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ASSOCIATION ACADÉMIQUE POUR LE DÉVELOPPEMENT EN ONCOLOGIE HÉMATOLOGIE DES PHASES PRÉCOCES EN FRANCE

CONFERENCE REPORT

November 22, 2019

2019 MEETING ON Early Phase Cancer Trials

How can France become more attractive for early phase cancer trials?

An event organized by

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1ST MEETING ON EARLY PHASE CANCER TRIALS - 2019 REPORT

Jean-Yves Blay
(Léon Bérard
Cancer Center, Lyon).

Christophe Massard
(Gustave Roussy
Cancer Center,
Villejuif).

How can France become the most attractive country for early phases trials in onco-hematology? This was the ambitious goal of the **1st Meeting on Early Phase Cancer Trials - 2019** that was organized to promote exchanges and discussion among all those who work in this field. More than 500 participants from various backgrounds —clinicians, agencies, pharmaceutical companies, ethics committees, health authorities, research institutes and foundations, and medical and patient associations—came together to discuss this question, giving everybody the opportunity to express themselves and share their point of view, and to carry out a general review of the situation of early phase clinical trials in France.

France now has several assets to increase its attractiveness: French centers have a unique experience in immunotherapies and the management of side effects; several hospitals have been certified by the National Cancer Institute (INCa) for early phase clinical trials in adult and pediatric oncology; and platforms for the characterization of the molecular genetics of cancer cells are also available. In addition, existing networks make it easier now to recruit patients, for example, for the expansion cohorts in phase I trials. Finally, the coordinated action of French practitioners to facilitate access of patients in the country to innovative treatments deserves to be praised.

This meeting, endorsed by the SCOPP (Academic Association for the Development of Early Phases Onco-hematology Trials in France), also focused on important changes that will contribute to the attractiveness of France: first of all, the "fast track" procedure of the French National Agency for Medicine and Health Product Safety (ANSM) with a response time of less than two months will bring about a marked improvement in the activation of early phase trials and access to innovative treatments; and secondly, as of March 2020, French Ethics Committees (CPP) will be reorganized to cope with the growing number of early phase clinical trials and to align with new European regulations that will soon come into effect.

Jean-Yves Blay
(Léon Bérard Cancer Center, Lyon)

Christophe Massard
(Gustave Roussy Cancer Center, Villejuif)

Recordings of all presentations from the meeting and slides are available on our website:

www.phases-precoces.fr

in the "Actualités" section.

1ST MEETING ON EARLY PHASE CANCER TRIALS - 2019 ENDORSED BY THE SCOPP ASSOCIATION

SCOPP (Academic Association for the Development of Early Phase Onco-hematology Trials in France) is a non-profit organization whose founding members are all involved in a general oncology-related activity and, above all, in the development of new drugs. Focusing on early phase trials, its members deal with the current questions and issues regarding trials in France and abroad.

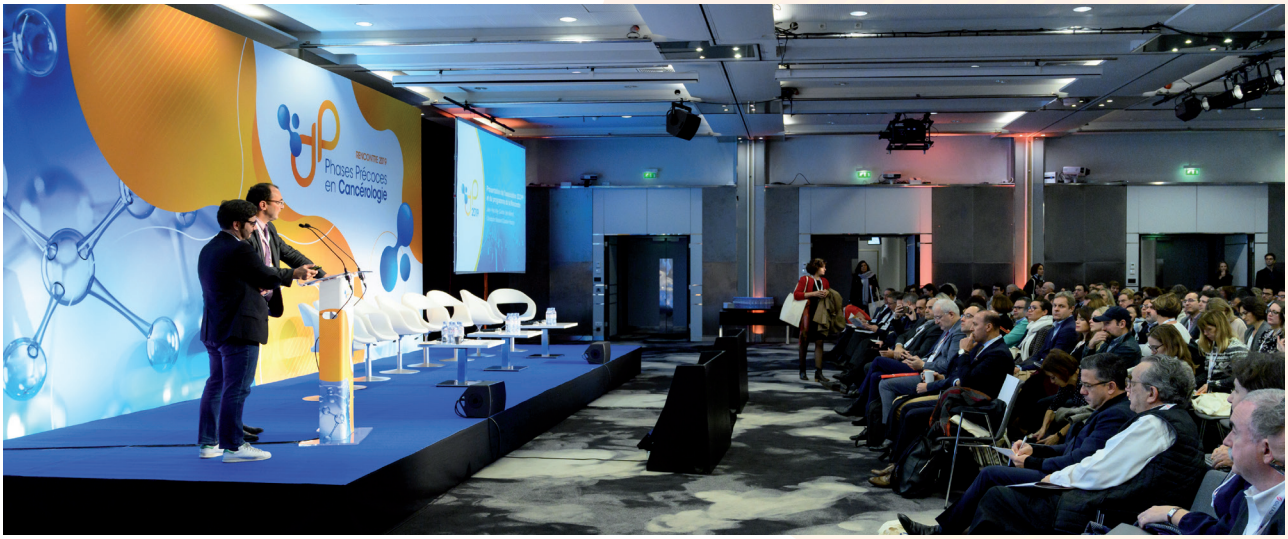
Moderators: Jean-Yves Blay (Léon Bérard Cancer Center, Lyon) **– Christophe Massard** (Gustave Roussy Cancer Center, Villejuif)

Jean-Yves Blay
(Director General of the Léon Bérard Cancer Center, Lyon).

Christophe Massard
(Gustave Roussy Cancer Center, Villejuif).

SCOPP has several goals:
To facilitate the implementation of early phase onco-hematology trials in France and **the rapid arrival of novel treatments for patients:** developing and activating early phase trials is increasingly complex in Europe and abroad due to high competition. As a result, the key to success is the ability to set up these trials quickly to help give patients access to new treatments.

- **To strive for patients to have** fast access to early phase **onco-hematology trials and also for these early phase trials to be extended** to frail populations (such as children and the elderly).
- **To be** a real intermediary for discussions **with decisionmakers in government and/or in health agencies and with the industry or patient groups involved in early phase cancer trials,** and bring all stakeholders together to overcome some of the hurdles involved in accelerating the process to enroll a first patient in an early phase clinical trial.
- **To represent a group of clinicians specializing in early phase cancer trials to defend these trials,** resolve difficulties and make France more attractive when it comes to this type of trial.
- **To rally clinicians involved in early phase onco-hematology trials** and encourage them to talk, exchange information and share their experiences.



- **To organize, manage and take part** in all activities to help promote early phase cancer trials.

- **To facilitate partnership contracts and agreements and plan training programs for the people involved in these early phase trials.**

The 1st Meeting on Early Phase Cancer Trials - 2019 was organized to promote discussions and debates with all stakeholders in this field who share the same goal: to make France more attractive for early phase onco-hematology trials This event was a huge success with over 500 attendees from different backgrounds: clinicians, the National Agency for Medicine and Health Product Safety (ANSM), pharmaceutical companies, ethics committees, the National Cancer Institute (INCa), research groups (LYSA), and foundations and associations involved in cancer research (ARC Cancer Research Foundation, *Ligue Nationale Contre le Cancer*), and patient groups. A wide range of subjects was addressed and debated in plenary sessions, several round tables, "speed conferencing" and pitches by start-ups, which enabled representatives from pharmaceutical companies, academia, institutions, regulatory authorities, patient groups and start-ups to share their opinions. ▲

HOW CAN FRANCE BECOME THE MOST ATTRACTIVE COUNTRY FOR EARLY PHASE INDUSTRY-SPONSORED CANCER TRIALS?

