RESEARCH

Activity report of the INCa-designated early-phase clinical trial centres (CLIP²) 2010-2012

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As the medical and scientific agency of reference devoted to cancer, the **French National Cancer Institute** stimulates, supports and implements a coordinated policy in the fight against the disease.

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INTRODUCTION

The designation and support of research centres specialising in early-phase clinical trials was part of measure 1.3 of the 2009-2013 Cancer Plan, entitled "Structure and stimulate research in the early phases of new cancer drug trials." In order to conduct these initiatives, INCa received support from the National center of industrial clinical trials' management (CeNGEPS), from ARC Foundation for Cancer Research, and from the Lilly Institute.

Thus, since the end of 2010, INCa has designated[1] and supported 16 early-phase clinical trial centres in oncology for a period of four years. These centres are distributed among 11 cancer centres and 5 university hospitals (Figure 1 and Appendix 3).

These centres have the particular role of:

- designing, planning, conducting and analysing early-phase clinical trials (phases I-II), both national and international, arising from both private and public cancer-related research, to the highest international quality standards, on innovative drugs (especially targeted therapies);
- responding to calls for proposals launched or managed by INCa, and to academic or industrial requests, according to their areas of expertise (organs, specialities, etc.).

Apart from this measure for structuring early-phase cancer research in France, measure 1.4 of the 2009-2013 Cancer Plan provided for the establishment of research and development partnerships between international research laboratories and players involved in cancer research.

Indeed, the emergence of targeted treatments in the management of cancer has brought about change in the way new drugs are developed. As a result of their mechanism of action, these drugs can be effective against a large number of tumors sharing the same molecular abnormality, thus multiplying the number of early-phase clinical trials required. This paradigm shift is leading pharmaceutical companies to create partnerships with academic teams that have expertise in early phase research.

This second measure to encourage the development of early-phase clinical trials was aimed at increasing the attractiveness of research, and enabling patients in France to benefit from new therapeutics supplied by pharmaceutical companies.

Designation of the CLIP² ends in October 2014. These actions will be continued under the 2014-2019 Cancer Plan, with a special effort in paediatrics, through the designation of centres active in paediatrics. As a result, it seems timely to carry out an initial activity review of these CLIP² based on the annual data they submit to INCa, and to assess the added value contributed by structuring these clinical research centres in France.

The present document summarises the activity of the centres designated between 2009 and 2012, based on data on patient enrollment in early-phase clinical trials (phases I, 1/II and II) provided by the 16 centres; and then presents a first review of the collaborations in place between INCa and the US National Cancer Institute (NCI) on the one hand, and with various pharmaceutical companies on the other hand.

This report is especially aimed at professionals affected by the early development of new drugs.

1 Following the generic procedure of identifying organisations working in the cancer area http://www.sante.gouv.fr/fichiers/bo/2010/10-02/ste_20100002_0100_0093.pdf

Key points from the 2010-2012 review of the CLIP²

▶ 16 centres specialised in early-phase clinical trials in cancer (I and II) have INCa designation since 2010.

- ✓ The services devoted to this type of research within care facilities (CHU and CLCC) have the staff and technical platforms needed to sponsor, establish and carry out these types of trials;
- ✓ They carry out their own trials, as well as those entrusted to them by other academic sponsors or pharmaceutical companies that wish to have the benefit of their expertise in the area;
- ✓ In 2012, 2,873 patients were enrolled and 187 new trials were opened in these early-phase clinical trial centres;
- ✓ 6,710 patients have been enrolled and 496 new trials carried out in total since designation.

▶ Since 2010, collaboration with the National Cancer Institute (NCI) has made it possible to set up two trials, and two trials are in preparation:

- ✓ CHONDROG, to evaluate a Hedgehog pathway inhibitor in chondrosarcomas, a trial sponsored by Insitut Bergonié, Bordeaux;
- ✓ AKTIL, to evaluate an AKT inhibitor in diffuse large B cell lymphomas, a trial sponsored by Centre Léon Bérard, Lyon;
- ✓ BrAVHo, to evaluate an anti-CD30 antibody in HIV-associated lymphomas, the French component of an American trial;
- ✓ a trial of cabozantinib, to evaluate an inhibitor of cMET and VEGFR2 in Ewing's sarcomas and osteosarcomas, sponsored by Institut Bergonié, Bordeaux;

▶ Since 2011, collaborations with pharmaceutical companies have made it possible to conduct 9 calls for proposals with respect to drugs supplied by 6 different pharmaceutical companies. Nine proposals for early-phase clinical trials were thus selected:

- ✓ PIK-ORL, to evaluate a P13K inhibitor in head and neck cancers, a trial sponsored by Centre Léon-Bérard, Lyon;
- ✓ CYCLIGIST, to evaluate a CDK 4/6 inhibitor gastrointestinal stromal tumors (GIST), a trial sponsored by Institut Bergonié, Bordeaux;
- ✓ OPTIMUM, to evaluate a CDK 4/6 inhibitor in metastatic melanoma, a trial sponsored by Hôpital Saint Louis (AP-HP), Paris;
- ✓ LAM-PIK, to evaluate a PI3K/mTor inhibitor in myeloid haemopathies and acute myeloid leukaemias, a trial sponsored by Institut Curie, Paris;
- ✓ TAKTIC, to evaluate an AKT inhibitor in metastatic or locally advanced HER2- breast cancers, a trial sponsored by Institut Paoli-Calmettes, Marseille;
- ✓ INPAKT, to evaluate an AKT inhibitor in advanced or metastatic cancers, a trial sponsored by Gustave Roussy, Villejuif;
- ✓ METROmaJX, to evaluate an oncolytic virus in breast cancers and advanced soft tissue sarcomas, a trial sponsored by Institut Bergonié, Bordeaux;
- ✓ OLYMPE, to evaluate a P38 MAPK inhibitor in metastatic or locally advanced breast cancers, a trial sponsored by Centre François-Baclesse, Caen;
- ✓ GLYRaD, to evaluate a P38 MAPK inhibitor in newly diagnosed glioblastomas, a trial sponsored by Centre Jean-Perrin, Clermont-Ferrand.

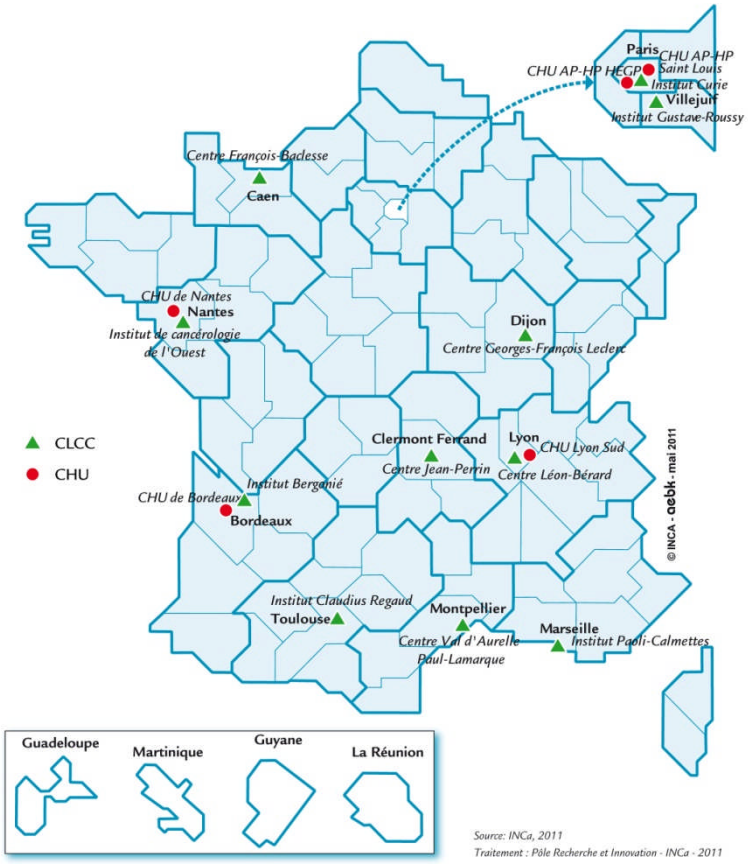
METHOD

Since 2010 and the designation of the early-phase clinical trial centres, INCa has launched an annual survey among the 16 CLIP² in order to compile information on their activity. The following data are thus collected:

- the number of new trials opened each year. These are trials with academic or industrial sponsorship, those for which the centres are sponsors and those for which they are participating centres;
- the number of patients enrolled during the year for each early-phase clinical trial conducted by the CLIP² centre;
- a description of each trial: title, EudraCT Number, sponsor and phase of the trial.

The data presented in the present document are the result of information submitted to surveys conducted from 2011 to 2013 on activity from 2010 to 2012.

Figure 1. INCa-Designated Early-Phase Clinical Trial Centres (CLIP²)



Since the CLIP² are incorporated into research and healthcare structures involved in activities other than early-phase clinical trials, we were careful to take into account only those data related to enrollment in early-phase clinical trials (I and II) in this first part.

As reminder recap, designation of the 16 centres took place at the end of 2010; this year thus constitutes T0 for the present review. As a result, the data from year 2011 can be considered as those from the first year of designation.

This first activity report for the CLIP² is interested only in data on enrollment and the number of new trials in these centres. However, patient enrollment in clinical trials is insufficient on its own to summarise the flow of a clinical trial. Indeed, prior to this step, the identification of patients presenting the full set of inclusion criteria and no exclusion criteria constitutes an important share of the activity of the centres. Similarly, subsequent to enrollment, treatment and monitoring of patients participating in these trials generate an active list of patients that is much larger than the number of patients enrolled in a given year. The present document therefore reflects only a part of the overall activity of these centres.

SUMMARY OF ACTIVITY DATA

1. ACTIVITY OF THE CLIP²

DEVELOPMENT OF CLIP² ACTIVITY BETWEEN 2010 AND 2012

During the 2010-2012 period, 496 early-phase clinical trials were opened for enrollment in the CLIP², and 6,710 patients were enrolled in a clinical trial within a CLIP².

Figure 2: Trend in the number of new clinical trials opened in the CLIP² – 2010-2012

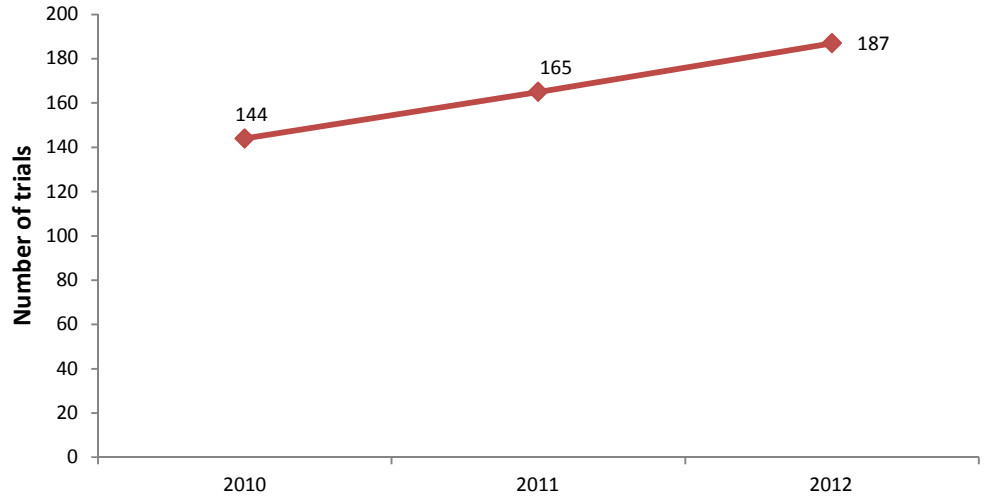
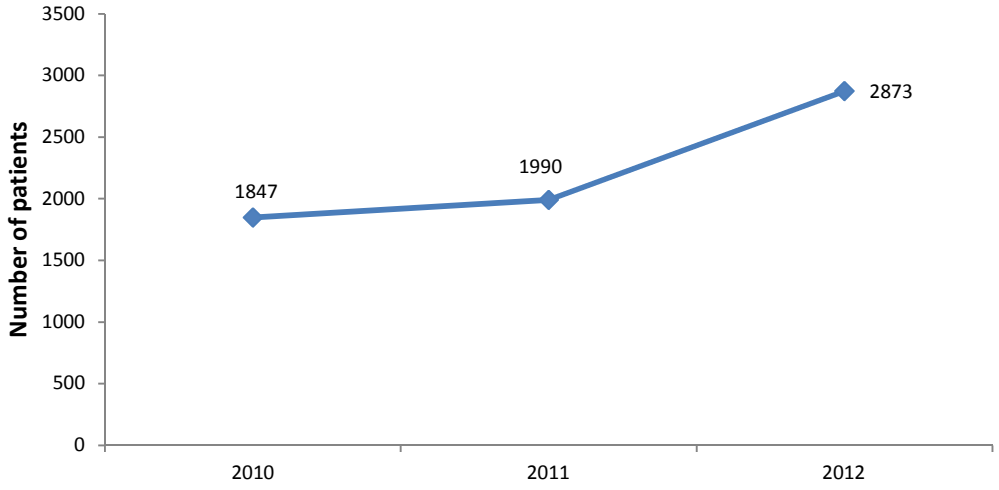


Figure 3: Trend in the numbers enrolled in clinical trials conducted by the CLIP² – 2010-2012



In 2012, 187 new trials were opened for recruitment in one or more designated centres (multicentre trials), i.e. an increase of 29% since 2010 (Figure 2). This growth is steady, with nearly 15% new trials opened every year in the CLIP².

At the same time, 2,873 patients were enrolled in one of the early-phase clinical trials within the 16 designated centres in 2012, i.e. an increase of 55% compared with 2010 (Figure 3). The increase in activity of the CLIP² is evidence of the effect of designating these centres (see page 13).

2. ACTIVITY ACCORDING TO TRIAL PHASE

Although clinical trials are classified into 4 phases (from I to IV), phases I and II are referred to as early phase, with a subtype, phase I/II.

- The main objective of phase I trials is to determine the maximum tolerated dose and dose-limiting toxicity of the drug being tested. They include trials of first administration to humans. They are conducted on a small number of patients (several tens of patients).
- The objective of phase II trials is to determine the optimum dose of the drug in terms of efficacy and tolerance in a limited and homogeneous patient population (several hundred).
- Phase I/II trials combine these two phases, with initial determination of the dose, followed by testing of efficacy, by treating a larger number of patients at the dose determined in the first part of the trial.

The activity of the CLIP² in early-phase trials can be detailed according to the different phases of clinical trials conducted, with respect to the number of patients enrolled as well as the number of trials initiated between 2010 and 2012.

