PRESS RELEASE
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Immunotherapy, circulating biomarkers, epidrugs, cancer vaccines... Institut Curie doctors at the ASCO 2023 Annual Meeting

From June 2 to 6 in Chicago, the American Society of Clinical Oncology (ASCO) will bring together the global scientific and medical oncology community. This annual event is attended by the world's leading oncology experts — including Institut Curie researchers and doctors — to showcase and discuss pioneering studies, groundbreaking findings, and new therapeutic strategies for fighting cancer.

"*Boasting over 2,000 posters and multiple sessions covering all fields of oncology, this year's ASCO meeting promises to be packed full of intense, fruitful exchanges. For yet another year, a great many Institut Curie doctors will be attending to present their original, breakthrough research,*" explains **Prof. Steven Le Gouill, Director of the Institut Curie Hospital Group.** "*From immunotherapy and new treatment combinations to real-world data studies and the clinical value of circulating biomarkers, Institut Curie's presentations are a testimony to the excellence and international reach enjoyed by our teams, all of whom work tirelessly for an ever better level of care and treatment for cancer patients*".

- Key Points –

BREAST CANCER/Circulating biomarkers: analyzing the role they play in the blood in patients with metastatic hormone receptor-positive breast cancer

HEMATOLOGY/The long-term benefits of immunotherapy on mantle cell lymphoma after autologous transplantation

EPIDRUGS AND IMMUNOTHERAPY/Highly encouraging results in squamous cell cancers

CANCER VACCINES/A study on an anti-HPV-16 therapeutic vaccine for anogenital cancers and a trial on personalized vaccines for ENT cancers

LUNG CANCER/Conclusive studies into real-world data in small cell lung cancer and research into thrombosis risk prevention

Circulating biomarkers: analyzing the role they play in the blood in patients with breast cancer

In late 2022, the results of the PADA-1 trial were published[1], demonstrating the clinical value of using liquid biopsies in treating metastatic hormone-sensitive breast cancer for the very first time. Sponsored by Unicancer and coordinated by Institut Curie medical oncologist Prof. François-Clément Bidard, PADA-1 revealed that — **following the detection of a certain type of mutation (ESR1) in the patients' blood — a change in hormone therapy delayed the onset of the cancer's resistance to treatment and doubled progression-free survival rates.**

"Through PADA-1, we demonstrated the clinical value of a new strategy underpinned by a combination of liquid biopsy via blood sampling, and the study of circulating tumor DNA in real time," says **Prof. François-Clément Bidard, medical oncologist at Institut Curie.** *"The current findings illustrate the clinical benefits of liquid biopsy, and over and above their impact in the clinical context assessed, they pave the way for a whole new wave of research aimed at mitigating resistance to tumor treatment".*

Circulating tumor DNA from 172 patients screened

In collaboration with the Cancéropôle de Toulouse, the Institut Curie team conducted an ultra-precise study of circulating tumor DNA in multiple blood samples taken from the 172 PADA-1 trial patients in whom mutations of the ESR1 gene had been detected. The ESR1 gene encodes an estrogen receptor and is involved in resistance to hormone therapy. How does circulating tumor DNA evolve over time? Does ESR1 mutation type impact on prognosis? **Tracking the kinetics of ESR1 mutations shows that ESR1 biomarkers disappear more rapidly in patients who switched treatment, and that this disappearance is linked to better prognosis.** Two months after switching hormone therapy, the ESR1 mutation had disappeared in 71% of the patients studied, compared to just 26% in those who did not switch treatment.

This pioneering academic trial paves the way for a new cancer treatment strategy that draws on the use of liquid biopsy to monitor and target resistance that crops up over the course of treatment. In the relatively rigid world of clinical research, the PADA-1 approach is somewhat of a rarity, and has already inspired a global trial conducted by a pharmaceuticals laboratory and approved by the European (EMA) and American (FDA) agencies to demonstrate the efficacy of a new drug that is even more promising than the one tested in PADA-1.

