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SUPPORT FOR THE DECISION

FRENCH NATIONAL NETWORKS FOR RARE CANCERS IN ADULTS

/Review and Outlook

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INSTITUT NATIONAL DU CANCER

The French National Cancer Institute (INCa) is the agency for health and scientific expertise in oncology with responsibility for coordinating action on cancer in France.

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KEY FIGURES ON RARE CANCERS IN ADULTS

- **18 of 19 candidate networks designated by INCa in 2014** (14 national clinical networks and 4 national anatomopathology networks for rare cancers in adults)
- **Over 12,800 patients** with a rare cancer benefited from expert care from the time of diagnosis in 2013
- The **coverage rate** for all networks combined was **75%** in 2013
- Over 8,300 patient files were discussed at multidisciplinary consultative meetings (RCP) during initial care
- **7,800 tumour specimens** for sarcomas, rare malignant neuroendocrine tumours, malignant mesotheliomas and rare peritoneal tumours were reread in the RRePS, TENpath and MESOPATH dedicated anatomopathology networks
- **Over 8,800 cases of lymphoma** were reread in the LYMPHOPATH dedicated network
- **138 clinical trials** involved rare cancers in 2013
- **56 clinical trials** related specifically to a rare cancer rare were opened for enrolment in 2013, and recorded in the French Registry for Clinical Trials in Oncology
- **1,300 patients** with a rare cancer were enrolled in a clinical trial in 2013
- **12 projects** related to rare cancers were supported and funded by INCa in 2013
- **Over 28,500 cases** were recorded in the national databases established in **17 of the 23 clinical networks**
- **9,160 cases of lymphoma** were recorded in the LYMPHOPATH database in 2013
- **17 websites** are specifically devoted to rare cancers
- **26 patient associations** are involved in the specific organisation for rare cancers

1. BACKGROUND

The French National Cancer Institute (INCa) has, in association with the French Directorate-General for Care Provision (DGOS), been entrusted with organising care for adult patients with rare cancers, thus completing the arrangement of reference centres and centres of competence for rare diseases established by the French National Plan for Rare Diseases. INCa is an autonomous public institution created by the Public Health Policy (France) Act of 9 August 2004. It is the national agency for health and scientific expertise in oncology.

There is no international consensus on the definition of a rare cancer. Although a prevalence of less than 50/100,000 defines a rare disease, the definition of a rare cancer is based on a low incidence. Thus, based on analysis of the cancer registries by cancer location and histological subtype, an incidence rate below 6/100,000 is proposed in Europe, and below 15/100,000 in the United States. The organisational structure established in France specifically for rare cancers in adults is aimed at cancers with an annual incidence below 6/100,000 people on the one hand, and cancers that require highly specialised care due to their particular location, their occurrence in a specific context, or their complex nature on the other hand. Rare histological or molecular subtypes of frequently occurring cancers are not covered by this specific organisation.

Alongside this organisation for rare cancer, an organisation for double reading of lymphomas has been established, in light of the extreme diversity of histological subtypes, the existence of some rare forms, and the importance of diagnosing histological subtype in patient care. The results of this structuring have been analysed together.

France has had three Cancer Control Plans since 2003. Two actions of the 2009-2013 Cancer Control Plan were devoted to rare cancers, namely Action 23.1, “Certify rare cancer reference centres,” and Action 20.3, “Support the anatomo-cytopathology profession’s quality process.” This specific organisation for adult patients with rare cancers was established via four successive calls for proposals from INCa-DGOS, starting in 2009, and has resulted in the establishment of 23 national clinical networks, as well as 4 national anatomopathology networks (http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares/les-cancers-rares-pris-en-charge/doc_download/11405-cancers-rares-de-ladulte--une-organisation-specifique-en-france).

In 2014, the 19 networks structured in 2009 and 2010 (15 clinical networks and 4 anatomopathology networks) were invited to apply for INCa designation, a recognition of excellence following 4-5 years of activity. Eighteen of the 19 national networks that applied were designated at the end of 2014, while one network was not retained (Appendix 1). A new round of designation is planned for 2018, which will also include the eight more recently structured national networks for rare cancers in adults (Appendix 2).

Each national network for rare cancers in adults comprises a national expert centre (or reference centre) and regional or interregional expert centres (or centres of competence).

The **national clinical expert centre** is responsible for structuring the national network, arranging double reading of tumour specimens, structuring referral multidisciplinary consultative meetings, contributing to clinical research on these rare cancers, enabling drafting of recommendations for good practice and their dissemination throughout the network, establishing a national database to contribute to the observation of these cancers, organising training for all health professionals involved, working in collaboration with the patient associations, and providing relevant information to patients and those close to them (Appendix 3).

A **regional clinical expert centre** is responsible for adapting these roles at regional level, including organising a regional referral multidisciplinary consultative meeting, enrolling patients in clinical trials, training health professionals at regional level, and developing coordination with health facilities authorised to treat cancer in order to optimise the patient pathway (Appendix 4).

The **national anatomopathology networks for rare cancers** are responsible for organising the procedure for double reading of slides, as well as drafting national recommendations for helping to diagnose these rare cancers, promoting research studies (basic, translational and clinical research), participating in the training of pathologists, and participating in epidemiological surveillance and observation by creating national databases (Appendix 5).

Thus, any patients with one of these rare cancers should be able to receive care in the facility of his/her choice, while being guaranteed a reliable diagnosis through the anatomopathological double reading of his/her tumour, discussion of his/her patient file in a referral RCP, a choice of appropriate therapeutic strategy, often innovative as part of a clinical trial, and the support of a patient association.

The 2014-2019 Cancer Control Plan is continuing to put this specific organisation in place, and is expanding it to include complex care. One of the Plan's objectives is indeed to guarantee all patients appropriate care in terms of competence and expertise, in order to avoid missing an opportunity, and to ensure fairness throughout the French national territory, regardless of where care is taking place.

Organisation for rare cancers in adults now has the benefit of annual funding of nearly €6 million under the French Social Security Finance Act (LFSS) for missions of general interest (MIGAC) (Assurance Maladie funding).

2. OBJECTIVE

This report monitors the specific organisation for rare cancers in adults in 2014, when the networks structured in 2009 and 2010 were designated.

It differs from the annual activity reports published every year since 2010, the last of which appeared in 2012 (http://www.e-cancer.fr/component/docman/doc_download/11402-organisation-prise-en-charge-patients-adultes-k-rares-bilan-activite-2012). Indeed, it includes not only quantitative activity data, but also includes qualitative data on patient care, as they appear in the application for designation.

It also presents the outlook for future developments that will be implemented in cooperation with all relevant stakeholders, during the 2014-2019 Cancer Control Plan, in order to further optimise the care of these patients.

It is intended for the relevant French Government ministries (Ministry of Social Affairs, Health, and Women's Rights, and the Ministry of Higher Education and Research), the regional health agencies, the French National Institute of Health and Medical Research (INSERM), ORPHANET, the French National Authority for Health, all health professionals involved in this specific organisation, the regional oncology networks, patient associations, and more widely the entire medical community (oncologists, radiotherapists, organ specialists, hospital-based and independent anatomopathologists, surgeons, general practitioners and researchers).

3. METHODOLOGY

Assessment of the 19 networks applying for designation (structured in 2009 and 2010), detailed in Appendix 6, comprised the following:

- a self-assessment, based on a self-assessment scoring sheet, completed by the candidate coordinator;
- an independent external assessment by an international jury.

The self-assessment scoring sheet, broadly based on the scoring sheet used in the centres of reference for rare diseases drafted under the aegis of the French National Authority for Health (HAS), included a summary of the missions of these national networks for rare cancers, a description of their implementation, measurement by quantitative and qualitative indicators of the degree to which these missions had been accomplished, and proposals for improving this scheme.

External assessment was done by a consultative committee of experts (CCE) composed of eight rapporteur members, who were recognised French and foreign individuals in the area of rare cancers, and not involved in the specific organisation in France.

Alongside this assessment of networks for designation purposes, **monitoring of the other 8 networks** structured in 2010 and 2011 continued, based on a monitoring questionnaire sent to each of the coordinators.

For this report, several sources of data were used:

- mainly self-reported data, both quantitative and qualitative, for completion of the self-assessment scoring sheet by the coordinators of each network applying for designation, and in the monitoring questionnaire for the other 8 networks;
- supplemented by analysis of the INCa database of calls for proposals, and the INCa registry of clinical trials in oncology.

The outlook for future development of the specific organisation for rare cancers stems from areas for improvement proposed by the coordinators in the self-assessment scoring sheet, from which all the networks may benefit.

4. CLINICAL ACTIVITY IN ALL OF THE RARE CANCER NETWORKS IN 2013

Clinical activity may be assessed by the number of new patients receiving care by the rare cancer structure over the year, the number of patient files discussed at referral RCP at the initiation of cancer treatment, the number of tumour specimens examined in a second anatomopathological reading to confirm the diagnosis of a rare cancer, and the type and number of recommendations or guidelines for care drawn up and disseminated by the national networks for rare cancers.

4.1. Activity in terms of new patients in 2013 and rate of coverage

A new patient in 2013 is a patient diagnosed with cancer during the year 2013. This activity varies greatly depending on groups of rare cancers, as shown in Table 1.

Table 1. Number of new patients who received care in 2013, by network

Type of rare cancer	Number of new patients 2013	Estimated incidence
Soft tissue and visceral sarcomas – Clinical	3,526	4,000
Rare sporadic and hereditary malignant neuroendocrine tumours – Clinical	1,592	1,200
Rare ovarian cancers	951	500
Cutaneous lymphomas	919	700
Osteosarcomas	521	630
Rare ENT cancers	486	900
Uveal melanomas	380	600
Primary ocular and brain lymphomas	287	350
Adrenal cancers	284	125
Malignant pleural mesotheliomas	267	900
Refractory thyroid cancer	255	400
High-grade oligodendrogliomas	285	600
Rare brain tumours	202	1,800
Rare skin cancers (other than cutaneous sarcomas)	131	950
Von Hippel-Lindau disease and other hereditary predispositions to renal cancer	120	200
Gestational trophoblastic tumours	118	180
Thymomas and thymic carcinomas	113	250
Gestational cancers	99	500
Rare peritoneal tumours	74	150
Lymphomas associated with coeliac disease	52	350
Rare renal cancers	31	1,000
Virally induced cancers in transplant recipients	31	110
Cancers in HIV+ subjects	0	700
Combined total	**12,832**	**17,095**

Thus **in 2013, over 12,800 patients with a rare cancer benefited** from expert care. In 2012, this figure was 8,100 (+58%).