Figure 4: Distribution of new trials opened in the CLIP² by phase type 2010-2012

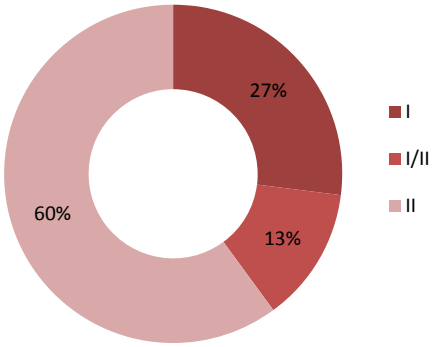
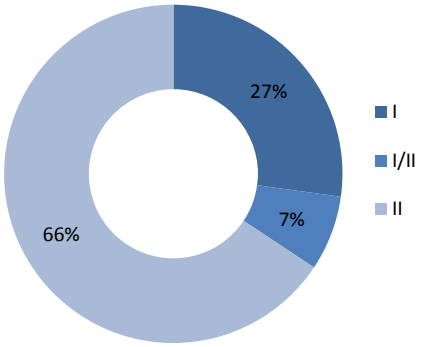


Figure 5: Distribution of patients enrolled in the CLIP² by phase type 2010-2012



The review of the first three years of designation shows that 27% of trials initiated in the CLIP² are phase I trials, and 60% are phase II trials (Figure 4).

Furthermore, 27% of patients enrolled in a trial were enrolled in a phase I trial, and 66% of patients were enrolled in a phase II trial (Figure 5).

Given the distribution of new trials in the CLIP² (Figure 4), the percentage of patients enrolled in a phase II trial should be higher than actually seen (Figure 5). Given that, according to the data from the French Registry of cancer research clinical trials (RECF), phase II trials enrol 2.5 times more patients on average than phase I trials[2], this ratio makes it possible to calculate, based on Figure 4, that 84% of patients should be enrolled in phase II trials and not 66% as observed. This discrepancy suggests that a proportion of patient enrollment in these phase II trials is done outside of the CLIP². Other healthcare facilities may be involved, or services located within the same healthcare facility as a CLIP², but not part of it. Moreover, again according to data from the RECF, the mean number of centres participating in a phase I trial is 4, and may be as high as 12. It is therefore legitimate to believe that the majority of centres participating in a phase I trial are CLIP². In contrast, with respect to phase II trials, the mean number of centres is 17, but this number may be as high as 94, explaining why patient enrollment in a phase II trial occurs outside of the CLIP².

2 © Registre des essais cliniques en cancérologie – Bilan 2007-2012 (French Registry for Clinical Trials in Oncology – Review 2007-2012), Activity Reports and Assessments collection, INCa, Boulogne-Billancourt, December 2013.

Figure 6: Trends in numbers of new trials by phase type – 2010-2012

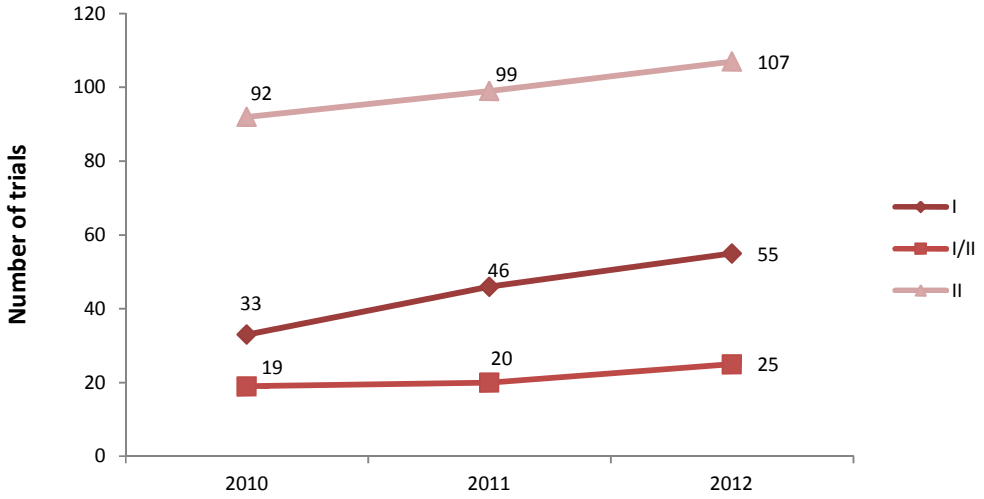
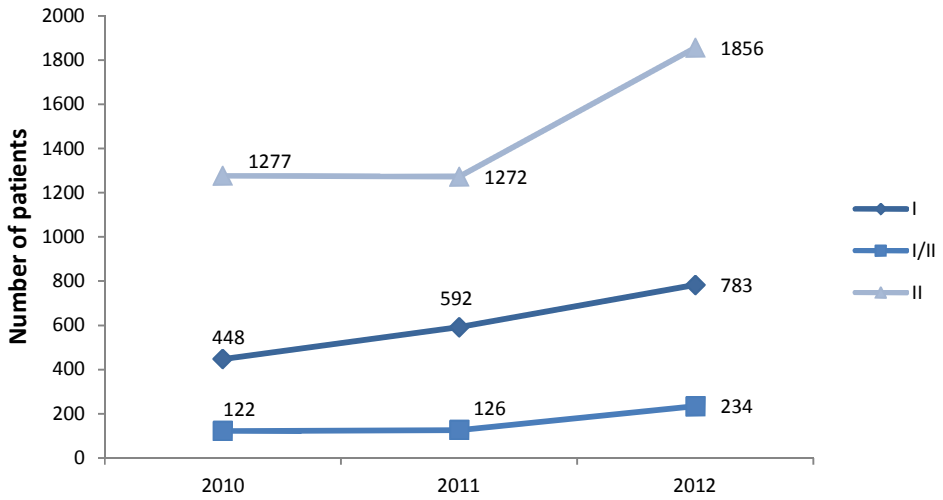


Figure 7: Trends in numbers of patients enrolled by phase type – 2010-2012



The number of new trials conducted in the CLIP² and the numbers enrolled increased steadily between 2010 and 2012 for the three phase types.

The number of new phase I trials increased by 66% during these three years. During the same period, phase I/II trials increased by only 31%, and phase II trials by 16% (Figure 6).

At the same time, the number of patients enrolled has greatly progressed for all types of trials, + 91% for phase I/II trials, + 75% for phase I trials, and + 45% for phase II trials (Figure 7).

It can be observed that the number of patients enrolled in a phase II trial increased much more rapidly than the number of new phase II trials (45% *vs* 16%), implying that one of the effects of designating the CLIP² has been to increase their capacity for recruitment into these trials, through an improved structure and reliance on additional dedicated staff.

3. ACTIVITY ACCORDING TO TYPE OF SPONSOR

Two types of sponsors of trials carried out within the CLIP² can be distinguished:

- academic sponsors comprise sponsors such as the CHU, CLCC, non-profit organisations and cooperative groups;
- industrial sponsors comprise private companies—pharmaceutical companies or service providers.

Figure 8: Distribution of new trials opened in the CLIP² by type of sponsor – 2010-2012

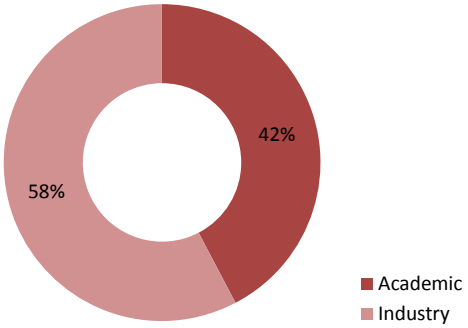
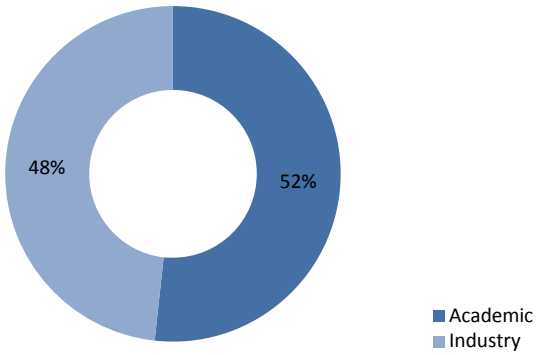


Figure 9: Distribution of enrollment in the CLIP² by type of sponsor – 2010-2012



The majority of trials conducted within the CLIP² are sponsored by industry (58%). This is a feature of the CLIP², related to the fact that they conduct early-phase trials, usually sponsor d by industry, in contrast to the RECF data, where only 40% of trials are sponsored by industry, regardless of the type of trial. On the other hand, patient enrollment for the same period is practically equally distributed between academic and industry-sponsored trials (48% *vs* 52%).

Figure 10: Trends in the number of new trials by type of sponsor – 2010-2012

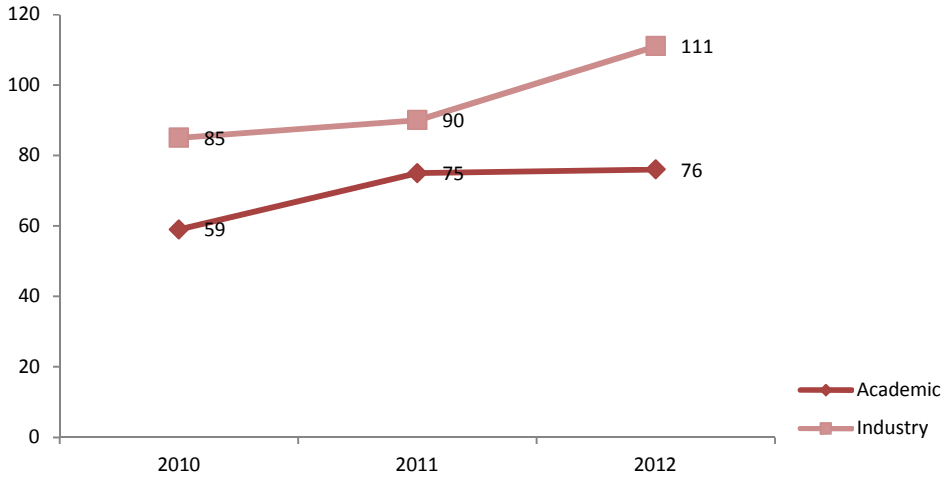
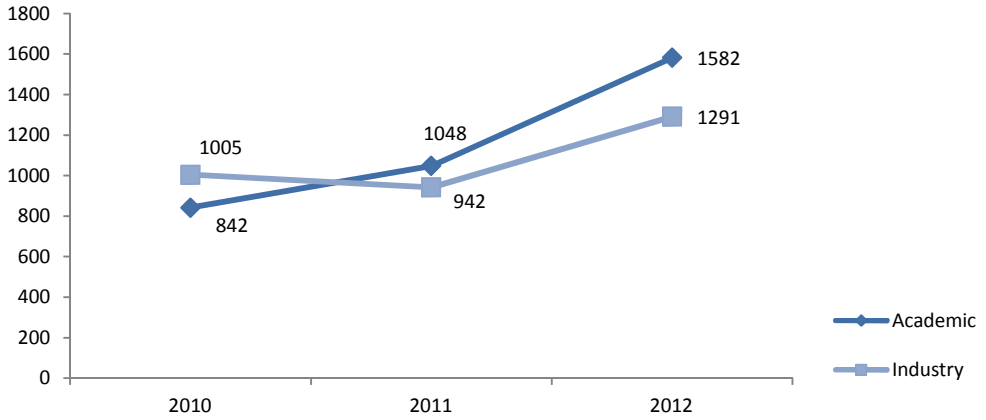


Figure 11: Trends in the numbers of patients enrolled in the CLIP² by type of sponsor – 2010-2012



Since 2010, the numbers of new academic and industry-sponsored trials have shown similar progress (approximately + 30%), and trials initiated by industrial sponsors have thus remained more numerous than those initiated by academic sponsors.

In contrast, the number of patients enrolled in academic sponsored trials has progressed more rapidly (+ 88%) than the number of patients enrolled in industry-sponsored trials (+ 28%). This observation is correlated with the predominant types of trials conducted by each type of sponsor, as evidenced by the analysis presented in the next chapter.

Thus, in 2012, more patients were enrolled in academic trials than in industry-sponsored trials (55%). The opposite was true prior to 2011: in 2010, 54% of patients were enrolled in industry-sponsored trials.

4. ACTIVITY ACCORDING TO TYPE OF SPONSOR AND TRIAL PHASE

The analysis of the overall distribution of new trials opened and patients enrolled can be refined according to the different phase types and nature of sponsorship.

New industry-sponsored phase I trials were four times more numerous than those with academic sponsorship (Figure 12). This confirms that phase 1 trials to evaluate new treatments are mainly conducted by industry. Academic sponsors do not generally have access to these innovative drugs until later. Indeed, 70% of academic phase 1 trials relate to treatment combinations, as against 46% of industry-sponsored trials. Five times more patients were enrolled in an industry-sponsored phase 1 trial than in an academic phase 1 trial (Figure 13).

Figure 12: Distribution of new trials by type of sponsor and trial phase – 2010-2012

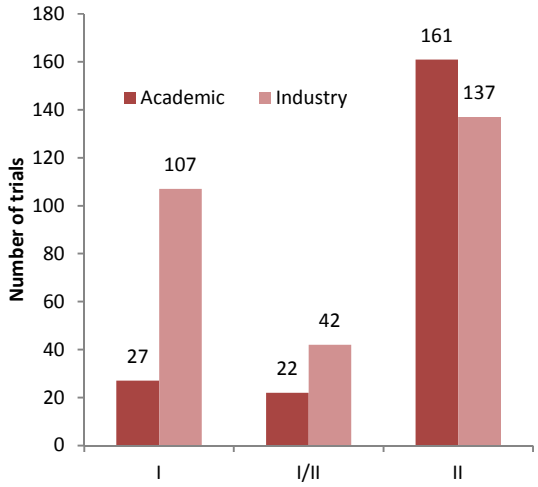
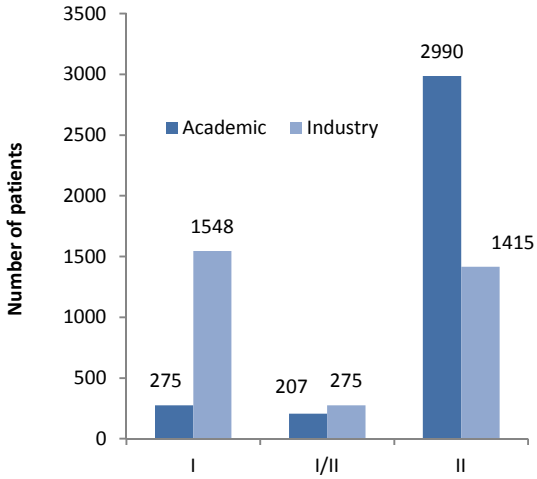


Figure 13: Distribution of enrollment in the CLIP² by type of sponsor and trial phase – 2010-2012



Conversely, although there were slightly more new academic phase II trials than industry-sponsored phase II trials (161 *vs* 137), twice as many patients were enrolled in academic phase II trials as in industry-sponsored phase II trials within the CLIP² (2,990 *vs* 1,415). Thus, academic phase II trials recruit relatively more patients than industry-sponsored phase II trials.

