PROTOCOL FOR THERAPEUTIC USE AND INFORMATION COLLECTION

Compounding of Birabresib, 20 mg capsule

Patient (adult and paediatric) with relapsed NUT tumour after at least one line of treatment

The request	
Speciality	BET (Bromodomain and Extra-Terminal) motif inhibitor
INN	OTX015 (Birabresib)
Award criteria *	*Validation by molecular MDT after progression of a first line of chemotherapy.*
Frequency of summary reports	*To be completed by the ANSM*
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Last update date: to be completed by the ANSM

GLOSSARY:

ANSM: French National Agency for the Safety of Medicines and Health Products
BETi: BET inhibitor
CR: Complete Response by RECIST 1.1 criteria
DPO: Data Protection Officer
ECG: Electrocardiogram
ECOG PS: Eastern Cooperative Group performance scale
FBC: full blood count
FISH: Fluorescence In Situ Hybridisation
HAS: French National Health Authority
ICI: immunotherapy blocking an immune checkpoint
IHC: Immunohistochemistry
INN: International non-proprietary name
MDT: Multidisciplinary Team Meeting
NGS: Next Generation Sequencing
NUT: NUclear protein in Testis
ORR: Overall Response Rate
PD: Progressive Disease (RECIST 1.1)
PD-L1: Programmed Death Ligand 1
PR: Partial Response by RECIST 1.1 criteria
PUI: Internal Pharmacy
PUT-SP: Protocol for Therapeutic Use and Patient Monitoring
RPVC: Regional Pharmacovigilance Centre
SD: Stable Disease by RECIST 1.1 criteria

CONTENTS

APPENDICES

1. Introduction

NUT tumours are extremely rare, under-diagnosed, and poor prognosis malignancies.[1–3] They were first described in 1991[4,5] and identified as a new entity in 2003.[6]

NUT tumors result from a single critical event, a fusion involving the NUT Midline carcinoma family Member 1 (*NUTM1*) gene, most commonly with the *BRD4* gene. This fusion results in the formation of an oncoprotein which, through epigenetic regulation, enhances transcription of genes such as *MYC, SOX2* and *TP63*, resulting in uncontrolled cell growth and de-differentiation.[1,7]

Clinically, NUT tumours affect patients of all ages, although it is more common in young people. It usually occurs in the chest, followed by the head and neck, but can occur anywhere in the body. Both the fusion partner and the primary site have been shown to have an impact on prognosis.[3] Its incidence is unknown, estimated at around one hundred cases per year in the US. This entity is largely underdiagnosed, both because it is rare and because of a lack of knowledge among healthcare stakeholders (oncologists, pathologists, etc.). Broad molecular profiles, particularly fusion panels, can incorporate *NUTM1* discomfort, and the diagnosis can now also be supported by molecular profiling.[8,9]

Due to its low frequency, most treatment data come from long retrospective series or consensus.[1,2,10–14] In general, a multimodal approach should be considered where possible.[1,11,12] In a non-curative setting, evidence remains limited, particularly due to the lack of effective systemic therapy. Ifosfamide-based regimens have been associated with a tendency to have better but transient responses.[1,11,15] The integration of immune checkpoint inhibitors (ICIs) into the therapeutic arsenal of NUT tumours has been less explored, although they have been reported to be stable in microsatellites, with low mutational burden and generally associated with low/negative PD-L1 expression.[16]

BET inhibitors (BETi) are a rational treatment option in NUT tumours. BETi are acetyl histone mimetic compounds that prevent the interaction between BET proteins and acetylated histone peptides, thereby disrupting chromatic remodelling and gene expression. Some clinical studies have assessed the role of BET inhibitors in solid tumours, including NUT carcinomas.[17–20]

In the study with Birabresib (OTX015/MK-8628), 9 patients with NUT carcinoma were treated and three achieved partial response, with response durations ranging from 1.4 to 8.4 months at the continuous dose of 80 mg/day. The dominant toxicities were thrombocytopenia, reversible, fatigue and hepatic function test abnormalities.[17] With Molibresib (GSK525762), 19 patients with NUT carcinoma were included with an ORR of 11% (95%CI 1.3%-33.1%). One expansion cohort (12 patients) showed two confirmed partial responses. The recommended dose was 80 mg/day, but haematological toxicity, including high grade thrombocytopenia, gastrointestinal effects and anaemia, limited dose escalation.[1,18] RO6870810, administered subcutaneously, was assessed in eight NUT patients with two partial responses (ORR 25%). The most common adverse reactions were fatigue, loss of appetite, local injection site reactions and cytopenias, sometimes complicated by febrile neutropenia.[20] ODM-207, assessed in Phase I studies in patients with advanced solid tumours, did not show objective responses in patients with NUT carcinoma, as enrolled patients either progressed within days of enrolment (3 of 4) or had very low plasma exposure to ODM-207 (1 patient). Despite this, treatment has confirmed its feasibility at increasing doses (up to 2 mg/kg), with haematological and gastrointestinal toxicities similar to other BETi.[21] Finally, BMS-986158 was assessed in a phase I/IIa trial involving 83 patients with solid tumours, including 7 with NUT carcinoma; of these, 1 patient had a partial response, while the majority of the other patients had stable disease.[19]

Table 1 presents a summary of the efficacy and toxicity profile of the different clinical trials conducted with BET inhibitors, including in patients with NUT tumours.