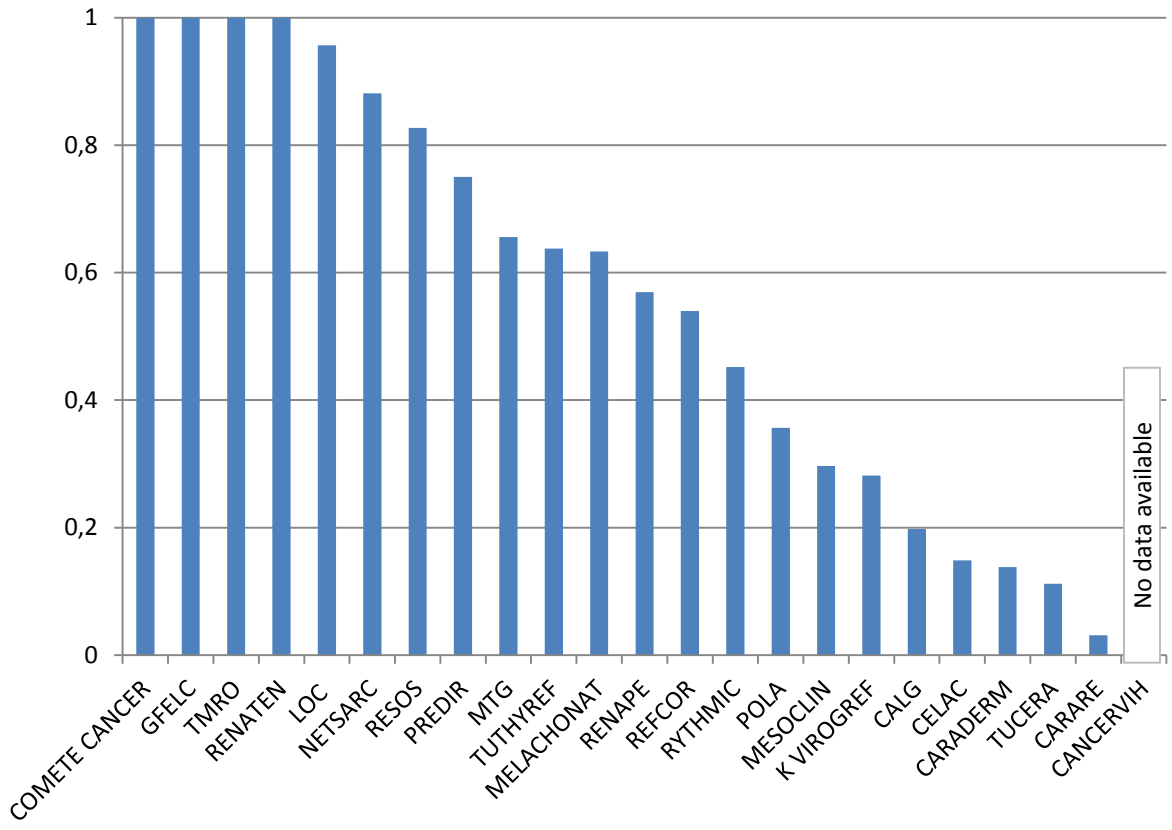
We observe a large variability among the different networks, from 3,500 new patients in the NETSARC network to approximately thirty new patients in the K-VIROGREF or CARARE networks.

Most of these new patients had their cases discussed at a referral RCP. However, for some pathologies, discussion is not systematic, and only the patient data are recorded in a dedicated national database.

The rate of coverage for a rare cancer network in 2013 is the ratio of the number of new patients (diagnosed with a rare cancer in 2013) who had access to expert review (file presented at a referral RCP and/or recording of the case in the national database) to the annual incidence (which is still usually an estimate of the incidence, since most cancer registries do not include data from patients with rare cancers).

Figure 1 illustrates the estimated rate of coverage of the national networks for rare cancers in 2013, based on the incidence estimated and provided by the coordinators when submitting initial proposals in 2009 and 2010.

Figure 1. Rate of coverage for the national clinical networks in 2013



The overall rate of coverage by the specific organisation for rare cancers, all networks combined, was 74.6% in 2013. However, it varies considerably between the networks. Although eight national reference networks have very good coverage, with over 70% of new patients discussed at a referral RCP or recorded in the corresponding databases, eight, on the other hand, have highly inadequate coverage, with fewer than 30% of patients having benefited from this specific organisation in 2013. However, six of these networks have only been structured in the last 1-2 years.

Nonetheless, these percentages should be interpreted with caution. Thus, for example, the TMRO network (rare ovarian cancers) had initially included all "borderline" tumours[1] in the list of pathologies under its care. It has been decided to include only "borderline" tumours with invasive

[1] Epithelial tumour of the ovary, on the borderline between benign and malignant

implants. In 2013, 162 borderline tumours were recorded, and 95 other tumours (including 50 carcinosarcomas, 14 low-grade serous tumours and 10 transitional cell tumours). The overall estimated incidence of 900 cases per year is therefore overestimated, and probably closer to 750 cases/year.

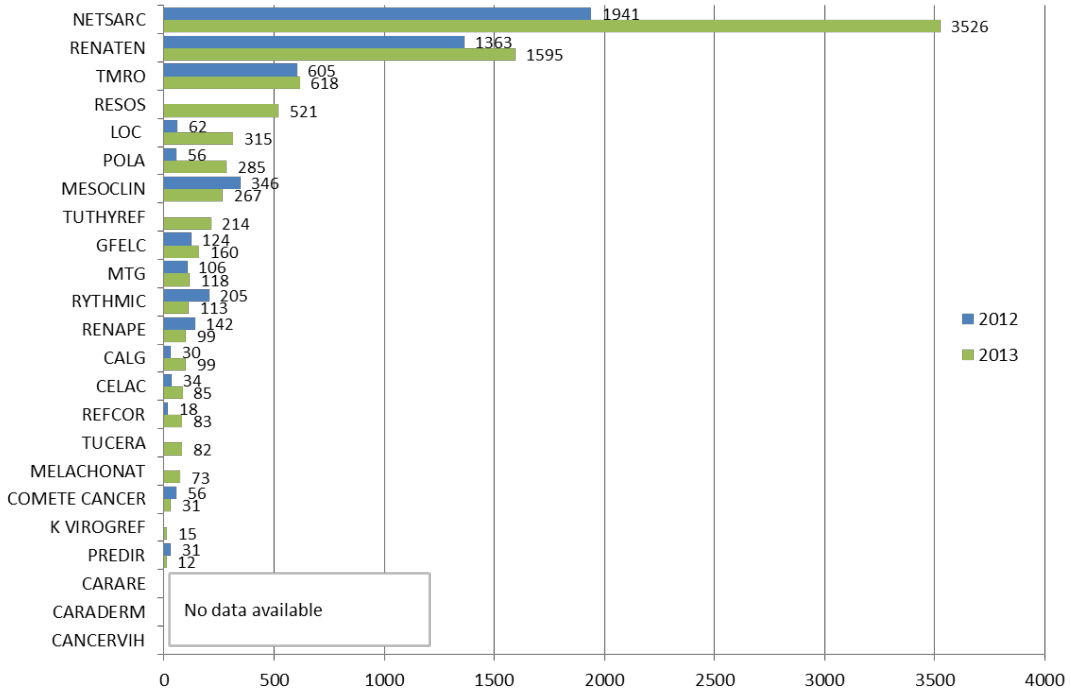
The annual incidence of high-grade oligodendrogliomas, estimated at 600 in 2009, also seems overestimated, with the actual incidence seeming closer to 350-400 cases/year in France. The coverage rate of the POLA network may be close to 80%.

The 284 new patients with adrenal cancer (COMETE-Cancer network) include 150 with malignant tumours (99 adrenocortical carcinomas and 51 malignant phaeochromocytomas and paragangliomas) and 134 with phaeochromocytomas and paragangliomas of uncertain malignancy, since the latter were not included when estimating annual incidence.

4.2. Activity in terms of referral RCP

The workload for all rare cancer experts involved in referral RCP, whether at national or regional level, varies greatly (Figure 2).

Figure 2. Trend in the total number of new patients discussed at referral RCP



This activity has clearly been growing since 2012, going from 5,865 new patients with rare cancers discussed at a referral RCP in 2012, to 8,311 in 2013 (+42%). It consumes a lot of time and resources, requiring a large number of experts for every referral RCP, especially as the patient file is often discussed not only at diagnosis, but also as the disease progresses.

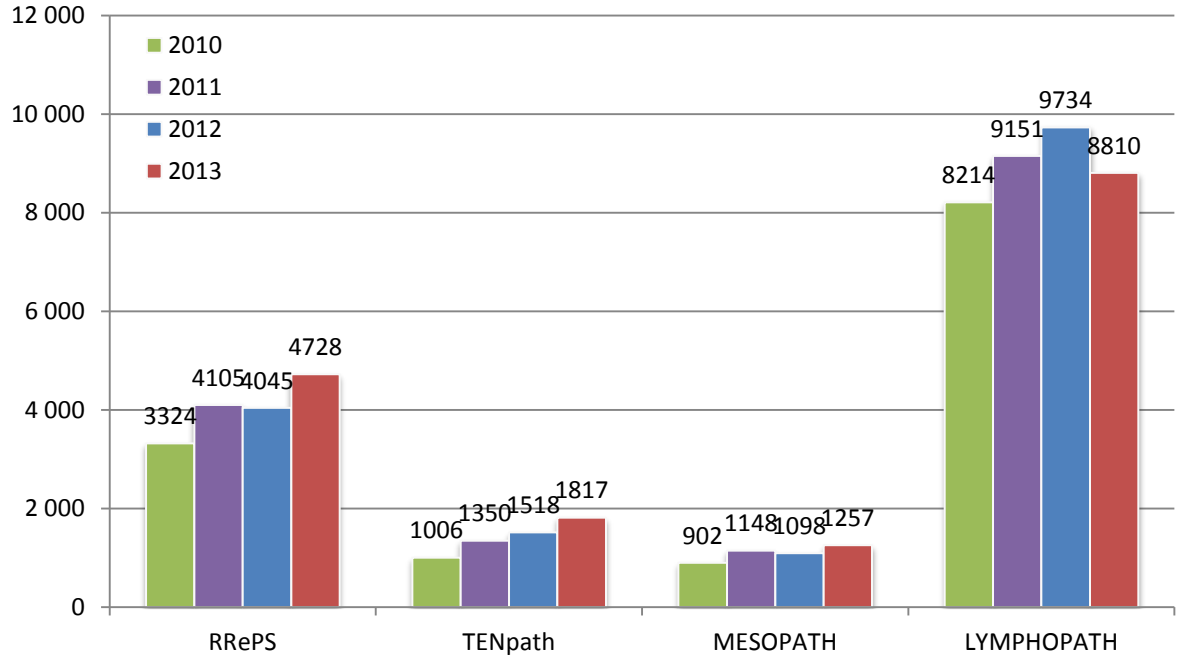
However, it remains inadequate in many networks. Here again, it is difficult to estimate the referral RCP activity in all the regional expert centres comprising a network. Better characterisation of the referral RCP and computerisation of the RCP file should enable a better assessment of this activity in future.

4.3. Double reading activity for tumour specimens within the four national anatomopathology networks in 2013

The main role of the four national anatomopathology networks listed in Appendix 1 is to provide systematic double reading of tumour specimens from cases of soft tissue and visceral sarcomas (RRePS network), rare malignant neuroendocrine tumours (TENpath network), malignant pleural or peritoneal mesotheliomas and other rare peritoneal tumours (MESOPATH network), and all cases of lymphoma (LYMPHOPATH), on a daily basis.

As shown in Figure 3, this double reading activity also increased from 2012 to 2013 in the RRePS network (+17%), the TENpath network (+28%) and the MESOPATH network (+14%), but is stabilising for lymphomas (-10%) (data regarding cutaneous lymphomas will be analysed later), with a total of 16,612 cases reread.

Figure 3. Trend in the number of patients who benefited from a double reading of tumour specimens within the four national anatomopathology networks for rare cancers in adults



When they are not taken within one of the expert centres comprising the network, these specimens are referred to one of the expert pathologists from the network for validation (confirmation) of the diagnosis, or more rarely for an opinion (second opinion), where no diagnosis has been made.