Dynamics and type of ESR1 mutations under aromatase inhibitor or fulvestrant combined with palbociclib after randomization in the PADA-1 trial. Prof. François-Clément Bidard - Oral Abstract Session: Breast Cancer—Metastatic, June 5, 2023

[1] Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial. Bidard, Francois-Clement et al. The Lancet Oncology, Volume 23, Issue 11, 1367 – 1377 https://doi.org/10.1016/S1470-2045(22)00555-1 / **Press release dated 09/30/2022: https://presse.curie.fr/etude-pada-1-un-suivi-par-adn-tumoral-circulant-ameliore-la-survie-de-femmes-atteintes-dun-cancer-du-sein-metastatique-hormono-sensible/?lang=fr**

Other breast cancer-specific sessions:

> Treating breast cancer in older women:

Dr. Etienne Brain, medical oncologist at Institut Curie, winner of the *ASCO B.J. Kennedy Geriatric Oncology Award 2022* in June 2022, will be taking part in an educational session on June 5 entitled: "**Not Too Little, Not Too Much: Optimizing More Versus Less for the Older Patient With Breast Cancer**". This session will focus on providing care for elderly patients with localized breast cancer that requires adjusting their treatment on both a loco-regional and (neo) adjuvant systemic level, on a frequent — if not near-constant — basis, taking into consideration underlying frailty, and not automatically following guidelines for younger adults, which are riskier for elderly patients, all while pulling back from traditional notions of dose intensity and escalation that are commonplace in oncology.

On June 4, Dr. Etienne Brain will also be presenting the efficacy results for a first-line metastatic hormone therapy treatment optimized through palbociclib, a CDK4/6 inhibitor, in hormone-sensitive breast cancer patients over the age of 70 taking part in the PALOMAGE program, the largest real-life study to be conducted in this context.

> HER2+ breast cancer: a new treatment sequence analyzed in real-life conditions for the first time

HER2-positive cancer (characterized by an overexpression of human epidermal growth factor receptor 2) accounts for around 15 to 20% of all breast cancer cases. Over 20 years ago now, trastuzumab — an antibody that specifically targets the HER2 receptor — proved life-changing for women living with HER2+ cancer. More recently, the arrival of antibody-drug conjugates such as trastuzumab-deruxtecan (new molecules that enable chemotherapy to target tumorous cells ultra-precisely) provided yet another leap forward for these women's chances of survival.

Today, trastuzumab deruxtecan is indicated as second-line treatment for HER2+ metastatic breast cancer. In terms of third-line treatment, doctors focus on a combination of three drugs (targeted therapy, antibodies and chemotherapy: tucatinib + trastuzumab + capecitabine (TTC)). But how effective is this combination after a course of treatment with trastuzumab deruxtecan? **For the first time, research conducted by several cancer centers and led by Institut Curie medical oncologist Dr. Delphine Loirat is offering up insight into the efficacy of this new therapeutic sequence.** A real-world French multi-center study of 101 patients has demonstrated significant efficacy of this TTC combination after exposure to trastuzumab deruxtecan among HER2-positive metastatic breast cancer patients previously exposed to the antibody-drug conjugate.

> First-line systemic treatment with palbociclib in women aged ≥70 years presenting with hormone receptor-positive advanced breast cancer: Results from the PALOMAGE program.
> *Efficacy of tucatinib+trastuzumab+capecitabine (TTC) after trastuzumab-deruxtecan (T-DXd) exposure in Her2-positive metastatic breast cancer: A French multicentre retrospective study.*
Discussion session poster - Breast Cancer—Metastatic (June 4, 2023)

HEMATOLOGY

The long-term benefits of immunotherapy on mantle-cell lymphoma after autologous transplantation

With nearly 200,000 people diagnosed every year worldwide, including around 600 in France, mantle-cell lymphoma accounts for 2 to 10% of lymphomas (cancer of the lymphatic system). These are rare non-Hodgkin lymphomas (NHL) that affect B cells in the immune system in a region of the lymph node called the "mantle zone". Often aggressive with high recurrence rates, they affect men more than women, and more frequently those over the age of 65.