This round table was a chance to take stock and discuss with all those involved in early phase trials the strategies to make France the most attractive country for early phase industry-sponsored cancer trials. Those directly in the field, clinicians, patients and drug developers spoke during the first part to share their views on France's attractiveness. It was then the turn of the public authorities to talk about how they see the near future and developments to come in this highly competitive international context.

Discussions moderated by Jean-Yves Blay (Director General of the Léon Bérard Cancer Center, Lyon)

→ SPEAKERS

- **Toufik Bendahmane** (Oncology Medical Director, Roche);
- **Pierre-Henri Bertoye** (President of the National Human Research Commission - CNRIPH);
- **Laetitia Gambotti** (Head of the National Cancer Institute's Clinical Research Department);
- **Laure Guéroult Accolas** (Patient, Founder and Director of *Patients en Réseau*);
- **Christophe Massard** (Head of the Department for Therapeutic Innovation and Early Phase Trials at Gustave Roussy Cancer Center);
- **Pascal Piedbois** (Medical Director, BMS);
- **Stéphane Vignot** (Medical Advisor for Early Phase Trials/Innovation, Division for Authorization and Innovation Policies, National Agency for Medicine and Health Product Safety).

THE PERSPECTIVE FROM PEOPLE IN THE FIELD

Christophe Massard (Head of the Department for Therapeutic Innovation and Early Trials, Gustave Roussy).

ASSETS FACILITATING EARLY PHASE ONCOLOGY TRIALS:

A clinician's perspective – **Christophe Massard** (Gustave Roussy, Villejuif).

France currently has a number of assets to help implement early phase trials:

- **For many years there has been support in the form of supervision, including from the French National Cancer Institute (INCa), and through the creation of spe-**

cialized units such as the DITEP (Department for Therapeutic Innovation and Early Trials) at Gustave Roussy, which has allowed us to conduct phase I clinical trials more professionally and gain recognition in Europe and internationally. Given the new development contexts of early phases and growing international competition, all the French centers involved in these early phases will need to organize themselves better, perhaps based on their expertise, and will need to coordinate nationwide.

- Having **unique expertise** (rare tumor network, expertise in thoracic oncology) makes **France a leader** in certain fields, with teams involved in routine care and the implementation of clinical trials based on actual demand in the field.

- **The French healthcare system model** gives all patients access to innovation, which facilitates the inclusion and management of patients in centers that conduct this type of early phase trial.

- In addition to these assets, partnerships between pharmaceutical companies, academic institutions and associations or foundations involved in cancer research must be strengthened and effort made to involve patients more at this stage of development.

THE LEEM'S PERSPECTIVE: AN ACTION PLAN DEVISED TO STRENGTHEN FRANCE'S ATTRACTIVENESS

Thomas Borel (Director of Scientific Affairs, LEEM, Paris).

From surveys conducted every two years on industry-sponsored clinical trials, the figures in 2017 showed a fall in the number of clinical trials in France, in particular early phase trials (a drop of around 20%) and **a decrease in France's relative attractiveness.** At the time, this was attributed to the complex regulatory situation and excessive time lags for setting up clinical trials. More recently,

Thomas Borel
(Director of Scientific Affairs, LEEM, Paris).

more reassuring data has been presented, but France is still in 5th place in Europe, behind Germany, the UK, Belgium and Spain, in terms of participation in early phase trials initiated by pharmaceutical companies. This is not as alarming as some publications have suggested, and recent efforts to facilitate clinical trials in France are encouraging. What is more, all those involved in clinical research, academics, medical societies, the French National Agency for Medicine and Health Product Safety, and pharmaceutical companies have **considered ways to strengthen clinical research in France.** This working group's report, endorsed by the Ministry of Health and the General Directorate for Healthcare (DGOS), is expected to be published soon.

FRANCE LESS POPULAR FOR FIRST-IN-HUMAN TRIALS: THE MANUFACTURERS' PERSPECTIVE

Toufik Bendhamane (Roche) and **Pascal Piedbois** (BMS)

Pascal Piedbois
(Medical Director, BMS).

Toufik Bendahmane
(Oncology Medical Director, Roche).

- **Toufik Bendhamane (Roche).** The fact that France is in 5th place in Europe for early phase trials is worrying and primarily concerns first-in-human trials. While ...

between 2008 and 2011, early phase trials in France were divided equally between phase I first-in-human trials, phase Ib trials and extension cohorts, the current ratio is around 80-85% for phase Ib trials/extension cohorts and 15-20% for phase I first-in-human trials. Pharmaceutical parent companies now tend to conduct trials in countries with easier and faster access to early phase trials such as Spain, Belgium, Korea, China and South America. **It is, therefore, now urgent to work together to promote France's expertise and start trials more rapidly.**

• **Pascal Piedbois (BMS).** Innovation is thriving. This is especially good news for patients, but given the level of competition from abroad, we must do all we can to develop France's expertise. This should involve all stakeholders, hospitals, the National Cancer Institute, ethics committees, the National Agency for Medicine and Health Product Safety, manufacturers and patient groups. But being competitive should not result in competition between those involved in early phase trials in France. Early phase trials in France will be what we make of them. The real challenge as far as industry-initiated trials and academic trials supported by the industry are concerned, relates to first-in-human trials that are more often conducted elsewhere. We cannot simply be good; we have to be better. The health authorities have already made considerable efforts, particularly in terms of response times (now around 50 days), and anything that can make France more appealing for early phase trials must be done. France has wonderful tools in place, trials in touch with daily medical practice, centers of expertise in different fields, constructive relations with the health authorities **and imminent EU regulations should help accelerate this progress.**

Laure Guéroult Accolas (Patient, Founder and Director of *Patients en Réseau*).

EARLY PHASE TRIALS, LARGELY UNKNOWN TO THE GENERAL PUBLIC - WHAT PATIENTS HAVE TO SAY

Laure Guéroult Accolas (Patient, Founder and Director of *Patients en Réseau*).

Although patients and patient advocacy groups are particularly active in some countries, in France, patients know little about and are rarely involved in early phase trials. Talking to the general public about these clinical trials and their specificities should be a top priority, stressing their importance, as they are a unique opportunity to access new treatments. It is vital to explain that these trials have strict inclusion criteria, so not all patients can be enrolled. Patients should be reassured that these trials are available to patients nationwide as there are expert centers throughout France, a list of which can be found on the National Cancer Institute website. Informing patients and helping them participate in these early phase clinical trials is an important goal.

THE AUTHORITIES' PERSPECTIVES

EARLY PHASE TRIALS: A SPECIAL ACTION PLAN IMPLEMENTED BY THE ANSM

Stéphane Vignot (Medical Advisor for Early Phase Trials/ Innovation, Division for Authorization and Innovation Policies, ANSM).