It is also interesting to note that more patients were enrolled in industry-sponsored phase I trials (1,548) than in industry-sponsored phase II trials (1,415), whereas there were more new industry-sponsored phase II trials than industry-sponsored phase I trials (137 *vs* 107). This is certainly due to the fact that there were centres opened for phase II trials other than the CLIP².

Figure 14: Trends in the number of new trials by phase and type of sponsor – 2010-2012

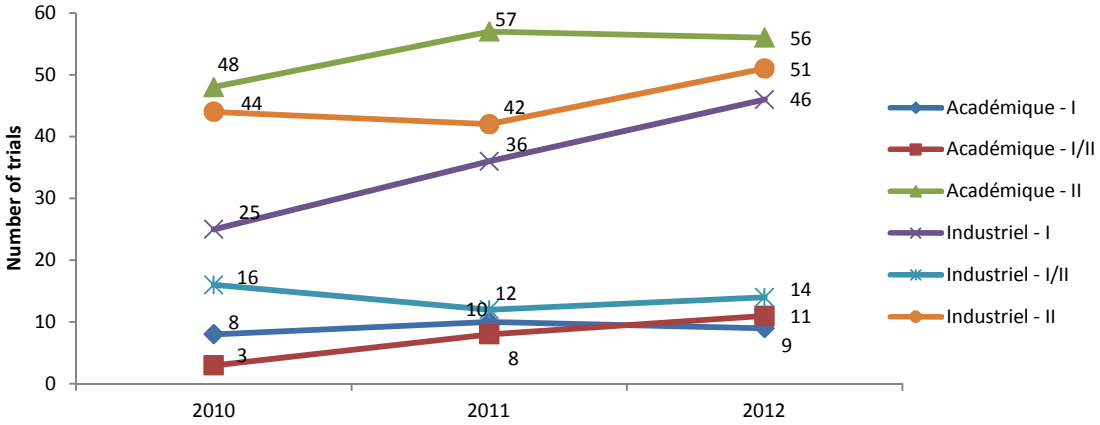
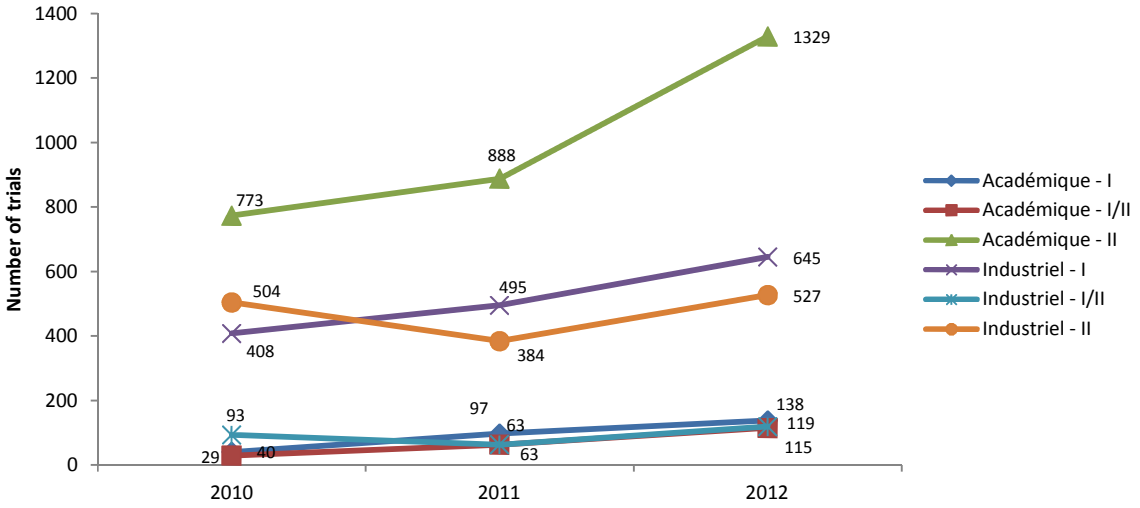


Figure 15: Trends in the number of patients enrolled by trial phase and type of sponsor – 2010-2012



Between 2010 and 2012, the trends in the number of new trials, as well as in the number of patients enrolled, varied depending on the phase of trial or type of sponsor.

Thus for the period examined, the number of new phase II trials showed rather slow progress, whether they were academic sponsored (+ 17%) or industry-sponsored (+ 16%) (Figure 14). On the other hand, while progress in the number of new academic phase I trials was rather slow (+ 12%), that of industry-sponsored phase I trials was very rapid (+ 84% in two years). This category of trial stands out clearly from the others. The strong increase in the number of industry-sponsored phase I trials is an indicator of the increased attractiveness of early-phase clinical oncology research in France, and meets one of the main objectives of the designation of early-phase expert centres, which was to attract new drugs under development into France. At the same time, the number of patients enrolled in industry-sponsored phase I trials increased by 58% from 2010.

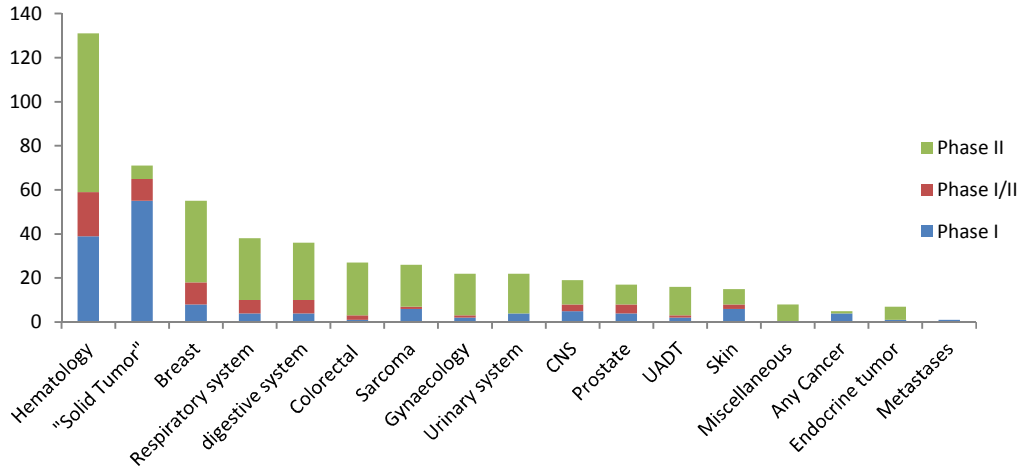
The data shown in Figure 15 allow a more detailed explanation of the difference in the trends observed between academic and industry-sponsored trials (Figure 11). Thus the strongly increased enrollment in academic sponsored trials is essentially due to increased enrollment in phase II trials (+ 72%), whereas the number of new academic phase II trials increased little during the same time (+ 16%). The number of patients enrolled in industry-sponsored phase II trials increased little (+ 4%), in correlation with the increase in the number of industry-sponsored phase II trials (+ 16%). The large increase in the number of patients enrolled in academic sponsored phase II trials leaves one to believe that this type of trial benefited strongly from the restructuring that followed the designation of the centres.

5. ACTIVITY ACCORDING TO ANATOMICAL GROUP

In this chapter, the data have been compiled by anatomical group, according to the classification set out in the INCa registry of clinical trials[3]. For information:

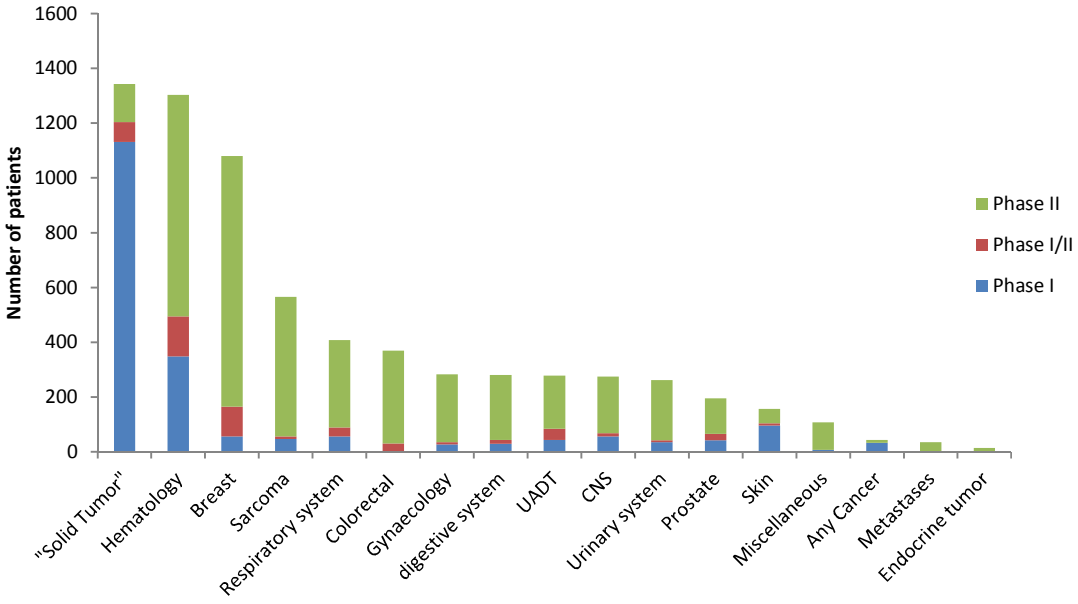
- the “Solid tumor ” group is a designation essentially associated with phase I trials aimed at determining tolerance to new drugs. In these trials, any patient with a cancer affecting a “solid” organ, as opposed to a malignant haemopathy, may be enrolled. This group also includes trials where pathologies in heterogeneous anatomical groups are compiled, generally phase II trials. Thus, in the following figures, the anatomical group “Solid tumors ” does not correspond to the sum of the various distinct anatomical groups such as “Breast,” “Respiratory system,” “Sarcoma” etc.;
- the “Metastases” group corresponds to trials concerned only with the treatment of metastases, and not with primary cancers;
- the “Any cancer” group comprises trials for which the pathology is not specified, or which deals with any type of “solid” or “liquid” cancer;
- the “Miscellaneous” group brings together rare pathologies that cannot be associated with an anatomical group.

Figure 16: Distribution of new trials in the CLIP² by anatomical group – 2010-2012



3 http://www.e-cancer.fr/recherche/recherche-clinique/registre-des-essais-cliniques/registre-des-essais-cliniques

Figure 17: Distribution of enrollment in the CLIP² by anatomical group – 2010-2012



Three anatomical groups stand out in terms of new trials and patient enrollment:

- haematology, which is the most represented pathology, with 25.3% new trials opened for recruitment, and 18.8% of patients enrolled;
- the "Solid tumor " group, which represents 13.7% of new trials, for 19.1% of patients enrolled;
- breast cancer, which, with 10.6% of new trials, represents 15.4% of enrollment. These three anatomical groups represent more than half of new early-phase trials and patients enrolled by the CLIP² between 2010 and 2012.

This representation is explained as follows:

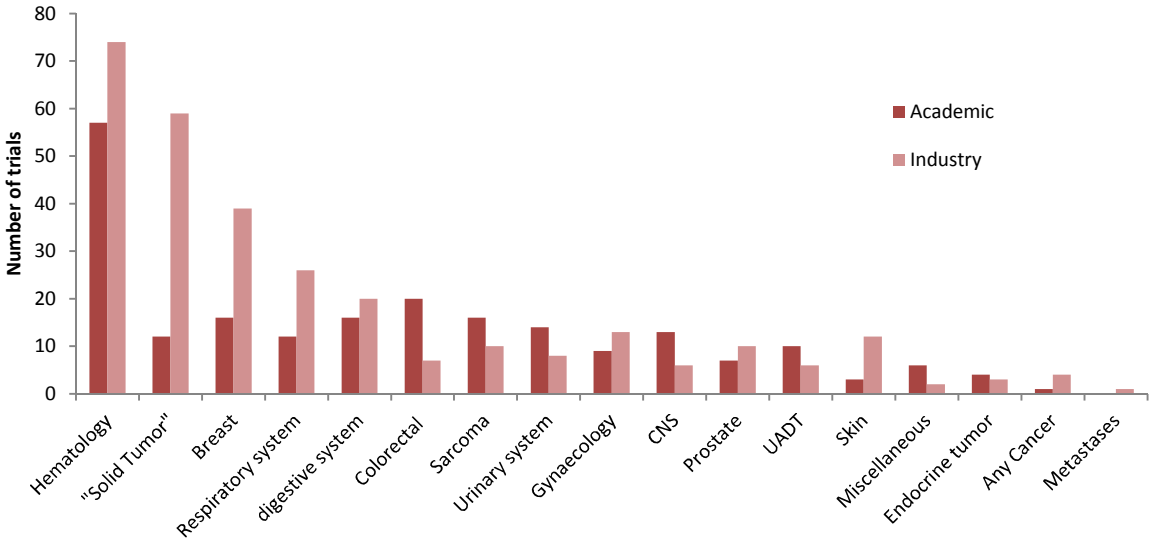
- in haematology, by the variety of different clinical situations and involvement of teams for whom it is the chosen field for clinical research. It is, however, surprising to observe that despite a much higher number of new trials, the number of patients enrolled is the same for haematology as for the "Solid tumor " group. This is all the more so since the "Solid tumor " group comprises mainly phase I trials (which on average enroll a smaller number of patients than phase II trials), unlike the haematology trials, which are phase II trials. Since malignant haemopathies are most often treated in the CHU, and since the latter are less well represented among the CLIP², one can believe that the discrepancy observed is related to the fact that a non-negligible share of the patients enrolled in the 131 new trials in haematology were enrolled outside the CLIP². In contrast, the majority of patients enrolled in phase I trials on solid tumors were enrolled in these centres.
- for "Solid tumor", by the phase I activity of the CLIP²;
- for "Breast cancer," because of its high incidence, and the attractiveness of clinical research for this pathology. Breast cancer is the pathology most studied in phase II trials, which clearly shows that breast cancer is one of the most explored development avenues.

We will also note the relatively small number of trials in prostate cancer, probably due to the existence of well-standardised treatments for local disease. The advent of new treatments for the advanced stages of the disease may change the current situation and result in more clinical trials for this pathology.

Conversely, we observe a strong representation of trials involving sarcomas. The relatively high number of trials in relation to the incidence of sarcoma may be explained by the interest taken by a number of CLIP² in these pathologies, with a high level of academic research activity.

These data show that the pathologies studied in early-phase trials are not correlated with the incidence of the cancers.

