PRESS RELEASE
October 11, 2023

Meeting of the International Society of Pediatric Oncology (SIOP) 2023

Pediatric cancers: Institut Curie's expertise at the forefront of the international scene

From October 11 to 14, 2023, in Ottawa (Canada), the world's scientific and medical community comes together to present the latest breakthroughs in pediatric oncology. Physicians and researchers from Institut Curie will in attendance with promising announcements to improve treatment of young patients. It will be an opportunity to communicate the excellent results of a new targeted therapy to treat the youngest patients suffering from infantile fibrosarcoma, and more effective and less invasive innovative therapeutic strategies for treating certain brain tumors and retinoblastoma.

"Through the progress achieved over the past thirty years, the survival rate for children with cancer is over 80% at 5 years, but more progress needs to be made. For these sick chidlren and their families, research is crucial in order to find new paths to recovery with the fewest possible side effects. At Institut Curie,, through our dedicated center: SIREDO (Care, Innovation & Research in Childhood, Adolescent & Young-Adult Oncology), our teams work each day to innovate and develop new therapeutic solutions and improve treatment. The attendance of our experts at the SIOP meeting is testimony to the quality of the work performed" agree **Prof. Alain Puisieux, Director of the Institut Curie Research Center and Prof. Steven Le Gouill, director of the Hospital Group at Institut Curie.**

- Institut Curie's major announcements at SIOP 2023-

Infant cancer /

- Larotrectinib: a **brand-new targeted therapy for infantile fibrosarcoma which is 80% more effective than classic treatments,** and which is administered very easily in the form of a syrup.
- A study to analyze spontaneous regressions in infantile fibrosarcoma.

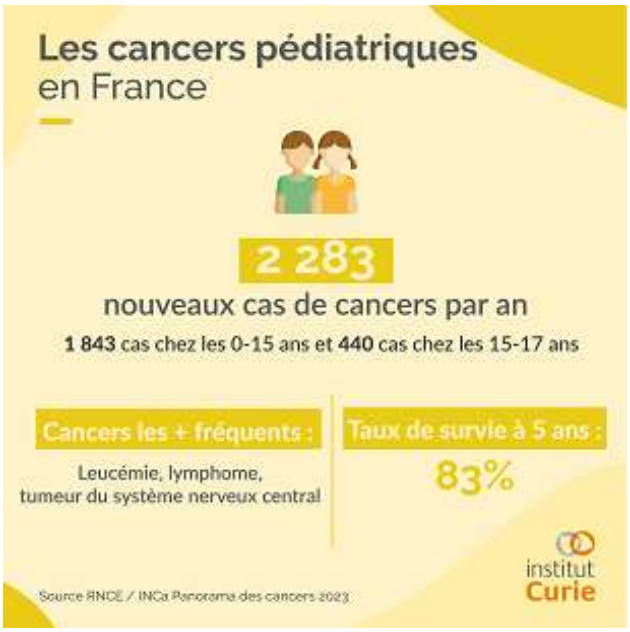
Liquid biopsies /

- Combining two **latest-generation circulating tumor DNA sequencing techniques to improve diagnosis and treatment of rhabdomyosarcoma,** the most common malignant mesenchymal tumor in children and adolescents.
- **Improving treatment of retinoblastoma** to map genetic anomalies using a sample of a few droplets of ocular fluid.

Proton therapy /

Results reveal the utility of **combining surgery and proton therapy in the treatment of craniopharyngioma, a rare brain tumor,** achieving improved quality of life, in particular enabling children to attend normal schooling

The detailed results of each study are presented in the annexed factsheets



Key figures and info

370 new patients (children and adolescents) treated each year at Institut Curie

70 scientists, **60** health professionals, **6** research teams

SIREDO (Care, Innovation & Research in Childhood, Adolescent & Young-Adult Oncology): **France's leading center for pediatric oncology care and research.**

Institut Curie's SIREDO center is headed by **Dr. Olivier Delattre**, pediatric oncologist and director of the Cancer, Heterogeneity, Instability and Plasticity unit (Inserm, Institut Curie) and winner of the Inserm 2022 Grand Prix.