Table 1Clinical trials assessing BET inhibitors, including in patients with NUT tumours

BET inhibitor	N	Response	Toxicity Any grade/Grade ≥ 3	Most common toxicities
Molibresib	19	ORR 11%	**83%/48%**	Thrombocytopenia, nausea, loss of appetite, vomiting, diarrhoea
	12 (expansion cohort)	2 confirmed partial responses		
Birabresib	9 (46)	**PR 3 (33%)** **SD 3 (33%)** PD 2 (22%) NE 1 (11%)	*Cohort A dose 80 mg* **15 (75%)/10 (50%)**	Nausea, vomiting Loss of appetite Factor VII deficiency Anaemia, thrombocytopenia
BM-986158	7 (83)	PR 1 Clinical benefit 57%	*Diagram A* **33 (71.7%)/19 (41.3%)**	Diarrhoea, nausea Thrombocytopenia, anaemia Fatigue *3 myocardial infarction
RO6870810/ RG6146/ TEN-010	8(74)	**PR 2** **SD 5** PD 1	**70 (94.6%)/22 (29.7%)**	Fatigue Loss of appetite Injection-related side effects Nausea, diarrhoea Anaemia, thrombocytopenia, elevation of ALT, AST and bilirubin
ODM-207	4 (35)	No CR/SD PD 3 NE 1	31 (89%)/> 10%	Thrombocytopenia Diarrhoea Nausea, vomiting Asthenia, fatigue, loss of appetite

PR = partial response, SD=stability, PD=progression, NE=not assessed

Among the various BETi presented, birabresib associates an acceptable toxicity profile with disease control in 66% of patients.

Given the rarity of this entity, no marketing application has been made, and no BET inhibitor is available for early access, neither in Europe nor in the United States. Given the biological rationale of BETi, the efficacy data reported, and the lack of treatment proven to be effective for patients with NUT tumours, this protocol aims to provide a framework for the use of birabresib in patients with NUT tumors.

2. Medicinal product:

Proprietary medicinal product(s) concerned

Birabresib dihydrate capsule 20 mg (expressed as base) size No. 4 in compounding

Medicinal product characteristics

BETi are small molecules mimicking acetylated lysine that competitively inhibit the interaction between bromodomain and acetylated histone, leading to the removal of BET proteins from chromatin. In the biology of NUT tumours, this interaction is a therapeutic vulnerability, not only in *BRD4-NUTM1* fusions, but also in *BRD3-NUTM1*, *NSD3-NUTM1* or *ZNF532-NUTM1* fusions.[1,22] OTX015/MK-8628 (birabresib) is a selective inhibitor of BRD2, BRD3 and BRD4, which blocks binding of these domains to acetylated H4 histones. In the phase Ib trial, nine patients with NUT carcinoma were treated; three had partial response, with durations of response ranging from 1.4 to 8.4 months on continuous treatment at 80 mg/day.[17]

3. Indication and awarding criteria

Name

Birabresib treatment is for all patients diagnosed with NUT with either (i) NUT-positive IHC with clone C52B1, or (ii) FISH or NGS confirming the presence of a *NUTM1* gene rearrangement, including paediatric patients, after at least one line of systemic therapy.

Patients eligible for curative treatment will be excluded.

All treatment initiations will be validated during the weekly molecular multidisciplinary team meeting at Gustave Roussy in order to jointly validate the indication for birabresib.

Treatment will continue as long as it is effective and well tolerated.

Safety data available for birabresib to support its use

A phase Ib trial including 10 patients diagnosed with NUT tumours recommended a phase II dose of 80 mg once daily with continuous dosing. Birabresib should be administered orally on an empty stomach with some water. 20 mg capsules will be manufactured to adjust the dose based on the safety profile (see Appendix E)

The 80 mg continuous dose cohort included 20 patients; 75% of patients experienced an adverse event, 50% had a grade 3-4 adverse event, and 7 patients had a serious adverse event, none of which resulted in death.

Overall, the **common adverse events** related to the treatment were diarrhoea, nausea, loss of appetite, vomiting, and thrombocytopenia.

Common treatment-related **serious adverse events** were thrombocytopenia, diarrhoea, nausea, hyperbilirubinaemia, increased ALT, loss of appetite, and acute kidney injury. Factor VIII deficiency has also been described.[17]

Most of these side effects are dose-dependent.