Stéphane Vignot (National Agency for Medicine and Health Product Safety - ANSM).

Clinical trials are the focus of a specific ANSM action plan that includes three priorities related to early phase trials. (Figure 1).

• **The Early Phase Trials Unit** created by the Agency takes a multidisciplinary team meeting approach to centralize the assessment of all early phase trials, assessing all aspects of the project with the help of specialized reviewers, considering issues affecting admissibility and risks, conducting discussions and forming a collegial decision. This operating method places more focus on the quality and relevance of the issues. The initial results are already encouraging, with a **30% increase in the number of early phase trials in 2018** (115 trials in 2017 vs. 144 in 2018) (Vignot et al. Ann Oncol. 2019; 30: 1694-6).

• **Streamlining measures** have been taken to digitize data, to simplify the format of intermediate letters and to draft questions in the language of the protocol to facilitate and accelerate communication between the ANSM and study sponsors.

• **Fast-track procedures,** which are optional to academic or industrial sponsors, involve a specific process to facilitate access to innovation. In practice, there are two main types of fast-track procedures:

- Fast Track 1 concerns early phase trials (excluding healthy volunteers) in pediatric oncology and rare

diseases, for which the Agency undertakes to submit questions before Day 21 and issue its final decision before Day 40.

- Fast Track 2 concerns clinical trials on a drug or combination of drugs already studied in France in a similar clinical context (where toxicology and quality data already exist), for which questions are submitted before Day 14 and a final decision is issued before Day 25.

To improve the process and response times, the ANSM offers slightly different submission methods for fast-track procedures. These procedures were implemented gradually, starting with an experimental phase in October 2018. They were then implemented definitively and extended to advanced therapy medicinal products (ATMPs) and complex designs in February 2019. One year after introducing the fast-track procedures, the ANSM has received 19 applications for novel drugs (Fast Track 1) including 18 industry-sponsored trials and 1 academic trial. The average decision time was 33 days. In addition, 20 development-related applications (Fast Track 2) were sent to the ANSM (18 industry-sponsored trials and 2 non-French academic trials) with the decision being rendered on average within 15 days.

The ANSM is continuing its efforts to facilitate access to novel treatments through clinical trials by:

- perpetuating these measures;
- creating an Innovation Desk (single contact at the agency for any application on novel treatments);
- increasing European investment and coordinating with the various European authorities (EMA, Heads of Medicines Agencies (HMA) and the European Commission);
- collaboration with ethics committees (EC) to prepare ANSM-EC coordination as outlined in the new EU regulations on clinical drug trials. (Figure 2).

...

Figure 1

ANSM: RECENT DEVELOPMENTS

Early Phase Trials Unit →	**Operating method:** • Admissibility stage: risk analysis (population concerned, drug knowledge) • Specialized reviewers • Group decision: multidisciplinary team meeting approach • Focus on admissibility barriers
Streamlining →	Digitization, format of intermediate letters, questions in the protocol language
Fast-track procedures →	**Specific process to facilitate access to novel treatments** Optional procedure, based on the decision of the academic or industry sponsors Method: improved application, formalized pre-submission

Figure 2

UPCOMING EUROPEAN MILESTONES

European milestones to prepare for

- Coordination between the ANSM and ECs
- Coordination with other member states:
  - shared evaluation doctrines
  - report format (in English)
  - adherence to deadlines
  - powers of persuasion
- Transparent decisions and reports
- **One protocol and one calendar for all EU states = strong attractiveness for Europe**

CERTIFIED EARLY PHASE TRIAL CENTERS (CLIP²)

Laetitia Gambotti (Head of INCa's Clinical Research Department).

Laetitia Gambotti (National Cancer Institute - INCa). CLIP² (INCa-certified early phase trial centers) are a valuable asset for clinical trials in France in terms of visibility and attractiveness. 16 centers have been certified since 2019, including 7 for adults and children, and other centers are expected to open in the near future. **They facilitate the conduct of quality early phase trials in France, have a reputation for excellence in academic and industry-sponsored research and help patients gain access to novel treatments.** Since their creation, the number of patients enrolled in trials at these centers has steadily increased to **approximately 5,000 in 2019.**

The public-private partnerships fostered by the INCa through calls for projects are also a means of promoting access to innovative therapies. Since their creation, 13 calls for projects involving 24 drugs in development have been submitted and around twenty projects have been funded.

Set up since 2006, **the 28 molecular genetics of cancer platforms, which are almost unique,** make it possible to identify "actionable" molecular targets and offer novel treatments to all patients treated in France. Discussions are currently taking place on the implementation of RNA sequencing (RNA-seq).

The INCa is also helping patients by cofunding the Ligue Nationale Contre le Cancer patient committees.

Pierre-Henri Bertoye (CNRIPH President).

ETHICS COMMITTEES AND EARLY PHASE CANCER TRIALS: A DELICATE SITUATION, AN ACTION PLAN LAUNCHED IN 2020

Pierre-Henri Bertoye (President of the National Human Research Commission - CNRIPH). There are currently 39 ECs in 7 regions of France, the new members of which were appointed by the regional

→ DISCUSSION

How do you view the broad partnership between pharma companies and INCa-certified early phase trial centers (CLIP²), in particular for first-in-human clinical trials?

Pascal Piedbois. "The organization in France is not always ideal for carrying out early phase trials, and we need to organize our healthcare and clinical research networks to enhance France's appeal."

Toufik Bendhamane. "Drug companies may choose centers to conduct these trials based on personal relationships and a positive experience with an expert and/or center. However, the priorities should be excellence and the center's reliability. It is no doubt important to communicate more efficiently with the parent companies and use existing networks to involve expert and non-expert centers, and thus increase the number of patients that can be included, the number of trials and the number of drugs in development in France."

Where does France stand in terms of academic early phase trials?

Pascal Piedbois. "France is doing well and French subsidiaries encourage their parent companies to carry out their trials in France. At BMS, two-thirds of clinical cancer trials in France are early phase trials, and France is one of the leading countries, probably due to academic expertise, which has achieved the highest recognition. Quality is still a major criterion."

Nicolas Albin. (Medical Advisor at the ANSM's Oncology and Hematology Department). "Each week the ANSM evaluates a dozen clinical cancer trials and one to two hematology trials. To stress the importance of cooperation between the ANSM and the ethics committees, it is important to know that the admissibility barriers that are resolved often concern a loss of chance compared to other therapeutic strategies, a scientific topic related to ethics. Lists of experts have been compiled by the ANSM, and we could of course share these with the ethics committees. I can confirm that we are processing more and more cases concerning early phase trials that are extension phases while the first-in-human trials are being conducted outside France."

Could systems in France giving access to novel treatments (such as Authorizations for Temporary Use) outside clinical trials be a reason that first-in-human trials are being conducted in other countries?

health authorities in June 2018. The administrative aspects of the ECs are overseen by the Directorate-General of Health; the CNRIPH set up in 2017 oversees their coordination, harmonization and practical evaluation; and the National Ethics Committee Presidents' Association (CNCP), a non-profit organization, federates the majority of the ethics committees.

