contraception methods from her male partner. 10. Male patients agree to use contraception methods from study entry to 6 months after the last day of treatment; 11. ECOG performance status 0 or 1

12. Subjects must have adequate haematological, renal and hepatic function;
    a. calculated creatinine clearance ≥ 60 mL/min as determined by the modified method of Cockcroft and Gault or by the EDTA method,
    b. absolute neutrophil count ≥1 500/µL,
    c. platelets ≥100 000/µL,
    d. haemoglobin ≥ 10 g/dL,
    e. aspartate (AST) and alanine transaminase (ALT) less than 3 times the upper limit of the normal range (ULN),
    f. total bilirubin ≤ 2.0 mg/dL,
    g. serum albumin >35 g/L.
13. QTcF interval ≤ 450 ms
14. Left ventricular ejection fraction (LVEF) within the institutional normal ranges as measured by echocardiogram (ECHO) or multigated acquisition (MUGA) scan;
15. No prior treatment with IAP inhibitors.
16. No use or requirement for use of aspirin or aspirin containing products with > 100 mg of aspirin per day;
17. No history of gastrointestinal bleeding within 1 year;
18. No active rheumatoid arthritis, active inflammatory bowel disease, chronic infections, or any other disease or condition associated with chronic inflammation.

Exclusion Criteria

1. Nasopharyngeal, paranasal sinuses, nasal cavity tumours or thyroid cancers;
2. Squamous cell cancer involving cervical neck nodes but from unknown primary site;
3. Metastatic disease;
4. Any prior or current treatment for invasive head and neck cancer of any kind. This will include but is not limited to: prior tyrosine kinase inhibitors, prior neoadjuvant therapy, prior surgical resection, or use of any investigational agent;
5. Weight loss of >10% during the last month;
6. Not compensated liver cirrhosis (Child-Pugh class C);
7. Gastro-intestinal disorders that could affect drug absorption (including, but not limited to, major abdominal surgery, significant bowel obstruction, ulcerative colitis, Crohn's disease);
8. Impaired bone turnover (serum C-terminal telopeptide [CTX] <300 pg/mL);1
9. Concurrent treatment with any other systemic anti-cancer therapy that is not specified as part of the protocol regimen;
10. Concomitant treatment with any drug on the prohibited medication list

	(provided separately); 11. Subjects with known history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure; 12. History of another malignancy within the last 5 years, with the exception of completely resected basal or squamous cell skin cancer, or successfully treated in-situ carcinoma. History of non-invasive lesion or in-situ carcinoma, including in the head and neck region that was successfully treated with surgery, photodynamic or laser, will be permitted; 13. Peripheral neuropathy ≥ grade 2; 14. Clinical hearing loss (to be confirmed by audiogram in doubtful cases); 15. If female, pregnant or lactating; 16. History of allergic reactions to appropriate antiemetics (e.g. 5-HT3 antagonists) to be administered with chemotherapy; 17. The investigator considers the subject unfit for the study as a result of the medical interview, physical examinations, or screening investigations.