PRESS RELEASE

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NATURE MEDICINE

A MAJOR INTERNATIONAL CLINICAL TRIAL SHEDS NEW LIGHT ON A PAEDIATRIC BRAIN CANCER

BIOMEDE 1.0, sponsored and coordinated by Gustave Roussy, is the largest clinical trial ever conducted in diffuse intrinsic pontine glioma, an aggressive paediatric cancer in which survival rarely exceeds one year. The findings, published in the journal *Nature Medicine*, chart a new biological map of the disease, identify patient response biomarkers, and document the prolonged survival of four children — opening concrete avenues for the therapies of tomorrow. This study was led principally by a team of researchers from Inserm, the Université Evry Paris-Saclay, the Université Paris-Saclay, and Gustave Roussy.

Diffuse intrinsic pontine glioma (DIPG) remains a paediatric tumour carrying a grave prognosis. Its deep location within the brain and its highly infiltrating nature, in proximity to areas governing vital functions, rule out surgery as a therapeutic option.

Radiotherapy remains to this day the only treatment to have demonstrated a transient benefit, without offering a cure. The median survival of patients is under one year — a prognosis that has not improved in 50 years. The development of new therapies, therefore, remains a pressing priority, with approximately 40 to 50 children and young adults diagnosed with DIPG each year in France.

The advances of precision medicine

Some fifteen years ago, knowledge of this tumour remained severely limited. No biological tools existed to characterise the disease, and research was hampered by the fragmentation of clinical trials — typically small-scale and yielding little in the way of meaningful scientific insight.

Progress in precision medicine has transformed this outlook. First, by enabling the identification of the H3K27M mutation, present in the vast majority of DIPGs. Discovered in 2012, this genetic abnormality provided, for the first time, a diagnostic marker specific to these tumours. Subsequently, several mechanisms exploited by the tumour to grow and survive were brought to light. In DIPGs, certain cancerous cells exploit receptors on their surface — such as PDGFRA or EGFR — to receive growth signals. Others rely on an internal signaling pathway, the PI3K/AKT/mTOR pathway, to resist treatments such as radiotherapy.

Drugs capable of blocking each of these mechanisms were accordingly developed and evaluated in clinical trials, most often in combination with radiotherapy: dasatinib to target PDGFRA, erlotinib to block EGFR, and everolimus to inhibit the PI3K/AKT/mTOR pathway.

The advances of precision medicine

Drawing on these new insights, Gustave Roussy launched the BIOMEDE 1.0 phase II study in 2014 — the first randomised international clinical trial dedicated to children, adolescents, and young adults with DIPG. This innovative trial was built upon a comprehensive genetic analysis of each patient's tumour, carried out via biopsy, which both confirmed the diagnosis (presence of the H3K27M mutation) and guided patients towards targeted treatments. Patients were subsequently allocated to one of the three treatment arms according to their tumour's molecular profile, receiving either erlotinib, everolimus, or dasatinib. The allocation between the three treatments was thus guided by tumour biomarkers, making BIOMEDE — sponsored by Gustave Roussy — the first precision medicine trial of this scale in DIPG.

All three treatments were administered alongside radiotherapy, then continued for as long as the disease showed no progression, with the primary objective of improving survival. In parallel, the teams at Gustave Roussy conducted an extensive research programme, analysing the patients' tumours in molecular detail. This work deepened understanding of the disease and identified potential avenues for tailoring treatments to each patient.

The trial, which randomised 233 patients between 2014 and 2019, brought together teams from France, the United Kingdom, Denmark, Sweden, Australia, Spain, and the Netherlands. France, as trial coordinator, enrolled most patients (72%). Each tumour underwent thorough molecular analysis, enabling the construction of the largest biological database ever assembled on this disease.

Major biological discoveries

The results of BIOMEDE 1.0, published in *Nature Medicine*, offer unprecedented biological insight into DIPGs. They identify the principal determinant of patient survival duration: mutation of the TP53 gene, which carries a poor prognosis. Patients whose tumours harboured this mutation sadly survived for shorter periods than others. This finding has now been incorporated to improve patient stratification in future trials and to adapt clinical management from the time of diagnosis.

As regards the three targeted therapies evaluated, none achieved a significant improvement in overall patient survival. In terms of tolerability, however, everolimus stood apart from the other two by virtue of a more favourable profile, with notably fewer adverse effects and a lower rate of treatment discontinuation due to toxicity (3%, compared with 14% for dasatinib and 20% for erlotinib). This outcome establishes it as the reference treatment for the next generation of trials.