Efficacy data available to support use

The phase 1 trial included 9 patients diagnosed with a NUT tumour in the "continuous dose cohort (eight patients 80 mg dose and one patient 100 mg dose". Best response per RECIST 1.1 was partial response in 3 (33%) patients, stability in 3 (33%), progression in 2 (22%), and 1 (11%) patient was not evaluable for response. The range of delayed response durations was 1-8.4 months.[17,22]

The Institut Gustave Roussy database includes 75 patients with NUT carcinoma, 17 of whom were treated with BETi. In the first-line setting (8 patients), 4 had a partial response and 3 had stable disease as best response. In the second line (7 patients), there is 1 persistent complete response, 2 disease stabilisations and 4 progressions. Survival analysis, performed in patients who have previously received other treatments including at least one systemic component, suggests a

longer overall survival in the BETi-treated group compared with other systemic treatments (15 months vs 8.86 months), without reaching statistical significance.

4. Conditions of prescription and supply and practical arrangements (access request)

The Birabresib 20 mg Compounding is subject to hospital prescription. The prescription is reserved for oncology specialists or doctors with oncology expertise.

See prescription circuit in Appendix C

5. Patient information

Before starting treatment, each patient, their legal representative or the trusted person they have designated, must be informed by the prescriber of the medicinal product and of the procedures for exceptional provision and reporting of adverse effects. A patient information sheet (appendix A) is given to them by the prescribing doctor with the explanations necessary for their understanding. The patient (their legal representative or trusted person) must read this information sheet and show it to any doctor consulted.

6. Eligibility criteria

Baseline

- child, adolescent or adult patient
- NUT tumour diagnosed by either (i) NUT-positive IHC with clone C52B1, or (ii) FISH or NGS confirming the presence of *NUTM1* gene rearrangement
- relapsing after at least one line of systemic therapy.
- after discussion and recommendation of prescription by the Gustave Roussy molecular MDT to take into account molecular profiling, if applicable, and to explore therapeutic medicinal product alternatives or possible therapeutic trials open to inclusion. The Gustave Roussy molecular MDT (maud.ngocamus@gustaveroussy.fr, laetitia.millier@gustaveroussy.fr) meets

every week to discuss and harmonise patient care according to the molecular profiling of their tumours. National and international cases from Gustave Roussy and other hospitals are presented and discussed.

Patients undergoing treatment with Birabresib dispensed abroad may enter the device, depending on the validation and prescription circuit. The circuit is detailed in Appendix C.

Non-inclusion

- patient who has not received a systemic line of therapy or is on treatment without progression
- no recommendation for prescription by the molecular MDT

7. Follow-up method

Visit schedule

	Request for authorisation from the ANSM	First administration (Initiation sheet)	Treatment follow-up and/or discontinuation (Follow-up sheets) every 3 to 4 weeks or according to progression
Dispensing of the patient information sheet by the prescribing doctor	X		
Collection of data on patient characteristics			
Declaration of compliance with the criteria for granting the guidelines	X		
Laboratory work-up, FBC	X	X	X At C2 then every 3 months or if clinically indicated
ECG	X		
Treatment history and disease history	X	X	X
Pregnancy test (if applicable)	X		
Physical examination	X	X	X

Performance status-ECOG	X	X	X
Collection of data on conditions of use			
Concomitant treatments and their dosage	X	X	X
Monitoring of adverse events			X
Treatment interruption			X
Collection of efficacy data (to be adapted according to the medicinal product)			
Survival data, if applicable			X
Efficacy outcome measure *(to be specified): imaging assessment (RECIST 1.1 assessment)*		X	X *Every 6-8 weeks and at progression*
Collection of safety data/special situations			
Monitoring of adverse effects/specific situations		X	X

The patient will join the "STING" protocol (Gustave Roussy Cancer Profiling), (NCT04932525), led by Gustave Roussy, sponsor of this research project. This study allows for the collection and use of clinical data. A "NUT tumour" cohort will be created.

Data from patients with an S2 form will be collected after signing the STING informed consent. For foreign patients who do not have an S2 form, the FRESH informed consent will be signed and a Data Transfer Agreement set up with the reference centres.

8. Procedure for reporting an adverse effect

Who should report?

Any doctor, dental surgeon, midwife or pharmacist who becomes aware of an adverse event likely to be due to the medicinal product must report it.

Other healthcare professionals may also report any adverse events suspected of being due to the medicinal product of which they become aware.

The patient or their authorised representative (trusted person designated by them, approved associations requested by the patient) may report any adverse effects that they or their family suspected of being linked to the use of the medicinal product.

What should be reported?