Difficult circumstances. The number of applications submitted to the ECs is continually increasing, rising by 25% between 2016 and 2019, making it difficult to manage the influx of applications and increasing response times. In 2019, 28% of category 1 applications (n=1,014) concerned cancer and 6%, hematology. In addition, the ECs, which normally have 28 members divided into 2 groups of 14 members, often encounter operational difficulties: insufficient staff, inadequate help from the CNRIPH, expertise hierarchy issues ...

Jean-Yves Blay. "Temporary Use Authorizations do not slow down the arrival of new drugs in France. It is also about arbitration and the doctor's responsibilities. Our country must have as many tools as possible to facilitate access to drugs."

Toufik Bendahmane. "The flexibility of the ANSM this year in and its efforts in granting Temporary Use Authorizations are good news for patients and send a strong message regarding the attractiveness of clinical research in France. As for the industry, the tools facilitating early access to novel treatments in France are very much appreciated by parent companies. In the past, France has been the first country to grant access to certain drugs via Temporary Use Authorizations. However, the regulatory hurdles to implement early phase trials and lack of concertation and coordination in France have long been perceived as an uphill battle. As we have just heard, a number of measures have been or will shortly be taken to improve this situation and it will be up to us, the French subsidiaries, to share information about these measures."

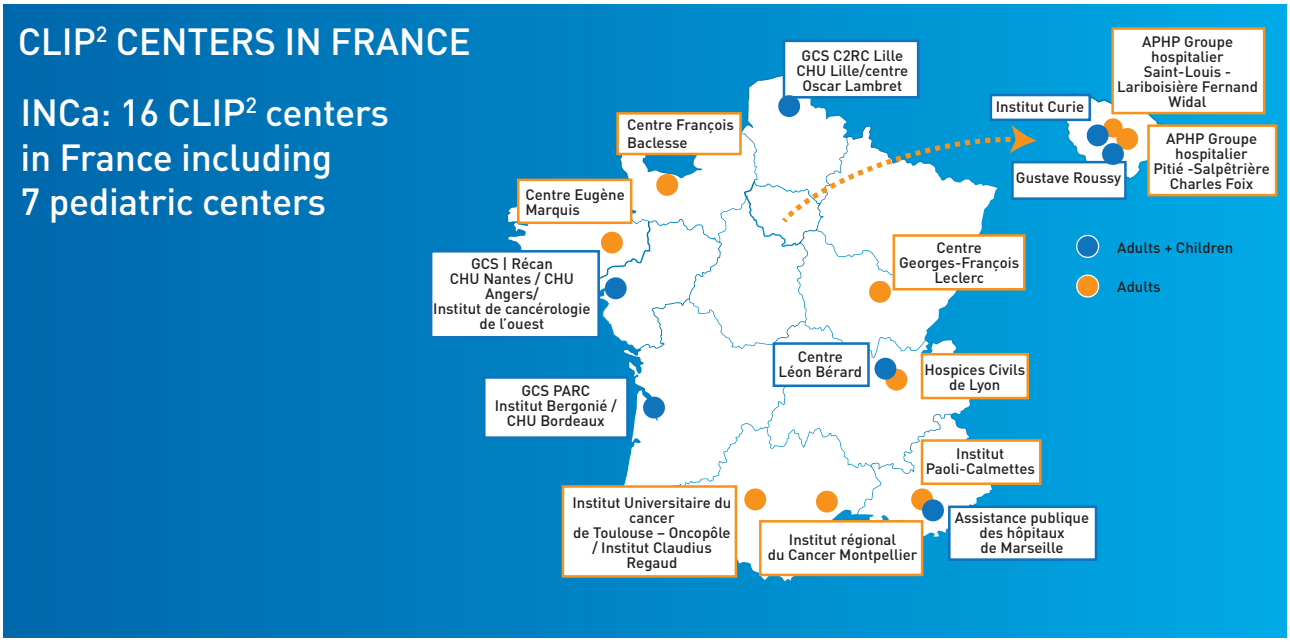
Stéphane Vignot. "Coordination between the ANSM and the ethics committees will be covered in the EU regulations: all questions relating to the protocol must be discussed with the ethics committees before being decided by the regulatory authorities, which significantly simplifies the procedure. However, the EU regulations impose deadlines. If an agency does not respond within the deadline, this will be taken as a favorable reply to the project, and if a sponsor does not respond within 12 days, the project will be considered withdrawn."

David Pérol. "The CLIP^2 networks have played a major part in developing trials in academic centers and in enrolling patients. I am, therefore, appealing to manufacturers to entrust us with more drugs in development and to continue fostering academic research."

Is the random selection of ethics committee really necessary?

Pierre Henri Bertoye. "The random selection cannot be eliminated. This procedure was requested by the Senate so it must be adapted as we mentioned earlier, and we have already managed to find volunteers."

Figure 3



... and a lack of workflow visibility due to the random selection system. These figures show that all parties concerned need to reflect on an organization strategy to guarantee adherence to response times. Review methods vary greatly depending on the use of working groups and training programs relating to sector expertise, methodology and complex designs, substantial modifications for new trials and the GDPR.

CURRENT SYSTEM DEVELOPMENTS

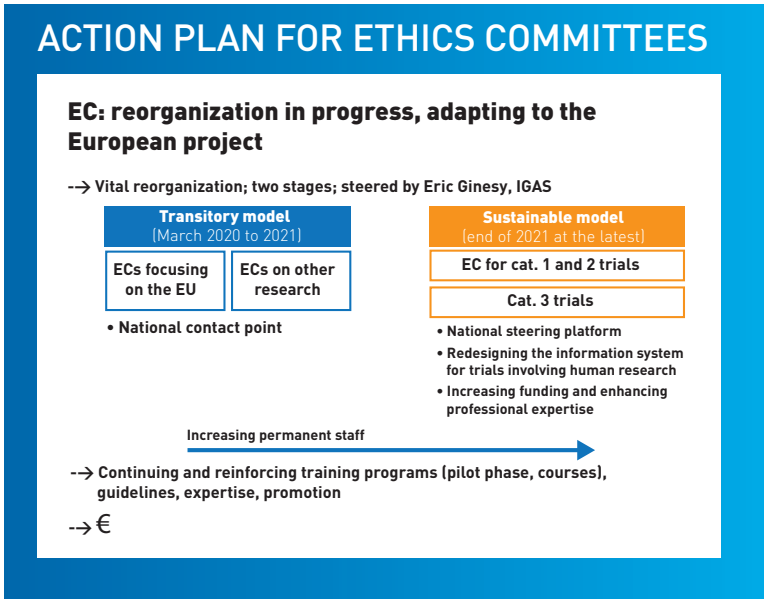
Different measures have been taken recently to improve the situation for ECs and speed up the implementation of clinical trials (Figure 3).

- **The random selection system is now adapted** to the availability and competence of the ethics committees.

- After an initial analysis phase, as of March 2020, the ECs will be reorganized with the various partner organizations (Interministerial Division of Public Transformation - DITP, the CNCP, Directorate-General of Health - DGS, ANSM and CNRIPH) in order to meet the requirements of the EU regulation in 2022. To this end, 15 ECs are now dedicated to European procedures, while continuing their usual work.