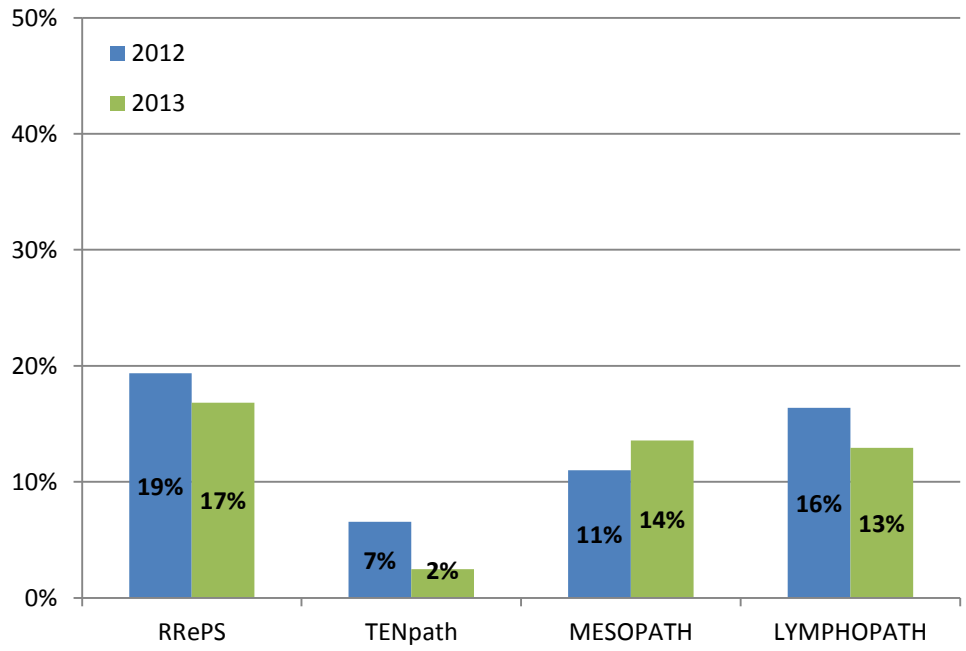
The **impact of double reading within the networks** is measured as the percentage of cases where the final diagnosis, after double reading, changes the initial care. This analysis is performed by the national anatomopathologist coordinator; it relates to all external cases referred to the network for double reading, whether for an opinion or confirmation. Criteria are defined in Table 2.

Table 2. Definition of results of double reading of tumour specimens in the four anatomopathology networks that have an impact on care

	RRePS	TENpath	MESOPATH	LYMPHOPATH
Definition of diagnostic modifications with an impact on care	Sarcoma vs benign tumour	Neuroendocrine vs non-neuroendocrine tumour	Mesothelioma vs metastatic carcinoma	Lymphoma vs benign lesion
	Sarcoma vs other neoplasia	Differentiated vs undifferentiated tumour	Mesothelioma vs sarcoma	Lymphoma vs nonlymphoid malignant tumour
	GIST vs non-GIST		Mesothelioma vs benign tumour	Lymphoma vs other haemopathy
	Desmoid vs non-desmoid tumour			

Results of this analysis are represented schematically in Figure 4.

Figure 4. Impact of double reading of specimens in the anatomopathology networks in 2012 and 2013 (as percentage of initial care plans that were subsequently modified)



The impact in 2013 was thus assessed at 17% (562 patients) in the RRePS network, 2% (23 patients) in the TENpath network, 14% (139 patients) in the MESOPATH network, and 13% (1,140 cases) in the LYMPHOPATH network.

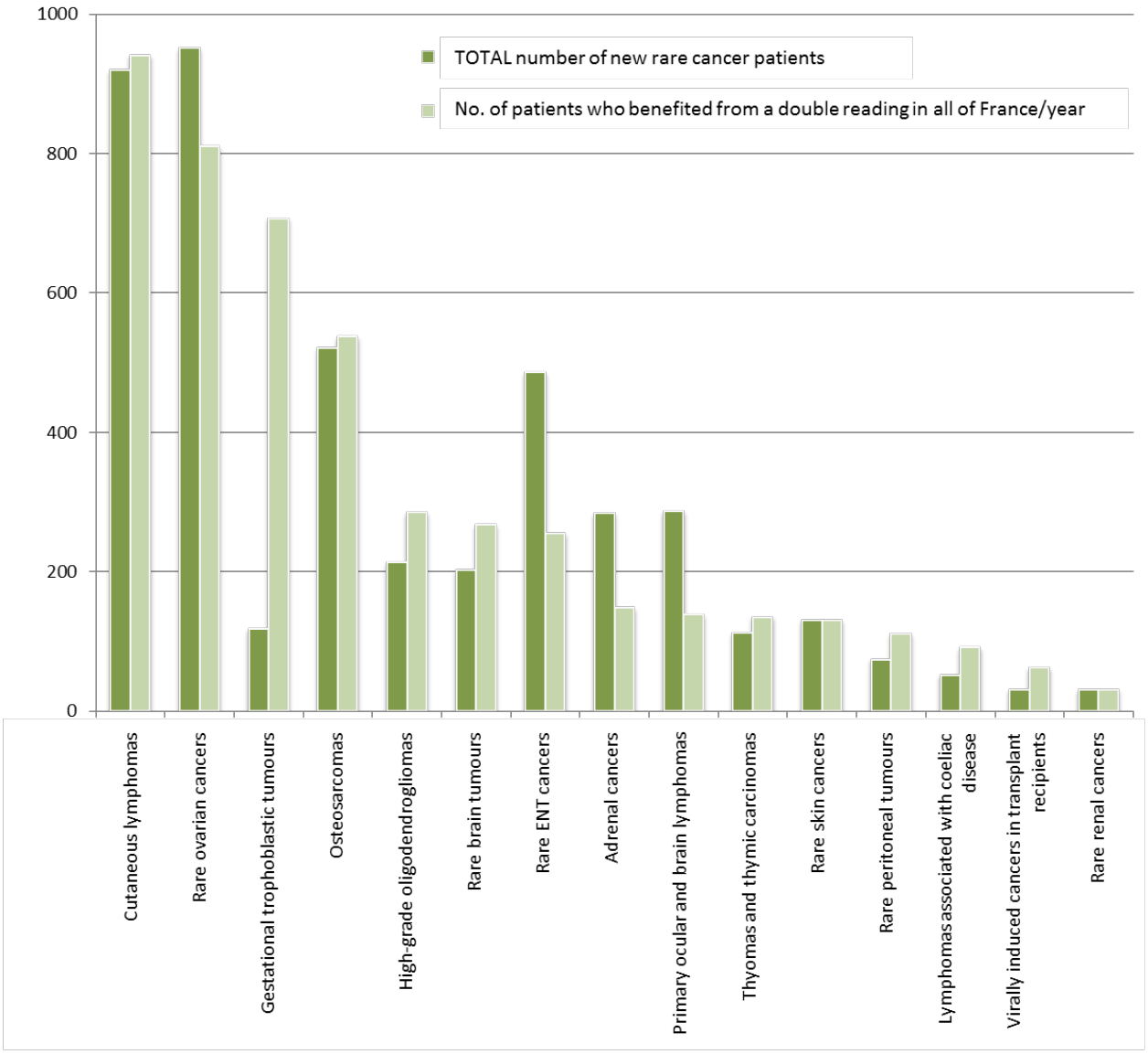
4.4. Anatomopathological double reading activity for tumour specimens from other rare cancers

Anatomopathological double reading activity for other rare cancers is incorporated into the corresponding clinical network, and provided by a small group of expert pathologists. Five networks are not involved in this double reading activity, since the diagnosis is undisputed, as the cancers are common, although they occur in a particular context or location; these are the TUTHYREF (refractory thyroid cancers), PREDIR (von Hippel-Lindau disease and other hereditary predispositions to renal

cancer in adults), CALG (gestational cancers), MELACHONAT (uveal melanomas) and CANCERVIH (cancers in HIV seropositive subjects) networks.

Figure 5 illustrates this activity for the 15 networks in question.

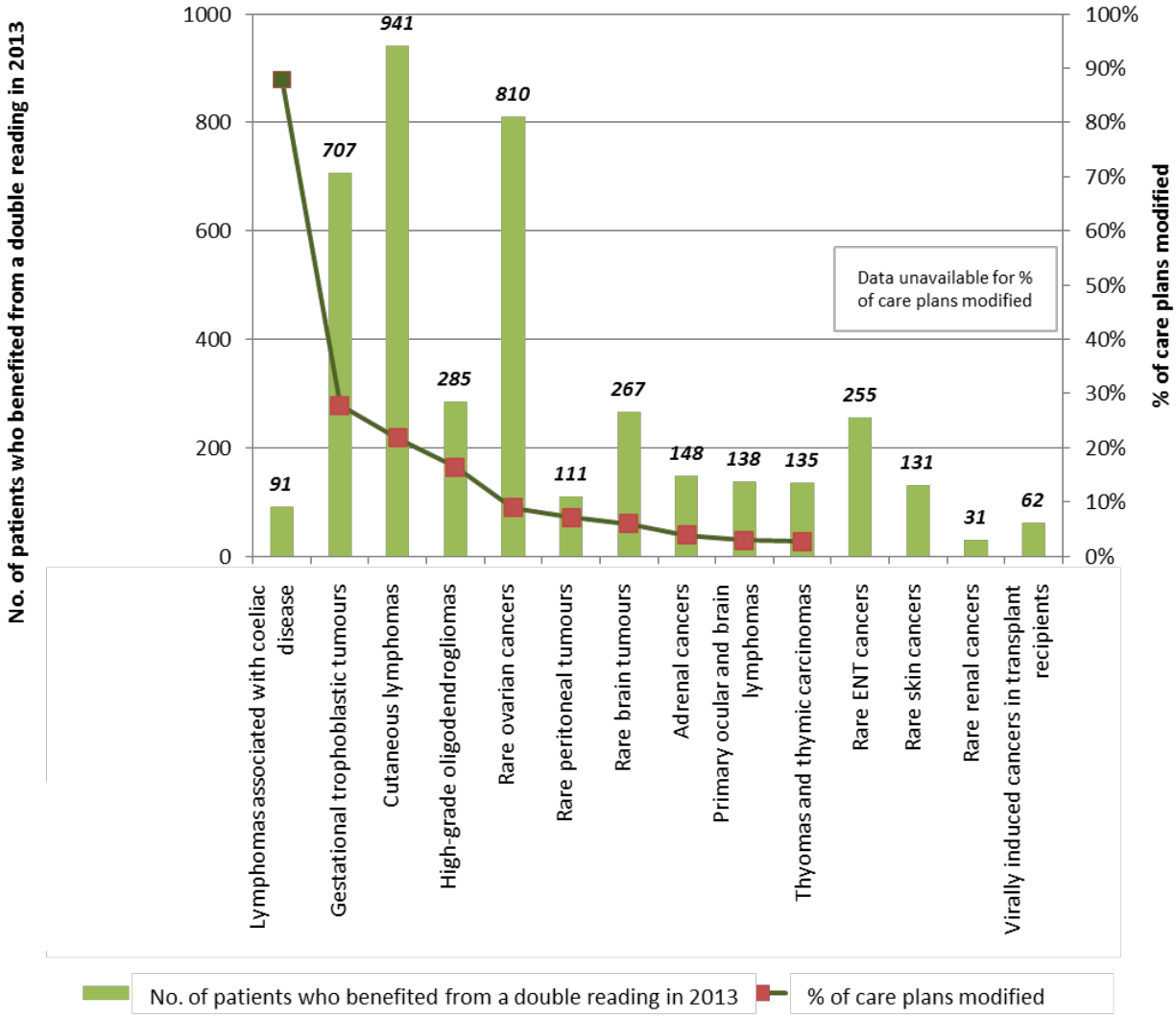
Figure 5: Double reading activity for tumour specimens from other rare cancers in 2013



Thus 4,412 tumour specimens from rare cancers were subjected to double reading within the clinical networks in 2013. The number of tumour specimens referred for a double reading may be higher than the number of new patients; thus, 285 cases were referred for confirmation of diagnosis of high-grade oligodendroglioma, but the diagnosis was confirmed for only 214 patients. In the MTG network (national network for gestational trophoblastic tumours), double reading generally relates to cases of hydatidiform mole, totalling 627 new cases/year, as against only 117 cases of gestational trophoblastic tumours.