All adverse events, including overdose, misuse, abuse, medication error, exposure during pregnancy or breast-feeding or paternal exposure, drug interaction and occupational exposure, and death.

It is also strongly recommended to report to the RPVC any special situation such as: exposure during pregnancy including paternal exposure even without adverse effects, any medication error without adverse effects, any suspicion of therapeutic inefficacy (partial or total) outside the natural progression of the underlying disease.

When should a report be made?

All adverse reactions should be reported as soon as the healthcare professional or patient or patient's legally authorised representative becomes aware of them

Reporting of suspected adverse reactions

Reporting suspected adverse reactions is important. It allows continuous monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals must report any suspected adverse reactions via the national reporting system (see section "How should a report be made?")

How should a report be made?

For healthcare professionals:

The report is made directly on the website www.signalement-sante.gouv.fr or using the adverse effect declaration form available on the ANSM website www.ansm.sante.fr (section Reporting an adverse effect). The statement must clearly state that the prescription was made as part of compounding

For patients:

The declaration is made directly on the website www.signalement-sante.gouv.fr. Other reporting media may be used, such as a letter, fax or telephone call,

addressed directly to the RPVC on which the person presenting the adverse effect depends geographically.

The prescription for Birabresib in the context of compounding must be specified.

9. References

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APPENDICES

A. Patient and/or Parent Information Sheets

B. Methods for collecting suspected treatment-related adverse reactions and special situations

C. Summary diagram of the Birabresib supply circuit

D. Validation and recommendation by the Gustave Roussy molecular MDT

E. Molecular MDT form

F. Product sheet

A. Patient and/or Parent Information Sheets

Information sheet on the authorisation of the Therapeutic Use Protocol

To be given to the patient before prescribing BIRABRESIB

In the event that the patient is unable to read this information, it will be given to their legal representative or, if applicable, to the trusted person designated by them

Your doctor has proposed treatment with Birabresib (OTX015) as part of a therapeutic use protocol (PUT).
The purpose of this note is to inform you so that you can accept the treatment offered to you with full knowledge of the facts. It is essential that you carefully read the leaflet, the text of which is reproduced below.

Confidentiality

In accordance with the General Data Protection Regulation (GDPR), Gustave Roussy, as data controller of your personal data, undertakes to take all necessary measures to ensure their security and confidentiality.

Your participation in this PUT involves the processing of information about you collected and generated as part of your care[1].

Your personal data will only be analysed for cancer research purposes. Unless you object, this data may be reused, in a confidential and secure manner, for future cancer research.

The processing of your data is justified by the legitimate interest of Gustave Roussy, as a cancer centre, to better understand the mechanisms of NUT cancers in order to better prevent and treat them.

Access to information that can identify you is strictly restricted to:

- professionals involved in the PUT

- where applicable, under strict contractual conditions, certain service providers[2] acting on behalf of Gustave Roussy;

- certain health authorities (e.g. ANSM, European Medicines Agency).

Your personal data is pseudonymised beforehand - i.e. it no longer shows your identity - before it is used by anyone other than those mentioned above.

After pseudonymisation, your personal data may be transmitted to Gustave Roussy's hospital, industrial and academic partners, to companies specialising in healthcare, as well as to the ANSM and, where applicable, to certain public authorities. Your data may be transferred outside France, including to non-European countries. In all cases, Gustave Roussy ensures that any third party with access to your data provides sufficient guarantees prior to sharing your data[3]. Gustave Roussy will make available to you, upon request, the list of third parties with whom your data is shared.

By guaranteeing your anonymity beforehand, the results of this PUT may also be communicated to the scientific community during seminars, conferences or published in the scientific press.

Unless you object, your information relating to this study will be kept for up to two years after the last publication of the results of the research or, if not published, until the signature of the final research report.

In accordance with the regulations, they will then be archived, with restricted access for at least 25 years.

1 The personal data collected and generated during your care are administrative, social and medical in particular. Certain data used may also relate to your personal life (e.g. tobacco, alcohol, drug consumption) and/or your professional life (e.g. socio-professional category, etc.), or even data generated by the analysis of biological samples collected from you as part of this PUT.

2 For example, the archiving of part of the medical-administrative files for Gustave Roussy clinical studies is carried out by a Gustave Roussy service provider

3 In the event of the transfer of personal data outside the European Union, Gustave Roussy shall first ensure that its non-European partners present sufficient legal guarantees to guarantee a sufficient and appropriate level of data protection (adequacy decision of the European Commission, standard contractual clauses of the European Commission, internal company rules, etc.). To find out more, you can contact the data protection officer of Gustave Roussy.

Your oncologist is offering you treatment with Birabresib, a treatment for NUT tumours. As this medicinal product does not have a Marketing Authorisation, its use as a medicinal product is subject to close monitoring by the French National

Agency for the Safety of Medicines and Health Products (ANSM) within the framework of a specific therapeutic use programme.