Figure 18: Distribution of trials in the CLIP² by anatomical group and type of sponsor – 2010-2012



Analysis of the distribution of new trials by anatomical group according to type of sponsor makes it possible to show that academic and industry sponsors each studies specific pathologies.

The greatest share of trials from the "Solid tumor " group is logically sponsored by industry, since these are strongly associated with phase I activity. It also seems that trials involving cancers of the breast, respiratory system (lung) and melanoma are mainly sponsored by industry. This highlights the priority tumour locations for industries in their development strategy. Although there is a high incidence of cancers of the breast and respiratory system, the same is not true of melanoma. For this pathology, the dynamism of industry clinical research may be explained by the identification of therapeutic targets and by evidence that immunotherapies are effective.

In contrast, trials involving colorectal cancers are mainly under academic sponsorship, although the incidence of this pathology is high. These differences can be explained by considerations of therapeutic indications taken into account by industries in their development strategy, as well as by the existence of well-standardised treatments for this tumour location. Similarly, sponsorship of trials is mainly academic for other tumour locations, such as sarcomas and CNS cancers.

6. ACTIVITY ACCORDING TO TYPE OF TREATMENT

TREATMENT CHARACTERISTICS

Table 1: Characteristics of early-phase trials – 2010-2012

Characteristic of trials	Number of trials	%	Number of patients	%
Type of treatment	496		6,710	
Drugs	451	90.9	6,095	90.8
Radiotherapy	13	2.6	159	2.4
Surgery	5	1.0	127	1.9
Other	7	1.4	99	1.5
Transplant	7	1.4	71	1.1
Biomarkers	1	0.2	66	1.0
Radiochemotherapy	4	0.4	46	0.5
Imaging	4	0.4	44	0.7
Radioimmunotherapy	4	0.4	29	0.3
Drugs	451		6,095	
Monotherapy	203	45	2,688	55.6
Combination	248	55	3,389	44.1
NA			18	0.3

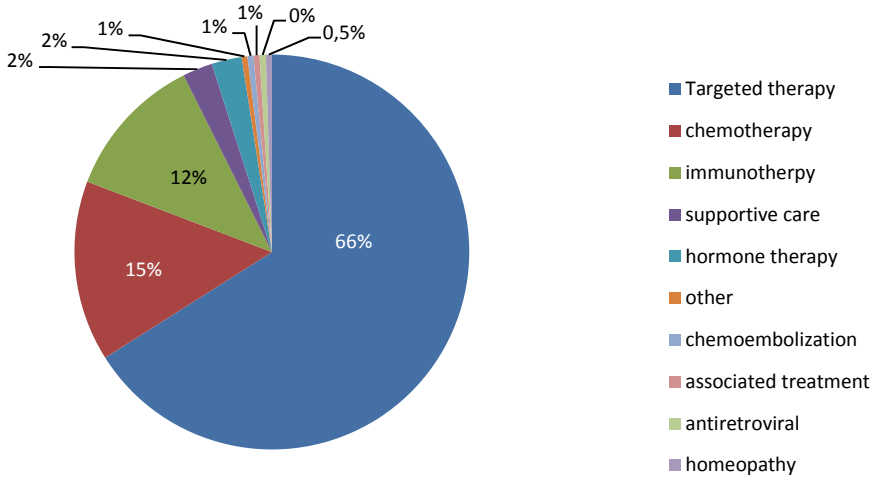
It is possible to distinguish the different types of treatments studied in new clinical trials carried out in the CLIP² during the 2010-2012 period. Thus, the vast majority of trials undertaken (90%) are to evaluate a drug, but the CLIP² also participate in trials to evaluate surgical strategies and radiotherapy trials (Table 1).

Of the "drug" trials conducted in the CLIP², 45% relate to the evaluation of a monotherapy (treatment with a single agent). In 66% of cases, this monotherapy has not yet obtained MA in France. The remaining 33% correspond to extensions of indication.

Trials of combinations including at least one drug without MA represent 51% of trials on drug combinations. We can note, although it is still marginal, the existence of trials on combinations of two drugs without MA. Thus five such trials were initiated in the CLIP² between 2010 and 2012, of a total of 248 drug combination trials, i.e. 2%.

In total, 59% of 451 "drug" trials, either monotherapy or combination, evaluated a drug which did not yet have MA, and 2,970 patients thus had access to an innovative drug in the CLIP² between 2010 and 2012 (i.e. 44% of patients enrolled in a clinical trial within the CLIP²).

Figure 19: Distribution of treatment type in drug monotherapy trials – 2010-2012



By the same token, monotherapy trials may be analysed as a function of the mechanism of action of the drug being examined (Figure 19). Of these trials, 66% evaluate targeted therapies, and 14% of them evaluate a chemotherapy, demonstrating the prominent place occupied by targeted therapies in industrial research and development in oncology.

Figure 20: Trends in the number of new monotherapy trials by type of treatment – 2010-2012

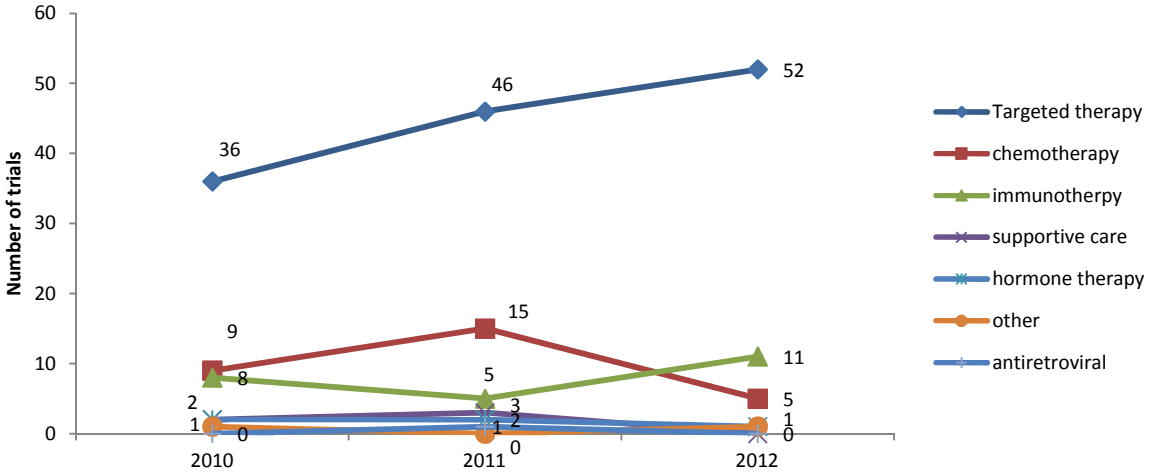
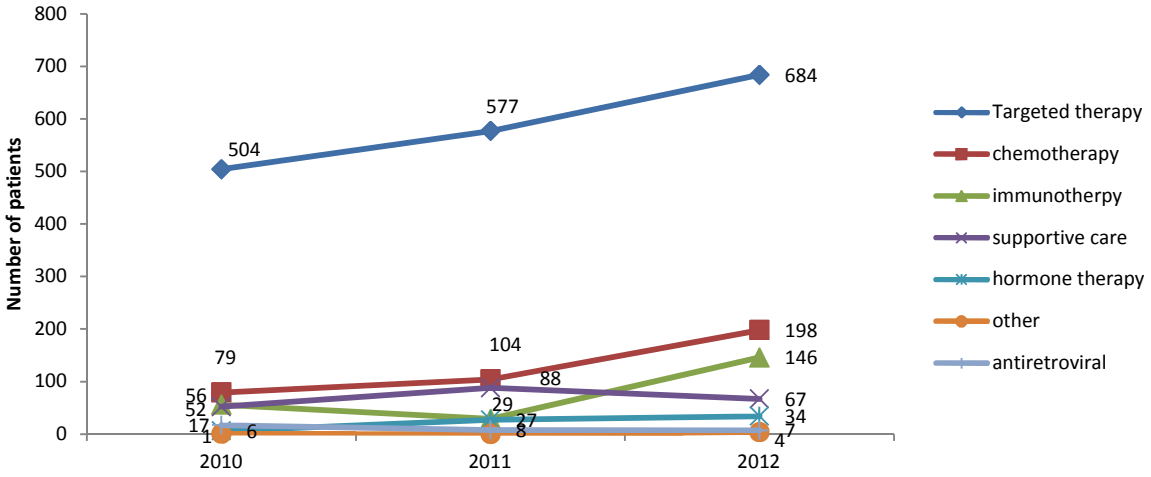


Figure 21: Trends in the number of patients enrolled in monotherapy trials by type of treatment – 2010-2012



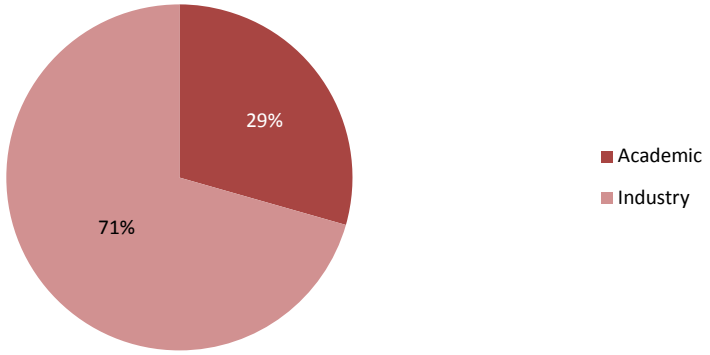
Between 2010 and 2012, the number of patients treated using a targeted therapy thus strongly increased, due to the large number of new trials on this type of drug.

Early-phase clinical trials to evaluate chemotherapies are holding their own in 2012, in terms of enrollment. However, since a drop in the number of new trials to evaluate a chemotherapy was observed between 2011 and 2012, it is possible that enrollment in trials evaluating a chemotherapy compound may decrease in 2013.

We also observe a clear increase in enrollment in immunotherapy trials from 2011 on. Since the curves for new trials in chemotherapy and immunotherapy cross between 2011 and 2012, the distribution of enrollment for these two types of treatment is likely to evolve in the coming years.

Early-phase monotherapy trials are mainly sponsored by pharmaceutical companies, which sponsored 71% of such trials initiated between 2010 and 2012 (Figure 22), compared with 58% of all new trials (Figure 8). These results show that the initial development of a new compound is brought about by monotherapy trials sponsored by the pharmaceutical industry, whereas academic sponsors are more likely to evaluate combinations. Thus, while the number of industry-sponsored trials is similar for monotherapy and combination trials, academic sponsored combination trials are twice as numerous as monotherapy trials.

Figure 22: Distribution of new monotherapy trials by type of sponsor – 2010-2012



DRUG CHARACTERISTICS

Table 2: Characteristics of drugs tested as a monotherapy9

Characteristics of drugs tested as a monotherapy	
Number of drugs **Number of trials**	108 134
Targeted therapy	70
Immunotherapy **Other (chemotherapy)** **Hormono therapy**	18 18 2
Targeted therapy	70
Antibodies	13
Small molecules	57
Immunotherapy	18
Antibodies Small molecules Vaccines	11 1 6
Targeted therapy	70
Signal transduction inhibitor	49
PI3K/AKT/mTor pathway RAF/MEK/ERK pathway Notch Hedgehog pathway JAK/STAT pathway Multikinase inhibitors HER receptors Other receptors HSP Miscellaneous	10 3 2 2 1 3 6 10 2 10
Regulation of gene expression/cell cycle	9
Apoptosis inducer	3
Antiangiogenics	4
Antibodies conjugated to toxic compounds	5
Immunotherapy Targeting surface receptors of haematopoietic cells Immune system activator	18 6 12

This table shows the different types of drugs evaluated in monotherapy trials conducted by the 16 CLIP². One hundred and eight different drugs were tested in 134 trials to evaluate a drug that had not yet obtained MA.

As previously observed, Table 2 shows a predominance of targeted therapies among these new treatments, and the growing share of immunotherapy.

Drugs classified as targeted therapy and immunotherapy can be distinguished according to their nature, whether they are antibodies or small molecules administered orally, or therapeutic vaccines for immunotherapy.

In the same way, with targeted therapies, it is possible to distinguish the mechanisms of action targeted by these new drugs, especially inhibitors of signal transduction pathways, which are currently the most studied. Thus 49 of these new drugs were tested between 2010 and 2012 in the CLIP². They target various signalling pathways, with the PI3K/AKT/mTor pathway being the most represented (Table 2). Other categories of targeted therapies can be distinguished among the trials carried out in the CLIP², such as drugs targeting the regulation of gene expression/cell cycle, apoptosis inducers or antiangiogenics. The high number of targeted therapies under development is therefore largely attributable to the great variety of therapeutic targets identified, and reflects the dynamism of early research.