- **Structural reinforcements will be undertaken** for administrative tasks, with new jobs created as of 2020 (allocated budget), **the creation of a national steering platform** (to monitor the ECs' work, harmonize practices **and provide regulatory support), and a complete overhaul of the information system** in early 2020.

Figure 4



In addition to these measures, **pilot phases** with drugs and medical devices will be introduced, **a specific training program** has been launched and **guidelines and recommendations** have been compiled by 8 working groups representing the Directorate-General of Health, CNRIPH, ECs, CNRIPH and sponsors.

The CNRIPH is a partner on the personalized medicine project as part of the **HORIZON 2020 program** which should commence in early 2020. **Lists of early phase trial experts will also be created,** who can be mobilized specifically for these early phase trials and for pediatric, pediatric oncology and radiotherapy trials (Figure 4). ▲

NEW "COMPLEX DESIGNS" FOR EARLY PHASE CANCER TRIALS: HOW CAN WE RESOLVE PROBLEMS WITH ETHICS COMMITTEE APPROVAL?

Discussions moderated by Jean-Pierre Delord (Toulouse University Cancer Institute)

→ SPEAKERS

- **Thomas Borel** (LEEM);
- **Bettina Couderc** (SOOM2 Ethics Committee);
- **Maryvonne Hiance** (France Biotech);
- **Louis Lacoste** (CNCP);
- **Stéphane Vignot** (ANSM);
- **Benoît You** (South Lyon Hospital).

Jean-Pierre Delord (Toulouse University Cancer Institute).

The ethics committees are divided into two groups:

- a scientific group made up of doctors, nurses and scientists;
- a non-scientific group made up of legal experts, social workers, patient representatives and ethicists in collaboration with at least two methodologists.

DAY-TO-DAY ETHICS COMMITTEE OPERATIONS AND OUTLOOK FOR REGULATORY DEVELOPMENTS

Bettina Couderc (SOOM2 Ethics Committee)

Ethics committees are committed to helping ensure that clinical trials are started as soon as possible and conducted under the best conditions.

Gaining expertise in oncology. The 39 ethics committees are committed to becoming **proficient in oncology within the next 2 years by having experts specializing in oncology, molecular genetics, and cell and gene therapy.**

Bettina Couderc (SOOM2 Ethics Committee).

The ANSM and ethics committees, therefore, conduct an additional analysis together on specific subjects. There is an administrative officer in each ethics committee who is specifically trained (often a former Clinical Research Associate) and who receives the applications and is responsible for exchanges between the ethics committee and the sponsors. ...

Thomas Borel
(LEEM).

Benoît You
(South Lyon Hospitals).

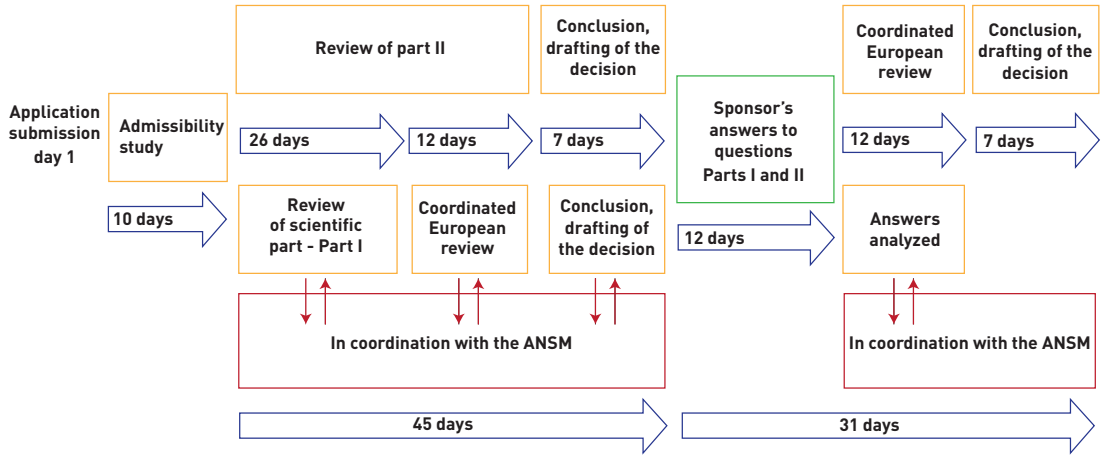
The submission of complete applications to speed up response times. Contrary to what is thought, most of the decisions rendered by ethics committees are favorable. Response times vary of course from one center to another, but overall all centers try to respond as fast as possible. The response time is largely dictated by the time it takes for the sponsor to provide a complete application. Less than half (44%) of all applications are actually complete when they are first submitted and each incomplete application is followed by multiple exchanges between the administrative officer and the sponsor. The response time is of course shorter when the application initially submitted is complete.

Upcoming EU regulations. The Directorate-General of Health organized several meetings in 2019 with the presidents of the 39 ethics committees to examine measures to ensure that applications are processed within the regulatory deadlines all year round, whatever the influx of applications or period of the year. The EU regulations will be implemented in

Figure 1

EUROPEAN PROJECTS

Ethics committee commitments to European projects for which France is the rapporteur State (March 2020)



March 2020 and the ethics committees will be bound by this regulation for European projects for which France is the rapporteur State. One key component of this EU regulation is the joint review of applications by the ANSM and ethics committees, with a joint decision written in English (Figure 1).

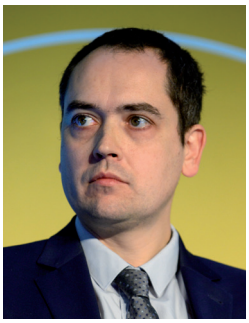
HOW DO THE ETHICS COMMITTEES HANDLE COMPLEX DESIGNS?

Louis Lacoste (CNCP).

Louis Lacoste
(CNCP).

The upcoming EU regulations on clinical trials adapt well to complex designs. The CNCP approached the Directorate-General of Health to work on information systems and digitizing applications, and the ANSM to set up a pilot drug phase that was launched in September 2015. The experiment was carried out in two phases: a first phase from 2015 to 2016 during which the applications were assigned to the ethics committees 21 days before the plenary session, and the second phase after the Jardé Act (implementation of the random selection and allocation of applications).

The Jardé Act was created to provide a single portal for all three human trial categories (type 1, 2 and 3), during a period when the ethics committees' workload had almost doubled. Random allocation helped to balance the workload between the 39 ethics committees and deal with potential conflicts of interest but meant that the monthly meetings no longer dealt with the applications arriving. In light of this extremely heavy workload that was difficult to anticipate due to the random selection and timelines not being met, in April 2018, the CNCP proposed ten areas for improvement. Although the information system (IS) needs to be updated, it currently provides a single portal (online application, operational database). In 2021, the 39 ethics committees should be able to handle all applications. New complex trial designs are handled in a specific way that facilitates approval from the ethics committees, involving:



Stéphane Vignot
(ANSM).