The impact of this double reading on these rare cancers is outlined in Figure 6.

Figure 6: Impact of double reading of tumour specimens for other rare cancers in 2013 (percentage of initial care plans that were subsequently modified)



The impact of establishing double reading can be currently assessed for only four pathologies: rare ENT cancers (255 cases), rare skin cancers (131 cases), rare renal cancers (31 cases) and virally induced cancers in transplant recipients (62 cases). The 88% impact on lymphomas associated with coeliac disease affects 91 cases, but the diagnosis is only retained in 52 cases.

Although the impact is major for rare lymphomas associated with coeliac disease, and substantial for cutaneous lymphomas, oligodendrogliomas and rare ovarian cancers, it is low for adrenal cancers and brain lymphomas, and the systematic nature of double reading for these pathologies deserves to be reviewed. Moreover, double reading of tumour specimens is not systematic for thymomas or thymic carcinomas, which seems justifiable given the 3% level of modification of care for the 135 cases reread.

Analysis of the impact of double reading in the MTG network (gestational trophoblastic tumours) is more difficult, since hydatiform moles are subject to double reading, while the diagnosis of gestational trophoblastic tumours most often relies on a biological assay.

4.5. Guidelines and recommendations for care

Framing good practice for patients with rare cancers is vital to ensure quality and fairness of care throughout the national territory.

Many documents have been produced and disseminated among the national clinical and anatomopathology networks for rare cancers in adults.

International recommendations of the American Thyroid Association have been translated and validated by the experts for thyroid cancers (TUTHYREF network for refractory papillary cancers, metastatic medullary cancers, and anaplastic cancers).

All the experts from the TMRO network (rare ovarian cancers) participated as authors or co-authors of the consensus recommendations for care of rare ovarian tumours proposed by the Gynecologic Cancer intergroup (GCIG), and published in the *International Journal of Gynecological Cancer* in 2013.

European recommendations (European Society of Clinical Oncology (ESMO) guidelines 2012) endorsed by all French experts provide the basis for diagnosis (RRePS network) and care of soft tissue and visceral sarcomas (NETSARC network) and osteosarcomas (RESOS network).

In 2012, ENETS (European Neuroendocrine Tumor Society) published "Consensus Guidelines" for the diagnosis and treatment of various neuroendocrine tumours, which should be translated and endorsed by all experts from the TENpath network. Care of rare neuroendocrine tumours currently relies on guidelines published by the French Society of Endocrinology (SFE) and the Endocrine Tumour Group (GTE) (RENATEN network).

Guidelines for the anatomopathological diagnosis of malignant mesothelioma were updated in 2012, but their endorsement by all French experts from the MESOPATH network is not specified.

A recommendation made by the MTG network for the care of gestational trophoblastic disease was given HAS/INCa approval and published in 2010.

National recommendations for good practice (or national guidelines), validated by all the experts, have been written and disseminated for the care of patients with primary lymphomas of the central nervous system (2013, LOC network), Merkel cell tumours (2011, CARADERM, K-VIROGREF, CANCERVIH network), high-grade oligodendrogliomas (2010, POLA network), low- and high-grade gliomas (2010, TUCERA network), rare ENT cancers (malignant tumours of the ear, salivary glands, nasal cavity and sinuses and upper aerodigestive tract excluding common squamous cell carcinoma) (2009, REFCOR network), thymomas and thymic carcinomas (2012, RYTHMIC network), rare ovarian cancers (TMRO), post-transplant lymphomas (K-VIROGREF) and malignant pleural mesotheliomas (2013 MESOPATH and 2005 MESOCLIN). Recommendations were published in 2010 for the care of cutaneous T-cell and B-cell lymphomas (GFELC network).

Two online thesauri for adrenal cancers have been published on the website of the COMETE-Cancer adrenal cancer network.

Recommendations of the PREDIR network regarding genetic diagnosis and clinical care of hereditary predisposition to renal cancer were published in 2013, in association with the oncology committee of the French Association of Urology (AFU). Specific international recommendations for renal tumours in patients with hereditary leiomyomatosis were defined at the international Symposium organised by the national coordinator of the PREDIR network in Paris in June 2013, and published in 2014.

These recommendations for good practice and these national guidelines make it possible, in theory, to harmonise practices throughout the national territory and ensure equity of care for all patients. Surveys must be done to assess the dissemination of these documents, their daily use, and the adherence of professionals to these recommendations.

Although the initial procedures for diagnosis and care are clearly defined for most rare cancers, recommendations for follow-up exist for only a few of these pathologies, such as von Hippel-Landau disease (2013, PREDIR network).

5. RESEARCH ACTIVITY

Assessment of research activity relies mainly on self-reported data from the project coordinators, supplemented by analysis of the INCa database of calls for proposals, and of the INCa registry of clinical trials in oncology.

5.1. Translational studies (coordinators' data)

Table 3 summarises the number of translational studies in the structured rare cancer networks in 2013.

Table 3. Number of translational studies by the rare cancer networks in 2013

Name of rare cancer network	Number of translational studies begun or ongoing	Number of translational studies completed
MTG	0	0
TENpath	0	0
CALG	0	0
CANCERVIH	0	0
CARADERM	0	0
CARARE	0	0
K VIROGREF	0	0
TUCERA	0	0
RYTHMIC	0	1
MESOCLIN	0	7
GFELC	1	0
MELACHONAT	1	3
PREDIR	3	0
MESOPATH	4	0
RESOS	4	0
REFCOR	4	0
CELAC	5	3
TUTHYREF	6	0
TMRO	7	2
RENAPE	8	2
LOC	10	3
COMETE CANCER	11	11
POLA	12	4
RENATEN	13	0
LYMPHOPATH	14	0
RRePS and NETSARC	39	34
Total	**142**	**70**

We count a total of 142 translational studies started or ongoing, 30% of them in the sarcoma networks (NETSARC, RRePS and RESOS), and 70 translational studies completed in 2013, 49% of them in the sarcoma networks.

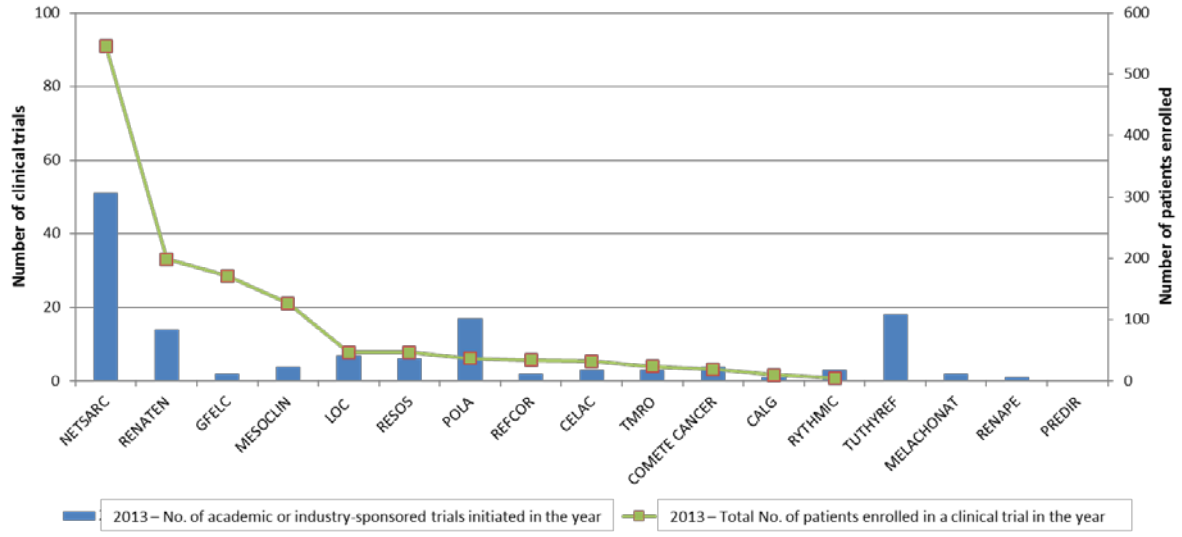
These figures have clearly increased in a year (+86% for studies started or ongoing, and +141% for studies completed).

5.2. Clinical trials in rare cancers and number of patients enrolled (coordinators' data)

The organisation for rare cancers with discussion of files at referral RCP and/or recording of cases in national databases acts as a lever for encouraging clinical trials, and facilitating access to innovative treatments.

Thus, in 2013, 138 clinical trials were started, ongoing or completed in the year, with a variable distribution depending on the network (see Figure 7). We counted 89 in 2012 (+55%).

Figure 7. Number of ongoing clinical trials in 2013, and numbers enrolled per network in 2013



The total number of enrolments in a clinical trial in 2013 is 1,298 patients with a rare cancer (largely unchanged compared with 2012).

The TUTHYREF network is a highly active network, with many clinical trials submitted by the network overall, but the number of patients enrolled within the network had not been reported at the time of writing this report.

5.3. Analysis of the INCa database of calls for proposals

Analysis of the **INCa database of calls for proposals** shows 12 projects on rare cancers supported and funded by INCa in 2013 (Table 4).

Table 4. Research projects on rare cancers started and funded by INCa in 2013

Type of CFP	Rare cancers	Title	Proponent	Proponent institution
BCB	Rare peritoneal cancers (RENAPE)	BIG-RENAPE: Clinical and biological database of peritoneal carcinomatoses of digestive origin	Olivier GLEHEN	Lyon General Hospitals (HCL)
GC	Sarcomas (NETSARC – RESOS – RRePS)	INTERSARC Cooperative Intergroup	Jean-Yves BLAY	French Sarcoma Group – Osteosarcoma Study Group (GSF-GETO)
CLIPP	Soft tissue sarcomas (NETSARC – RRePS)	METROmaJX: Phase Ib/II trial on advanced breast cancers and soft tissue sarcomas	Antoine ITALIANO	Bergonié Institute

Type of CFP	Rare cancers	Title	Proponent	Proponent institution
PHRC	Rare neuroendocrine tumours (RENATEN)	GEP-NOC: impact of [68Ga]-DOTANOC PET-CT on digestive neuroendocrine tumours	David TAIEB	Marseille University Hospital – La Timone Hospital
PHRC	GIST (NETSARC – RRePS)	GI-GIST: randomised trial of imatinib as adjuvant therapy for intermediate risk GIST	Sébastien SALAS	Marseille University Hospital – La Timone Hospital
PHRC	Anaplastic gliomas (POLA)	POLCA PCV alone versus radiotherapy and adjuvant PCV for anaplastic gliomas with 1p/19q co-deletion	Jean-Yves DELATTRE	Pitié Salpêtrière Hospital Group
PHRC	Rare skin cancers (CARADERM)	Phase II: somatostatin analogue for advanced Merkel cell carcinomas	Marie-Thérèse LECCIA	Grenoble University Hospital
PHRC	Rare brain tumours (TUCERA)	Everolimus octreotide for aggressive and progressive meningiomas	Thomas GRAILLON	Marseille University Hospital – La Timone Hospital
PHRC	Refractory thyroid cancers (TUTHYREF)	THYGEMOX01: Phase II, gemcitabine and oxaliplatin chemotherapy	Laurence LEENHARDT	Pitié Salpêtrière Hospital Group
PHRC	Malignant pleural mesotheliomas (MESOCLIN)	MESOPDT: Phase II multimodal treatment with extended pleurectomy/extensive decortication (eP/D), intraoperative photodynamic therapy and adjuvant chemotherapy	Arnaud SCHERPEREEL	Albert Calmette Hospital
PHRC	Primary lymphomas of the central nervous system (LOC)	BLOCAGE-01: Phase III, maintenance treatment versus surveillance following a complete response to first-line chemotherapy based on high-dose methotrexate in older patients	Khê HOANG-XUAN	Pitié Salpêtrière Hospital Group
PHRC	Rare tumours of the central nervous system (TUCERA)	"PROTONCHORDE01" cranial base and spine chordomas, surgery and proton therapy monitored by 18F- FAZA PET-CT	Hamid MAMMAR	Institut Curie

