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GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Press release

Relapsed or refractory acute myeloid leukaemia
Hope for complete remission with targeted oral therapy

The results of a phase II study led by Gustave Roussy, presented at an oral session of the 2021 ASCO Conference, offer hope for patients with refractory or relapsed acute myeloid leukaemia who have an IDH1 mutation. By selectively blocking the effects of this mutation, which prevents differentiation of immature blood cells, Olutasidenib, an oral targeted therapeutic agent, induces complete, long-lasting remission.

Oral presentation by
Dr Stéphane DE BOTTON

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READ THE ABSTRACT
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The acute myeloid leukaemias (AML) represent malignant proliferation of bone marrow precursors of blood cells combined with a block in maturation at an immature stage. This results in an accumulation of these immatures cells, or blasts, in the bone marrow, the blood and sometimes in other organs. In parallel, the bone marrow is unable to produce normal functioning cells. These are relatively rare conditions (around 5 per 100,000 population). Some 3,500 cases are diagnosed each year and frequency increases with age (median age around 67-70 years). If not subjected to onerous treatment, the patient succumbs within a limited time frame which depends on age, the "white cell" count on diagnosis and tumour cell cytogenetic and molecular abnormalities.

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Conventional therapy is based on first line treatment with a number of courses of intensive chemotherapy. *"In 7 cases out of 10, this can be followed with bone marrow transplantation to prevent relapse,"* explained Dr Stephane de Botton, Haematologist at Gustave Roussy and principal investigator for the phase II study. The results, presented at the ASCO Conference, offer new hope of remission for patients who have relapsed or those who are unable to tolerate standard therapy. In view of problems of tolerance linked to age, the type of AML and toxicity of these intensive treatment regimens, *"fewer than 1 patient in 2 over 65 years-of-age receives intensive chemotherapy and only 30% of those are suitable for transplantation,"* explained the Haematologist. *"And when it is refractory or in relapse, the disease becomes complex to treat and life expectation is restricted to 5-6 months."*

Olutasidenib, a selective IDH1 Inhibitor, might open the door to new therapeutic options for some of these patients. This small molecule selectively targets an enzyme mutation in type 1 isocitrate dehydrogenase (IDH1). Better known in the field of cerebral oncology, it is present in half of gliomas. A systematic search in acute myeloid leukaemia identified it in 6 to 10% of cases, such that it comprises one of the 200 genetic mutations associated with the condition. Researchers in the field believe that *"this enzyme mutation results in generation of a metabolite that prevents immature bone marrow cells from differentiating into normal blood cells,"* summarised Dr De Botton. *"Where the IDH1 mutation is present, in 30 to 40% of cases it appears to be responsible for the disease."*

By selectively targeting this mutation, Olutasidenib is believed to block its effects and restore the normal programme of blood cell differentiation. In this international phase II trial, 153 AML patients with the IDH1 mutation, who were refractory to treatment or in relapse, were given this oral medication. Of these, 123 (median age 71 years) received it for a sufficient period for assessment of its efficacy as monotherapy. All of them took this oral therapy exclusively and continued to do so until symptoms reappeared. *"Having an oral therapy which can be dispensed with monitoring at home already represents major progress in onco-haematology, where conventional treatment usually necessitates prolonged hospital admission. But, above all, the proportion of patients responding and the duration of the responses to this highly targeted agent have proved to be impressive and at least as effective as those reported with Ivosidenib, a molecule of the same class that has already been registered in the USA,"* observed Dr De Botton.

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A treatment response with disappearance of tumour cells from the blood and bone marrow and recovery of production of mature, normal functioning blood cells (complete remission) was seen in 30% of study participants. In 46% of patients tumour cells disappeared but complete recovery of normal production of blood cells did not occur. "Obtaining remission in a third is a great deal" and the response to treatment is all the more impressive in that it is long-lasting. *"The median survival period has not even been reached, which is absolutely unique,"* rejoiced Stéphane de Botton. *"Half of the responding patients are living beyond 15 months or even more if complete remission was achieved, compared with the usual 3 to 5 months".* This is an unheard of gain in survival achieved *"with an agent which is very well tolerated and without any additional toxicity when compared with other medication of the same class. The side effects proved to be completely acceptable,"* declared the Haematologist.

Two main complications were observed. Disturbed liver function tests (increased transaminases and alkaline phosphatase) necessitated temporary cessation of treatment in fewer than 10% of cases. 14% of the 123 patients enrolled in the trial developed a differentiation syndrome, which was fatal in only one case. Characterised by fever, pulmonary infiltrates and pleural effusions, this exaggerated response to the initiation of treatment is *"paradoxically a sign that it is working,"* explained Dr De Botton. Related to the reactivation of differentiation of blood cells, this syndrome, can, however, be controlled by high-dose corticosteroid therapy in hospital. *"Thus, this complication can generally be mastered over 48 hours, allowing normal blood cells to reappear very rapidly."*

At present, Ivosidenib, the first IDH1 inhibitor approved in the USA, is available in France through the ATU (authorisation for temporary use) system. It is currently being investigated in phase III trials in combination with standard therapies including intensive chemotherapy. While these targeted agents are not yet part of standard therapy, *"they will certainly become so for refractory or relapsed AML where the IDH1 mutation is present, thus broadening the range of options for a disease which is certainly uncommon, almost an orphan disease, and which has been very difficult to treat up till now before the advent of combined therapy with reference drugs,"* judges Dr De Botton.

ABOUT

GUSTAVE ROUSSY
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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. 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 specialised in the treatment of rare cancers and complex tumours and it treats all cancers in patients of any age. Its care is personalised 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**

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