GUSTAVE ROUSSY AT ASCO

PRESS RELEASE

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GUSTAVE ROUSSY IN THE FOREFRONT OF THERAPEUTIC INNOVATION WITH DITEP

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

ASCO 50 YEARS 1964-2014

ASCO American Society of Clinical Oncology
Making a world of difference in cancer care

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30 MAY

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PRESS RELEASE

ASCO

MAY 30th - JUNE 3rd 2014

50th congress
American Society of Clinical Oncology (Asco, Chicago, USA, May 30th - June 03rd 2014).

ABOUT GUSTAVE ROUSSY

Gustave Roussy in 2013:
First comprehensive cancer centre in Europe
2 630 professionals dedicated to care, research and learning
356 beds et 89 beds/chairs in day-car
47 000 patients
of which 11,200 first visits
3 690 patients included in a clinical trial
366 clinical studies
321 patients included in phase-1 early trials
88 patients included in phase-2-3 early trials
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EARLY TRIALS TO EVALUATE FUTURE TARGETED THERAPIES **THE INHIBITORS OF TOMORROW**

Gustave Roussy's medical researchers will be presenting their clinical and translational research papers at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO), the world's biggest oncology gathering. This year there will be 18 oral papers presented by the Institute's physician-researchers, including 10 on work carried out and 37 posters.

Latest news from Gustave Roussy at ASCO
from May 30th on
www.gustaveroussy.fr/asco2014

EARLY TRIALS TO EVALUATE **FUTURE TARGETED THERAPIES**

GUSTAVE ROUSSY IN THE FOREFRONT OF THERAPEUTIC INNOVATION WITH DITEP

Three oral communications during the session on new anti-cancerous agents gave the results of early studies evaluating the efficacy and safety of tomorrow's inhibitors on solid tumours.
Professor Jean-Charles Soria, head of the DITEP department, presented data on the activity and tolerance of lucitanib, a twin inhibitor of the FGFR and VEGFR pathways. A study undertaken by Dr Rastislav Bahleda, an oncologist at DITEP, has shown the benefit of a second generation FGFR inhibitor (JNJ-42756493).
Finally, Dr Eric Angevin, an oncologist at DITEP, presented the results obtained with an MET pathway inhibitor (SAR125844) in MET amplified patients.

The objective of these first three studies in man was to determine the dose (dose escalation, dose limiting toxicity, recommended dose for use), to show the efficacy, to establish the safety profile and the dosage regimen of these new compounds whilst confirming their benefit in extension cohorts during recruitment.

ASCO 2014

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A TWIN INHIBITOR OF FGFR AND VEGFR

FGF (FGFR1 to 4) receptors are transmembranous proteins implicated in numerous physiological processes such as cellular proliferation and growth in size of the cell. Data from the literature establishes a causal link between changes in FGFR genes and the development of cancers (urothelial, pulmonary and cerebral tumours in particular). Targeting of the FGFR pathway appears therefore to be a very promising approach. VEGFR receptors as such are key players in angiogenesis. These signalization pathways are therefore essential for tumour growth, survival and angiogenesis.

Lucitanib (E-3810), a potent inhibitor of the tyrosine kinase activity of FGFR1-3 and of VEGFR1-3, blocks these two proteins and thus prevents the tumour from nourishing itself and from growing. In certain tumours, the FGFR protein is also implicated in the proliferation of tumour cells themselves. Currently, there is no marketed treatment available for patients suffering from tumours presenting with an alteration in their FGF pathway (FGFR1 or amplified FGF3/4/19).

1. A phase I/IIa study evaluating the safety, efficacy, pharmacokinetics and pharmacodynamics of lucitanib in advanced solid tumours.
Jean-Charles Soria, Filippo G. De Braud, Ratislav Bahleda, Barbara Adamo, Roberta Cereda, Maria Gabriella Camboni, Renata Robert, Jeffrey D Isaacson, Jason B. Litten, Andrew R. Allen, Lindsey Rolfe, Josep Tabernero

A THERAPY IS SAID TO BE TARGETED WHEN IT ACTS SPECIFICALLY ON A MOLECULAR ABNORMALITY WHICH PLAYS A ROLE IN THE PROGRESSION OF CANCEROUS CELLS.

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2. Phase I study of JNJ-42756493, a pan-fibroblast growth factor receptor (FGFR) inhibitor in patients with advanced solid tumours.
Rastislav Bahleda, Rodrigo Dienstmann, Barbara Adamo, Anas Gazzah, Jeffrey R. Infante, Bob Zhong, Suso J. Platero, Hans Smit, Timothy Perera, Kim Stuyckens, Jacqueline Bussolari, Vijay Peddareddigari, Jean-Charles Soria, Feng Roger Luo, Josep Tabernero

Presented by **Prof. Jean-Charles Soria**, this open phase I/IIa study was carried out in 76 patients, divided into 3 groups, suffering from solid tumours at an advanced stage, some of which presenting with an alteration in the FGF pathway. Doses of 5 to 30 mg were administered by mouth and the dose-limiting toxicity was ascertained at 30 mg. The pharmacological profile of the compound permits a single administration per day. Anti-tumour activity was observed at all doses, but interestingly, the overall response level is 22% and 10 patients out of 58 evaluable patients derived a benefit in excess of one year. The sub-group of patients with breast cancer and an abnormality of the FGF pathway had a 50% response level and a median survival without progression of 9.6 months.

