GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

PRESS RELEASE

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FIRST SCIENTIFIC EVIDENCE FOR EFFECTIVENESS OF A TREATMENT FOR RARE NEUROENDOCRINE TUMOURS.

For the first time an international academic randomised double-blind trial (conducted by Gustave Roussy and presented at the presidential session at the ESMO Congress) has demonstrated the effectiveness of a treatment for rare malignant neuroendocrine tumours.

Sunitinib is a targeted therapy that is already well established in oncology. It is an anti-angiogenic inhibitor of tyrosine-kinase and has been authorised for 15 years for the treatment of advanced or metastatic kidney cancer and for pancreatic neuroendocrine tumours. Following presentation at ESMO 2021 (20th September, 3.05 pm) of the results of the study demonstrating its safety and efficacy conducted by Gustave-Roussy teams in collaboration with other French and European units (COMETE and ENSAT), it should now also become the standard treatment for patients with active malignant paragangliomas and phaeochromocytomas.

This is a first: "*no anticancer drug has ever been evaluated with a comparable level of positive evidence,"* emphasised Dr Eric Baudin, leader of the endocrine and neuroendocrine tumour unit at Gustave Roussy, and lead author of this phase II randomised study which will become a landmark. Up till now, none of the therapies used to delay progression of these diseases has ever been subject to an academic, randomised, placebo-controlled, double-blind trial with the reliability of the results justifying publication.

It took over ten years to conduct this unprecedented trial properly. "*Many thought that we would not manage it because of the difficulty in recruiting a sufficient number of patients and because of the complexity of these orphan diseases,"* stated Dr Baudin. 40% of these neuroendocrine tumours have a familial component and they are very rare. The annual incidence of paragangliomas, which develop in endocrine cells in nerve pathways along major blood vessels extending from the head and neck via the vertebral column and the abdomen to the pelvis, is 1 in 100,000. That of phaeochromocytomas, which arise from the central portion of the adrenal glands (adrenal medulla), is 1 per 500,000.

In 85% of cases the tumours remain benign and localised. But there are malignant forms which seed tumour cells to secondary locations. "*15% of affected individuals develop a metastatic*

form," summarised Dr Baudin. This means that less than one patient per million is at risk of developing this tumour. It is difficult to diagnose because this requires complex imaging investigations. Disease progression is also difficult to predict. "*In half of patients with metastatic disease whose median survival period is about 7 years, the condition is quite indolent and progresses only slowly,"* thus needing monitoring only. For those in whom progression is significant, treatment options are limited to vector-targeted radionuclide therapy (metabolic radiotherapy) with or without the addition of standard chemotherapy (dacarbazine ou temozolomide), "*the effectiveness of which is poorly evaluated as it has been assessed by retrospective or rare phase II studies only."*

Treating these rare conditions, as with evaluating therapeutic options, is subject to additional complexity. Whether they are progressing or not, "*they may cause significant comorbidity because of their special capacity to secrete hormones, which in 10 to 30% of patients can be more of a threat to life than the disease itself,"* continued Dr Baudin. Indeed, some paragangliomas secrete hormones, usually catecholamines, which cause hypertension and/or severe constipation that can lead to bowel perforation. These well recognised functional manifestations of the disease require specific treatment. "*When conducting a trial the risks they pose require great care in handling interactions between medication and hormone secretions."*

Given these complex elements in the risk-benefit ratio, researchers from 15 centres located in four countries worked in concert to recruit 78 patients from December 2011. The median age was 53 and all had metastatic disease, some of them having been treated previously for this. However, none had previously received anti-angiogenic treatment or had had uncontrolled hypertension. They were randomised into two groups, in one of which the patients received oral sunitinib (37.5 mg/day); patients in the second group were given placebo. Neither the doctors nor the patients knew who was receiving what.

The main assessment criterion was survival at 12 months without progression. "*Our initial hypothesis was that the treatment would double this (from about 20 to 40%) in comparison with the placebo group. To conclude that sunitinib was effective, it was necessary to observe progression-free survival in at least 11 of the 37 patients in the sunitinib arm. This objective was met, in that it was finally achieved in 14 of these patients with a value of 35.9% for progression-free survival in the sunitinib group,"* specified Dr Baudin.

With only 18.9% progression-free survival in the placebo group, the study findings also support the initial hypothesis: "*if treatment is not given, the disease does not progress significantly in less than 20% of patients."* Side effects of treatment were acceptable overall, in the main being restricted to fatigue (18%) and worsening of hypertension (10%).

In view of the difficulties in conducting trials in these rare conditions, "*it is not possible to require a phase III study,"* declared Dr Baudin, "*but at the conclusion of this phase II trial, sunitinib now has the highest published level of efficacy, thus justifying its becoming standard therapy in these active cancers."*

Background on Gustave Roussy

Classed as the leading European Cancer Centre and the fifth on the world stage, Gustave Roussy is a centre with comprehensive expertise and is devoted entirely to patients suffering with cancer. The

Institute is a founding member of the Paris Saclay Cancer Cluster. It is a source of diagnostic and therapeutic advances. It caters for almost 50,000 patients per year and its approach is one that integrates research, patient care and teaching. It is specialized in the treatment of rare cancers and complex tumors and it treats all cancers in patients of any age. Its care is personalized and combines the most advanced medical methods with an appreciation of the patient's human requirements. In addition to the quality of treatment offered, the physical, psychological and social aspects of the patient's life are respected. 3,200 health professionals work on its two campuses: Villejuif and Chevilly-Larue. Gustave Roussy brings together the skills, which are essential for the highest quality research in oncology: a quarter of patients treated are included in clinical trials.
For further information**: www.gustaveroussy.fr/en, Twitter, Facebook, LinkedIn, Instagram**

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