An extensive phase 3 study sparking change in standard treatment

In 2017, the findings to come out of an extensive phase 3 study (LYMA) coordinated by Prof. Steven Le Gouill demonstrated that **adding immunotherapy (rituximab, an anti-CD20 antibody) for three years following induction chemotherapy improves overall survival rates in patients with mantle-cell lymphoma** (aged under 66 at the time of diagnosis) [2].

"Five years ago, our findings helped change the standard maintenance therapy treatment for mantle-cell lymphoma. Now for the very first time, I'm proud to present the highly positive long-term data to come out of our randomized phase 3 LYMA study," said **Prof. Steven Le Gouill, hematologist, Director of the Institut Curie Hospital Group, Chairman of the LYSA and coordinator of the LYMA study**.

75% of the patients who responded to immuno-chemotherapy had not progressed seven years later

The question at the heart of the study was to find out whether if, upon stopping their maintenance therapy, patients would see their cancer return and lose the benefits of immunotherapy. In fact, the long-term results (seven years after treatment) show that **the immunological benefits persist after treatment has been stopped. 81% of recurrences arise in the three years of rituximab maintenance therapy. 19% occur once rituximab is stopped, which is low.**

However, while the number of long-term recurrences dropped, it is important to note that around 15% of patients experience recurrence early, and for these patients in particular, **therapeutic solutions are vital, despite the arrival of new molecules that did not exist when this study was launched.**

"Just a few years ago, median overall survival for patients with this rare form of lymphoma was around four years. Today, 75% of patients are alive seven years later, which points to considerable progress. Now, ***our goal is to identify the 15% of patients who are refractory to conventional approaches right from the beginning of treatment in order to provide them with suitable alternatives*** *such as Car-T cells or bispecific antibodies...which still remain to be explored,"* concludes **Prof. Steven Le Gouill.**

Very long-term follow-up of rituximab maintenance in young patients with mantle cell lymphoma included in the LYMA trial, a LYSA study. Pr Steven Le Gouill – Oral abstract session - "Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia" – June 6, 2023

[2] **Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma.** Steven Le Gouill, M.D., Ph.D. et al. for the LYSA Group. September 28, 2017. N Engl J Med 2017; 377:1250-1260 . DOI: 10.1056/NEJMoa1701769

Other hematology sessions:

Central nervous system lymphoma is a rare (2% of non-Hodgkin lymphoma) and aggressive form of cancer, with approximately 300 new cases occurring in France each year. For this pathology, Institut Curie hematologist Dr. Carole Soussain presents the results to come out of the LOC-R01 phase 1 dose escalation study sponsored by Institut Curie, which aims to improve first-line induction chemotherapy by combining either ibrutinib (a tyrosine kinase inhibitor) or lenalidomide (an immunomodulatory agent) with conventional immunotherapy chemotherapy. The top-line results paved the way for establishing the doses of the two therapies (ibrutinib and lenalidomide) that can be combined with conventional induction chemotherapy. Phase 2 of the study has been kick-started, with half the expected patients already included.

Final analysis of the phase IB part of the LOC-R01 trial, a non-comparative randomized phase IB/II study of escalating doses of lenalidomide and ibrutinib in association with R-MPV for patients with a newly diagnosed primary central nervous system lymphoma (PCNSL) – Poster session Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia (June 5).

Dr. Carole Soussain will also be chairing a ***"case-based panel discussion" on primary central nervous system lymphoma on June 2.*** *This group will discuss therapy options for patients with newly diagnosed primitive lymphoma of the central nervous system, including induction and consolidation strategies, while reviewing treatment options for recurrent and refractory illnesses.*

INNOVATIONS: FROM EPIDRUGS TO CANCER VACCINES

Epidrugs and immunotherapy: highly encouraging results in squamous cell cancers

The PEVO clinical trial sets out to evaluate a ground-breaking therapeutic approach: **combining immunotherapy (pembrolizumab) with an epigenetic drug (vorinostat).** The trial was rolled out across 112 patients affected by squamous cell carcinoma recurring in several locations (the ENT area, the lungs, the cervix, the vulva, the penis, the anal canal). These types of cutaneous tumor involve similar molecular alterations that justify shared therapeutic strategies.

