Press release

October 20, 2023

The European Society for Medical Oncology 2023 meeting

Bispecific antibodies, nanoparticles, epidrugs…: institut Curie's latest progress at the ESMO Annual Meeting 2023

The European Society for Medical Oncology Annual Meeting will take place from October 20 to 24, 2023, in Madrid. Institut Curie's physicians and researchers will be present for this essential event in European oncology research. There they will present the latest clinical progress, innovative molecules and original treatments, which in years to come could change the landscape for cancer patients.

"This 2023 edition of the ESMO meeting once again conveys the momentum and quality of the clinical research conducted at Institut Curie", enthuses **Prof. Steven Le Gouill, director of the Hospital Group at Institut Curie.** "The combination of our expertise in certain locations with high-level research has brought our teams to the forefront of European oncology, with increasingly innovative and promising approaches for patients".

– L'essentiel –

Bispecific antibodies/New effective strategies in rare lung cancer and metastatic uveal melanoma

- For the first time, a bispecific antibody is transforming the treatment of a rare form of lung cancer
- Long-term results confirm the effectiveness of a bispecific antibody for treating metastatic uveal melanoma

Epidrugs/Towards new innovative anti-cancer therapies: promising results from the combination of an epidrug and immunotherapy in squamous cell carcinoma

Nanoparticles/A new milestone reached in ENT cancers for a unique and original class of drugs

Bispecific antibodies/New effective strategies in lung cancer and uveal melanoma

The principle: Bispecific antibodies are able to bind to two separate sites: one recognizes a site in the tumor cells, and the other recognizes a second site on these cells or on the immune system cells. These antibodies, by binding to the two sites or to two different cells, enable them to more deeply inhibit the intracellular signaling pathways or enable two different cells to move closer together to facilitate the destruction of cancer cells.

Immumotherapy changing the landscape in a rare form of lung cancer

For the first time, an international phase-3 trial (PAPILLON) assessed the effectiveness of the combination of a bispecific antibody, amivantamab, with chemotherapy on 308 patients with a rare lung cancer (advanced non-small cell with a rare EGFR (Epithelial Growth Factor Receptor) Exon 20 mutation.

The results of this study will be presented on Saturday October 21, 2023, by Prof. Nicolas Girard, respiratory oncologist, head of the Medical Oncology department at Institut Curie, coordinator at the Curie-Montsouris Chest Center and principal investigator on the PAPILLON trial.

Oral communication, Presidential -Saturday October 21 (5:47 pm - 5:59 pm) - *Prof. Nicolas Girard*
Amivantamab Plus Chemotherapy vs Chemotherapy as First-line Treatment in EGFR Exon 20 Insertion-mutated Advanced Non-small Cell Lung Cancer (NSCLC): Primary Results From PAPILLON, a Randomized Phase 3 Global Study

=> *Press release to be released on October 24, 2023 on the Results of PAPILLON*

Effectiveness in the long term of a bispecific antibody for treating metastatic uveal melanoma

With 500 to 600 new cases each year in France, uveal melanoma is the most common form of eye cancer in adults. **Each year, Institut Curie, the leading national and European center, treats around two thirds of new uveal melanoma cases in France.** In one in three patients, the disease spreads in the form of metastases (most frequently in the liver) and until now there was no really effective therapy for treating these metastases.

Now **a bispecific antibody, tebentafusp (Tebe), is changing the landscape for around 45% of metastatic patients** (those with a certain tissue type HLA-A*02:01, needed to trigger this anti-melanoma immunity). By redirecting the patient's T CD3+ lymphocytes against the glycoprotein gp100 expressed by the skin's cells and the melanoma tumor cells, Tebe stimulates a targeted anti-tumor immune reaction.

In 2021, **the results of an international randomized phase-3 trial (IMCgp100-202) coordinated in France by Dr. Sophie Piperno-Neumann, medical oncologist at Institut Curie,** revealed that Tebe significantly increases overall patient survival, compared with existing treatments. **At the ESMO 2023 meeting Dr. Sophie Piperno-Neumann will present an update of these results with follow-up of at least three years for all patients in the trial. The data confirm the advantage of Tebe, which continues to provide patients with a long-term survival benefit (27% compared with 18% with existing treatments).** The clinical benefit rate is 46% vs. 27%, and one third of patients still responded to Tebe after 18 months of treatment. These long-term data also show that there are no longer side effects or toxicity. Furthermore, the role of circulating tumor DNA (ctDNA) was assessed as a biomarker to identify patients who benefit most from Tebe. The early disappearance of ctDNA in

37% of patients is associated with improved survival, including in patients with radiological progression.

"The first results reported after 14 months of follow-up in 2021 are now largely consolidated; **after median follow-up of 43 months, the long-term data confirm the first-line status of Tebentafusp, this bispecific antibody, in HL A02:01-positive patients with metastatic uveal melanoma**", continues Dr. Sophie Piperno-Neumann.

Note also that a real-life retrospective study conducted among 72 patients with metastatic uveal melanoma and monitored in France, in particular at Institut Curie, strengthens the results of the phase-3 trial in the long term.