NUT tumours are rare and aggressive tumours. They are most often located in the chest, then in the head and neck, but can appear anywhere in the body. To date, no treatment has been shown to be effective.

Based on tumour biology, birabresib targets one of the distinctive molecular characteristics of NUT tumours, i.e. a ‘flaw’ in the biology of this tumour. Your referring oncologist, after discussion in a multidisciplinary consultation meeting and taking into account your clinical and biological data, proposes treatment with this molecule

Birabresib is a medicine that works by blocking certain proteins called bromodomains (BETs). These proteins play a key role in controlling genes involved in cancer cell growth and survival. In NUT tumours, an abnormal gene excessively activates these proteins, resulting in a rapid multiplication of tumour cells. By inhibiting the action of bromodomains, birabresib can slow or stop the growth of cancer cells and help limit the progression of the disease.

Birabresib will be administered to you in the form of compounding performed by the pharmacy of Gustave Roussy Cancer Campus. This preparation is reimbursed by health insurance.

Birabresib is presented as capsules to be swallowed with liquid, taken once daily continuously until you or your oncologist decide to stop it for insufficient efficacy, or for possible unexpected or excessive side effects.

The dose should be taken on an empty stomach, i.e. up to 30 minutes before or at least 2 hours after a meal.

Given the previous data, stabilisation or even reduction of the disease is expected, but for a possibly limited duration.

This medicine has already been assessed in adult patients and has been well tolerated. Of the notable side effects, those of digestive origin (nausea, vomiting, diarrhoea), fatigue and changes in blood cell counts were described as the most common. The table below describes the side effects reported in patients treated with Birabresib (N = 9).

Table 2 Adverse effects and frequency

Adverse effects	**%**
Gastrointestinal .- Diarrhoea .- Nausea .- Vomiting .- Decreased appetite .- Dysgeusia	 10 25 20 20 15
Constitutional .- Fatigue	 15
Haematological .- Anaemia .- Thrombocytopenia	 5 5
Biological .- Factor VII deficiency	 20

- Dysgeusia is a change in the taste of food and liquids ingested.
- Anaemia is a decrease in haemoglobin in the blood, linked to a change in red blood cells.
- Thrombocytopenia is a decrease in the number of platelets in the blood, which can lead to bleeding.
- Factor VII deficiency is an abnormality of haemostasis, i.e. the ability of the blood to create blood clots in case of bleeding.

What commitments should you make? What are your constraints?

As there is little hindsight on the use of the medicinal product proposed to you, its use is monitored and described in detail in the protocol for therapeutic use and patient monitoring (PUT-SP) available on the website of the French National Agency for the Safety of Medicines and Health Products (ANSM).

Your feedback on this treatment is essential. This is why your opinion on this medicine and the effects it has on you will be collected in two ways: at each consultation with your doctor and at any time between visits in case of side effects.

At each visit

Your doctor will ask you questions about how you are feeling with this treatment and collect personal data about your health.

At home, between visits

If you do not feel the same as usual or if you have any new or unusual symptoms, talk to your doctor, pharmacist or nurse.

It is important that you report the side effects of the medicine, i.e. the unexpected or unpleasant consequences of the treatment that you may experience (pain, nausea, diarrhoea, etc.).

Processing of your personal data

Treatment with a medicine prescribed under a PUT involves the collection of personal data concerning your health.

It will be suggested to you by your doctor that the safety and efficacy data for the medicine you receive will be collected anonymously in the STING study. You will be given a separate information document. The collection of this information is not mandatory to gain access to the medicine Birabresib.

Patient associations involved in your disease can provide you with help and support. Ask your study staff for more information.

B. Methods for collecting suspected treatment-related side effects and special situations

How the patient reports side effects

In the event that a side effect occurs, you should notify your oncologist immediately, who will advise you of the action to be taken. These data will be collected for all patients as and when the tolerance of this prescription is monitored.

Your oncologist is responsible for administering and monitoring this treatment.

You can also report any side effect likely to be related to this medicine directly on the website www.signalement-sante.gouv.fr or using the side effect reporting form available on the ANSM website www.ansm.sante.fr (section Reporting a side effect). By reporting side effects, you can help provide more information on the safety of this medicine.

Who should report?

Any doctor, dental surgeon, midwife or pharmacist who becomes aware of a side effect likely to be due to the medicine must report it. Other healthcare professionals may also report any suspected side effects of which they become aware.

In addition, healthcare professionals are encouraged to report any special situations.

The patient or their authorised representative (trusted person designated by them, approved associations requested by the patient) can report any side effects/special situations that they or their loved ones suspect are related to the use of the medicine.

What should be reported?