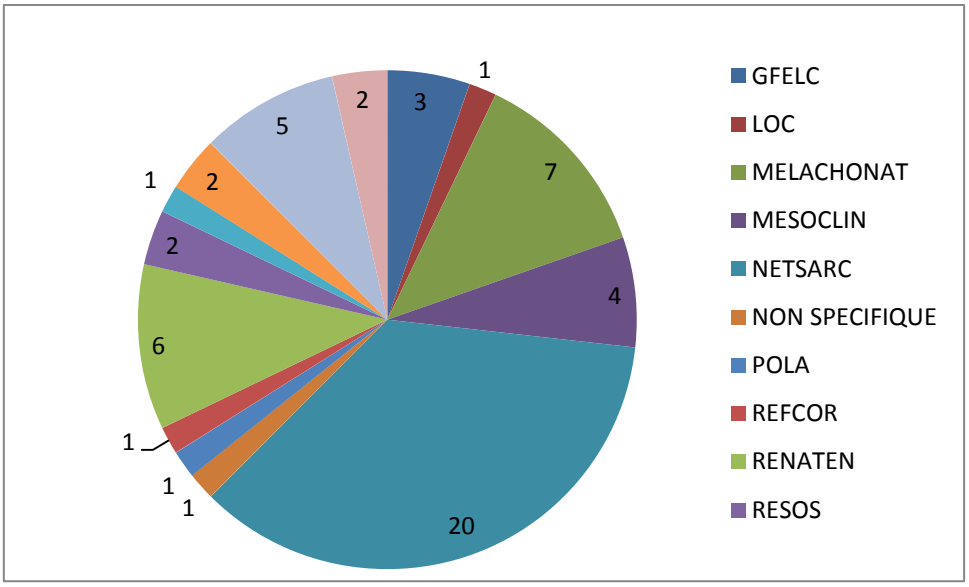
BCB: clinical and biological database – GC: cooperative intergroup – CLIP2: designated early-phase clinical trial centre – PHRC: hospital clinical research programme

Projects in the area of rare cancers, aimed at helping to structure clinical research as well as helping to access innovative treatments, were thus funded for a total amount of €4.7 million in 2013.

5.4. Analysis of the French Registry for Clinical Trials in Oncology

The analysis covers clinical trials open as of 31 December 2013. It has counted 56 clinical trials open for enrolment in 2013, distributed among 8 early phase clinical trials, 32 Phase II trials, 11 Phase III trials, and 10 trials in Phase IV or of no phase. These trials are sponsored by the cancer centres (22), university hospitals (10), cooperative groups (140) and industry (10). Fifteen pathologies structured into networks for rare cancers in adults had at least one open clinical trial in 2013. Figure 8 shows the distribution of these trials among the different rare cancer networks.

Figure 8. Distribution of clinical trials recorded in 2013 related to one or more specific network-based rare cancer themes



We have found a large predominance of trials on sarcomas, which have an incidence of approximately 5,000 patients; however, even some very rare cancers are the subject of several clinical trials.

The number of 56 trials in the registry and 138 declared by the coordinators may reflect a certain delay in the recording of trials in the registry, and probably a more restrictive analysis of data from the registry.

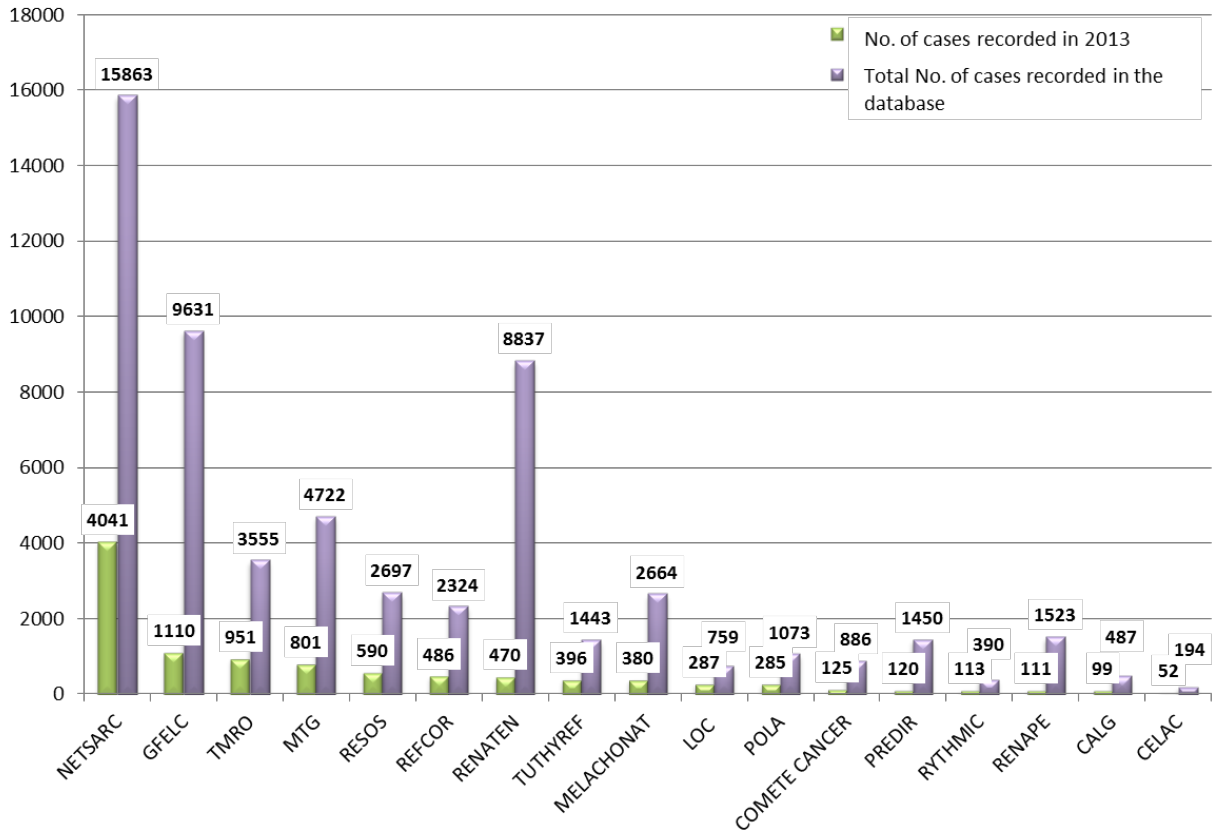
6. OBSERVATION – ANALYSIS OF NATIONAL AND INTERNATIONAL DATABASES

Epidemiological surveillance is essential for improving the knowledge of these rare pathologies. Moreover, most of them are excluded from the general cancer registries. And the few cases included in these registries do not include diagnostic certification by systematic double reading of tumour specimens. Furthermore, one of the duties of the national networks for rare cancers is to create a national database by rare cancer type, and to systematically record all cases.

Seventeen of the 23 clinical networks for rare cancers have established a national database for recording cases. However, follow-up data, especially data on survival without recurrence and on overall survival are most often not recorded.

Figure 9 details the number of cases recorded in 2013 (28,508 cases). Over 135,000 cases were recorded in these 17 dedicated national databases. The TUCERA (rare brain tumours), CARADERM (rare skin cancers), MESOCLIN (clinical network for malignant pleural mesotheliomas), CARARE (rare renal cancers), CANCERVIH (cancers in HIV seropositive subjects) and K-VIROGREF (virally induced cancers in transplant recipients) networks do not currently have systematic recording of all cases receiving care within the network.

Figure 9. Number of cases recorded in the national databases in 2013, by clinical network



These databases, many of them established for several years, constitute a major tool for research and for improving knowledge of these rare pathologies.

The NETSARC national database (www.netsarc.org) for soft tissue and visceral sarcomas contains 35 items divided into three themes: characteristics of the patient and tumour, key steps in care and

follow-up, and successive presentations of the file and decision making at RCP. This database is shared with that of the RESOS network (osteosarcomas) and that of the reference anatomopathology network for soft tissue and visceral sarcomas (RRePS). This database, which has a long history, records data from nearly 16,000 patients. Indicators of patient quality of care enabling the assessment of practices are regularly analysed, such as the rate of repeat surgical excision where residual tumour has been found, or the mean waiting time between diagnosis and presentation at a sarcoma RCP. A quality assurance programme has been established for this database, and an external audit is planned in order to ensure the quality of medical data recorded.

The GTE/RENATEN database for rare sporadic and hereditary neuroendocrine tumours was established in November 2000, but without systematic recording. It has now been reorganised, with implementation at regional level in each of the expert centres. Approximately 4,700 cases are recorded in the **TENpath database**, including 1,817 cases recorded in 2013. Unfortunately, the RENATEN and TENpath databases are still not shared.

The national database of high-grade oligodendrogliomas is clinical and biological, and linked to a tumour bank and collection of DNA from blood or plasma.

The national lymphoma database, established by the LYMPHOPATH network in 2010, comprises more than 30,000 cases of lymphoma, 9,160 of which were recorded in 2013. From an anatomopathological point of view, this is the largest data bank for confirmed lymphomas in the world. Analysis of these data by the coordinators makes it possible to show that the incidence of different types of lymphomas in France is comparable to that of countries of a similar socioeconomic level, with the exception of angioimmunoblastic T-cell lymphomas, which have a higher incidence than peripheral T-cell lymphomas. It also makes it possible to monitor, in association with the French Medicine Agency (ANSM), cases of breast implant-associated anaplastic large cell lymphomas.

The cutaneous lymphoma database is also evolving into a clinical and biological database, facilitating translational and clinical research studies.

For the 759 cases of **lymphomas of the central nervous system recorded in the LOC network,** including nearly 300 in 2013, 13 studies were established in 2013. In addition, analysis of these data allows real-time assessment of practices, such as use of radiotherapy as a first-line treatment in older subjects, prescription or non-prescription of rituximab, or type of consolidation therapy for young subjects, making it possible to optimise recommendations for good practice and requirements for clinical trials.

The database from the PREDIR network records patients with **conditions that predispose them to renal cancer**, together with the results of the different genetic analyses performed. It includes 1,450 cases, including 436 updated in 2013, but is probably still not exhaustive.

Systematic recording of **malignant mesothelioma** cases in the MESOPATH, MESOCLIN and RENAPE networks actively contributes to the mandatory notification of this pathology established by the French Institute for Public Health Surveillance (InVS) in January 2012.