Oral communications at SIOP 2023 /

SOFT TISSUE SARCOMAS session, October 14, 2023

> Comparison of Clinical Outcomes of Patients With Infantile Fibrosarcoma Treated With Larotrectinib in the SCOUT Study Versus Historical Cohort - THE EPI-VITRAKI STUDY **(Dr. Daniel Orbach, speaker)**

*> Should we consider alveolar soft part sarcomas in children and young adults in the same way? The French National Netsarc+ Network experience (***Dr. Daniel Orbach, last author)**

> *Sequential genomic analysis using a multisample/multiplatform approach to better define rhabdomyosarcoma progression and relapse* **(Dr. Gaelle Pierron, last author)**

INTERESTING SOLID TUMORS session, October 14, 2023

> Does spontaneous infantile fibrosarcoma regression exist? **(Dr. Daniel Orbach, speaker)**

Press contacts:

Catherine Goupillon-Senghor - catherine.goupillon-senghor@curie.fr/+33(0) 6 13 91 63 63
Elsa Champion – elsa.champion@curie.fr/+33(0)7 64 43 09 28
Mélany Mandikian – melany.mandikian@havas.com/+33(0)1 58 47 89 48

About Institut Curie

Institut Curie, France's leading cancer center, combines an internationally-renowned research center with a cutting-edge hospital group, treating all types of cancer, including the rarest. Founded in 1909 by Marie Curie, Institut Curie employs 3,700 researchers, physicians, and health professionals across three sites (Paris, Saint-Cloud, and Orsay), all of whom contribute to its three missions of treatment, teaching, and research. A foundation with public utility status, Institut Curie is authorized to accept donations and bequests, and thanks to the support of its donors, is able to accelerate discoveries and improve patient treatment and quality of life. Find out more at: **curie.fr**

INFANT CANCER FACTSHEET

Infantile fibrosarcoma: targeted therapies that are 80% more effective than chemotherapy


© Institut Curie/Pedro Lombardi

Infantile fibrosarcoma is a soft-tissue sarcoma in children, affecting newborns and infants aged on average less than three months. In order to treat it, if surgery is not possible, two options can be considered: classic chemotherapy or a new targeted therapy named larotrectinib. This medication very specifically targets tumors carrying a genetic anomaly, almost constant in the cells of infantile fibrosarcoma (*neurotrophic tyrosine receptor kinase*).

The first comparative study between larotrectinib and chemotherapy

In order to characterize the benefits of this new molecule, the team of Dr. Daniel Orbach, head of the clinical department of the Care, Innovation & Research in Childhood, Adolescent and Young-Adult Oncology center, SIREDO, at Institut Curie, compared this targeted therapy with classic chemotherapy used historically, within the context of a study (EPI-VITRAKVI). The results are conclusive.

"There is an 80% lower risk of relapse and need for additional treatment, such as radiotherapy, amputation or second-line treatment, with larotrectinib," explains Dr. Daniel Orbach. "It is all the more interesting since the new medication is also much simpler to administer than chemotherapy: a spoonful of syrup given morning and evening to the very young children at home by the parents, as opposed to a central catheter and chemotherapy injections weekly in the outpatient department."

Better treatment for all chidlren suffering from infantile fibrosarcoma in France

Dr. Daniel Orbach, with the help of Bayer, the laboratory that launched the molecule, presented these promising results to the *Haute Autorité de Santé* (HAS), which led to authorization of reimbursement for larotrectinib in France in March 2023. "These means that all infants with this soft tissue tumor in France can receive this new molecule," enthuses Dr. Orbach. "Until now, this targeted therapy was proposed only as part of a prospective protocol, named SCOUT, which took place mainly in Ile-de-France (greater Paris region)."

Today the research continues. We have to check whether the molecule causes adverse effects in the long term. "The study is also continuing to analyze the effectiveness of larotrectinib for patients with other tumors carrying the NTRK anomaly, such as common adult cancers and brain tumors in children," continues Dr. Orbach.

Oral communication/- SOFT TISSUE SARCOMAS Session, October 14, 2023 - Dr. Daniel Orbach - *Comparison of Clinical Outcomes of Patients With Infantile Fibrosarcoma Treated With Larotrectinib in the SCOUT Study Versus Historical Cohort - THE EPI-VITRAKI STUDY*

Spontaneous regression remains very rare in infantile fibrosarcoma

Infantile fibrosarcoma is a rare malignant tumor (4.3 cases per million children per year) that occurs mainly in children under one year of age. For this reason it may be tempting to hope for spontaneous regression to avoid treating newborn babies. But is this a good idea? To find out, **Dr. Daniel Orbach and his colleagues collected cases of infantile fibrosarcoma that regressed alone in France, Germany, Dublin and a part of Italy between 2006 and 2016. The result? Fewer than 5% of them regressed spontaneously.** "Given that this cancer carries a good prognosis, waiting to see how it evolves dos not seem like a reasonable option," explains Dr. Daniel Orbach. "The tumors grow quickly and even though they do not frequently metastasize, they may end up requiring disfiguring surgery. It may be possible to delay the operation for a few weeks, to give a newborn some more time, but in most cases the tumor will not disappear by itself."

As for the question of which mechanisms may cause the occasional spontaneous regression of infantile fibrosarcoma, it remains unanswered. As this physician-researcher explains, "there are so few cases that there is not enough data to study the subject."