All side effects, serious and non-serious, occurring under conditions of use compliant or non-compliant with the terms of the authorisation, including overdose, misuse, unintended use, abuse, medication error, occupational

exposure, drug interaction, a defect in the quality of a medicine or fraudulent medicine, exposure during pregnancy (maternal or via semen), paternal exposure (potential alteration of sperm), exposure during breast-feeding.

In addition, it is also necessary to report any special situation: any medication error without adverse effects, whether proven, potential or latent, any suspicion of therapeutic inefficacy (partial or total), other than the natural progression of the underlying disease (in particular with vaccines, contraceptives, treatments for life-threatening diseases, unexpected resistance to drug treatments or any other situation considered clinically relevant), any suspicion of transmission of infectious agents linked to a medicine or medicinal product, any exposure to a medicine during pregnancy or breast-feeding without the occurrence of a side effect; any situation considered relevant to report.

When should a report be made?

All side effects/special situations should be reported as soon as the healthcare professional or patient becomes aware of them.

How should a report be made, and to whom?

For healthcare professionals:

The report is made via the PUT-SP declaration sheets to the laboratory.

For patients and/or patient associations:

As soon as possible, after the occurrence of the side effect(s)/special situation(s) with the doctor, pharmacist or nurse. It is also possible to report side effects/special situations directly via the reporting portal: www.signalement-sante.gouv.fr.

Other reporting media may be used, such as a letter, email or telephone call, addressed directly to the RPVC on which the person presenting the side effect depends geographically. The list indicating the address and departments covered by each RPVC is available on the ANSM website.