Maryvonne Hiance
(France Biotech).

- taking into account and disseminating recommendations, particularly those published by the CFTG ("Clinical Trial Facilitation and Coordination Group");
- specific training implemented by the CNRIPH and CNCP since 2017.

In conclusion, the ethics committees are currently making real efforts to adapt to the growing number of clinical trials, EU regulations and the new context of complex trial designs. ▲

→ DISCUSSION

Benoît You. "Complex trial designs include several aspects of clinical trials: methodology, dose escalation, choice of treatment based on biomarkers, specificities of rare tumors. The difficulties that ethics committees face create uncertainty and anxiety among us clinicians. As already mentioned, there is huge competition. Setting up a clinical trial, especially if it is an academic trial, requires about 3 years of negotiations with manufacturers and multiple phases to draft the protocol. A huge amount of work has already been done before an application is submitted to the ethics committee and we are then faced with this period of uncertainty, made worse by the random selection, questions over the ethics committee's expertise and deadline issues.

Based on this, I suggest 4 areas for improvement:

- to contact the Ligue Nationale Contre le Cancer for their opinion and additional information. We have already tried this with success;
- organizing a short meeting (20 minutes) between the principal investigator and the ethics committee during its meeting to discuss and answer the simplest questions. This could avoid or reduce the number of exchanges later on;
- improving ethics committee training and reports;
- and perhaps reconsidering roles, in particular the assessment by ethics committee of trial merits and methodology that are in any case reviewed by the ANSM."

Louis Lacoste. "We would very much like to be able to talk to investigators and sponsors, if they could make themselves available for the meetings. If the ethics committees' questions can be answered clearly within 12 days, the application does not necessarily have to be discussed again in a meeting and a favorable decision can be rendered immediately."

Bettina Couderc. "I would like to stress that in the cover letter with the application, the sponsor or investigator can ask that a specialist provide information on specific points."

Public. "The way informed consent forms are written is sometimes catastrophic and improving this could speed up responses from the ethics committees."

Maryvonne Hiance. "France Biotech, which represents French biotech firms, publishes an overview of clinical trials every year. The results confirm that while France

has a good reputation for scientific quality, there are still few early phase trials. Indeed, a large number of companies conduct their early phase clinical trials in Belgium, in Eastern Europe, the United States and even in China. This finding led us to create a working group with LEEM, CRO associations, the French association of clinical research organizations (AFCROs), and other experts, to improve this situation. The next overview that will be published soon shows more positive results, with a rise in the number of clinical trials, no doubt thanks to the substantial efforts of all stakeholders and in particular the ANSM. The new EU regulations should also help to improve this situation. For biotech firms that obtain funding for a given period, time is crucial.

Lastly, I would like to stress the importance of meetings like such as this, which bring together all those involved in healthcare and clinical trials."

Stéphane Vignot. "At a European level, working groups are tackling regulatory issues revolving around complex designs, and the level of experience varies greatly between the different agencies. France is a leader when it comes to knowledge and experience. Transparency, in particular data transparency, is also the subject of much discussion at a European level."

How does the ANSM intend to work with the ethics committees?

Stéphane Vignot. "With the upcoming EU regulations, everyone's scope of activity will be clearer when it comes to both initial approvals and amendments. All medical and quality aspects will be handled by the agency and ethical matters as defined in the EU regulations will be dealt with by the ethics committees. But it is true that some situations concern both medical and ethical aspects (such as repeat biopsies). In any case, the questions discussed in advance by the ethics committees and/or the ANSM will ultimately be handled by the ANSM in France."

EARLY PHASE TRIALS AND RARE CANCERS: WHAT CAN BE CHANGED?

EXAMPLES FROM PEDIATRIC ONCOLOGY

Moderators: Nicolas Albin (ANSM), **Jean-Philippe Spano** (Pitié-Salpêtrière University Hospital, Paris)

→ SPEAKERS

- **Nathalie Gaspar** (Gustave Roussy, Villejuif);
- **Gilles Vassal** (Gustave Roussy, Villejuif).

ACADEMIC ORGANISATIONS INVOLVED IN CLINICAL PEDIATRIC ONCOLOGY TRIALS

Gilles Vassal (Gustave Roussy, Villejuif).

Childhood cancers are rare, extremely rare in fact. To give children refractory to treatment access to novel treatments, **the European ITCC network** (Innovative Therapies for Cancer in Children), created in 2003, today represents **55 investigating centers in 14 countries and 25 translational and fundamental research teams** (Figure 1). With this unique network, 2,204 children and adolescents were able to participate in 34 trials between 2015 and 2019, two thirds of which were industry-sponsored and a dozen, first-in-child trials. France enrolled around 50% of these patients, a testament to the involvement and motivation of the French teams, the importance of the CLIP^2 and the effects of the **AcSé eSMART** protocol.

Gilles Vassal (Gustave Roussy, Villejuif).

Since 2015, we have a strategy in place that consists of:

- **performing a biopsy for all children refractory to treatment when relapse occurs to analyze and sequence the tumor;**
- **offering all children a place in phase I and II trials with a treatment that is adapted to the molecular profile of the tumor;**
- **aggregating all clinical and biological data to try to get a better understanding of these cancers and identify new therapeutic targets for specific development.** ...

Figure 1

CLINICAL RESEARCH ON "PRECISION MEDICINE IN CHILDREN" WITHIN THE EUROPEAN NETWORK ITCC

The ITCC network and its precision medicine program

1. Tumor molecular profiling for each patient

"Targeted" clinical trials at relapse

WES, RNA-seq, methylome analysis, immunophenotyping

- **INFORM** (Germany, Poland, Switzerland, etc.)
- **MAPPYACTS** (France, Spain, Italy, Ireland, etc.)
- **iTHER** (Netherlands)
- **SM-PAED** (UK)
- **Nordic PCM** (Northern Europe)

Platform, pipeline and data harmonization

Aggregation of clinical and biological data for research

ACHIEVEMENTS:

- 39 children included in the phase I larotrectinib trial
- 2,300 exomes at relapse in Q4 2019

Jean-Philippe Spano (Pitié-Salpêtrière University Hospital, Paris).

Nicolas Albin (ANSM).