Oral communication/INTERESTING SOLID TUMORS Session - October 14, 2023 - Dr, Daniel Orbach – *Does spontaneous infantile fibrosarcoma regression exist?*

LIQUID BIOPSIES FACTSHEET

An innovative method for better monitoring of rhabdomyosarcoma

© Institut Curie/Thibaut Voisin

In rhabdomyosarcoma (RMS), the most common malignant mesenchymal tumor in children and adolescents, genetic alterations may be of different types, affecting the number, structure or sequence of chromosomes and the genes that they carry. How can we detect and identify those that may constitute appropriate therapeutic targets? Dr. Gaëlle Pierron, assistant head of Institut Curie's somatic genetics unit at Institut Curie, and her team, have found a solution: combining two tumoral DNA Next Generation Sequencing (NGS) techniques.

Combining exhaustive sequencing and targeted sequencing

The first will focus on a panel of around forty genes and areas of interest in RMS, to identify the mutations (part of the gene contains a writing error) but also the translocations (part of the gene has been moved to another area of the genome). Since few genes are sequenced in this first analysis, they can be sequenced a significant number of times, which provides a high level of sensitivity. The second, known as shallow sequencing, will be less sensitive, but will analyze the entire genome, thus identifying areas gained or lost in the sample studied.

"By combining these two methods we can identify different types of alterations and draw up a molecular identity map for each tumor," announces Dr. Gaëlle Pierron. The bioinformatics tools needed for the full analysis of this sequencing have been successfully developed and tested. **The method was applied to 35 tumors and helped identify mutations presented at diagnosis, as well as those that appeared at relapse.**

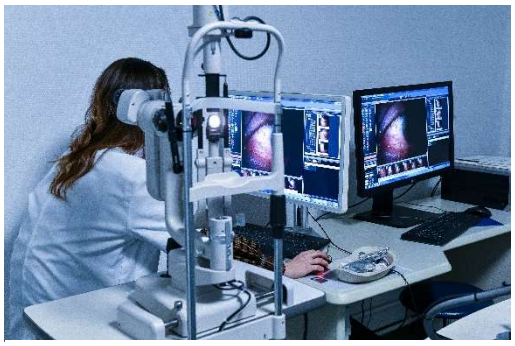
Monitoring the patient, anticipating relapse and adapting treatment

"This offers three opportunities: firstly, to obtain the tumor's properties at the time of diagnosis and thus define appropriate treatment targets; secondly, to observe the effects of the treatment via changes in the circulating tumor DNA; and lastly, to detect any relapse at a early stage", summarizes Dr. Gaëlle Pierron. **The method developed does not require direct access to the tumor, since it uses a liquid biopsy (via blood sample).** Any relapse can therefore de detected on the circulating tumor DNA isolated in the plasma, via a simple blood sample.

The next step will involve making these tools widely available: the new FAR-RMS protocol to be implemented on an international scale by the end of the year will aim to use the method in a clinical setting. Routine access to the molecular portrait of RMS, as well as monitoring throughout treatment of alterations identified, will enable clinicians to adapt treatment for each patient and offer innovative treatments.

Oral communication/SOFT TISSUE SARCOMAS Session - October 14, 2023 - Sequential genomic analysis using a multisample/multiplatform approach to better define rhabdomyosarcoma progression and relapse – last author: Dr. Gaëlle Pierron, Speaker Dr. Henri De Traux

Retinoblastoma: no demonstrated connection between molecular markers of aggressiveness and intensity of treatment



© Institut Curie

Retinoblastoma affects one child in 15-20,000. This tumor of the retina can be easily treated if diagnosed on time, often via chemotherapy followed by ophthalmological treatment (laser, cryotherapy) or with ophthalmological treatment alone (sometimes with the need to remove the eye if the disease is advanced).

Today new options are becoming available, with the possibility for doctors to sample droplets of aqueous humor in the rear chamber of the eye to map the genetic anomalies of the tumor. Using this method, some scientists have proposed using this information to improve patient treatment: if molecular markers of aggressiveness are identified, they could be used to classify retinoblastomas and thus adapt the level of treatment.

The connection between molecular markers, a histological risk factor and use of additional treatment is in question

A leading national center for retinoblastoma, Institut Curie has studied the relationship between molecular markers of aggressiveness and the histological analysis of tumors sampled, in order to guide the intensity of post-operative treatment.

"We selected 87 patients with retinoblastoma who had already undergone enucleation", explains Dr. Yassine Bouchoucha, assistant chief resident in Institut Curie's pediatrics department "to map the molecular identity of the disease by sequencing fragments of the tumor DNA."