C. Summary diagram of the Birabresib supply circuit

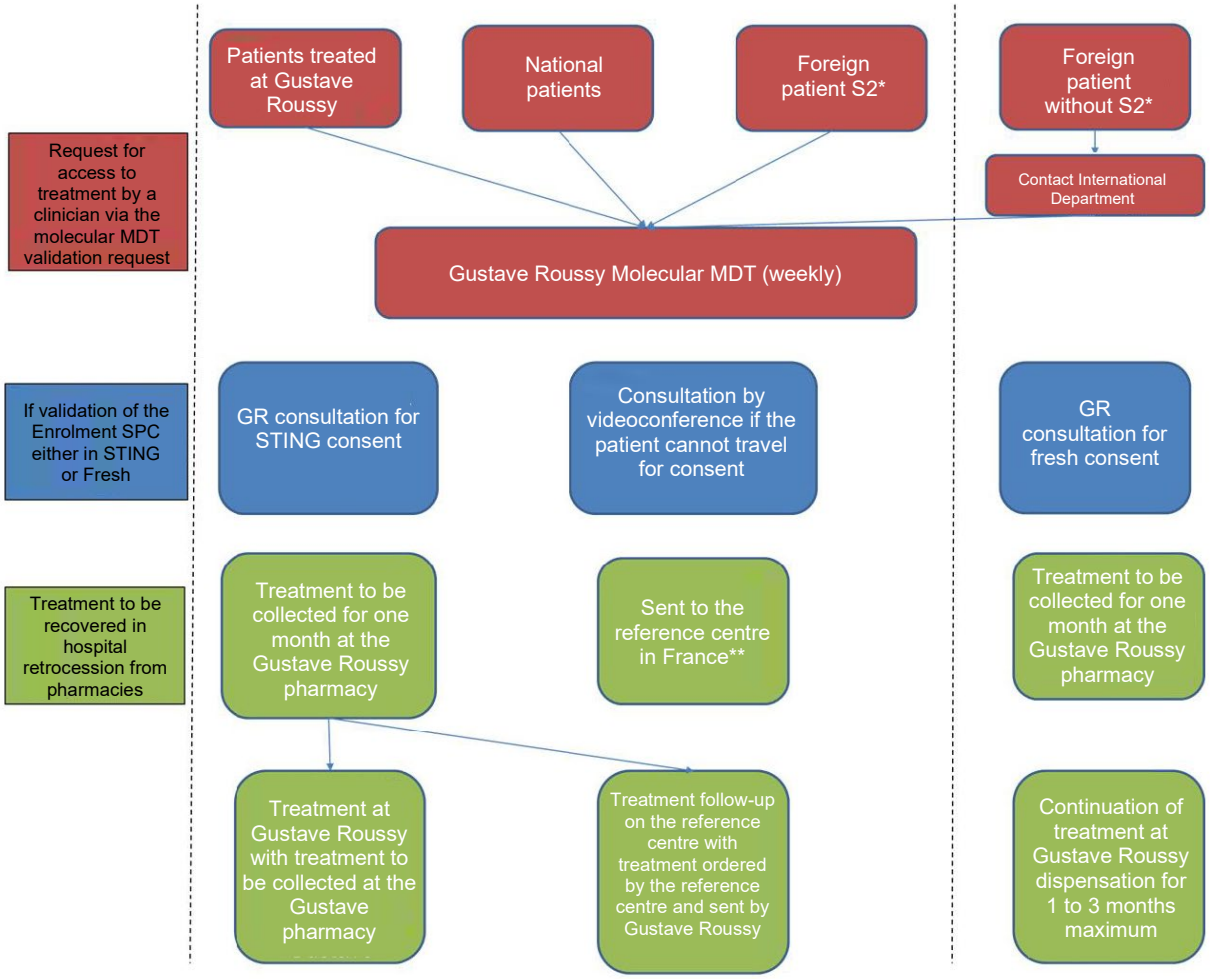
Circuit

1. Report of IHC, FISH, or NGS diagnosis of a NUT tumour is sent to the oncologist who confirms the NUT tumour diagnosis
2. Discussion at the Gustave Roussy molecular MDT (with at least 3 physicians with a separate speciality in attendance) The Gustave Roussy molecular MDT (maud.ngocamus@gustaveroussy.fr, laetitia.millier@gustaveroussy.fr) meets every week to discuss and harmonise patient care according to the molecular profiling of their tumours. National or international cases from Gustave Roussy and other hospitals are presented and discussed.
3. MDT treatment recommendation based on disease history, prior therapies and available molecular information
4. If the proposed treatment is Birabresib, the written recommendation from the Gustave Roussy molecular MDT is sent to the patient's referring medical oncologist and the information is sent at the same time to the Gustave Roussy PUI.
5. The doctor informs the patient or parents and explains to them the participation in STING during an inaugural consultation at Gustave Roussy. They collect their non-opposition to the collection of data by signing the informed consent form for the FRESH programme. A Data Transfer Agreement may be put in place for the collection of data.

Teleconsultation may be offered if the patient cannot travel.

6. After informing the parents or the patient, the doctor prescribes Birabresib according to the PUT and the prescription is sent to the Gustave Roussy PUI with the recommendation of the MDT.
7. The therapeutic units (treatment for one month) are sent by the Gustave Roussy PUI to the hospital PUI where the patient is cared for.
8. The hospital pharmacy makes treatment available to the patient by retrocession
9. Monthly renewal requests are made by the referring doctor according to the same circuit without further evaluation by the national molecular MDT

10. After initiation of treatment, the doctor records the patient in STING and completes the medical follow-up and therapeutic evaluation in accordance with the terms of the PUT.



Overall diagram of the Birabresib circuit.

*for foreign patients who cannot benefit from an S2 form, the international department of Gustave Roussy must be contacted secretariat.di@gustaveroussy.fr, in order to send the files to the molecular MDT.

**To be able to send the treatment to a French centre, it must have a subcontracting agreement with the Gustave Roussy pharmacy. To do so, they can contact: pharmacie.preparatoire@gustaveroussy.fr. The invoicing and reimbursement procedures then follow the traditional channel via subcontracting agreements and retrocession channels

Validation and recommendation by the Gustave Roussy molecular MDT

The Gustave Roussy Molecular MDT meets once a week to discuss the therapeutic indications for drug treatment based on the molecular analysis results for relapsed patients. This is a national MDT conducted at Gustave Roussy. The clinical cases of patients at Gustave Roussy and other (national) hospitals are discussed.

Contact: birabresib@gustaveroussy.fr

maud.ngocamus@gustaveroussy.fr, laetita.millier@gustaveroussy.fr

In practice, a form is sent to the MDT contact. The patient's doctor is invited to participate in the discussion. A written recommendation is sent to the attending doctor.

D. Molecular MDT form

The form is to be completed on Redcap Gustave Roussy

Patient Administrative Information

Date of request

Requesting Doctor's Institution:

Gustave Roussy ☐

Other ☐

Committee:

Dermatology ☐

Digestive ☐

Miscellaneous-Without entry door (ACUP) ☐

Miscellaneous staff ☐

Early Tests ☐

Gynaecology ☐

Haematology ☐

Neurology ☐

Oncogenetic ☐

ENT ☐

Paediatrics ☐

Lung ☐

Sarcomas and mesenchymal tumours ☐

Breast ☐

Endocrine tumours ☐

Genitourinary ☐

Surname of Patient

First Name of Patient

Sex

Date of Birth

File No. (PIN)

Referring Doctor

Form completed by (if different referring doctor)

Cancer Pathology

Signed consent(s) for the protocol(s)

Speciality:

ACUP ☐

Dermatology ☐

Digestive ☐

Endocrinology ☐

Gynaecology ☐

Neurology ☐

ENT ☐

Sarcomas ☐

Breast ☐

Thoracic ☐

NET ☐

Urology ☐

Haematology ☐

Paediatrics ☐

Location of the primary tumour:

Histology

Current WHO

0 ☐

1 ☐

2 ☐

3 ☐

4 ☐

Metastatic

Yes ☐

No ☐

Brain metastasis(es)