7. ACTIVITY BY CENTRE

OVERALL ACTIVITY OF CENTRES

Figure 23: Trials initiated by CLIP² – 2010-2012

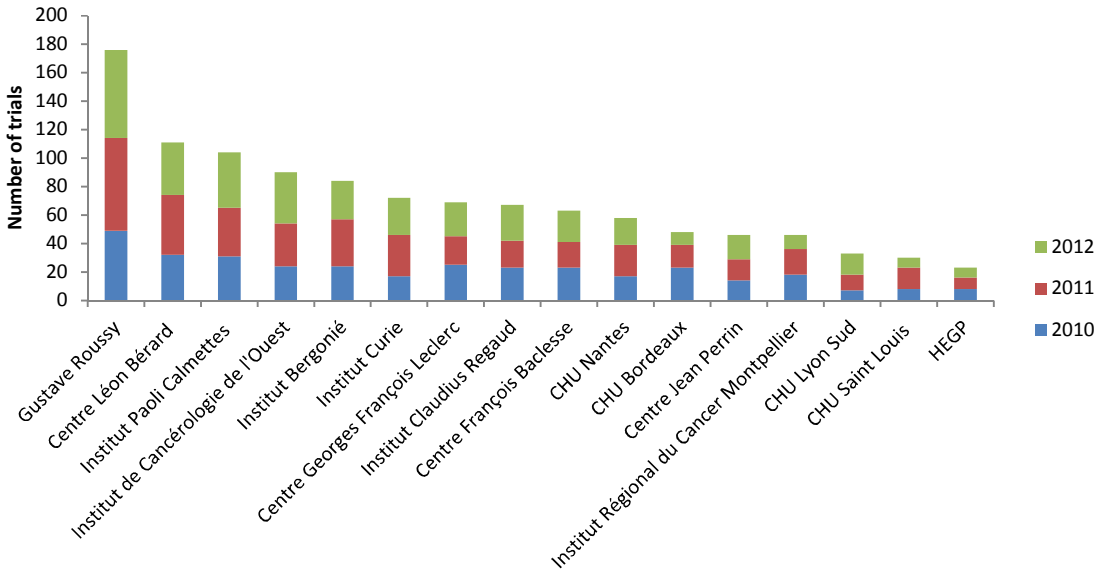
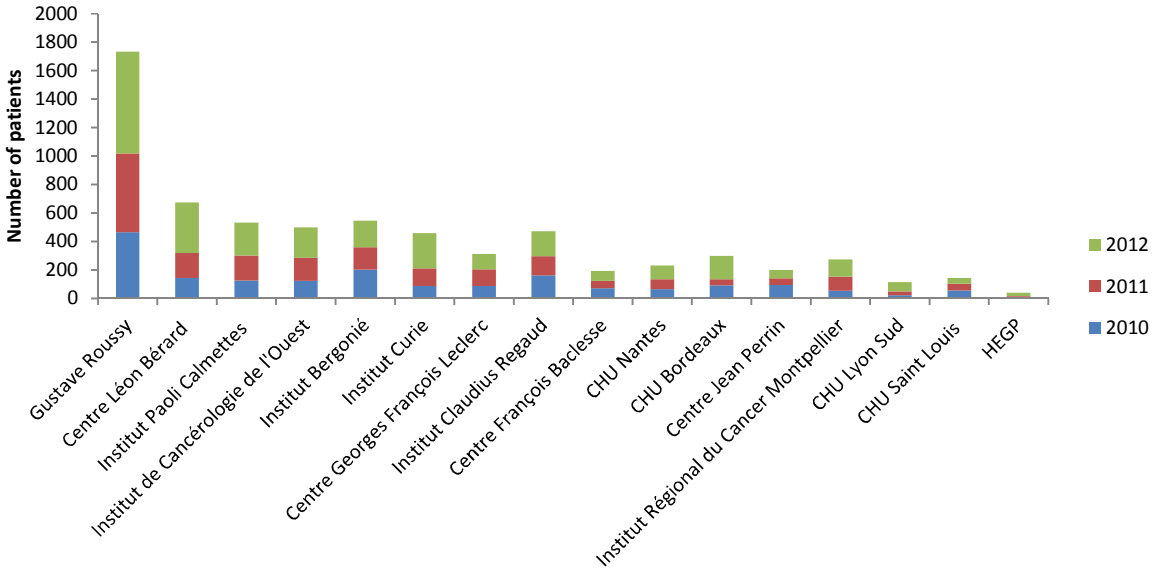


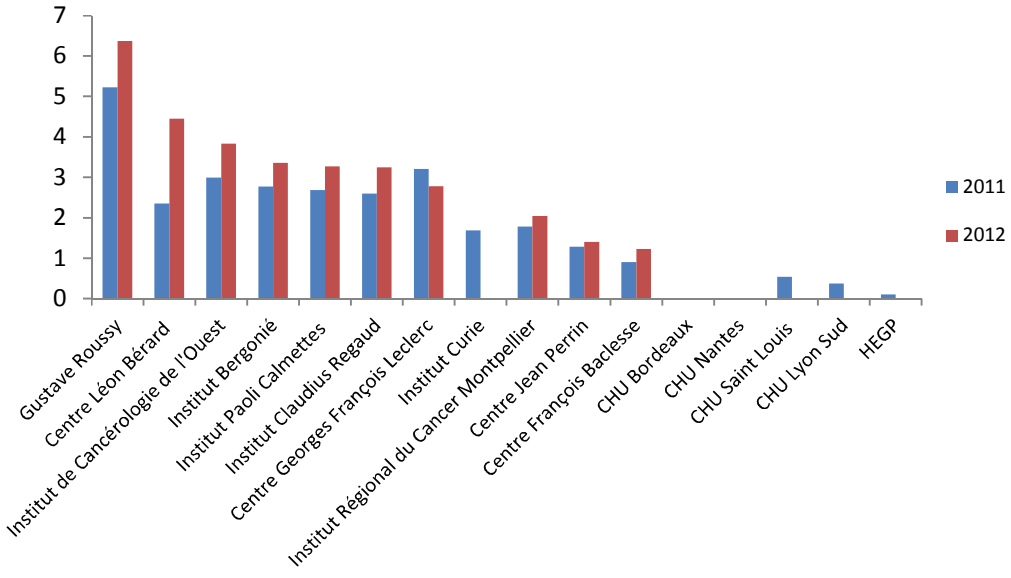
Figure 24: Patient enrollment by CLIP² between 2010 and 2012



The median activity of a CLIP² between 2010 and 2012 is 305 [40-1,731] patients enrolled, for 65 [23-176] new trials opened for enrollment. For the 2010-2012 period, the 16 designated centres reported a highly variable level of activity, with respect to the number of new trials being conducted (up to 10-fold variability) as in the number of patients enrolled (up to 50-fold variability) (Figures 22 and 23).

It should be noted that most of the centres have experienced a steady increase in activity. The designation of the CLIP² has enabled better structuring of the centres, and in particular the recruitment of new staff, either medical or paramedical. Analysis of activity data for 2013 and 2014 will make it possible to see whether the initial trend observed following designation is confirmed. However, since early-phase clinical trials require specific logistics, a plateau may be reached in some of the centres, particularly for phase I trials.

Figure 25: Enrollment rate in the CLIP² as a function of the number of patients being managed for – 2011 and 2012[4]



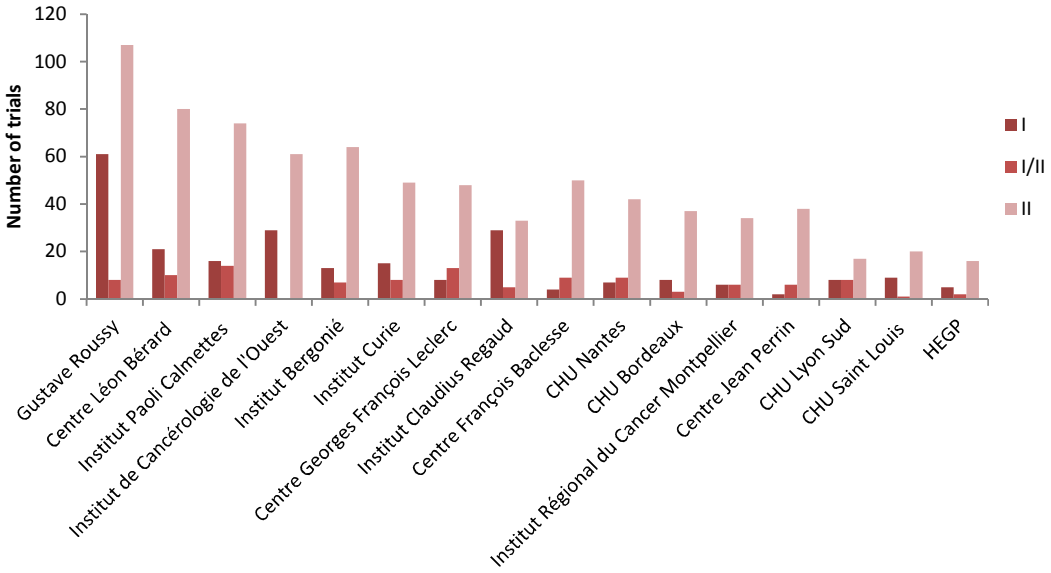
4 For Bordeaux and Nantes University Hospitals (CHU), the PMSI (Programme for the Medicalisation of Information Systems) data do not allow one to distinguish between the different CHU facilities. For the Lyon Sud, Saint Louis and HEGP University Hospitals, the 2012 data are unavailable For Institut Curie, the data from 2011 and 2012 are non-uniform, since patients from René Huguenin Hospital are included from 2012 on.

Data from PMSI[5] allow comparison of figures on cancer care per facility hosting a CLIP² (hospital admissions), with figures for patient enrollment in each CLIP². Thus, for most of the centres, a rate of recruitment into the early-phase clinical trials reported by the CLIP² can be calculated for years 2011 and 2012 (Figure 25). As with enrollment data, this rate varies strongly between centres, going form 0.1% to over 6%, showing that enrollment activity is not related to the overall oncological activity of the facility. Substantial room for improvement therefore remains for centres with the lowest rate.

However, this observation must be qualified by the difference in organisation of each centre. In the CLCC, the early-phase research unit cares for all patients eligible for an early-phase trial, regardless of indication, whereas in the CHU, patients cared for in the specialist organ services are likely to be enrolled in trials carried out within these services, and are not counted as part of the early-phase clinical trial activity.

ACTIVITY OF CENTRES ACCORDING TO PHASE TYPE OF TRIALS

Figure 26: Trials initiated by CLIP² by phase type – 2010-2012

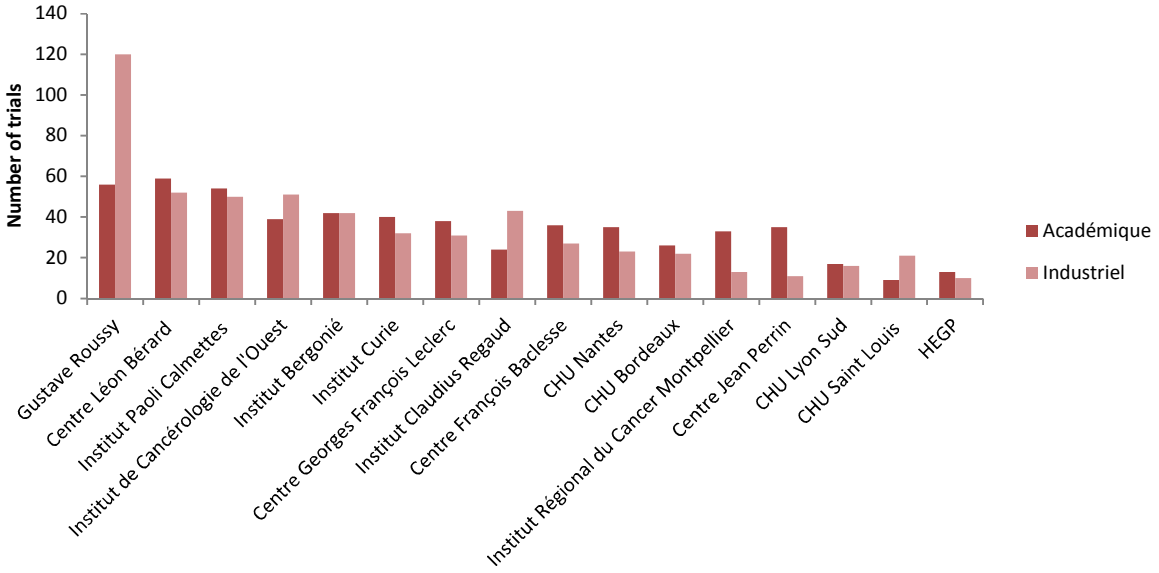


We can note that the predominant activity of the centres is phase II (Figure 26). Only Gustave Roussy (GR), Institut de Cancérologie de l'Ouest (ICO), and Institut Claudius Regaud (ICR) are distinguished by strong phase I activity, representing respectively 35, 32 and 43% of new trials carried out in these centres.

5 Source of data: PMSI MCO 2011-2012.

ACTIVITY OF CENTRES ACCORDING TO TYPE OF SPONSOR

Figure 27: Trials initiated by CLIP² by type of sponsor - 2010-2012



Centres such as GR, ICO and ICR show more industry-sponsored activity than academic activity (Figure 27), which is explained by the strong activity in phase I trials. In contrast, the Centre Jean-Perrin and Institut regional du Cancer de Montpellier have predominantly academic activity.

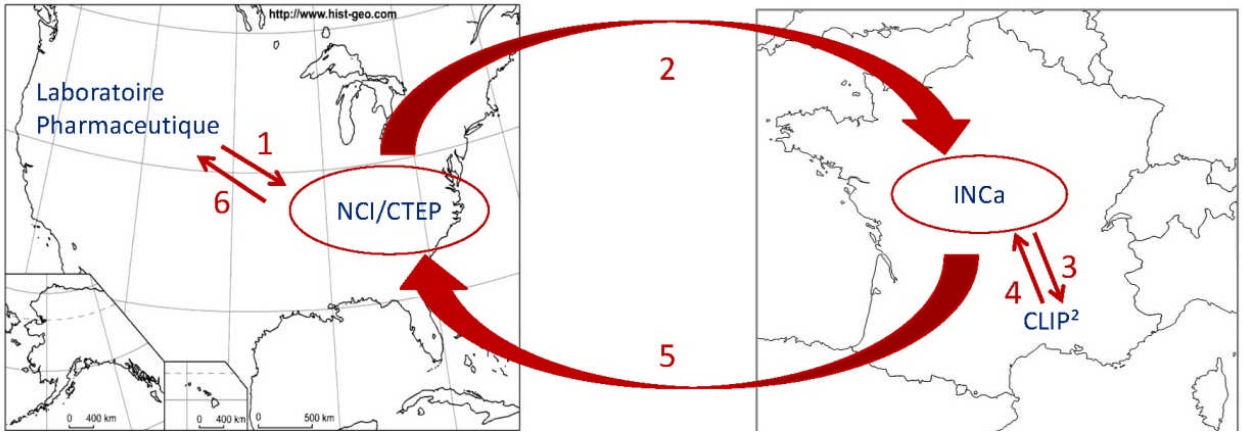
REPORT OF COLLABORATION WITH THE NATIONAL CANCER INSTITUTE (NCI[6])

1. ESTABLISHMENT OF THE NCI-INCa COLLABORATION

From January 2008, INCa and the Division of Cancer Treatment and Diagnosis (DCTD) of NCI decided to cooperate, especially in the area of early-phase clinical trials, under the Cancer Therapy Evaluation Program (CTEP). On 31 March 2010, the two institutes signed a collaboration agreement setting out the terms for participation by French centres with expertise in early-phase trials in NCI calls for proposals, and especially, provisions for making innovative drugs available to these centres by NCI.

This collaboration is implemented and articulated according to a specific procedure

Figure 28: Schema of the NCI-CTEP collaboration with INCa for early-phase clinical trials



The pharmaceutical companies supply drugs to NCI for specific indications that are non-priority in their development programme.

1. The CFP launched by NCI-CTEP is open to France via INCa.
2. INCa informs the CLIP².
3. The CLIP² submit letters of intent (LOI).
4. The LOI, following review by INCa, are submitted to NCI for competitive examination by CTEP and then by the company.
5. NCI-CTEP and the company evaluate and select the LOI. When an LOI is selected, the CLIP² sponsor writes the protocol and launches the trial in the French centres.

This collaboration encourages the participation of French centres in phase I and II trials to test new drugs that had not previously been available in France.

6 The National Cancer Institute is the American agency coordinating the programme of action on cancer in the United States.

2. TERMS OF THE COLLABORATION

The collaboration with NCI involves a certain number of obligations for the CLIP², most of which are described in the collaboration agreement signed between NCI and INCa, and based on the regulatory responsibilities of NCI.