For example, the **MAPPYACTS trial** offers children with leukemia or a solid tumor in relapse a biopsy, a complete genome analysis and a discussion of their situation in a molecular multidisciplinary team meeting to identify possible treatment options (Figure 1). A total of 770 patients have been included in France since 2016, and centers have opened in Spain, Ireland and Italy. This trial was supported by a hospital clinical research program, the ARC Cancer Research Foundation and the Imagine for Margo – Children without Cancer Foundation. The 2025 France Génomique plan should take over from 2020 on the SeqOIA and AURAGen platforms. Other similar programs have been developed in different European countries. *For example, the 2,300 tumor exomes analysed in 2019 identified 39 children and adolescents in Europe with a NTRK (or NTRAC) gene fusion-positive tumor who were able to be included in the phase I larotrectinib trial.*

Other initiatives promote clinical research in pediatric onco-hematology:

- **The opening of 7 CLIP² centers for children and adult patients** which enable interregional multidisciplinary team meetings to systematically discuss the situation of all the children at diagnosis. Funding received from the Ligue Contre le Cancer, the National Cancer Institute and the ARC Foundation is vital to support academic programs for rare diseases such as pediatric cancers.
- **The U-link site** (www.u-link.eu) created by the French Society for the Fight Against Child and Adolescent Cancer and Leukemia (SFCE) and the National Union of Associations of Parents with Children with cancer or leukemia (UNAPECLE), is a **database accessible to parents and health professionals. The site lists all active clinical pediatric oncology and onco-hematology trials in France** and offers financial assistance to families (costs related to the child's treatment or participation in a clinical trial).
- **The SACHA project,** is an observational study initiated by Pablo Berlanga (Villejuif) involving the prospective collection of clinical information on new cancer drugs prescribed through a Temporary Use Authorization or off-label, in children and adolescents with relapsed cancer who cannot be included in a clinical trial. The cases are discussed in a multidisciplinary team meeting and all the information is collected in a database. If the results are promising a phase III trial may be launched.

This means that from 2020, access to novel pediatric cancer treatments in France will include:

- **the prescription of a molecular tumor analysis for children refractory to treatment at each of the 30 SFCE centers, followed by a multidisciplinary team meeting discussion;**
- **tumor molecular profiling on the SeqOIA or AURAG platforms in connection with the MAPPYACTS trial;**
- **and three possible options: participation in phase I or phase I-II trials in CLIP² centers, the ASCé-ES-MART trial or the SACHA project.**

The regulatory environment for pediatric trials has improved in recent years. The US Research to Accelerate Cures and Equity (RACE) for Children Act, which came into effect in 2018, promotes the conduct of pediatric clinical drug trials related to an actionable therapeutic target.

THE FAIR WORKING GROUP (ACCELERATE)

Nathalie Gaspar (Gustave Roussy, Villejuif).

The ACCELERATE platform is an international platform that brings together academics, parents, pharmaceutical companies and regulatory authorities through working groups and organized forums **to facilitate the development of pediatric cancer drugs** (www.accelerate-platform.org).

Within the ACCELERATE group, the **Working Group on Fostering Age Inclusive Research (FAIR)** coordinated by Nathalie Gaspar is specifically interested **in clinical development for adolescents and young adults** (www.accelerate-platform.org/fair-trials/). It represented all concerned: pharmaceutical companies, academics, pediatric oncologists and medical oncologists involved in drug development, parent and patient associations and regulators (EMA). This group's work led to the publication of an article on the advantages and limits of conducting clinical trials for both adolescents and adults, on the basis of scientific rationale right from the early phase

(including first-in-human trials) (*Gaspar et al. Ann Oncol 2018*).

Such trials are entirely feasible and there are actually few arguments for not conducting them.

- Medically, the pharmacokinetics (dosing based on weight or body surface area) appear to be similar in adults and young adolescents, and acute toxicity is often less severe in adolescents.
- Such trials can detect biological specificities in adolescents and adults.
- From a legal point of view, these trials are feasible. There are no legal barriers to including adolescents in adult trials, even in the absence of pediatric phase I data.
- For pharmaceutical companies, this type of data can be included in a pediatric investigation plan.
- For parents and patients, these trials provide a secure framework for prescribing a new drug.

The FAIR group's objectives are:

- to identify and launch "promising" trials that do not exclude patients based on age or that include adolescents in adult trials or young adults in pediatric trials (FAIR survey www.accelerate-platform.org/fair-trials/early-drug-development-adolescents-oncology-protocols-survey; FAIR stamp (www.accelerate-platform.org/fairtrials/fair-trials-resources/fair-aya-stamp/);
- to disseminate the results of this working group to all stakeholders: cooperative groups, pharmaceutical companies, regulators, ethics committees, parent associations, etc.;
- to offer a ready-to-use toolkit to investigators, academics or manufacturers who want to include adolescents in adult trials, to give them all the information necessary to conduct such trials. This toolkit is available online (www.accelerate-platform.org/fair-trials/fair-trials-resources/fair-toolkit/);
- and get support from regulators. The EMA sent a positive official letter to the ACCELERATE group which is available online; this letter can be downloaded and included in clinical trial submission files (www.accelerateplatform.org/wp-con tent/uploads/sites/4/2019/07/PDCO-letter-to-FAIR-Group-supporting-age-inclusive-research-1.pdf).

Nathalie Gaspar (Gustave Roussy, Villejuif).

Within this group, a task force has been set up in France with pediatric oncologists and medical oncologists to get involved in clinical research on tumors found in both children and adults, such as sarcomas, lymphomas or even brain tumors. Parents and representatives of associations, including Imagine for Margo and UNAPECLE, are involved in this process and extremely useful in gaining access to multiple contacts (LEEM, MPs, legislators) and ethics committees (such as the Ethics Group on Pediatric Research - CERPed). National institutions such as INCa and the ANSM are also very involved, and pediatric CLIP^2 centers, that are greatly admired by our European neighbors, contribute significantly to progress in this area. In addition, funders are made aware of the importance of trials in patients under 18 years of age. ▲

→ DISCUSSION

Gilles Vassal. "As you can see, thanks to these collective efforts, we have set the ball rolling with the launch of several great projects."

Nicolas Albin. "Pediatric oncology is a good illustration of how the agency has tried to facilitate the implementation of the eSMART and MAPPYACTS trials. The investigators presented these "complex design" trials to the ANSM at an early-stage meeting, which considerably facilitated the review process. In addition to clinical trials, real-life data is useful, especially when the marketing authorization is issued with little data, because this makes it possible to continue evaluating the drugs and possibly obtain reimbursement. The ANSM is also working on a tool to centralize/obtain all the information on clinical trials accessible in France at a given time and the drugs available (clinical trials, temporary use authorizations, temporary use recommendations, marketing authorizations, reimbursement status), that should be especially useful for molecular multidisciplinary team meetings."

Public. "Is it more difficult to convince a parent to include a young patient or child than an adult?"

Gilles Vassal. "Generally speaking, the inclusion rates for pediatric trials are higher than for adult trials. Parents or young adults are often very eager to get access to a clinical trial."

ADVANCED THERAPY MEDICINAL PRODUCTS (ATMP/GENE AND CELL THERAPIES) AND EARLY PHASE ONCOLOGY TRIALS

Moderator: Thierry Lamy de la Chapelle (Rennes University Hospital)

→ SPEAKERS

- **Marc Martin** (ANSM);
- **Catherine Thieblemont** (Saint-Louis Hospital, Paris).

Thierry Lamy de la Chapelle (Rennes University Hospital).

Thierry Lamy de la Chapelle. Advanced therapy medicinal products (ATMP) include four treatment categories: somatic cell therapy medicines, gene therapy medicines, tissue-engineered medicines, and novel combination therapies. These treatments have been under specific legislation since 2011 with the assumption that pharmacies must be involved in dispensing these new drugs.

ARRIVAL OF CAR T-CELLS IN FRANCE

Catherine Thieblemont (Saint-Louis Hospital).