Yes ☐

No ☐

Other Concomitant active cancer

Yes ☐

No ☐

Processing on the date of creation of the file

Number of PREVIOUS lines of therapy (metastatic only)

For each line of treatment:

Molecule: *please specify*

Current anti-cancer therapy line:

Molecule: *please specify*

Situation of the patient on the date of request for transition to molecular MDT

Before any metastatic therapy

Before current treatment

Currently being treated

On current treatment (stable patient or in response)

Currently on treatment (progressing patient)

After Current Treatment or On Standby or Monitoring

Known mutations (previous molecular portraits):

Free comments:

E. Product sheet

Packaging:

20 mg Birabresib capsules, prepared by the Gustave Roussy PUI

The capsules are size 4 (formulation suitable for pts who cannot swallow during development)

All preparations are stored at room temperature.

Posology and method of administration

- In adults, 80 mg orally on an empty stomach once daily continuously
- In children and adolescents, 40 mg/m^2 orally on an empty stomach once daily

Dose adjustment of birabresib in the paediatric population:

Patient weight (kg)	theoretical dosage	number of capsules/day	actual posology	posological delta
15	20	1	20	0
20	24	1	20	-17%
25	33	2	40	21%
30	40	2	40	0%
35	46	2	40	-15%
40	53	3	60	12%
45	60	3	60	0%
50	67	3	60	-11%
55	73	4	80	9%
60	80	4	80	0%

The capsules should not be opened or crushed. Swallow with liquid.

Precautions for use/warnings

<u>Treatment initiation criteria:</u>

- Hepatic and renal function tests normal
- Absolute neutrophil count > 1.5 x 10^9/L and platelets > 100 x 10^9/L and haemoglobin > 8 g/dL

An ECG is performed before the start of treatment and at the end of treatment visit for all patients.

Drug interactions

The following are prohibited: avasimibe, carbamazepine, phenytoin, rifampicin, St. John's wort, boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, voriconazole.

The following substances should be avoided: amobarbital, dexamethasone, efavirenz, felbamate, nevirapine, omeprazole, phenobarbital, pioglitazone, primidone, rifabutin, tamoxifen, troglitazone, atazanavir, amiodarone, amprenavir, aprepitant, cimetidine, cyclosporine, darunavir, delavirdine, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, miconazole, suboxone, verapamil, phenobarbital, rifampicin, ketoconazole, methoxsalene, pilocarpine, tranylcypromine, coumarin, halothane, losigamone, methoxyflurane, nicotine, quinoline, SM-12502, valproic acid.

Contraception

Women of childbearing potential/Contraception in men and women

Women of childbearing potential should be advised to avoid becoming pregnant while taking Birabresib. Patients must use an effective method of contraception (methods associated with a pregnancy rate of less than 1%) throughout the duration of treatment and continue for at least 1 month after the last dose. Men with a sexual partner who is pregnant, potentially pregnant, or who may become pregnant must use condoms during treatment with Birabresib and for at least 1 month after the last dose.

Pregnancy

There are no adequate and well-controlled studies in pregnant women to rule out a risk associated with the product.

Women of childbearing potential must have a blood pregnancy test within 72 hours before starting treatment with Birabresib.

Breast-feeding

It is not known whether Birabresib is excreted in breast milk. There are no data on the effects of Birabresib on breast-fed infants or on milk production. Due to the risk of serious side effects in breast-fed infants, women should not breast-feed during treatment and for 2 months after the last dose.

Fertility

No data are available on the effect of Birabresib on human fertility.

Management of toxicities

Dose interruption, dose reduction or permanent suspension may be justified according to individual tolerability according to the table below:

Starting dose	Toxicity grade	Management	Dose adjustment
80 mg	3*	Suspension until resolution Symptomatic treatment if applicable	*After resolution to grade ≤ 1 (first occurrence of toxicity)*, decrease to 60 mg level: 40 mg in the morning and 20 mg in the evening (40 mg- 0 – 20 mg) *If the toxicity appears for the second time:* Permanent suspension
60 mg	3*	Suspension until resolution Symptomatic treatment if applicable	*After resolution to grade ≤ 1 (first occurrence of toxicity)*, decrease to the 40 mg level: 20 mg in the morning and 20 mg in the evening (20 mg- 0 – 20 mg) *If the toxicity appears for the second time:* Permanent suspension

40 mg	3*	Suspension until resolution Symptomatic treatment if applicable	*After resolution to grade ≤ 1 (first occurrence of toxicity),* decrease to 20 mg level: 20 mg in one dose in the morning (20 mg-0-0) *If the toxicity appears for the second time:* Permanent suspension
All doses	4*	Final suspension	Final suspension

Dose adjustment of birabresib according to toxicity

**Except for asymptomatic biological or haematological testing*