Two European clinical and biological databases (clinical and biological data, and virtual tumour bank) for **sarcomas** are managed by the NETSARC clinical and RRePS anatomopathology networks: these are Conticabase, devoted to mesenchymal tumours (currently with nearly 14,800 recorded cases), and ConticaGist, devoted to GIST (comprising nearly 2,000 cases). These databases collect anonymised data on the tumour, treatment and follow-up, together with a tumour sample and molecular biology analyses.

Under the VRE project (Virtual Research Environment), two European clinical and biological databases have been developed for adrenal tumours, one for **adrenocortical carcinomas** (ENS@T-ACC), and the other for cases of **phaeochromocytoma and paraganglioma** (ENS@T-phéo). They are linked to collections of tumour specimens. The expert centres for adrenal cancers are involved in the implementation of these two databases.

The RENAPE network is involved in the establishment of a prospective international registry for **pseudomyxoma peritonei.**

Use of these databases by the scientific community in general still often seems insufficient.

7. TRAINING AND INFORMATION

On the e-cancer website, a page devoted to rare cancer organisation was updated in February 2015: http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares

Seventeen websites have been designed by members of the rare cancer network, and provide high-quality information for health professionals, patients and the general public alike (Appendix 7). They provide detail on the organisation of the network, with a list of the experts in each regional centre and the *modus operandi* of the referral RCP, and disseminate recommendations for good practice or national guidelines for these pathologies.

Information for patients and the general public is often written with the relevant patient associations. Twenty-six patient associations work closely with the national networks for rare cancers, and contribute actively to the quality of care of these patients (http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares/les-associations).

8. FUNDING AND PROCEDURES FOR SPENDING ALLOCATED BUDGETS

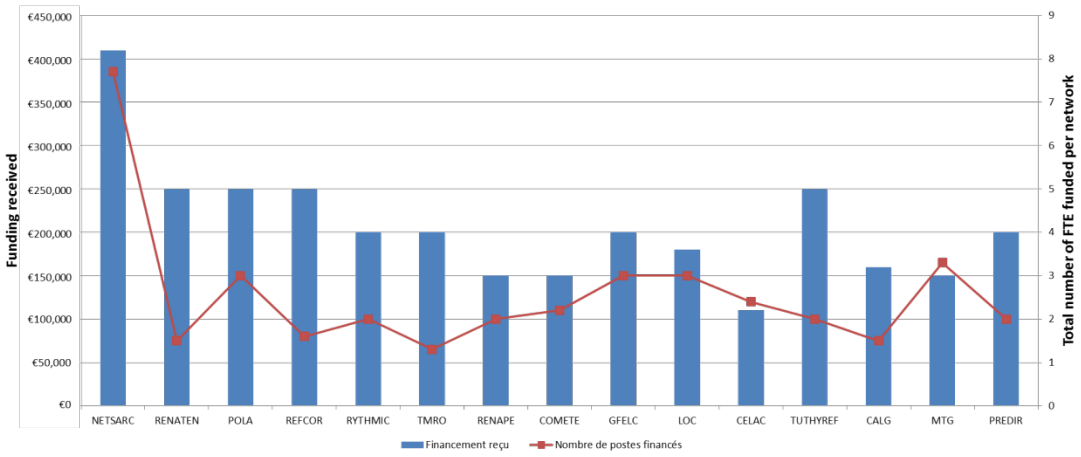
Since 2009, the specific organisation for rare cancers has received funding from Assurance Maladie (French national health insurance scheme), and, since 2010, additional grants from INCa.

❖ Funding of the national clinical networks for rare cancers

In 2013, a total budget of €5,872,850 in Assurance Maladie funding was transferred for this organisation for rare cancers. Appendix 8 details the amount of funding for each of the clinical networks and the phase (budget circular) of transfer of these monies.

Figure 10 shows the amounts of funding transferred to the 15 clinical networks applying for designation, and the number of positions funded in 2013.

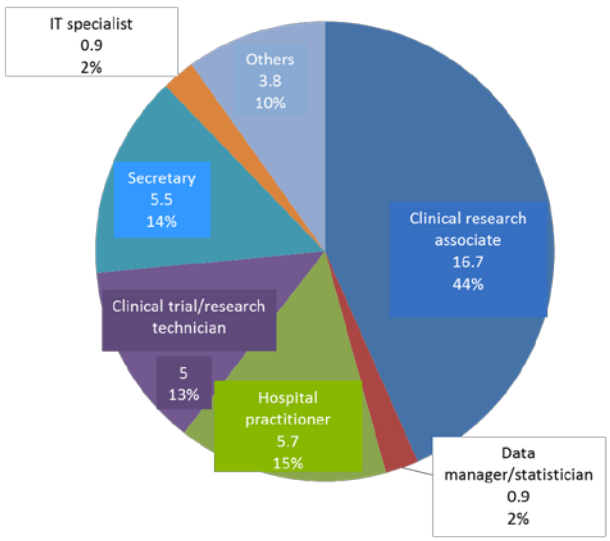
Figure 10. Funding received and positions funded in 2013 for the 15 national clinical networks for rare cancers applying for designation



Funding received / Number of positions funded

Figure 11 represents the distribution of these positions (in full-time equivalents or FTE) for these 15 clinical networks.

Figure 11. Distribution of positions funded (38.5 FTE) in the rare cancer networks in 2013



The funds allocated are mainly used to fund positions for clinical research associates (CRA) or technicians (57%).

❖ **Funding for anatomopathology networks:**

Since 2009, the anatomopathology networks have received funding from Assurance Maladie, worth €1,270,000 in 2013.

Moreover, since 2010 INCa has granted additional grants totalling €853,000 to the LYMPHOPATH and RRePS networks to cover the additional cost of double reading.

A summary of this funding is shown in Table 5.

Table 5. Procedures for funding the 4 national anatomopathology networks for rare cancers

Networks	Assurance Maladie funding (€ thousand/year) in regular funding since 2009	Additional grants from INCa (€ thousand)
RRePS	350	623
TENpath	150	
MESOPATH	350	
LYMPHOPATH	420	230

9. OUTLOOK FOR DEVELOPMENT

This report reviews the specific organisation for adult patients with rare cancers implemented during the 2009-2013 Cancer Control Plan, just when the 2014-2019 Cancer Control Plan was beginning. It will provide the baseline for final assessment of the developments made during this third Cancer Control Plan, with the expectation that they will meet the ambitious objectives of the 2014-2019 Plan.

Eighteen networks were designated for three years in 2014. Other networks are continuing to scale up their organisation. All the networks will be called upon to apply for a renewal of their designation in 2018. This time will be used to reflect upon and develop this scheme as a whole.

Developments will be made in consultation with the relevant supervisory bodies, health professionals and patient associations. They will particularly rely on the proposals made by some of the national coordinators of the rare cancer networks, as part of their application for designation for their network.

Prospects for development relate to the specific organisation, but also include research, training, information and observation in this area of rare cancers.

9.1. Proposals for changing the organisation of double reading of tumour specimens for rare cancers

❖ Proposal to establish preconditions

It has often been argued that arranging “systematic” double reading for rare cancers is disheartening for the pathology community. Setting preconditions, with, for example, one or two immunostains before sending the slides for double reading, obviously helps to guide diagnosis, but also gets the requesting pathologist involved. Established in the TENpath network, it could be extended to the entire organisation for rare cancers.

It is for the pathologists to define together the preconditions for the pathologies involved.

❖ Diagnostic anatomopathological algorithms

These algorithms, developed by the experts after analysis of cases referred for double reading, and then validated by pathologists selected randomly within the community, constitute a tool for assisting diagnosis, and make it possible to target the indications for double reading. Thus 6 algorithms have been developed to help diagnose cutaneous lymphomas (GFELC network). This approach can be proposed for certain lymph node lymphomas, certain types of sarcomas and probably for other rare cancers. It will make it possible to dispense with systematic double reading without, however, reducing the quality of diagnosis, which would be controlled.

It is for the expert pathologists to analyse the data accumulated over the last five years, propose algorithms to assist diagnosis, and then to have them tested and validated.

❖ Procedure for emergency rereading

Double reading in rare cancers is intended to guarantee the quality of diagnosis, but should not cause any delay in patient care. Moreover, for some rare cancers, the therapeutic strategy varies according to the histological subtype, stage or degree of differentiation. It may be useful to define those cases that justify the establishment and dissemination of a procedure for emergency rereading. This reflection, conducted in the RYTHMIC network, should be shared.

It is for the expert clinicians and pathologists to define the cases that justify emergency rereading, and for the expert pathologists to define its organisation.

❖ Assessing the impact of double reading of tumour specimens in rare cancers

Better guidance needs to be provided for this assessment. It should be noted that cases referred to an expert pathologist without a proposed specific diagnosis should not be included in impact assessment (and the requesting pathologist should not receive compensation from the expert network since it is a matter of assisting diagnosis).

Impact assessment of double reading should apply to all cases referred for validation of a diagnosis. "Internal" cases, read in an expert centre at the outset, are excluded from this assessment.

Since impact of double reading on care is defined as involving a modification to this care, it cannot be analysed solely by a pathologist or pathologists. Impact assessment of double reading of tumour specimens in rare cancers should be anatomoclinical.

❖ Sharing of knowledge

The establishment of double reading of tumour specimens in rare cancers should contribute to the education of all pathologists, and the sharing of information should benefit all.

It is to be hoped that each network or group of expert pathologists organise, like the expert pathologists from the RYTHMIC network, an annual meeting, and invite pathologists who have referred slides for double reading to this session on rereading, offering them the opportunity to review one of their reread cases if they so wish.

❖ Formalisation of links with the clinical networks

Validation of a diagnosis of a rare cancer, which is a sign of quality, loses its meaning if the patient does not then have the benefit of clinical expertise. It therefore seems necessary to formalise the links between expert pathologists and expert clinicians. The formal report sent by the expert pathologist should include recommendation for discussion of the file at a referral RCP for rare cancers, which is already the formal arrangement in the RRePS and TENpath networks.

It could be proposed to each of the networks or groups of pathologists that they formalise the double reading report, and include a recommendation to discuss the patient file at a referral RCP for rare cancers. This report should feature a link to the website of the appropriate clinical network.

9.2. Proposals for developing the organisation of clinical care

❖ Provide guidance for submission of files for referral RCP

Reflection has been initiated within the NETSARC network, and has a bearing on all networks.

Referral RCPs involve a considerable number of health professionals and are very time-consuming. To make the best use of this time, it is important that the files presented be of high quality. A minimum content can be defined, at least for some rare cancers, and the submission form for each file submitted to a referral RCP validated by the relevant cancer care coordination centres (3C).

It is the role of the national coordinators from each rare cancer network to liaise with the managers of the expert centres to discuss the procedure for submission of files, and, if necessary, to prepare a minimum content sheet for the referral RCP.

Preparation of standardised reports for surgery and imaging would help to improve the quality of files being presented.

❖ **Assess the quality of the referral RCP**

This mission is the responsibility of the 3C. It is desirable that the 3C establish a procedure for assessing regional referral RCPs for rare cancers (frequency, quorum, technological support, virtual or traditional means of organisation, etc.), regularly or occasionally.

It is the duty of INCa to implement and monitor this mission, by including it in the frame of reference for the 3C.

❖ **Assess the adherence to proposals made at referral RCP**

It is essential to ensure adherence to recommendations for care made by experts at referral RCP and to understand the reasons for nonadherence where it occurs. This assessment, carried out in the NETSARC, TMRO, TUTHYREF and LOC networks, should be systematic throughout the networks.

It is proposed that the national coordinators for each rare cancer network arrange an annual assessment, on a random selection of 30-50 files discussed at RCP, and compare the proposals made at this RCP with the patient data.

