PRESS RELEASE

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NATURE

INTRA-TUMOUR IMMUNOTHERAPY: MOBILISING THE IMMUNE SYSTEM AGAINST CANCER WHILE AVOIDING TOXICITY TO THE BODY

Published in the journal *Nature*, the NIVIPIT study, led by Gustave Roussy and conducted by researchers from Inserm and the University of Paris-Saclay, demonstrates the benefit — in terms of both efficacy and safety — of administering an immunotherapy treatment intratumorally that is typically given intravenously. This approach, carried out via interventional radiology — a field in which Gustave Roussy is a leading actor — involves injecting the treatment directly into the patient's tumour to increase its effectiveness while limiting side effects.

Immunotherapy treatments have revolutionized cancer management over the last decade. The immunomodulatory antibodies ipilimumab (anti-CTLA4) and nivolumab (anti-PD1) belong to the class of T-lymphocyte checkpoint blockers. They aim to train the patient's immune system to attack their cancer more effectively. In the case of metastatic melanoma, a form of skin cancer that previously had a poor prognosis, advances in research have now made it possible to achieve a ten-year survival rate of 52%.

However, intravenous administration of these two immunotherapies is associated with severe adverse effects in approximately 60% of patients. Some of these effects may be irreversible or even lead to death in rare cases, which limits the use of this combination to around one in two patients in routine practice, despite its benefits in terms of efficacy.

The rationale for intratumoral injection

It was to address this issue — and thereby enable a greater number of patients to benefit from immunotherapy — that the NIVIPIT phase 1b randomized trial was developed, with results now published in *Nature*. This multicentre study was led by the dermatology team of Prof. Caroline Robert at Gustave Roussy, in collaboration with the teams of Prof. Stéphane Dalle at the Hospices Civils de Lyon, Prof. Céleste Lebbé at AP-HP (Paris), and Prof. Nicolas Meyer at the CHU de Toulouse. It was conducted at Gustave Roussy within the BIOTHERIS Clinical Investigation Centre (CIC), a structure funded by the DGOS and Inserm dedicated to intratumoral immunotherapy. This innovative treatment, based on the technical expertise of interventional radiology, consists of injecting the treatment directly into the core of the tumour rather than administering it intravenously throughout the body. Intratumoral immunotherapy

allows the use of lower doses while powerfully stimulating the immune system precisely where the cancer is present, thereby reducing adverse effects for patients.

In total, 61 patients with metastatic melanoma who had never previously received immunotherapy were enrolled in the trial between 2016 and 2019. They were then randomly assigned to one of two groups: the first received the standard treatment for this indication combining two intravenous immunotherapies, an anti-PD-1 (nivolumab) and an anti-CTLA-4 (ipilimumab), while the other group received an innovative approach combining intravenous nivolumab with ipilimumab — the more toxic of the two immunotherapies — injected directly into the tumour at high concentration but at a total dose ten times lower than the dose typically administered intravenously. The objective of NIVIPIT was to evaluate the safety, tolerability and efficacy of this strategy by analysing tumour response and adverse effects over the first six months, as well as patients' overall survival.

A safer approach

The results indicate that the primary endpoint of the study was achieved. Severe autoimmune side effects (colitis, skin rashes, hepatitis, etc.) were far less frequent in patients who received the direct intratumoral injection (22.6%) than in those treated intravenously with both molecules (57.1%), representing a reduction of more than half in severe toxicity. The safety profile observed with the intratumoral approach is comparable to that of anti-PD1 monotherapy alone. Achieving such a level of safety for a treatment combining two molecules demonstrates the value of intratumoral immunotherapy in limiting side effects.

Regarding the efficacy of the approach, the results are again very encouraging: 65.7% of tumours treated with intratumoral immunotherapy regressed, and 50% of "distant" lesions (those not injected) also regressed.

Discovery of predictive markers

Beyond the clinical results, the NIVIPIT trial researchers succeeded in decoding the mechanism underlying the anti-tumour immune response. By precisely analysing the tumour microenvironment, they discovered a counter-intuitive phenomenon: for the treatment to work, the tumour must present a specific immune balance between cancer-fighting cells (lymphocytes) and cells known to prevent the immune system from recognising and attacking tumour cells (macrophages and regulatory T cells).

This immune trio, detected before the start of treatment, makes it possible to predict which patients will benefit from a durable response. The study shows that once the treatment is administered, the cells previously considered to be allies of the cancer disappear from within the tumours, giving way to a significant increase in cancer-killing molecules (granzymes). These biological findings were made possible by technical and logistical innovations enabling immediate analysis of fresh tumour biopsies, whereas the current diagnostic routine relies on fixed or frozen tissue.

This cutting-edge expertise in therapeutics and tumour biology confirms that the intratumoral approach is not only less toxic but represents a strategy for the future — one that can strike cancer with surgical precision from the earliest stages of the disease.

"*By using interventional radiology to directly target the core of the tumour, we have shown that it is possible to trigger a powerful immune response while halving toxicity for the patient. This is a paradigm shift: the precision of the local procedure makes it possible to overcome the side effects of conventional intravenous treatments, thus opening the way to an earlier and safer use of these therapeutic combinations,*" comments Prof. Lambros Tselikas, Deputy Head of the Department of Anaesthesia, Surgery and Interventional Medicine at Gustave Roussy, Professor of Interventional Radiology at the University of Paris-Saclay, and Director of CIC BIOTHERIS.

"*Beyond clinical innovation, our in-depth biological analyses have revealed a crucial mechanism: the local injection does not merely destroy the targeted tumour — it reprogrammes the patient's immunity. We observed that the initial presence of certain regulatory cells, which were thought to be associated with a poor prognosis, is in fact a favourable context for this treatment to effectively awaken the body's natural defences. These results now allow us to better understand the tumour ecosystem to identify, from the point of diagnosis, the patients who will benefit most from this strategy*," explains Prof. Aurélien Marabelle, medical oncologist, Professor of Clinical Immunology at the University of Paris-Saclay, Director of the Translational Research Laboratory in Immunotherapy at Gustave Roussy, and Scientific Director of CIC BIOTHERIS.

"*This is the first time that the benefit of injecting this type of immunotherapy directly into the tumour has been demonstrated, and this first study conducted in patients with metastatic melanoma has proven it, particularly in terms of toxicity. We have already initiated a new clinical study for localised melanomas in which the combination of both immunotherapies is administered intratumorally before surgery (NCT07230613), to reduce relapses while protecting patients from potential treatment-related toxicities*," concludes Prof. Caroline Robert, Head of the Dermatology Department within the Department of Oncological Medicine at Gustave Roussy, Professor of Dermatology at the University of Paris-Saclay, and Principal Investigator of the NIVIPIT study.

Source

Safety and Efficacy of Intratumoral Anti-CTLA4 with Intravenous Anti-PD1
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Lambros Tselikas, Sandrine Susini, Matthieu Texier, Andrey Yurchenko, Emilie Routier, Mona Amini-Alde, Edi Tihic, Séverine Mouraud, François-Xavier Danlos, Sami Ammari, Thibault Raoult, Séverine Roy, Delphine Bredel, Siham Farhane, Lydie Cassard, Irma Molinaro, Alexander Eggermont, Jean-Charles Soria, Laurence Zitvogel, Christophe Massard, Angelo Paci, Thierry de Baere, Jean-Yves Scoazec, Nathalie Chaput, Sergey Nikolaev, Nicolas Meyer, Céleste Lebbé, Stéphane Dalle, Caroline Robert, Aurélien Marabelle

The journal's editor has published a 'Clinical Briefing' article on the study in the same issue of *Nature*.

Background on 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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