These requirements relate to:

- additional regulatory procedures under the American authorities;
- reporting of adverse events to NCI;
- ownership of clinical data and results of research;
- the conduct, on request from NCI, of independent audits in centres participating in the research;
- the drug circuit.

3. RESULTS

From the beginning of the collaboration until 2012, the French centres responded to six invitations from NCI. Six letters of intent were selected by NCI, including a collaborative project with an American cooperative group (Table 3).

This collaboration between NCI and a foreign institution, the first of its kind, ended in the establishment of a first early-phase clinical trial in advanced chondrosarcomas, to test a new drug that inhibits the Hedgehog pathway. The first French patient was enrolled on 8 February 2011. He was the first to receive this drug in France. This first trial made it possible to demonstrate the feasibility of such a partnership, and the competence of the French centres. Indeed, all the patients were enrolled within one year, albeit for an extremely rare indication. The initial results were presented in an oral communication at the 2012 international meeting of the American Society of Oncology (ASCO)[7] and were published at the end of 2013[8].

A second trial, on large B cell lymphomas, began in 2011, and 22 patients were enrolled of 51 expected, in a little over a year. It was interrupted following the interim analysis provided for in the protocol.

Two projects are presently being discussed. The first is on Ewing's sarcomas and osteosarcomas. The synopsis has been accepted by NCI, and the protocol is being written. The second, a French-American collaboration, is on HIV-associated lymphomas. For this American-initiated project, the French investigators were contacted by NCI in order to participate in this project. It should be finalised in 2014, thereby establishing new collaborations between France and the United States.

7 Italiano A, Le Cesne A, Cassier PA, Ray-Coquard I, Domont J, Piperno-Neumann S, Duffaud F, Penel N, Takebe N, Blay JY, Bui B. GDC-0449 in patients with advanced chondrosarcomas: A French Sarcoma Group (FSG)/French and U.S. National Cancer Institute phase II collaborative study. J. Clin. Oncol., 2012 ASCO Annual Meeting Proceedings (Post-Meeting Edition). No 15_suppl (May 20 Supplement), 2012: 10005.

8 Italiano A, Le Cesne A, Bellera C, Piperno-Neumann S, Duffaud F, Penel N, Cassier P, Domont J, Takebe N, Kind M, Coindre JM, Blay JY, Bui B. GDC-0449 in patients with advanced chondrosarcomas: a French Sarcoma Group/US and French National Cancer Institute single-arm phase II collaborative study. Ann Oncol. 2013 Nov; 24(11):2922-6. doi: 10.1093/annonc/mdt391

Table 3: Table summarising the results of responses of French early-phase clinical trials to calls for proposals from NCI under the collaboration between INCa and NCI

Drug	Proposals submitted by the CLIP²	Project selected	State of progress
Hedgehog pathway antagonist	6	Chondrosarcomas–CHONDROG trial Institut Bergonié, Bordeaux	46 patients enrolled of 41 expected
Notch inhibitor	9	Triple negative breast cancer Gustave Roussy, Villejuif	Abandoned, following cessation of development of the drug
AKT inhibitor	11	Diffuse large B cell lymphomas–AKTIL trial Centre Léon-Bérard, Lyon	22 patients enrolled of 51 planned. Trial stopped
IGF-1R pathway inhibitor	12	Endocrine tumors Institut Paoli Calmettes, Marseille	Collaboration stopped following reorganisation of the company
Aurora kinase A inhibitor	1	Sarcomas Institut Bergonié, Bordeaux	Ultimately, the American cooperative group sponsoring the trial did not wish to include French centres in the project.
cMet and VEGFR2 inhibitor	9	Ewing's sarcoma and osteosarcoma Institut Bergonié, Bordeaux	Trial accepted by NCI and the company that owns the drug; protocol in preparation
Anti-CD30 antibody	NA	HIV-associated lymphoma	Discussion in progress

4. DEVELOPMENTS IN THE COLLABORATION

Today, the collaboration with NCI-CTEP has evolved, following a reduction in the number of American cooperative groups recognised by NCI. CLIP² are now asked to join with these American cooperative groups when responding to sollicitations from NCI-CTEP.

This new rule makes collaboration more difficult: CLIP² must now rapidly identify the network of American centres that might agree to collaborate on a common theme, and convince them of the interest of conducting an international trial. Indeed, even when the American principal investigator wishes to undertake a joint project with a CLIP², many practical arrangements need to be defined: a shared database, a common case report form, the drug circuit, and choice of sponsor. NCI has formed a focus group (NCI Group International Planning Committee [GIPC]), bringing together the United States and some European and Asian countries in order to improve international collaboration regarding clinical trials. Meanwhile, other arrangements for collaboration with NCI-CTEP are emerging, particularly the opportunity for the CLIP² to propose letters of intent regarding drugs available to NCI outside of these CFPs.

REPORT OF COLLABORATION WITH PHARMACEUTICAL COMPANIES

Alongside the collaboration with NCI, INCa initiated discussions with some French and international pharmaceutical companies in order to establish research and development partnerships between international companies and players involved in oncology research.

The goal of this initiative is to conduct early-phase clinical trials under academic sponsorship for previously unexplored indications, and outside these companies' own clinical development plans, with drugs that do not have marketing authorisation. The ultimate objective is to give patients early access to innovative therapies. This principle was approved by the INCa Ethics Committee on 27 June 2011 (Appendix 2). The entire programme receives joint funding from ARC Foundation for Cancer Research.

1. DESCRIPTION OF THE PROCESS

This collaboration is implemented according to a specific procedure (Figure 29). Five stages, from the identification of drugs until the launch of clinical trials, have been defined, together with the duration of each.

Figure 29: Procedure for collaboration between INCa and pharmaceutical companies in France

IDENTIFICATION OF DRUGS BEING MADE AVAILABLE

The identification of drugs likely to be made available by a pharmaceutical laboratory takes place during discussions between INCa and the pharmaceutical company that owns these drugs. INCa then requests the opinion of the CLIP² coordinators on the scientific opportunity of launching a CFP for early clinical trials with each drug identified. The decision to launch a CFP regarding a given drug leads to the signing of a collaboration agreement between INCa and the pharmaceutical company, describing the obligations of the parties. These terms and agreements are subsequently included in the contract linking the CLIP² sponsor of the trial with the company.

COMPETITIVE CALLS FOR PROPOSALS DIRECTED AT THE CLIP²

INCa launches a CFP reserved for the CLIP². The text of the CFP specifies the company's own areas of investigation, which are therefore outside the scope of the present call for proposals. The company also supplies the necessary data on the drug. This documentation, generally the Investigator's Brochure for the drug, contains confidential information. For this reason, INCa is careful to obtain a confidentiality agreement in advance from the legal representative of the centre to which the CLIP² is attached.

This stage takes a maximum of 12 weeks.

EVALUATION OF PROPOSALS

The CLIP² teams prepare a letter of intent (synopsis), which will be evaluated by three reviewers, each with clinical, pharmacological or methodological expertise. Initially, INCa will make sure that none of these reviewers has any conflicts of interest with the CLIP², project sponsor or the company that owns the drug at the centre of the CFP.

The applications are then reviewed in committee by these same reviewers, and given a final rating. Applications likely to be supported are sent to the company.

This evaluation process takes place in the six weeks following receipt of the applications by INCa.

FINAL SELECTION

The company has one month to return to INCa the list of proposals that it does not agree to support. Each rejected proposal must be accompanied by a justification. The reasons for rejection may be of a scientific nature, where new clinical data on the drug render the research area proposed for the project irrelevant, or of a technical nature, where the company has not the dosage form of the drug required for the project. Another reason for rejection may be the launch of an identical clinical trial in another country with the same drug.

INCa chooses the trial or trials that will be funded from the list reviewed by the company, based on the rating established by the evaluation committee. A maximum of two trials are funded by INCa for the same drug.

LAUNCH OF THE STUDY

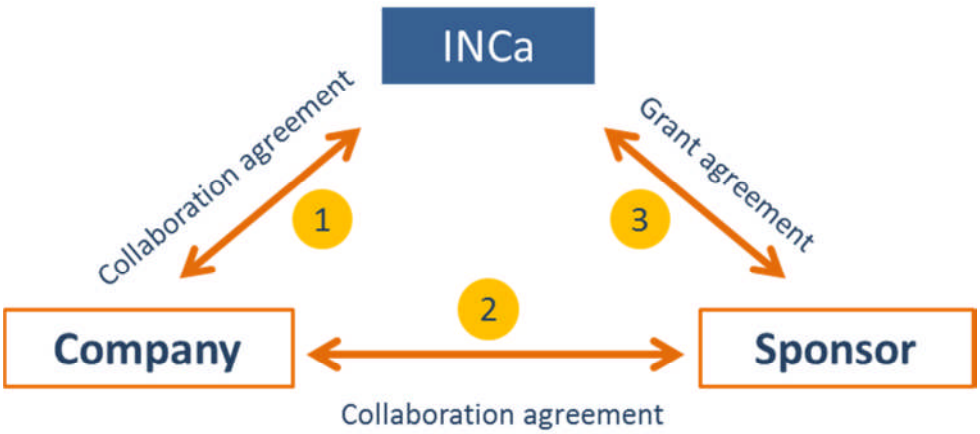
Once the trial has been selected, the CLIP² sponsor must write the trial protocol and sign an agreement with the company within the following three months.

Once this agreement has been signed, and a copy submitted to INCa, the financial agreement between INCa and the managing body to which the CLIP² is attached can be signed.

In total, three types of contract are drawn up during this procedure (Figure 30):

- a collaboration agreement between INCa and the company supplying the drug;
- a contract between the company and the CLIP² sponsoring the study, regarding the arrangements for supplying the drug;
- a grant agreement between INCa and the CLIP² sponsoring the study.

Figure 30: The contracting process



2. ROLE OF THE DIFFERENT PARTIES

ROLE OF THE PHARMACEUTICAL COMPANY

- To make innovative drugs available, free of charge, and to supply all information regarding the drug.
- To submit the "pharmaceutical dossier" to the competent authorities, at the same time as the protocol is submitted by the sponsor.
- To ensure, under its responsibility, the release of the product, labelled "clinical trial" according to the legislation in force, and its delivery to the centres participating in the study or to a services company designated by the sponsor.
- To inform the sponsor, for the duration of the clinical trial, of all data on the drug that might affect patient health, have an impact on the running of the trial, or modify the authorisation of the competent authorities to pursue the clinical trial.

Apart from the above-mentioned points, there may be no involvement of the company in either the running of the trial or in the analysis of the data.

ROLE OF THE SPONSOR

- To assume responsibility for the study in accordance with the public policy provisions of Article L.1121-1 of the Public Health code.
- To ensure that the clinical trial is run in accordance with the relevant legislation, regulations, and good practices.
- To provide INCa with activity reports and financial reports.
- To organise audits in each centre participating in the clinical trial conducted under this collaboration.

3. TERMS OF THE COLLABORATION

OWNERSHIP OF RESULTS

The data and results from the trial are completely and entirely owned by the sponsor; however, the sponsor is obliged to provide them to the company that owns the drug.

The latter has the opportunity to acquire the totality of data and results from the trial (especially for purposes of registration in the context of an application for marketing authorisation), subject to payment of financial compensation, the amount of which will be decided in good faith between the company and the sponsor. In particular, the price must take into consideration the grant paid by INCa under the agreement, the cost borne by the sponsor in carrying out the trial, and the impact of the results of the trial on the development of the drug.

In this case, the sponsor agrees to reinvest, up to the amount of the grant paid by INCa, the sum thus received in early-phase clinical trials carried out within the CLIP².

FUNDING

Funding for these early-phase clinical trials is provided by the French National Cancer Institute (INCa) in partnership with ARC Foundation for Cancer Research. A collaboration agreement between INCa and ARC Foundation for Cancer Research was signed on 24 August 2011 for the duration of designation. ARC Foundation for Cancer Research reserves the right to agree or otherwise to provide matching funding for each early-phase clinical trial proposed by INCa.

4. RESULTS

INITIAL COLLABORATION – NOVARTIS

The first two collaboration agreements were signed between INCa and the Novartis pharmaceutical company. The first agreement involved a drug that inhibits the PI3kinase signalling pathways, and the second involved a drug that inhibits the PI3kinase and mTor signalling pathways.

Key dates:

- INCa-Novartis collaborative agreement: 26 September 2011;
- publication of the call for proposals: 7 November 2011;
- submission of applications: 21 December 2011;
- review committee: 3 February 2012;
- final selection of applications by INCa 21 March 2012.

At the end of the procedure described in Figure 29, INCa selected one project per drug, according to the rating given by the evaluation committee. These were the project proposed by Prof. Céleste Lebbé of CLIP² Saint-Louis on Kaposi's sarcomas, and that of Jérôme Fayette of CLIP² Centre Léon-Bérard on cancers of the head and neck. However, after the results of these two CFPs were announced, and following new data on the drug, and with the agreement of the company, Prof. Lebbe's trial did not proceed.

With respect to Dr Fayette's trial, an agreement was signed between Centre Léon-Bérard, the sponsor, and Novartis. This agreement contains the terms and agreements specified in the collaboration agreement between INCa and the company. The protocol was prepared concurrently.

Submissions for authorisation of the clinical trial were made to the Committee for Protection of Individuals (CPP) and to ANSM. The application obtained a favourable opinion from the CPP on 18 September 2012, and obtained authorisation from ANSM on 25 September 2012. The first centre was opened in December 2012, and the first patient enrolled on 4 January 2013. Since then, 8 patients have been enrolled.

Following the announcement of the project selection, a coordination task was carried out by INCa between the CLIP² sponsor and the company. For this reason, less than 11 months elapsed between launching the call for proposals and receipt of authorisations for this trial.

OTHER COLLABORATIONS

Since signing the first collaboration agreements with Novartis, INCa has signed collaboration agreements with six other companies, to make ten additional drugs available (Table 4).

Table 4: Summary of calls for proposals for early-phase clinical trials

Drug	Number of proposals submitted	Type of project selected	PI/Centre	State of progress
Novartis				
PI3K inhibitor: BKM120	4	Head and neck cancer	Dr Fayette, Centre Léon-Bérard	Open for recruitment
PI3K/mTor inhibitor: BEZ235	18	Kaposi's sarcoma	Prof. Lebbé, protocol abandoned	
Pfizer				
PI3K inhibitor: PF	13	Myeloid leukaemia and myelodysplasia	Dr Vargaftig, Institut Curie	Finalisation of protocol
CDK4/6 inhibitor: PD-0332991	7	GIST	Dr Italiano, Institut Bergonié	Open for recruitment
		Melanoma	Prof. Lebbé, Hôpital Saint Louis	Open for recruitment
Lilly				
p70/AKT inhibitor	20	Solid tumour	Prof. Soria, Gustave Roussy	Open for recruitment
		Breast cancer	Prof. Goncalves, Institut Paoli Calmettes	Open for recruitment
Roche				
Anti-EGFR: GA-201	14	Project abandoned		
Transgene				
Oncolytic virus: JX-594	7	Breast cancer and soft tissue sarcoma	Dr Italiano, Institut Bergonié	Finalisation of protocol
Lilly				
P38/MAPK inhibitor: LY2228820	8	Breast cancer	Dr Levy, Centre François-Baclesse	Finalisation of protocol
		Glioblastoma	Dr Durando, Centre Jean-Perrin	Finalisation of protocol
Sanofi				
Anti-HER3 antibody: MM-121	8	Call for proposals in progress		
Ipsen				
Antineoplastic: tasquinimod	12	Call for proposals in progress		

CONCLUSIONS AND OUTLOOK

The initiatives and support actions of the French National Cancer Institute for early-phase clinical trials have achieved their main objectives, namely, the designation of expert centres for the conduct of early-phase clinical trials, and making innovative drugs available to patients in France.