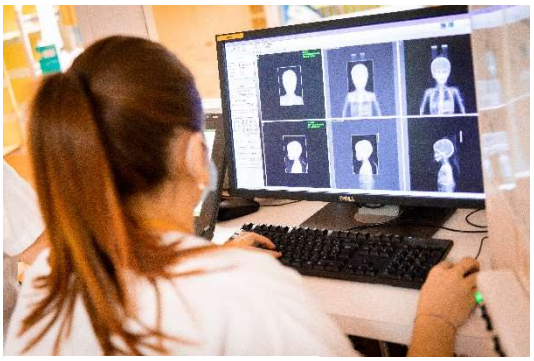
The study found no connection between the biomarkers and the necessary intensity of post-operative treatment. In particular, children whose tumor showed DNA fragments with aggressiveness markers (corresponding to amplification of the MYCN gene) did very well without the need for additional chemotherapy. Additional studies are therefore needed in order to use molecular markers in a new risk classification for retinoblastoma, and achieve better adaptation of treatments for each patient.

Usefulness of aqueous humor biopsy for genetic counseling

Sampling a few droplets of aqueous humor, now a routine practice at Institut Curie, is already helping to improve genetic counseling. These biopsies help identify children affected by retinoblastoma with a genetic predisposition, linked to a constitutional anomaly of the RB1 gene, and thus a higher risk of sarcoma in adulthood. "This systematic biopsy of aqueous humor in children's eyes (with the parents' consent), allows us to search for various markers of aggressiveness," concludes Dr. Yassine Bouchoucha. "These results provide the substrate necessary for the studies that will ultimately help reduce treatments for children whose retinoblastoma has no markers of aggressiveness, with the ultimate goal of reducing long-term after-effects. It is an avenue that merits exploration."

Poster presentation: Prognostic value of molecular markers in unilateral retinoblastoma treated by first-line enucleation. Yassine Bouchoucha, Jessica Le Gall, Alexandre Matet, Sarah Mezghani, Hrant Ghazelian, A. Savignoni, Meriam Mahmoudi, Clément Hua, Jennifer Carrière, Marion Gauthier-Villars, Arnaud Gauthier, Paul Fréneaux, Hervé Brisse, Nathalie Cassoux, Livia Lumbroso-Le Rouic, Isabelle Aerts, François Doz, François Radvanyi, Liesbeth Cardoen, Lisa Golmard.

Craniopharyngioma: an appropriate and effective therapeutic approach



© Institut Curie/Thibaut Voisin

Craniopharyngioma is a rare tumor (6 to 9% of brain tumors in children and adolescents), derived from embryonic tissue. It is generally benign, but is located in a complex area, close to the optic chiasma, the hypothalamus and the pituitary gland. **Development of this tumor therefore produces risks of visual deterioration, but also loss of the feeling of fullness, leading to morbid obesity if it infiltrates the hypothalamus.**

The issue of conservative surgery followed by proton therapy

Treatment of craniopharyngioma is first of all surgical, with the need to avoid visual pathways and the hypothalamus. "This is why the therapeutic approach via partial surgery, preserving the areas at risk and followed by radiotherapy (to eliminate the tumor residue), has now achieved consensus, particularly when the craniopharyngioma has invaded the hypothalamus," explains Dr. Claire Alapetite, oncological radiotherapist at Institut Curie.

Proton therapy is the preferred treatment for children, rather than classic radiotherapy using X-ray technology: when focused on the tumor, it helps spare the surrounding brain parenchyma. "The aim of our study was to confirm the effectiveness of this combined therapy in young patients," continues Dr. Claire Alapetite. "Furthermore, we attempted to assess the feasibility of increasing proton doses in the tumor volume, with the aim of limiting the risk of relapse, which occurs in 10 to 15% of cases."

Fewer relapses ... and schooling problems

The results of this study, involving 33 patients (included from 2010 to 2015) with median follow-up of 9 years, show the utility of this approach. "Children monitored for craniopharyngioma often experience memory and attention problems, leading to difficulties in school. Combined therapy enabled 24 patients to have a normal school experience," Dr. Claire Alapetite. "It also helped reduce the risk of obesity, to preserve normal visual acuity at least for one eye in 21 patients, and to delay the occurrence of any relapse: six patients experienced a relapse, but it was delayed, occurring at an average of 7 years after treatment."

However, the study could not establish a connection between an increased proton dose and control of the tumor - since increase of the dose, according to tolerance of the visual pathways, was possible in only five children. "Given that these five young patients experienced neither relapse nor excessive reaction, an increase in the dose for the tumor volume could be suggested in selected cases, and could bring about a drop in the risk of relapse," concludes Dr. Claire Alapetite. "To confirm these benefits, multi-disciplinary follow-up of young patients suffering from craniopharyngioma is vital in the long term, in terms of both control of the disease and quality of life."

Poster presentation. M. Cornen et al., Combined Approach for Craniopharyngioma in Children with conservative Surgery and Protontherapy: late Analysis of a Phase II Study to examine Feasibility of Dose Escalation (last author: Dr. Claire Alapetite).