❖ **Make it mandatory to present the file at a referral RCP or carry out certain procedures at an expert centre?**

Absence of access to expert review may be a cause of missed opportunity for the patient. Currently, this access to expert review is not mandatory, but simply recommended. Action 2.8 of the 2014-2019 Cancer Control Plan incorporates this concept of complex care, from diagnosis to treatment, and as stipulated in this action, to “change the regulatory framework for cancer treatment if this is justified.” Thus surgical resection of a soft tissue sarcoma or thymoma may be considered complex. The stakeholders will be involved in the implementation of this action of the Cancer Control Plan.

❖ **Facilitate access for all to highly specialised technical platforms**

Certain techniques used in imaging, functional imaging, and biology are highly specialised and are not always in place for a given pathology in all expert centres.

The criteria for referral to these technical platforms should be specified, and a map produced and distributed to facilitate access for all patients involved. The regional oncology networks should contribute to the dissemination of this information.

❖ **Specify the indications for transferring the patient to an expert centre**

Although the specific organisation for rare cancers in adults has favoured keeping the patient in the facility of his/her choice, with double reading of specimens by sending slides to expert pathologists, and discussion of the file at a referral RCP by expert clinicians, transfer of a patient to one of the regional or national expert centres may be necessary for diagnosis, treatment, enrolment in a clinical trial or access to an innovative treatment. Data regarding the care pathways of these patients and the reasons for transfer to an expert centre are presently too scarce and poorly known.

The coordinators of the national networks for rare cancers are requested to provide details on the number of patients transferred, and the indication for transfer to an expert centre. These data are essential in eventually facilitating better coverage of these transfers by Assurance Maladie.

9.3. Research

There is ongoing support for research projects on the theme of rare cancers.

Rare cancers may also benefit from the **AcSé programme**, which is aimed at providing certain patients with secure access to targeted therapies. The first clinical trial in the AcSé programme involves crizotinib. This drug obtained MA in 2012 for patients with lung cancer whose tumour shows a translocation that activates the ALK gene. In 2013, this test was performed on 27 patients with rare cancers (sarcomas, rare cancer of the kidney or ovary, or refractory thyroid cancers), and demonstration of a translocation of the ALK gene gave these patients the opportunity to have crizotinib treatment (http://www.e-cancer.fr/recherche/recherche-clinique/le-programme-acse).

Several international organisations have united to facilitate clinical research on very rare cancers, and formalised these collaborations in 2011 by forming **IRCI (International Rare Cancers Initiative)** (http://www.irci.info/). INCa is a member of IRCI. The goal is to bring together investigators and organisations with the capacity to conduct these studies, to define innovative methodologies enabling organisation of trials for these very rare cancers, and to spur the achievement of results by helping to overcome the problems involved in international trials. Priority has been given to interventional trials, particularly randomised trials. Nine clinical research groups have been established within IRCI, each targeting one very rare cancer.

9.4. Training for health professionals

University training for medical oncologists does not currently include education in rare cancers. Some of the coordinators propose the establishment of an inter-university diploma (DIU) in rare cancers, with an emphasis on sarcomas, rare ovarian cancers, and refractory thyroid tumours. Organisation of postgraduate medical studies is currently being restructured, especially with respect to postgraduate diplomas (DES) in specialist cross-disciplinary training (FST). Reflection should therefore include the theme of “rare cancers.”

As a first step, coordinators of the national networks for rare cancers who have not already done so are asked to urge the managers of regional expert centres to organise training for health professionals in their region.

9.5. Informing patients and the general public

Seventeen of the 23 national networks for rare cancers have formal links with one or more patient associations. These associations are involved in writing information documents for the network, in drawing up the procedure for informed consent for clinical trials, and are above all an essential element in the care pathway and in the general support of patients and those close to them.

All coordinators of rare cancer networks should formalise their links with patient associations (where such associations exist), particularly by arranging regular meetings, involving patient associations in writing documents for the network, and providing feedback to patient associations on the results of clinical trials completed within the rare cancer networks.

The managers of the regional or interregional expert centres should relay information to patients and the general public on rare cancers in the regions.

9.6. Observation: constitution and exploitation of national rare cancer databases

❖ **Include data from medium- and long-term follow-up, especially data on overall survival and progression-free survival**

These data are essential in assessing any impact of the organisation for rare cancers on patient outcome.

It is the duty of the coordinators of each network to promote collection of these data and to audit them annually, and exploit the data in their entirety every year.

❖ **Arrange systematic quality control of databases**

The collection of data on rare cancers should be as comprehensive as possible, to help improve the knowledge of these pathologies in the long term.

It is for the coordinator of each network to establish systematic quality control for the relevant national database.

These databases from the rare cancer networks are designed to record a maximum of information, but cannot prove the completeness of the cases. At the same time, the cancer registries provide exhaustive records of all cases over a geographic area, regularly updating the vital status of the individuals, but collect more limited information. Synergy between these two players is therefore desirable, with one providing knowledge, and the others ensuring the completeness and hence quality and robustness of the results.

9.7. Developments in structuring

INCa and DGOS have to oversee this scheme.

Thus, the terminology defined by DGOS and published in April 2012 distinguishes three levels of referral: the highest grade (reference centre), at national or interregional level; intermediate grade (centre of competence), at interregional or regional level, attached to a reference centre; and the specialist structure, at regional level—in oncology, this corresponds to the facilities authorised to treat cancer.

The designation of 2014 has clarified this structure for some time, with a list produced by the national coordinators of the expert centres and their managers that constitute each of the 18 designated networks.

Although the governance of the rare cancer networks clearly relies on the national coordinator, it is important to define the rules for changing governance and to reflect on governance itself, especially the place of patient associations in this governance, in accordance with Objective 14 of the 2014-2019 Cancer Control Plan, to breathe life into health democracy.

The regional oncology networks should be more involved in publicising the structure within their region, and in disseminating the guidelines for rare cancers. They should also act as a conduit to the ARS, by describing to them the specific organisation for rare cancers in their region.

The 2014-2019 Cancer Control Plan will be a good use of time to harmonise the scheme for rare cancers, in particular through consolidation in order to make gains in transparency and efficiency, by possibly opening to other pathologies such as chronic myeloid leukaemia and by extending the scope

of some of these expert networks to include cancers in children. However, this organisation is perhaps not appropriate for all rare cancers. Thus, it does not seem efficient for gestational cancers, and reflection on optimising access to expert review and accurate and comprehensive information will have to rely on other European models.

Better gauging of funding of the organisation for rare cancers, a harmonisation of funding for the additional cost of double reading and better traceability of Assurance Maladie monies dedicated to this specific organisation are all matters for reflection by INCa in association with DGOS.

The Hospitalisation Committee has validated the creation in 2015 of a new Education, Research, Information and Innovation Programme (MERRI) devoted to reference centres for rare cancers, thus making it easier to track this funding.

10. CONCLUSION

The keys to success for this specific organisation for rare cancers in adults, the building of which started five years ago, have indisputably been:

- an integrated approach, with major involvement of health professionals, researchers, academics and patient associations, as well as supervisory bodies, regional health agencies, and the relevant State agencies;

- the establishment of an equitable care offering, with access to clinical and anatomopathological expertise, whether at regional or national level, regardless of the initial place of care, in one of the 881 public or private facilities authorised for cancer treatment;

- optimal individualised and often innovative care via clinical trials;

- rigorous institutional monitoring, with annual reporting of activity in each of the domains involved in this organisation.

The impediments identified are:

- the still imperfect knowledge of this specific organisation by the relevant stakeholders, despite strong involvement by the regional health agencies, regional oncology networks and patient associations;

- the absence of systematic adherence to the recommendations for care stemming from the referral RCP, sometimes due to inadequate access to certain therapeutic agents or because of their cost;

- inadequate links between the anatomopathological and clinical arrangements, with confirmation of a rare cancer diagnosis by double reading, but without submission of the file to a referral RCP;

- financial resources often not pooled within the network.

Many challenges need to be met in the coming years:

- clarify and harmonise the organisation for rare cancers and its funding;

- better define the pathway of these patients and the potential indications for transferring them to an expert centre;

- better assess the impact of this specific organisation on patient survival and quality of life, since up to now the data have been very fragmentary;

- reconsider this specific organisation in terms of the 2014-2019 Cancer Control Plan.

11. APPENDICES

Appendix 1. National reference networks for rare cancers in adults designated in 2014

Name of network	Rare cancers	National coordinator and co-coordinators	National expert centre
NETSARC	Soft tissue and visceral sarcomas	Prof. Jean-Yves BLAY Dr Antoine Italiano Dr Axel Le Cesne	Centre Léon Bérard Bergonié Institute Gustave Roussy Institute
RENATEN	Rare malignant neuroendocrine tumours	Prof. Patricia Niccoli	La Timone Hospital, AP-HM
POLA	High-grade oligodendrogliomas	Prof. Jean-Yves Delattre Prof. Dominique Figarella-Branger	Pitié-Salpêtrière Hospital, AP-HP La Timone Hospital, AP-HM
REFCOR	Rare ENT cancers	Dr François Janot Prof. Bertrand Baujat	Gustave Roussy Institute Tenon Hospital, AP-HP
RYTHMIC	Thymomas and thymic carcinomas	Dr Benjamin Besse Prof. Nicolas Girard	Gustave Roussy Institute Louis Pradel Hospital, HCL
TMRO	Rare ovarian cancers	Dr Isabelle Ray-Coquard Prof. Eric Pujade-Lauraine Dr Patricia Pautier	Centre Léon Bérard Hôtel-Dieu, AP-HP Gustave Roussy Institute
RENAPE	Rare peritoneal tumours	Prof. François-Noël Gilly	Lyon Sud Hospital, HCL
LOC	Primary lymphomas of the central nervous system	Prof. Khê Hoang-Xuan Dr Carole Soussain	Pitié-Salpêtrière Hospital, AP-HP Institut Curie, Saint Cloud site
CELAC	Lymphomas associated with coeliac disease	Prof. Christophe Cellier Prof. Olivier Hermine	Georges Pompidou European Hospital (HEGP), AP-HP Necker Hospital for Sick Children, AP-HP
TUTHYREF	Refractory thyroid cancers	Prof. Martin Schlumberger Prof. Françoise Borson-Chazot	Gustave Roussy Institute Lyon General Hospitals (HCL)
MTG	Gestational trophoblastic tumours	Prof. François Golfier	Lyon Sud Hospital, HCL
PREDIR	Von Hippel-Lindau disease and hereditary predispositions to renal cancer	Prof. Stéphane Richard	Bicêtre Hospital, AP-HP
COMETE-Cancer	Adrenal cancers	Prof. Jérôme Bertherat Dr Eric Baudin	Cochin Hospital, AP-HP Gustave Roussy Institute
GFELC	Cutaneous lymphomas	Prof. Martine Bagot	Saint-Louis Hospital, AP-HP
RRePS	Anatomopathology network for soft tissue and visceral sarcomas	Prof. Jean-Michel Coindre	Bergonié Institute
MESOPATH-IM@EC	Anatomopathology network for malignant pleural mesotheliomas and rare peritoneal tumours	Prof. Françoise Galateau-Sallé	Caen University Hospital
TENpath	Anatomopathology network for rare malignant neuroendocrine tumours	Prof. Jean-Yves Scoazec	Gustave Roussy Institute
LYMPHOPATH	Anatomopathology network for lymphomas	Prof. Pierre Brousset Prof. Philippe Gaulard	Toulouse University Hospital Henri Mondor Hospital, AP-HP