Mini-oral session – Melanoma and other skin tumors – Saturday October 21, 2023 (3:10 pm - 3:15 pm)
LBA50 - Three-year survival with tebentafusp in previously untreated metastatic uveal melanoma in a phase 3 trial - *Speaker*: Dr. Piperno-Neumann
Three-Year Overall Survival with Tebentafusp in Metastatic Uveal Melanoma, ***New England Journal of Medicine***
Jessica C. Hassel, M.D., Sophie Piperno-Neumann et al. ; 21 octobre 2023 - DOI: 10.1056/NEJMoa2304753

Poster session "Melanoma and other skin tumors" - – Sunday October 22, 2023 - Tebentafusp (Tebe) in an ongoing cohort of 72 French patients (pts) with metastatic uveal melanoma (mUM)

Translational research focus

Better understanding of the heterogeneity of tumors and exploring the clinical utility of liquid biopsies: application in ENT cancer

Is there an association between the level of heterogeneity of an ENT cancer and the risk of recurrence? Does detection of tumoral DNA in circulating blood enable us to identify patients who have undergone surgery at risk of recurrence? **Using data from the SCANDARE trial, Dr. Grégoire Marret, medical oncologist in the Early clinical trials department at Institut Curie (D3i), conducted several analyses among the cohort of patients with ENT cancer.** SCANDARE is a prospective study in which tumor and blood samples are collected for translational research in ovarian cancer, triple negative breast cancer and ENT cancer. Its goals include **better understanding of tumor heterogeneity, the role of the immune environment, and the characterization of sensitivity biomarkers and biomarkers of resistance to cancer drugs.**

=> A first analysis shows that in **63% of patients who initially underwent surgery for localized ENT cancer, detection of tumoral DNA in the circulating blood during monitoring helped anticipate clinical recurrence by around 10 months.** These results raise the issue of the utility of additional post-surgical treatment guided by the detection of circulating tumor DNA.

=> By studying histological sections of ENT tumors, intra-tumor heterogeneity was able to be quantified and correlated to the risk of recurrence. Annotation of these heterogeneous regions by a pathologist then helped to guide the molecular analyses in order to be able to understand the heterogeneity at the genetic level. **This multi-region sequencing approach guided by pathological interpretation has never before been reported in these tumors**.

Two poster presentations session "Head and neck cancers, excl. thyroid" – Sunday October 22, 2023
> Prognostic value of pathological intratumor heterogeneity in patients with head and neck squamous cell carcinoma treated with upfront surgery
> Serial cell-free tumor DNA in prognosing survival in patients with head and neck squamous cell carcinoma treated with upfront surgery

Epidrugs/Towards new innovative anti-cancer therapies

The principle: Epidrugs are molecules that act on epigenetic mechanisms, i.e. reversible biological processes that influence gene expression without altering the DNA sequence itself. These molecules are able, for example, to inhibit methylation of DNA or to target the alterations of histones, these proteins surrounding the DNA. Among epidrugs, vorinostat is an inhibitor of histone deacetylases (HDAC) which, by binding to active sites of HDAC enzymes, can modulate the epigenome.

Epidrugs and immunotherapy: highly encouraging results in squamous cell cancers

The PEVO clinical trial (phase 2, open, non-randomized, multi-center) sets out to evaluate a ground-breaking therapeutic approach: combining immunotherapy (pembrolizumab) with an epidrug (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).

Squamous cell carcinoma affects the skin cells and accounts for around 20% of skin cancers. This type of cutaneous tumor is potentially aggressive and involves similar molecular alterations that justify shared therapeutic strategies.

"We chose this original combination because the preliminary data indicated that the epidrug, by modulating the expression of certain genes, could improve the efficiency of immunotherapy", explains **Prof. Christophe Le Tourneau, medical oncologist, head of the Early clinical trials department (D3i) at Institut Curie and head of the PEVO trial.** "We are now very satisfied since our results show highly encouraging anti-tumor activity, particularly in cancer of the anal canal".

The results obtained in each of the five cohorts will be presented at the ESMO 2023 meeting. In particular, the PEVOsq study met its main assessment criterion, **reporting promising anti-tumor activity with the combination of the epidrug (vorinostat) and immunotherapy in patients with squamous cell carcinoma of the anal canal.** The results have also revealed encouraging anti-tumor activity in patients with ENT squamous cell carcimona, as in cervical cancer. The effectiveness is also encouraging in patients with cancer of the vulva.

Mini Oral presentation - Gastrointestinal tumors, lower digestive- Sunday October 22, 2023 - Phase II trial evaluating the efficacy of pembrolizumab combined with vorinostat in patients with recurrent and/or metastatic anal squamous cell carcinoma – subgroup analysis of the PEVOsq basket trial. C. Coutzac, F. Bigot, D. Vansteene, M. Dos Santos, F. Ghiringhelli, B. You, A.Lambert, C. Gomez-Roca, C. Abdeddaim, C. Neuzillet, E. Jeannot, E.Guerini Rocco, G. Frige, L. Mazzarella, C. Dupain, M. Kamal, F. Legrand, M. Jimenez, T. Filleron, C. Le Tourneau.