Four long-term surviving patients

BIOMEDE 1.0 documented four so-called "long responder" patients — diagnosed with DIPG more than six years ago and still alive today. In a disease where median survival does not exceed eleven months, these cases represent far more than mere exceptions: they constitute an unprecedented scientific window onto the mechanisms that can, in rare circumstances, allow the body to achieve durable control over the tumour.

In-depth analysis of the tumours of these four survivors, along with approximately ten other patients who survived beyond two years, offers a preliminary explanation. Whilst they share no common genetic profile — thus ruling out the hypothesis of a simple pre-existing favourable biological anomaly — their tumours do exhibit a tumour microenvironment distinct from that of other patients, suggesting a more active local immune response. These observations place immunotherapy targeting the tumour microenvironment at the forefront of the next generation of trial development.

"*BIOMEDE 1.0 is the culmination of ten years of collective effort to finally deliver a rigorous answer. The results have given us a solid foundation on which to build the next steps. We continue to investigate why these four children are in long-term remission*," said Dr Jacques Grill, paediatric oncologist, co-director of Inserm Research Unit U1360 and member of the Genomics and Oncogenesis of Paediatric Brain Tumours team at Gustave Roussy.

"*Making biopsy a condition of entry into the trial was a bold undertaking in 2014. Yet it is precisely thanks to this approach that we now hold the largest biological database ever assembled on this disease. The TP53 mutation, the mTOR pathway, and the microenvironment of long survivors are all keys that BIOMEDE has enabled us to identify*," added Professor Marie-Anne Debily, Professor at the Université Evry Paris-Saclay and researcher within Inserm Unit U1360 (Université Paris-Saclay) at Gustave Roussy.

Two new clinical trials already underway

Armed with these new biological insights, the teams at Gustave Roussy have already launched BIOMEDE 2.0, the only international comparative clinical trial dedicated to malignant gliomas of the midline and brainstem — a family of malignant brain tumours that encompasses DIPGs but extends further, affecting other deep structures of the brain and spinal cord in both children and adults. Open across ten European countries, it is recruiting 368 patients over four years and comparing everolimus — now established as the new therapeutic standard through BIOMEDE 1.0 — with ONC201, the first representative of a new class of anticancer agents.

In parallel, Gustave Roussy is leading BIOMEDE IA, a pioneering research programme harnessing artificial intelligence to analyse the biological, genomic, and imaging data accumulated throughout the trial, to identify information beyond the reach of human analysis. "*BIOMEDE 2.0 and BIOMEDE IA embody the promise that the data from BIOMEDE 1.0 will serve the children who will be diagnosed tomorrow*," concluded Dr Grill.

This work was supported by a Hospital Clinical Research Programme from the INCa and by the associations Imagine For Margo, l'Étoile de Martin, les Amis d'Antoine, La Ligue contre le cancer du 74 et du 94, La marche de l'écureuil, the association Lisa Forever, and all donors to the "*Guérir le cancer de l'enfant au 21e siècle*" campaign of the Fondation Gustave Roussy. BIOMEDE 1.0, BIOMEDE 2.0, and BIOMEDE IA have all been made possible through the support of the association Imagine for Margo.

Source

Targeted therapies plus radiotherapy for diffuse intrinsic pontine glioma: the randomized phase 2 BIOMEDE trial

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About Gustave Roussy

Ranked first in France, first in Europe and sixth in the world, Gustave Roussy is a centre of global expertise entirely dedicated to patients living with cancer. The Institute is a founding pillar of the Paris-Saclay Cancer Cluster. Source of therapeutic innovations and diagnostic breakthroughs, the Institute welcomes more than 54,000 patients each year, including 2,760 children and adolescents, and develops an integrated approach combining research, care and teaching. An expert in rare cancers and complex tumours, Gustave Roussy treats all cancers at all stages of life. It offers its patients personalised care that combines innovation and humanity, taking into account both care and the

physical, psychological and social quality of life. With 4,000 employees at two sites, Villejuif and Chevilly-Larue, Gustave Roussy brings together the expertise essential for high-level cancer research; 40.5% of treated patients are included in clinical studies. To find out more about Gustave Roussy and follow the Institute's news: www.gustaveroussy.fr/en , X, Facebook, LinkedIn, Instagram et Bluesky.

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