Since August 2018, two anti-CD19 CAR T-cells have been available to patients with refractory or relapsed diffuse large B-cell lymphoma (DLBCL) and one of them is also indicated in acute lymphoblastic leukemia in children. **To date, 12 centers throughout France can administer these treatments, with more expected this year.**

The majority of clinical trials currently conducted with CAR T-cells concern hematological indications (myeloma, chronic lymphocytic leukemia, lymphomas, acute leukemia), but progress is also being made in non-oncological indications (HIV/AIDS, lupus (SLE) and myasthenia gravis).

CAR T-cells fundamentally change the way things are organized and our needs in terms of medical resources. Organization on a national level varies and is more or less centralized in the different European countries. **In France, the population that can benefit from this new approach is currently estimated to be 600 patients with diffuse large B-cell lymphoma or acute leukemia,** and this figure is expected to increase significantly with the other hematology indications currently in development.

Marc Martin (ANSM).

Catherine Thieblemont (Saint-Louis Hospital).

A SPECIFIC EVALUATION SYSTEM PROPOSED BY THE ANSM FOR ATMPs

Marc Martin (ANSM).

The ANSM is responsible for working on the ATMP evaluation process in order to give patients access to these products as fast as possible. **Since 2015, 10 marketing authorizations have been granted for ATMPs, 7 of which are gene therapies and 3 cell therapies, and 15 to 25 clinical trial authorizations have been issued for ATMPs.** ATMPs are special because, since they are "living" products, they have to go through additional channels and require approval by biomedicine agencies. Specific tests must also be performed regarding safety and quality, along with a GMO authorization for gene therapies.

The ANSM works at various levels with the European Medicines Agency on ATMPs, in particular regarding the evaluation of clinical trials (scientific opinions, new procedures). Given the importance of speeding up their approval in France, the ANSM decided to grant ATMPs a fast-track procedure in February with

a system for early phase trials in pediatrics and rare diseases, and a final decision within 110 days. For ATMPs already evaluated in France, the decision is given within 60 days. The fast-track procedure for the submission and review of ATMP applications includes a pre-submission meeting to discuss key points and quality, clinical and non-clinical issues that could be problematic during the evaluation. The ANSM has already received 5 Fast Track 1 applications, 4 of which are under review and 1 of which was approved in 110 days. Two Fast Track 2 applications have been submitted, 1 of which is under review and the other was approved within 27 days, which has already made it possible to open a center in France and give a patient access to treatment for the first time worldwide. ▲

→ DISCUSSION

Catherine Thieblemont. "These results are extremely encouraging but unfortunately not well known in the pharmaceutical industry. This data needs to be published and shared."

Marc Martin. "Investigators, industry sponsors and academics are all asking that a positive signal be sent to parent companies."

KEY POINTS

● PROGRESS IS NEEDED TO IMPROVE FRANCE'S STATUS FOR EARLY PHASE FIRST-IN-HUMAN TRIALS.

● PATIENTS AND PATIENT ASSOCIATIONS MUST BE INVOLVED AND THE GENERAL PUBLIC NEEDS SPECIFIC INFORMATION ON EARLY PHASE TRIALS.

● AGENCIES AND REGULATORS ARE BECOMING MORE OPEN-MINDED, AND THE ANSM HAS DEVISED A SPECIFIC ACTION PLAN FOR EARLY PHASE TRIALS WITH:

- early phase trial group and centralized data;
- streamlining to facilitate and speed up communication between the ANSM and sponsors;
- optional fast-track procedures for early phase trials in pediatric oncology and rare diseases, and for drugs already tested in France;
- the creation of an Innovation Desk to facilitate discussions with sponsors and investigators;
- and joint efforts to anticipate coordination between the ethics committees and the various European agencies.

● ETHICS COMMITTEES ARE BEING REORGANIZED TO ADAPT TO THE FORTHCOMING EU REGULATION.

- To cope with the growing number of early phase clinical trials and to comply with the forthcoming EU regulation.
- With specific expertise in oncology and molecular biology in each ethics committee.
- Complex designs: specific training and recommendations.

● A FAVORABLE CONTEXT IN FRANCE WITH THE SUPPORT OF PUBLIC BODIES SUCH AS THE NATIONAL CANCER INSTITUTE (INCA), THE CREATION OF CERTIFIED CENTRES SPECIALIZING IN EARLY PHASE TRIALS (CLIP²), WORLD-RENOWNED SCIENTIFIC EXPERTISE AND THE POSSIBILITY FOR ALL PATIENTS TO HAVE ACCESS TO INNOVATIVE THERAPIES.

● ACADEMIC RESEARCH AND EARLY PHASE TRIALS

- Academic research in France is supported by the ANSM, INCa, the Ligue Contre le Cancer and the ARC Cancer Research Foundation.
- Two thirds of the trials submitted to the ANSM are academic trials.
- The INCa funds 40 academic trials each year and the institute's ACSé program is a success.

● VERY ACTIVE SUPPORT FOR ONCO-PEDIATRIC TRIALS IN FRANCE AND EUROPE WITH:

- the ITCC network and the MAPPYACTS trial;
- INCa certification for 7 pediatric CLIP² centers;

- the U-Link platform, which lists all ongoing trials in France in oncology and pediatric oncology;
- the SACHA project for children with relapsed cancer who are not eligible for inclusion in clinical trials;
- less stringent regulations for pediatric trials;
- creation of the FAIR group to design clinical trials for both adolescents and young adults.

● ADVANCED THERAPY MEDICINAL PRODUCTS (ATMP): SPECIFIC LEGISLATION AND IN-DEPTH REORGANISATION:

- 12 centers approved in France to administer CAR T-cell therapy;
- work in progress at the ANSM to organize the clinical development of these novel therapies with the possibility of a fast-track procedure.

● MEASURES TO DEVELOP PERSONALIZED MEDICINE IN FRANCE:

- molecular screening, a way to accelerate enrolment in early phase trials;
- the 2025 France Génomique Plan for access to genomic medicine for all concerned (patients and families as indicated) with high throughput sequencing available throughout the country.

● THE DIGITAL REVOLUTION: REMOTE TOOLS TO PROMOTE CLOSE MONITORING OF PATIENTS AND THEIR DISEASE.

● AND SOON AN ARTIFICIAL INTELLIGENCE TOOL TO COMPILE AND ANALYSE DATABASES, AND CREATE SYNTHETIC CONTROL GROUPS.

→ CONCLUSION

This first 2019 Meeting on Early Phase Cancer Trials with over 500 attendees provided an overview of early phase clinical trials in France with contributions from various stakeholders on subjects rarely addressed such as clinical research in pediatric oncology, complex clinical trial designs or the issues raised by the development of advanced therapy medicinal products.

At the start of a new era with, on the one hand, genomic profiling and personalized medicine, and on the other, the arrival of new technologies and artificial intelligence, this was a chance for the attendees to familiarize themselves with a number of projects or new approaches that were presented.

SAVE THE DATE

We look forward to seeing you at the 2nd Meeting on Early Phase Cancer Trials - 2020

On Thursday, November 26, 2020

At the Marriott Rive Gauche Hotel

17 boulevard Saint-Jacques, 75014 Paris

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