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Plateformes du DO
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Indication	Mélanome métastatique ou carcinome à cellules de Merkel métastatique
Title	A Phase I, exploratory, intra-patient dose escalation study to investigate the preliminary safety, pharmacokinetics, and anti-tumor activity of pasireotide (SOM230) s.c. in patients with metastatic melanoma or metastatic Merkel cell carcinoma
Protocol ID	**Novartis SOM230**
Phase	**Phase I**
Sponsor	Novartis
Local Principal Investigator	Prof. O. Michielin
Primary Objective	Assess the safety profile of pasireotide s.c. in patients with confirmed unresectable and/or metastatic melanoma (without BRAF and NRAS mutation) or confirmed unresectable and/or metastatic Merkel cell carcinoma during the first 8 weeks of treatment with pasireotide s.c.
Inclusion/exclusion criteria	**Key Inclusion Criteria** 1. Adult male or female, age ≥18 years 2. Female patients of child bearing potential must have a negative pregnancy test at screening 3. Histologically or cytologically confirmed unresectable (stage III) and/or metastatic (stage IV) melanoma or unresectable and/or metastatic Merkel cell carcinoma 4. No mutation in BRAF and NRAS genes (for melanoma patients only) 5. Patients should have at least 1 (one) lesion suitable for standardized uptake value (SUV) measurements on 18FDG-PET (e.g., $\geq$ 1.5 cm in longest diameter by CT and with a tumor-to-background ratio (TBR) $\geq$ 1.5). 6. Patients must have skin lesions that can be biopsied 7. Presence of measurable or non-measurable disease according to RECIST 1.0 (Appendix 14.1) a. In order to be considered measurable, skin or superficial lymph nodes must be $\geq$ 1 cm in longest diameter. b. Lesions in previously irradiated areas should not be considered measurable, unless they have clearly progressed since the radiotherapy 8. Assessable metastases (skin or superficial lymph nodes, minimal diameter 1 cm) 9. ECOG Performance Status of 0 or 1 10. Patients with a known history of impaired fasting blood glucose (glucose >100 and <126 mg/dL) may be included at the discretion of the PI. These patients should be monitored closely throughout the trial and treatment adjusted as necessary. Patients that are deemed ineligible due

	to elevated glucose may be re-screened again after adequate medical treatment 11. Adequate organ function • Adequate bone marrow function • WBC ≥ 2.5 x 109/L • ANC ≥ 1.5 x 109/L • Platelets ≥ 100 x 109/L • Hemoglobin ≥ 9 g/dL • Serum creatinine ≤ 1.5 mg/dL or estimated glomerular filtration rate (eGFR) > 40 ml/min/m2 • Serum lipase ≤ 1.5 ULN 12. Life expectancy of at least 12 weeks 13. Written informed consent obtained prior to any screening procedures **Key Exclusion Criteria** 1. Patients with unknown BRAF or NRAS mutational status (for melanoma patients only) 2. Primary ocular melanoma 3. Patients with symptomatic CNS metastases who are neurologically unstable or requiring increasing doses of steroids to control their CNS disease 4. Prior treatment with somatostatin analogue or radiolabeled somatostatin analogs 5. Patients with a known hypersensitivity to somatostatin analogs or any component of the pasireotide s.c. formulations or their excipients 6. Patients for whom standard treatment is available and indicated due to rapidly progressive or aggressive disease 7. Patients who received more than 2 prior lines of systemic therapy for the treatment of the disease (the wash out period has to be 4 weeks prior to baseline). 8. Patients receiving any anti-neoplastic therapy within the 4 weeks prior to baseline 9. Patients receiving an investigational drug within 1 month prior to baseline 10. Patients who have undergone major surgery/surgical therapy for any cause within 1 month prior to baseline. Patients must have recovered from the treatment and have a stable clinical condition before entering this study 11. Patients who have received prior radiation therapy ≤ 4 weeks, or limited field radiation ≤ 2 weeks, prior to baseline or the side effects of such therapy have not resolved to ≤ grade 1. 12. Patients unwilling to perform repeated biopsies

13. Patients with known gallbladder or bile duct disease, acute or chronic pancreatitis (patients with asymptomatic cholelithiasis and asymptomatic bile duct dilation can be included)

14. Patients with abnormal coagulation (PT or PTT elevated by 30% above normal limits)

15. Patients on continuous anticoagulation therapy. Patients who were on anticoagulant therapy must complete a washout period of at least 10 days prior to baseline and have confirmed normal coagulation parameters before study inclusion

16. Patients who are not biochemically euthyroid

- Patients with known history of hypothyroidism are eligible if they are on adequate and stable replacement thyroid hormone therapy for at least 3 months prior to baseline

17. QT-related exclusion criteria

- Baseline QTcF >450 ms
- History of syncope or family history of idiopathic sudden death
- Known history of prolong QT syndrome
- Sustained or clinically significant cardiac arrhythmias
- Patients with risk factors for torsades de pointes such as uncorrected hypokalemia, uncorrected hypomagnesemia, clinically relevant cardiac failure (NYHA class III or IV), clinically significant/symptomatic bradycardia or high-grade AV block
- Concomitant medications known to prolong the QT interval
- Known concomitant disease(s) that could prolong QT such as autonomic neuropathy (caused by diabetes mellitus or Parkinson's disease), HIV, liver cirrhosis, uncontrolled hypothyroidism or cardiac failure
- Patients with unstable angina, sustained ventricular tachycardia, ventricular fibrillation, high grade (NOT advanced!) heart block or history of acute myocardial infarction less than one year prior to baseline

18. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

- Uncontrolled diabetes as defined by HbA1c > 8% despite adequate therapy
- Patients with the presence of active or suspected acute or chronic uncontrolled infection or with a history of immunodeficiency, including a positive HIV test result (ELISA and Western blot). A HIV test will not be required; however, previous medical history will be reviewed
- Non-malignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with this study treatment
- Liver disease or history of liver disease such as cirrhosis,

	decompensated liver disease, or chronic active hepatitis B and C or chronic persistent hepatitis • Life-threatening autoimmune and ischemic disorders 19. Patients who have a history of another primary malignancy, with the exception of locally excised non-melanoma skin cancer and carcinoma in situ of uterine cervix. Patients who had no evidence of disease from another primary cancer for 3 or more years are allowed to participate in the study 20. Patients who have any current or prior medical condition that may interfere with the conduct of the study or the evaluation of its results in the opinion of the Investigator or the Sponsor's Medical Monitor 21. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study 22. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL) 23. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are • Women whose sexual orientation precludes intercourse with a male partner • Women whose partners have been sterilized by vasectomy or other means • Using a highly effective method of birth control (i.e. one that results in a less than 1% per year failure rate when used consistently and correctly, such as implants, injectables, combined oral contraceptives, and some intrauterine devices (IUDs); periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) is not acceptable) 24. Baseline ALT or AST > 3 x ULN 25. Baseline total bilirubin > 1.5x ULN 26. Presence of Hepatitis B surface antigen (HbsAg) 27. Presence of Hepatitis C antibody test (anti-HCV) 28. History of, or current alcohol misuse/abuse within the past 12 months prior to visit 1 (baseline)