4 poster presentations: Phase II trial evaluating the efficacy of pembrolizumab combined with vorinostat in patients with recurrent and/or metastatic head & neck squamous cell carcinoma / squamous cell cervix carcinoma / vulvar and vaginal squamous cell carcinoma / penis squamous cell – subgroup analysis of the PEVOsq basket trial.

Nanoparticles/A new milestone reached in ENT cancers for a unique and original class of drugs

The principle: Metal hafnium nanoparticles (known as NBTXR3) are injected directly into the tumor and help enhance the anti-tumor effect of radiotherapy. By interacting with the hafnium, the rays generate nine times more free radicals than in "standard" radiotherapy. These free radicals destroy tumor cells without affecting the neighboring tissues.

Highly compelling results in ENT cancer and a phase-3 trial underway

Many patients with ENT cancers, given their advanced age and co-morbidities, do not tolerate standard treatment by chemotherapy. This is why the **development of therapeutic alternatives adapted to a vulnerable population is required**. It is within this context that treating these patients with nanoparticles appeared as a new and original therapeutic option.

A first phase-1, multi-center trial was conducted with patients suffering from locally advanced ENT cancers not eligible for chemotherapy. This so-called "dose escalation" study helped establish a tolerance without toxicity profile and determine the correct dose of nanoparticles to be injected in the operating room into the tumor. **A second part of the trial, the "dose expansion", was conducted in 56 patients recruited in 20 centers in Europe, who had all received the same nanoparticle dose.**

Presented at ESMO 2023, the results obtained are encouraging: they reveal that the treatment is well tolerated and that the anti-tumor effectiveness is lasting. In 44 patients, a response was obtained in the lesion injected in 81.8% of patients, of which 63.6% achieved a full response. In all lesions the overall reponse rate was similar, i.e. 79.5%. The complete response rate was 52.3%. The median overall survival rate was 23.1 months in these patients (compared with 12 months). **These results confirm the treatment that is currently being tested in older patients with advanced ENT cancer as part of the international phase-3 trial underway (NANORAY-312).**

"For over 10 years Institut Curie has been working on this extremely original therapy with the company Nanobiotix, which developed these NBTXR3 nanoparticles. Positive results have already been shown in sarcoma and today, with the highly promising results in ENT cancer, the therapeutic potential of this entirely original strategy has been confirmed", confides **Prof. Christophe Le Tourneau, medical oncologist, head of the Early clinical trials department (D3i) at Institut Curie and principal investigator for the trial.** "We are now impatient to collect the first data from the phase-3 NANORAY-312 trial, which has started up internationally."

Poster presentation session "Head and neck cancers, excl. thyroid" – Sunday October 22, 2023 - **Antitumor Activity of the Radioenhancer NBTXR3 on Injected Lesions to Estimate Overall Survival: Exploratory Analyses from a Phase I in Cisplatin-Ineligible Locally Advanced HNSCC Patients.** Christophe Le Tourneau, (…) Maria Lesnik

On the agenda for the educational and special sessions at ESMO 2023

Prof. Anne Vincent-Salomon, head of the pathology department at Institut Curie, director of the Institut des cancers des femmes, will co-chair a **special session devoted to artificial intelligence in cancer prognosis**, and will take part in a presentation on breast cancer: how can AI be used in pathology for breast cancer diagnosis and prognosis, which tools are currently available? What are the opportunities and what are the biases for these new uses?

Artificial Intelligence in prognostication – October 23 from 2:45 pm to 4:15 pm

Dr. Etienne Brain, medical oncologist at Institut Curie, will chair a special session devoted to oncogeriatrics, during which he will speak specifically about optimizing **treatment of elderly patients with advanced breast cancer;** including these patients in clinical trials while adapting to give them true access to innovation.

In collaboration with SIOG (International Society of Geriatric Oncology): Fundamentals in geriatric oncology in clinical practice – October 20 from 2:00 pm to 3:30 pm

- Dr. Emanuela Romano, medical oncologist, medical director of the Cancer Immunotherapy Center at Institut Curie, will chair 2 special sessions:

- ESMO Clinical Practice Guidelines 1 – October 22 from 10:15 am to 11:45 am

- ESMO Clinical Practice Guidelines 2 – October 22 from 2:45 pm to 4:15 pm

Prof. Sylvie Bonvalot, an oncological surgeon specializing in soft-tissue sarcomas at Institut Curie, will present during a special session devoted to genetic predisposition to sarcoma. **"How to treat patients with bone sarcoma, soft tissue sarcoma and GIST (gastrointestinal stromal tumors) with a hereditary predisposition: A surgeon's viewpoint"**

Educational session *- Genetic predisposition in patients with sarcoma – October 23 from 2:45 pm to 4:15 pm*

Prof. Nicolas Girard, head of the Medical Oncology department at Institut Curie and coordinator at the Curie-Montsouris Chest Center, will present on **predictive biomarkers for adjuvant/neoadjuvant immunotherapy in non-small cell lung cancer.**

Educational session *- Adjuvant / neoadjuvant therapy of operable NSCLC in 2023 – October 23 from 4:30 pm to 6:00 pm*

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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.

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