"*We developed this unprecedented combination due to the fact that because the epidrug modulates some gene expression, it could improve immunotherapy efficacy,*" explains **Prof. Christophe Le Tourneau, medical oncologist, head of Institut Curie's Early Clinical Trials department (D3i), and head of the PEVO trial. "The results point to highly encouraging anti-tumor activity, particularly in cancer of the anal canal and cervical cancer."**

The efficacy results are very encouraging, with response rates sitting around 31 to 39% (compared to 13 to 15% with conventional treatment). Furthermore, patients with cancer of the anal canal had an overall survival rate of over 18 months, which is significant.

The trial is financed by European funding and the ARC. The project is coordinated by Dr. Maud Kamal, head of the D3i's scientific coordination cell.

Breakthroughs in cancer vaccines

✓ The anti-HPV-16 therapeutic vaccine in anogenital cancer

Human papillomavirus type 16 (HPV-16) is linked to a number of different types of cancer for which therapeutic options are restricted to the metastatic stage. The results of a randomized phase 2 study comparing the effects of a vaccine aimed at some HPV-16 proteins and immunotherapy in patients with anogenital cancers (anal, vulva, cervix, penis) are presented here.***"Our study reveals that the vaccine induces an immune response in almost all patients,"*** says study coordinator Prof. Christophe Le Tourneau. "*Furthermore, this research offers up some encouraging preliminary data on the vaccine's efficacy.*"

✓ Personalized vaccines for ENT cancers

Prof. Christophe Le Tourneau will also be presenting the findings to come out of a randomized phase 1 study conducted among patients with ENT cancer. Until now, immunotherapy has only had a limited impact on treating ENT cancers, but this breakthrough trial aims to assess another vaccine strategy that draws on **personalized vaccines. Each vaccine is developed individually based on individual tumor sequencing with the help of artificial intelligence-powered tools.** The results show that vaccination was well tolerated, and no recurrence was observed in the group of patients who were vaccinated at the end of treatment after a median period of 10.4 months of follow-up. *"The study also shows that all the patients developed an immune response with the personalized vaccine: a highly positive, highly promising sign going forward,"* adds **Prof. Christophe Le Tourneau.**

"Phase II basket trial evaluating the efficacy of pembrolizumab (PE) combined with vorinostat (VO) in patients (pts) with recurrent and/or metastatic squamous cell carcinoma (SCC)" and *"Immunogenicity and clinical activity of tipapkinogen sovacivec (TG4001), an HPV-16 cancer vaccine: A randomized phase 2 study in advanced anogenital cancers"*
Poster session Developmental Therapeutics—Immunotherapy (June 3).
"Safety and Immunogenicity of TG4050; a personalized cancer vaccine in head and neck carcinoma".
Poster session "Head and Neck Cancer" (June 5)

LUNG CANCER

✓ Conclusive studies into real-world data in small cell lung cancer

Lung cancer is the leading cause of cancer death throughout the world, with around 1.8 million deaths in 2020[3]. It is the third most prevalent cancer in France, and its incidence is rising sharply among women. Among the two main types of lung cancer, small cell lung cancer accounts for up to 15% of lung cancer diagnoses in France.

A new marine algae-derived molecule

For patients with recurring small cell lung cancer, there is currently no satisfactory therapeutic option. **Lurbinectedine is a new drug (derived from marine algae, with anti-tumor properties as a result of its action on tumor DNA) available in France with early access for these patients.** Conducted with the Intergroupe Francophone de Cancérologie Thoracique (IFCT), the LURBICLIN study analyzed real-world data from French patients who had received lurbinectedine to assess this new drug's effectiveness. The results show that lurbinectedine is a viable therapeutic option with seemingly better efficacy than conventional drugs.