In conclusion, lucitanib has demonstrated its anti-tumour activity with an acceptable secondary effects profile in patients suffering from advanced solid tumours, notably in those presenting with an alteration in the FGF pathway. Phase II studies are ongoing in Europe and in the United States to evaluate this treatment in patients suffering from breast cancers (Principal Investigator: **Prof. Fabrice Andre**) or in non-small-cell epidermoid lung cancer presenting with an alteration in the FGF pathway.

SECOND GENERATION INHIBITOR OF THE FGFRS

JNJ-42756493 acts on the tyrosine kinase activity of the FGFRs (1, 2, 3 and 4). It has shown anti-tumour activity in vitro on cell lines and in vivo in animal models presenting with an alteration in the FGFR pathway.

The 2 first parts of the phase I trial undertaken by **Dr Rastislav Bahleda** evaluated the safety, efficacy and the pharmacokinetic and pharmacodynamic parameters of JNJ-42756493 in patients presenting with a solid tumour or an advanced or refractory lymphoma.
Thirty seven patients were treated at 6 dosage levels (0.5, 2, 4, 6, 9 and 12 mg per day continuously). The 9 mg dose per day was selected for the phase II study. At the recommended dose, JNJ-42756493 had a good pharmacological profile. Seven patients presented with significant undesirable effects, including one death, but none were attributed to the medicine. The third part of the trial only involved patients in whom the tumour had a molecular FGFR abnormality (amplification of FGFR1, 2 or 4). In these 8 patients, a total and partial response to treatment was observed in 2 patients at the recommended dose; the disease was stable in 4 patients. Responses were seen in particular in cancers of the bladder and in glioblastomas with FGFR translocations.

In conclusion, JNJ-42756493, which has demonstrated its anti-tumour activity in patients presenting with an abnormality of the FGFR pathway, has favorable pharmacological properties with

manageable secondary effects at the recommended dose, encouraging the pursuit of its clinical development.

INHIBITOR OF THE MET PATHWAY

Over-expressed in numerous tumours (kidney, thyroid, lung, melanoma...), the MET receptor is associated with a poor prognosis and is often a sign of aggressive cancers. A powerful and highly selective kinase inhibitor of the MET pathway, SAR125844 has demonstrated its safety and its efficacy in preclinical models on amplified MET tumours. The study presented by **Dr Eric Angevin** included 33 patients suffering from solid tumours presenting with an elevated expression of MET membranous protein or an amplification of the c-MET gene. They received increasing doses from 50 to 740 mg/m2 of SAR125844 once a week by perfusion.
The anti-tumour activity of SAR125844 was observed at 540 mg/m2. A complete response to treatment was obtained in one patient suffering from a pulmonary tumour involving an amplification of the c-MET gene and 7 patients not presenting with amplification of c-MET benefited from a lasting stabilization (more than 3 months) of their illness.

In conclusion, SAR125844 is well tolerated on the whole and two cohort extensions, currently ongoing, will confirm the 540 mg/m2 dose.

DITEP ACCELERATES THERAPEUTIC INNOVATION

A department dedicated to early clinical trials (phase I) at Gustave Roussy, DITEP (Department for Therapeutic Innovations and Early Trials) has the task of offering patients in therapeutic failure access to innovative compounds and of accelerating the development of new treatments in cancerology.
It has been labeled as an Early Phase Center (CLIP) by the National Institute of Cancer.

With this unique organization in France, which enables the enrollment of patients across the board, Gustave Roussy has become an essential partner in phase I trials both in adults and in children.
The activity of DITEP is managed by a multidisciplinary committee of experts in medical oncology, radiotherapy, hematology, imaging, biology and pathology.

In 2013, 371 patients were able to be included in early phase trials at Gustave Roussy. The principal objective of DITEP is to increase the number of patients treated in early trials to attain 490 patients treated per year from now to 2015 with a significantly increased percentage of patients benefiting from a molecular profiling and a precision approach.

DITEP
NEWSLETTER

3. A first-in-human (FIH) phase I study of SAR125844, a novel selective MET kinase inhibitor in patients (pts) with advanced solid tumours: Dose escalation results.
Eric Angevin, Gianluca Spitaleri, Antoine Hollebecque, Tommaso De Pas, Jean-Charles Soria, Marzia Harnois, Florent Mazuir, Sylvie Assadourian, Filippo De Marinis Tabernero

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