Indeed, by designating them and providing them with financial support, INCa has enabled the 16 centres to recruit dedicated staff and to restructure themselves for optimum operational organisation. In addition, this designation has increased the visibility of the CLIP², and attracted a growing interest from French subsidiaries of pharmaceutical companies and their parent companies.

These initiatives have contributed to an increase in the number of early-phase clinical trials and the number of patients enrolled in these trials since 2010. This increase has been observed for industry-sponsored phase I trials in particular, demonstrating the attractiveness of the CLIP² for pharmaceutical companies. The latter have been more strongly persuaded to open phase I trials in French centres.

The public/private partnership procedure established by INCa to enable early-phase clinical trials for indications that are not included in the pharmaceutical companies' development priorities has been readily and favourably received.

Indeed, the range of drugs on offer has not ceased to grow since the programme was created. Eleven pharmaceutical companies have already offered drugs, and discussions are underway with additional companies. Furthermore, from now on the companies will be making more drugs available under this partnership.

Patients can benefit from this programme through earlier access to innovative drugs that may prove effective. Thus, this programme has enabled a growing number of patients to access these drugs before they are given MA, or to receive combinations of innovative drugs.

Designation of the CLIP² ends in October 2014. Based on the recommendations of the 2014-2019 Cancer Plan, designation of the CLIP² will be repeated starting in 2014, with improvement in territorial coverage, and specific identification of centres active in paediatrics.

A next step will be to also increase the number of early-phase clinical trials combining several drugs under development, in order to limit resistance developed by tumour cells against targeted treatments, to combine the effects of treatments and to increase their efficacy. For this to happen, collaboration between companies is indispensable, and will stimulate collaboration with academic teams.

The 2014-2019 Cancer Plan also emphasises the importance of research on rare cancers and paediatric cancers. The number of clinical trials in these areas will thus have to be increased.

For rare cancers, recruitment is often difficult, and the size of trials too small to allow definite conclusions to be drawn. For this reason the Cancer Plan also recommends having a Europe-wide system of support for early-phase trial centres to enable trials to be carried out collaboratively. It will involve following the CLIP² model and organising public/private partnerships between companies and recognised expert centres in early-phase trials in Europe.

APPENDICES

APPENDIX 1. CLINICAL TRIALS

NCI COLLABORATION

CHONDROG	
Drug	**GDC-0449 – vismodegib: Hedgehog pathway inhibitor**
Coordinating investigator	Dr Antoine Italiano, Institut Bergonié (Bordeaux)
Title	A Phase 2 Study of GDC-0449 in Patients with Advanced Chondrosarcomas.
Number of patients	41 evaluable patients will be enrolled in 6 centres.
Main objective	To evaluate the antitumor activity of GDC-0449 in terms of 6-month non-progression rate (Complete response, partial response and stable disease, as per the Response Evaluation Criteria in Solid Tumors, Revised RECIST criteria 2009).
Secondary objectives	• Best overall response (as per the revised RECIST criteria 2009); • 1- and 2-year progression-free survival; • 1- and 2-year overall survival; • GDC-0449 safety; • Pharmacogenomic analysis of predictive markers of treatment outcome
Participating centres	• Institut Bergonié • Centre Léon-Bérard, Lyon • Gustave Roussy, Villejuif • Centre Oscar-Lambret, Lille • Institut Curie, Paris • Hôpital la Timone, Marseille
State of progress as of 31 March 2014	Recruitment into the Chondrog trial has been finished since February 2012.

AKTIL	
Drug	**MK-2206: AKT inhibitor**
Coordinating investigator	Dr Hervé Ghesquières, Centre Léon-Bérard (Lyon)
Title	A Phase 2 Study of MK-2206 in Patients with relapsed or refractory Diffuse Large-B Cell Lymphoma.
Number of patients	51 evaluable patients will be enrolled in 11 centres.
Main objective	To evaluate the antitumor activity of MK-2206 in terms of objective response rate (ORR) at 4 months as per 2007 Cheson international response criteria.
Secondary objectives	• To evaluate the antitumor activity of MK-2206 in terms of • ORR at 4 months as per 1999 Cheson international response criteria. • Duration of response • Progression-free survival (PFS) • Overall survival (OS) • MK-2206 safety..
Participating centres	• Centre Léon-Bérard, Lyon • Centre Hospitalier Lyon Sud, HCL, Pierre-Bénite • Centre Henri-Becquerel, Rouen • Hôpital Henri Mondor , AP-HP, Créteil • CHRU de Lille, Lille • CHU Nancy, Nancy • Hôpital Necker, AP-HP, Paris

Continued >>

	• Gustave Roussy, Villejuif • Institut Bergonié, Bordeaux • Institut Paoli Calmettes, Marseille • Hôpital Saint Louis , AP-HP, Paris
State of progress as of 31 March 2014	22 patients were enrolled in 6 centres, corresponding to the first stage of Simon's design. The trial was interrupted following interim analysis.

COLLABORATION WITH PHARMACEUTICAL COMPANIES

INCa-Novartis collaboration	
Drug	**BKM120: PI3K inhibitor**
PIK-ORL	
Coordinating investigator	Dr Jérôme Fayette, Centre Léon-Bérard (Lyon)
Title	A Phase II, multicenter trial aiming to evaluate BKM120 in monotherapy in patients with metastatic head and neck cancer recurrent or progressive under platin and cetuximab-based chemotherapy.
Number of patients	70 evaluable patients will be enrolled in 8 centres.
Main objective	To determine the activity of BKM120 as measured by the 2-month disease control rate (Complete response + Partial Response + Stable disease according to RECIST 1.1) in adult patients with recurrent or metastatic head and neck cancer progressive under platin and cetuximab-based chemotherapy.
Secondary objectives	• To further assess the activity of BKM120 as measured by progression-free survival (PFS), overall survival (OS), objective response rate (ORR), duration of response, time to progression (TTP) and time to treatment failure (TTF). • To assess the safety and tolerance of BKM120 in this patient population. • To assess the 18F-FDG-PET changes reflecting the inhibition of the tumor metabolic activity.
Participating centres	• Centre Léon-Bérard, Lyon • Centre Oscar-Lambret, Lille • Centre Antoine-Lacassagne, Nice • Institut Curie, Paris • Institut régional du cancer de Montpellier • Hôpital Saint André , Bordeaux • Centre Hospitalier Lyon-Sud, HCL, Pierre-Bénite • Gustave Roussy, Villejuif
State of progress as of 31 March 2014	Of the 8 participating centres, 5 have already enrolled at least 1 patient of the 18 patients enrolled.

Continued >>

INCa-Pfizer collaboration	
Drug	**PD-0332991 – palbociclib: CDK 4/6 inhibitor**
Cycligist	
Coordinating investigator	Dr Antoine Italiano, Institut Bergonié (Bordeaux)
Title	Efficacy and Safety of PD-0332991 in Patients with Advanced Gastrointestinal Stromal Tumors Refractory to Imatinib and Sunitinib: A Phase 2 study
Number of patients	63 evaluable patients will be enrolled in 10 centres.
Main objective	To assess the antitumor activity of PD-0332991 in terms of non-progression at 16 weeks
Secondary objectives	• To evaluate the six-month non-progression rate. • To evaluate one-year progression-free survival. • To evaluate the objective response at six-months. • To evaluate one-year overall survival. • To evaluate the toxicity associated with PD-0332991 (NCI-CTC v4). • Pharmacogenomic analyses: to identify markers predictive of sensitivity to PD-0332991 using tumour samples from consenting patients.
Participating centres	• Institut Bergonié, Bordeaux • Centre Georges-François-Leclerc, Dijon • Centre Oscar-Lambret, Lille • Centre Léon-Bérard, Lyon • Hôpital de La Timone , Marseille • Centre Alexis-Vautrin, Nancy • Institut de Cancérologie de l'Ouest, Saint-Herblain • Hôpital Saint Antoine, AP-HP, Paris • Hôpital Robert Debré Reims • Gustave Roussy, Villejuif
State of progress as of 31 March 2014	Six centres are open for enrollment, and 3 patients are enrolled.
Optimum	
Coordinating investigator	Prof. Céleste Lebbé, Hôpital Saint Louis (Paris)
Title	An open label multicentre, phase I-II study with tumour molecular pharmacodynamics (MPD) evaluation and pharmacokinetics of PD-0332991 combined with vemurafenib in patients suffering metastatic melanoma with BRAF V600E/K mutated and CDKN2A loss defined by either low CDKN2A mRNA expression, or mutation or loss of CDKN2A gene (in accordance to Mac Arthur recent data ASCO 2012) and expression of Rb
Number of patients	40 evaluable patients will be enrolled in 5 centres.
Main objective	To establish the Maximum Tolerated Dose (MTD) of PD-0332991 in association with vemurafenib in patients with metastatic melanoma with BRAF V600E/K mutation and CDNKN2A loss defined by either low CDKN2A mRNA expression, or mutation or loss of CDKN2A gene
Secondary objectives	• To establish the biologically active dose based on pharmacodynamics and pharmacokinetics parameters of PD-0332991 combined with vemurafenib • To estimate the efficacy of this dose
Participating centres	• Hôpital Saint Louis, AP-HP, Paris • Hôpital Saint André, CHU Bordeaux • Centre Léon-Bérard, Lyon • CH Lyon Sud, HCL, Pierre-Bénite • Hôpital Hôtel-Dieu, CHU Nantes
State of progress as of 31 March 2014	Trial to open for enrollment shortly

Continued >>

Drug	PF-05212384 – PKI-587: PI3K/mTOR inhibitor
LAM-PIK	
Coordinating investigator	Dr Jacques Vargaftig, Institut Curie, Paris
Title	Phase II study to evaluate the efficacy and tolerance of double inhibition of the PI3K/AKT/mTOR pathway by PF-05212384 (PKI-587) in patients with myeloid haemopathy secondary to radiochemotherapy (t-AML/MDS) or de novo refractory or relapsed AML.
Number of patients	39 evaluable patients will be enrolled in 9 centres.
Main objective	To evaluate the efficacy of PF-05212384 (PKI-587) on the global response after a four month treatment, calculated by the proportion of complete responses, complete responses with incomplete recovery and partial responses, according to the IWG AML and MDS criteria (by Cheson BD)
Secondary objectives	• Tolerance and toxicity. • One-year progression-free survival. • Overall survival. • Quality of life.
Participating centres	• Institut Curie, Paris • CHU André-Mignot, Le Chesnay • Gustave Roussy, Villejuif • Hôpital Saint Louis, AP-HP, Paris • Institut Paoli Calmettes, Marseille • Hôpital Cochin, AP-HP, Paris • CHU Purpan, Toulouse • CHU Haut Lévêque, Pessac • CHU Hôtel-Dieu, Nantes
State of progress as of 31 March 2014	Protocol being finalised

Continued >>

INCa-Lilly collaboration	
Drug	**LY2780301: AKT inhibitor**
TAKTIC	
Coordinating investigator	Prof. Anthony Gonçalves, Institut Paoli-Calmettes, Marseille
Title	A prospective, multicentre, uncontrolled, phase Ib/II study of LY2780301 in combination with weekly paclitaxel in her2-negative metastatic or locally advanced breast cancer in patients with and without PI3/AKT/S6 pathway activation
Number of patients	Maximum of 18 patients for phase Ib, and then 55 patients for phase II, will be enrolled in 9 centres.
Main objective	• Phase Ib part: To determine the recommended phase II dose (RP2D) of daily LY2780301 when administered orally in combination with weekly intravenous (IV) paclitaxel in HER2-negative, inoperable locally advanced or MBC patients. • Phase II part: To estimate the efficacy of daily LY2780301 when administered orally at the RP2D in combination with weekly intravenous (IV) paclitaxel in HER2-negative, inoperable locally advanced or MBC patients, in the overall population and in patients with activation of PI3/AKT/S6 pathway
Secondary objectives	• To evaluate tolerance and safety of the combination. • To estimate clinical benefit and duration of response of the combination. • To estimate progression-free survival (PFS). • To determine pharmacokinetics of LY2780301 and paclitaxel.
Participating centres	• Institut Paoli Calmettes, Marseille • Centre Georges-François-Leclerc, Dijon • Institut Claudius Regaud, Toulouse • Institut de Cancérologie de l'Ouest, Saint-Herblain • Centre Léon-Bérard, Lyon • Hôpital Saint Louis, AP-HP, Paris • Institut Curie, Paris • Centre François-Baclesse, Caen • Hôpital Saint Louis, AP-HP, Paris
State of progress as of 31 March 2014	Three patients enrolled for the first dose level.
INPAKT	
Coordinating investigator	Prof. Jean-Charles Soria, Gustave Roussy, Villejuif
Title	A Phase 1b, open-label, dose escalation study of the safety, tolerability and efficacy of LY2780301 (a p70/Akt inhibitor) in combination with Gemcitabine in Patients with Advanced or Metastatic Cancer
Number of patients	6-12 patients in the dose escalation phase, and up to 32 patients in the dose expansion phase, will be enrolled in 4 centres.
Main objective	• Dose escalation: To determine the recommended phase2 dose of LY2780301 in combination with gemcitabine • Expansion cohort: To determine preliminary signs of anti-tumor activity among patients with ovarian cancer and among other cancer patients with molecular alterations of the PI3K/AKT/mTOR pathway. **Continued >>**