"By analyzing real-world data sourced from 312 patients in France who had received this drug, we are able to demonstrate that lurbinectedine is a new therapeutic option for patients with small cell lung cancer," says study coordinator **Prof. Nicolas Girard, pulmonologist and coordinator of the Curie-Montsouris Chest Center.** *"As a sponsor of a great many studies of this type, these results are a clear indication of Institut Curie's commitment to assessing innovative cancer therapies based on patients' real-world data".*

The results of the **retrospective CLINATEZO study,** also conducted with the IFCT, are further proof of this. The study aims to evaluate real-world effectiveness and tolerance to the combination of immunotherapy (atezolizumab) and first-line chemotherapy in patients with small cell lung cancer, again.

✓ Thrombosis risk prevention in lung cancer

Patients with lung cancer are four times as likely to develop venous thromboembolism, or thrombosis (blood-clotting in the veins). Some drugs can also heighten the risk, which would appear to be the case in a combination of new drugs, lazertinib and amivantamab, being evaluated in advanced stage lung cancer clinical studies at Institut Curie.

[3] https://www.who.int/fr/news-room/fact-sheets/detail/cancer

"The data we have collected is prompting us to offer personalized preventative measures to a certain number of patients receiving these targeted treatments. Accurately identifying and analyzing the risk of thrombosis is key to preventing these treatments being stopped, when they are effective over the long term," explains Prof. Nicolas Girard. *"Institut Curie is particularly alert to the issue of the risk of thrombosis arising in cancer patients.* ***The institute coordinates an entire program dedicated to this issue, in fact. DASTO*** *aims to cross-reference data sourced from several French cancer centers with data from the social security system to understand the risk factors, improve patient treatment, make changes to the care pathway, and prevent this unwanted occurrence from arising."*

"IFCT-2105 lurbiclin real-world effectiveness and treatment sequences in patients (pts) with extensive-stage small cell lung cancer (ES-SCLC) who received lurbinectedin as part of the French Early Access Program (EAP-ATU)" and "Long-term effectiveness and treatment sequences in patients with extensive stage small cell lung cancer receiving atezolizumab plus chemotherapy: Results of the IFCT-1905 CLINATEZO real-world study. "
Poster session - Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers (June 4)

Risk factors for venous thromboembolism (VTE) among patients with EGFR-mutated advanced non-small cell lung cancer (NSCLC) receiving amivantamab plus lazertinib versus either agent alone.
Poster session - Lung Cancer—Non-Small Cell Metastatic (June 4)

UVEAL MELANOMA

Uveal melanoma is the most common form of eye cancer in adults, with 500 to 600 new cases diagnosed annually in France. Every year, Institut Curie treats around two-thirds of all new cases of uveal melanoma in France. **A leading national and European center for treatment of this disease, Institut Curie is internationally renowned for its expertise in this type of cancer.**

Dr. Sophie Piperno-Neumann, medical oncologist at Institut Curie, will be taking part in an educational session dedicated to metastatic melanoma. This presentation will cover what we know about uveal melanoma, the treatments developed over the past few years, future pathways — particularly with the arrival of tebentafusp, a new immunotherapy molecule — challenges in treatment and monitoring, and more.

"The Changing Landscape of Uveal Melanoma"/The Evolving Management of Stage IV Melanoma -
Dr. Sophie Piperno-Neumann – Education session (June 6, 2023) -
https://ascopubs.org/doi/full/10.1200/EDBK_397478?cid=DM13580&bid=271570067

Pediatric cancers/ As an INCa-designated early-phase clinical trial center (CLIP²), Institut Curie coordinated a phase 1 clinical trial to evaluate a combined treatment (niraparib + dostarimab) in children with refractory tumors, particularly neuroblastomas and osteosarcomas. This research assessed the toxicity levels of this combination and established the recommended dose for pediatric patients before conducting studies into the efficacy of this combination.

Safety and PK (pharmacokinetic) profile of niraparib (nir) + dostarlimab (dost) in pediatric patients (pts) with recurrent or refractory (RR) solid tumors: SCOOP study – Poster session Pediatric Oncology (June 5)

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**