PRESS RELEASE

ESMO 2024 – *Proffered Paper Session*

Villejuif, 14 September 2024

METASTATIC LUNG CANCER: NEW THERAPEUTIC AVENUES ARE OPENING UP THANKS TO THE IDENTIFICATION OF RESISTANCE TO TARGETED TREATMENTS

Targeted therapies represent a major breakthrough in the management of locally advanced or metastatic lung cancers. But resistance to these treatments in the medium term means that new solutions have to be found. The team of Prof. Benjamin Besse, Director of Clinical Research at Gustave Roussy, participated in an international study aimed at analysing and understanding these resistances to learn how to overcome them.

Late breaking abstract no. 55 presented orally by Prof. Benjamin Besse on Saturday 14 September at 9.30 am.

Watch the video online.

Nearly 10% of metastatic non-small cell lung cancers have an EGFR gene mutation. Patients can then benefit from targeted osimertinib therapy. However, after an average of 18 months, the tumour becomes resistant to this drug, through two main types of mechanism that have been identified. One is said to be on-target, i.e. new mutations appear on the EGFR gene, making the drug ineffective. The other is called off-target: new abnormalities, other than in the EGFR gene, particularly in the MET gene, prevent the drug from acting. The most common mechanisms of resistance to osimertinib are therefore modifications of the EGFR and MET pathways. To combat these resistances, new drugs have been developed. Amivantamab is a bispecific antibody against both EGFR and MET.

The MARIPOSA phase 3 multi-centre trial, published in 2024 January in the *New England Journal of Medicine*, involving more than 1,000 patients, had already shown that amivantamab, combined with lazertinib (another anti-EGFR), allows double EGFR blockade and MET blockade. In this trial, patients with advanced or metastatic lung cancer with an EGFR mutation benefited from an improvement in progression-free survival compared with osimertinib alone. However, the tumour becomes resistant to these treatments after 24 months

on average. This new treatment is now approved in the US as a first-line treatment for these forms of lung cancer. In France, amivantamab is available for early access in combination with chemotherapy for patients resistant to osimertinib.

The study presented at ESMO by Prof. Besse aims to analyse and understand the mechanisms of resistance to the combination of amivantamab and lazertinib in patients included in the MARIPOSA trial. Tumour DNA analysis was performed using fluid biopsies (on blood samples) before and after treatment in patients who became resistant.

This work reveals that amivantamab combined with lazertinib significantly reduces the occurrence of MET abnormalities and EGFR mutations compared to osimertinib alone. Thus, MET abnormalities are 4.4% with the combination, compared to 13.6% with osimertinib alone. Also, EGFR resistance mutations affect 0.9% of patients with the combination versus 7.9% in the other group. Moreover, the combination, compared to osimertinib, reduces the risk of tumour transformation into small-cell lung cancer, faster progression, and worse prognosis.

"Combining the two targeted therapies increases progression-free survival through better control of two therapeutic targets," concludes Professor Besse. *This work is preliminary because some of the patients in the study are still being treated. We will continue to analyse the mechanisms of resistance to this new treatment in order to work on new targeted treatments. It is possible that, for patients who benefit from prolonged disease control, the mechanisms of resistance will be different."*

***Late breaking abstract* no. 55**

Mechanisms of Acquired Resistance to First-line Amivantamab Plus Lazertinib Versus Osimertinib in Patients With EGFR-mutant Advanced Non-Small Cell Lung Cancer: An Early Analysis from the Phase 3 MARIPOSA Study.

Saturday 14 September 2024 | 9:30 am.

About Gustave Roussy

Ranked first in France, first in Europe and fourth 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 nearly 50,000 patients each year, including 3,500 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 4,100 employees at two sites, Villejuif and Chevilly-Larue, Gustave Roussy brings together the expertise essential for high-level cancer research; 40% 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.

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