Secondary objectives	• To characterize the safety and toxicity profile ofLY2780301 when administered in combination with gemcitabine ; • To document any antitumor activity observed with LY2780301 in combination with gemcitabine in patients harbouring a molecular alteration of the PI3K/Akt/mTOR pathway (basket group and specific ovarian cancer group) ; • To document the progression-free survival (PFS) and response rate (RR) in patients with advanced or metastatic cancerafter treatment with LY2780301 and gemcitabine especially in patients harbouring a molecular alteration of the PI3K/Akt/mTOR pathway ; • To estimate the pharmacokinetic (PK) parameters ofLY2780301 when administered in combination with gemcitabine.
Participating centres	• Gustave Roussy, Villejuif • Institut Bergonié , Bordeaux • Centre Léon-Bérard, Lyon • Institute Paoli Calmettes, Marseille
State of progress as of 31 March 2014	Nine patients have been enrolled, and the 4 participating centres are active.
Drug	**LY2228820: P38 MAPK inhibitor**
Olympe	
Coordinating investigator	Dr Christelle Levy, Centre François-Baclesse, Caen
Title	A randomized open-label phase II multicenter trial assessing the efficacy and safety of tamOxifen plus LY2228820 in advanced or Metastatic breast cancer Progressing on aromatasE inhibitors
Number of patients	114 patients will be enrolled in 14 centres.
Main objective	• To evaluate the progression-free survival at six months.
Secondary objectives	• To evaluate the toxicity profile. • To evaluate progression-free survival. • To evaluate overall survival. • To evaluate the overall response rate • To evaluate the duration of response.
Participating centres	• Centre François-Baclesse, Caen • Institut Paoli Calmettes , Marseille • ICO (Institut de Cancérologie de l'Ouest), Nantes • Centre Henri-Becquerel, Rouen • Gustave Roussy, Villejuif • Centre Georges-François-Leclerc, Dijon • Institute Claudius Regaud, Toulouse • Institut Curie, site de Saint Cloud • Centre Léon-Bérard, Lyon • Centre Jean-Perrin, Clermont-Ferrand • Institut Bergonié , Bordeaux • Centre Eugène-Marquis, Rennes • Hôpital Saint Louis, AP-HP, Paris • Hôpital Européen Georges-Pompidou (HEGP), AP-HP, Paris
State of progress as of 31 March 2014	Protocol being finalised
GLYRad	
Coordinating investigator	Dr Xavier Durando, Centre Jean-Perrin, Clermont-Ferrand
Title	Phase I/II study of LY2228820 with radiotherapy plus concomitant TMZ in the treatment of newly diagnosed glioblastoma.
Number of patients	50 patients will be enrolled in 6 centres.
Main objective	• Phase I (dose escalation part) : To determine the recommended dose of LY2228820 in combination with TMZ and radiotherapy during chemoradiotherapy period • Phase II : To estimate the 6-month progression free survival (PFS) rate of patients treated with LY2228820 when administered at the recommended

	dose in combination with radiotherapy and concomitant TMZ
Secondary objectives	• To evaluate the tolerance profile for LY2228820 combined with temozolomide and radiotherapy. • To evaluate the twelve-month progression-free survival rate. • To evaluate the median progression-free survival. • To evaluate overall survival. • To evaluate the objective response rate. • To evaluate the patient's neurological status.
Participating centres	• Centre Jean-Perrin, Clermont-Ferrand • Centre Paul-Strauss, Strasbourg • Centre François-Baclesse, Caen • CHU d'Amiens • Centre Georges-François-Leclerc, Dijon • Institut Bergonié, Bordeaux
State of progress as of 31 March 2014	Protocol being finalised

Continued >>

INCa-Transgene collaboration: JX-594 METROmaJX	
Product	JX-594: oncolytic virus
Coordinating investigator	Dr Antoine Italiano, Institut Bergonié (Bordeaux)
Title	A phase I/II study of metronomic cyclophosphamide and the oncolytic poxvirus JX-594 in patients with advanced breast cancer and soft tissue sarcoma.
Number of patients	Maximum of 20 patients for phase Ib, and then 104 patients for phase II, will be enrolled in 7 centres.
Main objective	• Phase Ib: to establish the maximum tolerated dose and/or phase II recommended dose for JX-594 association with metronomic cyclophosphamide. • Phase II: to evaluate the antitumour activity of JX-594 combined with metronomic cyclophosphamide, in patients with advanced breast cancer or soft tissue sarcoma, in terms of improved objective response for breast cancers, and non-progression at six months for soft tissue sarcomas (RECIST v1.1).
Participating centres	• Institut Bergonié • Centre Léon-Bérard, Lyon • Centre Georges-François-Leclerc, Dijon • Gustave Roussy, Villejuif • Centre Oscar-Lambret, Lille • Institut Claudius Regaud, Toulouse • Institut de Cancérologie de l'Ouest, Saint-Herblain
State of progress as of 31 March 2014	Applications for regulatory authorisations in progress.

APPENDIX 2. OPINION OF THE ETHICS COMMITTEE

OPINION OF THE ETHICS COMMITTEE OF 27 JUNE 2011 ON RELATING TO INCA'S COLLABORATION WITH THE PHARMACEUTICAL INDUSTRY " ON ACCESS TO INNOVATIVE DRUGS"

The members of the ethics committee are in favour of the planned framework of the collaboration with the pharmaceutical industry to promote access to innovative molecules.

This framework should adhere to the following main principles:

1. Prior to signing with an industrial party, INCa undertakes to obtain the opinion of the experts committee of the INCa-certified early-phase clinical trial centres (CLIP²) on the interest of the molecule belonging to said industrial party and that would be provided to the CLIP² free of charge
2. INCa undertakes to conduct a call for proposals targeted to the CLIP²
3. INCa shall preselect the clinical trial projects submitted within the scope of this call for proposals and forward them to the industrial party
4. After receiving the industrial party's opinion, INCa shall select no more than two clinical trial projects per molecule from among the preselected projects
5. INCa undertakes to fund no more than two clinical trial projects thus selected
6. The industrial party undertakes to refrain from being involved in the conduct of the clinical trial and the analysis of the corresponding data
7. The sponsor, owner of the data and results of the clinical test, undertakes to forward them to the industrial party and to INCa. Prior to any communication to the public or publication relating to the clinical test, it undertakes to inform the industrial party and INCa accordingly
8. If the sponsor sells the data to the industrial party, the sponsor undertakes that:
   1°) the price takes into account in particular the grant paid by INCa
   2) the corresponding amount of the grant paid by INCa is reinvested in the early-phase clinical trials conducted in the CLIP²
   3°) INCa is informed accordingly.

APPENDIX 3. THE CLIP²

Centres labellisés	Etablissements	Coordonnateurs
Service des innovations thérapeutiques précoces de l'Institut Gustave Roussy	Institut Gustave Roussy CLCC VILLEJUIF	Pr Jean-Charles SORIA
Unité d'investigation clinique de l'Institut Curie	Institut Curie CLCC PARIS	Dr Véronique DIERAS
Centre d'essais précoces du centre Léon Bérard	Centre Léon Bérard CLCC LYON	Dr Philippe CASSIER
Unité essais précoces de l'Institut Bergonié	Institut Bergonié CLCC BORDEAUX	Dr Antoine ITALIANO
Unité de recherche clinique de l'Institut Claudius Regaud	Institut Claudius Regaud CLCC TOULOUSE	Pr Jean-Pierre DELORD
Unité de recherche clinique de phase précoce en hématologie du CHU Hôtel Dieu de Nantes	CHU de Nantes NANTES	Pr Philippe MOREAU
Unité de développement thérapeutique précoce du centre René Gauducheau	Institut de Cancérologie de l'Ouest SAINT-HERBLAIN	Pr Mario CAMPONE
Site des essais cliniques de phases I et II précoces du CHU de Bordeaux	CHU de Bordeaux TALENCE- BORDEAUX	Pr Alain RAVAUD
Centre d'essais précoces des services d'hématologie clinique et oncologie médicale du CH Lyon Sud	Hospices Civils de Lyon (HCL) LYON	Pr Bertrand COIFFIER
Centre d'investigations cliniques de l'hôpital Saint-Louis	Assistance Publique - Hôpitaux de Paris (AP-HP) -Hôpital Saint louis PARIS	Pr Jean-Jacques KILADJIAN
Unité « centre d'essais précoces en cancérologie (CEPEC) » du service d'oncologie médicale de l'hôpital européen Georges Pompidou	Assistance Publique - Hôpitaux de Paris (AP-HP) - hôpital européen Georges Pompidou PARIS	Pr Stéphane OUDARD
Unité de phase précoce du centre Georges-François Leclerc	Centre Georges-François Leclerc CLCC DIJON	Pr Pierre FUMOLEAU
Centre d'essais cliniques de phase précoce de l'Institut Paoli-Calmettes (IPC)	Institut Paoli-Calmettes CLCC MARSEILLE	Pr Norbert VEY
Unité de recherche clinique du centre Jean Perrin	Centre Jean Perrin CLCC CLERMONT-FERRAND	Dr Xavier DURANDO
Centre d'essais cliniques de phase précoce du centre Val d'Aurelle - Paul Lamarque	Institut régional du Cancer Montpellier CLCC MONTPELLIER	Pr Marc YCHOU
Unité de phases précoces du centre François Baclesse	Centre François Baclesse CLCC CAEN	Pr Florence JOLY-LOBBEDEZ

APPENDIX 4. ACRONYMS AND ABBREVIATIONS

AKT	Serine/threonine protein kinase B
AML	Acute myeloid leukaemia
AML	Acute myeloid leukaemia
ANSM	Agence nationale de sécurité du médicament et des produits de santé (French Medicine Agency)
AP-HP	Assistance Publique-Hôpitaux de Paris (Paris public hospital system)
ASCO	American Society of Oncology
CDK	Cyclin-dependent kinase
CFP	Call for proposals
CHU	Centre hospitalier universitaire (university hospital)
CLCC	Centre de lutte contre le cancer (comprehensive cancer centre)
CLIP²	Centre labellisé INCa de phase précoce (INCa-designated early-phase clinical trial centre)
CNS	Central nervous system
CPP	Comité de Protection des Personnes (Committee for Protection of Individuals)
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCTD	Division of Cancer Treatment and Diagnosis
ERK	Extracellular-signal-regulated kinase
GIPC	Group International Planning Committee
GIST	Gastrointestinal stromal tumour
GR	Gustave Roussy
HEGP	Hôpital Européen Georges-Pompidou (Georges-Pompidou European Hospital)
HER	Human epidermal receptor
HIV	Human immunodeficiency virus
HSP	Heat shock protein
ICO	Institut de Cancérologie de l'Ouest
ICR	Institut Claudius-Regaud (Claudius Regaud Institute)
IWG	International Working Group
JAK	Janus kinase
LOI	Letter of intent
MA	Marketing Authorisation
MAPK	Mitogen actived protein kinase
MDS	Myelodysplastic syndrome
MEK	Mitogen-activated extracellular signal-regulated protein kinase
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NCI	National Cancer Institute
PFS	Progression-free survival
PI3K	Phosphatidyl-inositol-tri-phosphate kinase
RAF	Rapidly Accelerated Fibrosarcoma
RECF	Registre d'Essais Cliniques Français en Cancérologie (French Registry of cancer research clinical trials)
RECIST	Response evaluation criteria in solid tumor
RP2D	Recommended phase II dose
STAT	Signal transducer and activator of transcription
UADT	Upper aerodigestive tract
VEGFR2	Vascular endothelial growth factor receptor 2

NOTES

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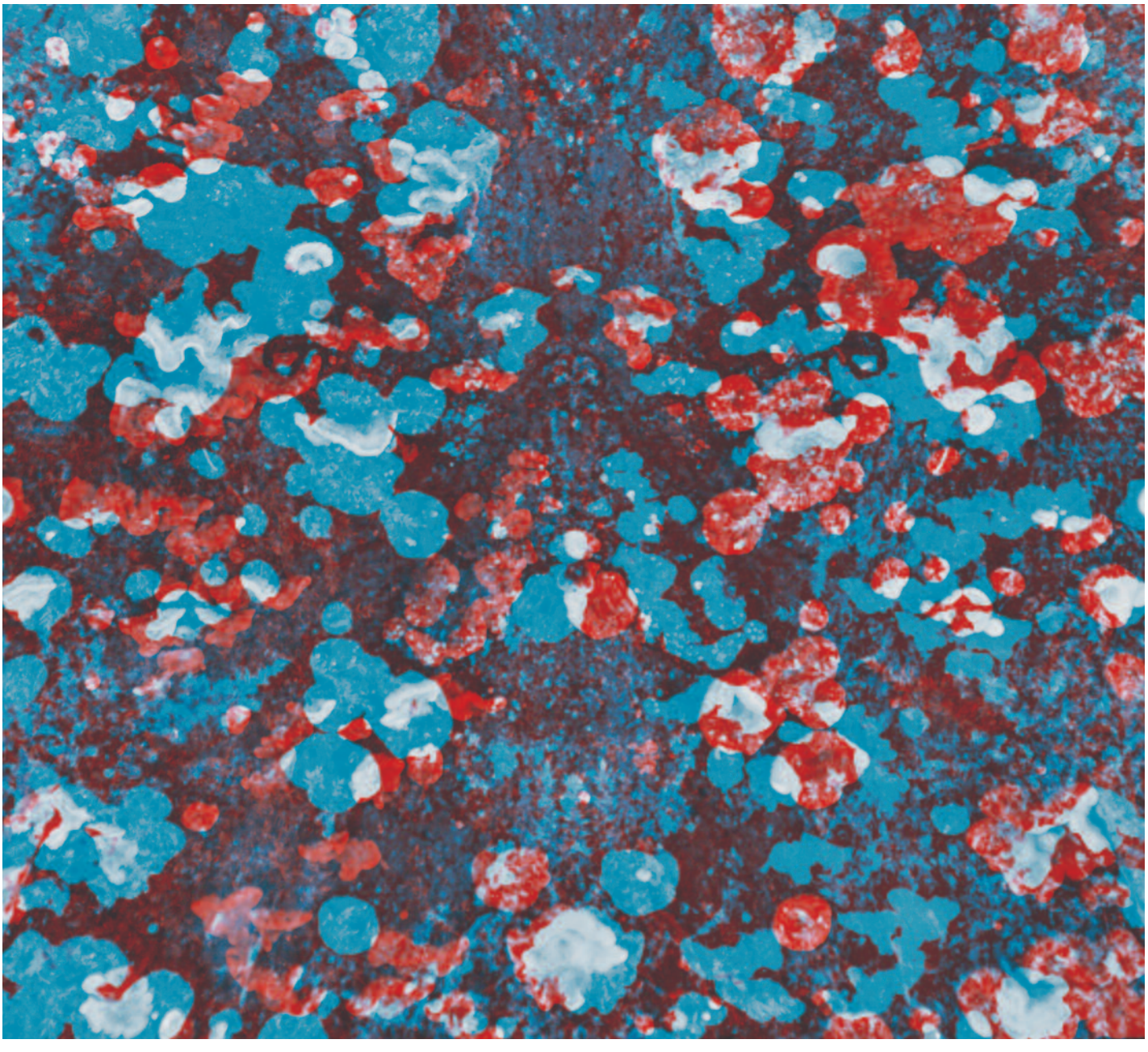

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