Appendix 2. Other national networks for rare cancers in adults (structured by call for proposals in 2011 and 2012)

Rare cancers	Name of network	Year of structuring	National coordinator (and co-coordinator)	National expert centre (one or several sites)
Osteosarcomas	RESOS	2012	Prof. François Gouin	Nantes University Hospital
Rare brain tumours	TUCERA	2012	Prof. Hugues Loiseau	Pellegrin Hospital, Bordeaux University Hospital
Rare skin cancers	CARADERM	2012	Prof. Laurent Mortier	Lille Regional University Hospital
Malignant pleural mesotheliomas	MESOCLIN	2011	Prof. Arnaud Scherpereel Prof. Françoise Le Pimpec-Barthes Prof. Jacques Margery	Lille Regional University Hospital Georges Pompidou European Hospital (HEGP), AP-HP Gustave Roussy Institute
Rare renal cancers	CARARE	2012	Dr Bernard Escudier	Gustave Roussy Institute
Uveal melanomas	MELACHONAT	2012	Dr Laurence Desjardins	Institut Curie
Cancers in HIV+ subjects	CANCERVIH	2012	Prof. Jean-Philippe Spano Dr Isabelle Poizot-Martin Prof. François Boue	Pitié-Salpêtrière Hospital, AP-HP St Marguerite Hospital, AP-HM Antoine Béclère Hospital, AP-HP
Virally induced cancers in transplant recipients	K-VIROGREF	2011	Prof. Véronique Leblond Dr Corinne Bezu Prof. Camille Francès	Pitié-Salpêtrière Hospital Group, AP-HP Tenon Hospital Tenon Hospital

AP-HM: Assistance Publique-Hôpitaux de Marseille (Marseille public hospitals); AP-HP: Assistance Publique-Hôpitaux de Paris (Paris public hospitals); HCL: Hospices Civils de Lyon (Lyon general hospitals)

Appendix 3. Specific missions of an expert national clinical centre

Missions	Description
Selection and structuring of expert centres	Defining the procedures for selection
Clinical referral	Organisation of a national referral RCP where applicable Liaising with the pathologist responsible for organising double reading and access to molecular typing tests
Research	Sponsoring multicentre studies in basic, translational and clinical research
National recommendations for good clinical practice	Drafting or updating
Epidemiological surveillance and observation of cancers	Establishment of a national database
Training	Organisation of training for caregivers
Information for patients	Establishment of formal relations with the national patient associations Participation in communication with the general public
Monitoring of expert centres	Establishment and monitoring of indicators

Appendix 4. Specific missions of an expert regional clinical centre

Missions	Description
Clinical referral	Establishment of a regional or interregional referral RCP
Participation in clinical research	Enrolment of patients in clinical trials
Training and information	Participation at regional level in training caregivers, and providing information to patients and their entourage
Structuring the care sectors	Coordination with facilities authorised to treat cancer

Appendix 5. Missions of a national anatomopathology network for rare cancers

Missions	Description
Selection of experts	Defining the procedures for selection
Establishment of double reading	Organisation of the procedure: technical, flow Liaison with the corresponding clinical network
National recommendations for good practice	Definition of diagnostic criteria
Research	Active participation in the biological resource centres Sponsorship or coordination of multicentre studies in basic, translational or clinical research
Training of pathologists	Sharing of expertise as part of continuing professional development
Epidemiological surveillance and observation of cancers	Establishment of a national database International collaborations
Monitoring of this specific organisation	Establishment and monitoring of indicators

Appendix 6. Assessment of the call for applications for designation of the national reference networks for rare cancers in adults/methodology and results

Assessment comprised a **self-assessment**, based on a self-assessment scoring sheet completed by the candidate coordinator and an **independent external assessment** by an international jury.

External assessment comprised, on the one hand, the analysis of each self-assessment scoring sheet by two reviewers, and second, an oral presentation by the candidate coordinator on his/her application before a consultative committee of experts, followed by a collegial discussion. An opinion was then formulated, based on consensus between all members of the consultative committee of experts.

The **consultative committee of experts** (CCE) was constituted by the Chairperson of INCa. It was composed of eight reporting members, who were recognised French and foreign individuals in the area of rare cancers, and not involved in the specific organisation in France. This committee was attended by a representative of DGOS, a representative of the Regional Health Agencies (ARS), a representative from the French National Rare Disease Plan, 2 representatives from Orphanet-INSERM, and a users' representative (a member of the INCa Users and Professionals Committee).

Analysis of public declarations of interest by members of this committee showed no conflicts of interest regarding this expert review of the organisation for rare cancers.

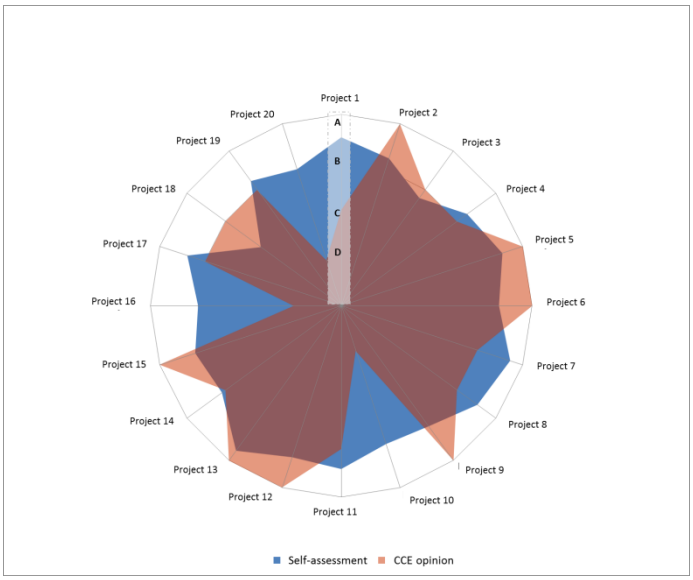
Nineteen national networks for rare cancers applied for designation. One project was presented twice, with different national coordination, bringing to twenty the number of projects received.

The CCE judged 7 projects excellent, 9 good, 1 needing rapid adjustments, and 3 unsatisfactory, including the duplicated project.

Comparison between self-assessment and external assessment

Figure 12 below outlines the results of self-assessment and the opinion of the CCE.

Figure 12. Comparison of grades from self-assessment and from the consultative committee of experts regarding applications for designation of the rare cancer networks



Comparative analysis of grades estimated by the project proponents themselves when submitting applications (self-assessment) and grades awarded by the committee reviewing the applications (CCE opinion) highlights three situations: applications for which the grade estimated by the project proponents was clearly higher than the opinion returned by the CCE (20%); applications for which the grade estimated by the project proponents was close to or even identical to the opinion of the committee (50%); and applications for which the grade awarded by the expert committee is maximal and clearly higher than self-assessment (30%).

We can therefore emphasise that although the majority of projects were self-assessed with discernment and objectivity (50%), or even humility (30%), those projects assessed/judged inadequate (20% of applications graded C and D by the committee) were overvalued by their respective proponents. Moreover, we observe that of the projects assessed as excellent (graded A), impediments were described with great relevance, and the proposed areas of improvement proposed were entirely appropriate.

Appendix 7. Websites of the national expert centres for rare cancers in adults

Rare cancer	Name of network	Website
Soft tissue and visceral sarcomas	NETSARC	https://netsarc.sarcomabcb.org/home.htm
Osteosarcomas	RESOS	https://netsarc.sarcomabcb.org/home.htm
Rare malignant neuroendocrine tumours	RENATEN	www.sfendocrino.org/categorie/9
Rare brain tumours	TUCERA	www.anocef.org
High-grade oligodendrogliomas	POLA	wwww.reseau-pola.org
Rare skin cancers	CARADERM	
Rare ENT cancers	REFCOR	www.refcor.org
Malignant thymomas and thymic carcinomas	RYTHMIC	www.rythmic.org/01/
Malignant pleural mesotheliomas	MESOCLIN	http://mesoclin.chru-lille.fr/
Rare renal cancers	CARARE	
Rare ovarian cancers	TMRO	www.ovaire-rare.org
Rare peritoneal tumours	RENAPE	www.renape-online.fr
Adrenal cancer	COMETE-Cancer	www.sfendocrino.org/categorie/53
Cutaneous lymphomas	Network of experts from the French Study Group on Cutaneous Lymphomas (GFELC)	www.gfelc.org
Primary lymphomas of the central nervous system	LOC (ocular and brain lymphoma)	www.reseauloc.org
Lymphomas associated with coeliac disease	CELAC	
Uveal melanomas	MELACHONAT	
Refractory thyroid cancer	TUTHYREF	www.tuthyref.com
Cancers in HIV+ subjects	CANCERVIH	
Gestational trophoblastic tumours	MTG	www.mole-chorio.com
Von Hippel-Lindau disease and hereditary predispositions to renal cancer	PREDIR	www.predir.org
Virally induced cancers in transplant recipients	K-VIROGREF	

Appendix 8. Amount of funding for each clinical network and budgetary phase of transfer of these monies

LFSS funding for rare cancers – Cancer Control Plans												
Regions	Institutions	Reference centres	Coordinator	2009 funding, phase 2 renewable	2009 funding, phase 3 renewable	2010 funding, phase 3 non-renewable	2011 funding, phase 1 renewable	2011 funding, phase 3 renewable	2011 funding, phase 3 (NR)	2013 funding, phase 1 renewable	2014 funding, phase 2 renewable	Total renewable amounts in 2014
Aquitaine	Bergonié Institute	Soft tissue sarcomas	Prof. Coindre		€350,000						€586,000	€936,000
	Bordeaux University Hospital	Rare brain tumours	Prof. Loiseau							€250,000		€250,000
Lower Normandy	Caen University Hospital	Anapath mesotheliomas	Prof. Galateau-Sallé	€350,000								€350,000
Île de France	Gustave Roussy Institute – Villejuif	Malignant thymomas	Prof. Besse			€150,000	€200,000					€200,000
		Rare ENT cancers	Prof. Janot			€250,000	€250,000					€250,000
		Rare renal cancers	Dr Escudier							€250,000		€250,000
		Refractory thyroid cancers	Prof. Schlumberger	€250,000								€250,000
	Pitié-Salpêtrière University Hospital	CNS lymphomas	Prof. Hoang-Xuan			€180,000	€180,000					€180,000
		Virally induced cancers in transplant recipients	Prof. Leblond					€192 000				€192 000
		Cancers in HIV seropositive subjects	Prof. Spano							€150 000		€150 000
		Oligodendrogliomas	Prof. Delattre	€250,000								€250,000
	Cochin University Hospital	Adrenal cancer	Prof. Bertagna	€150,000								€150,000
	Bicêtre University Hospital	Von Hippel Lindau disease	Prof. Richard	€200,000								€200,000
	St Louis University Hospital	Cutaneous lymphomas	Prof. Bagot			€200,000	€200,000					€200,000
	Institut Curie – René Huguenin	Uveal melanomas	Dr Desjardins							€150,000		€150,000

LFSS funding for rare cancers – Cancer Control Plans

Regions	Institutions	Reference centres	Coordinator	2009 funding, phase 2 renewable	2009 funding, phase 3 renewable	2010 funding, phase 3 non-renewable	2011 funding, phase 1 renewable	2011 funding, phase 3 renewable	2011 funding, phase 3 (NR)	2013 funding, phase 1 renewable	2014 funding, phase 2 renewable	Total renewable amounts in 2014
	Tenon University Hospital	Gestational cancers	Prof. Rouzier			€160,000	€160,000					€160,000
	HEGP	Lymphomas in coeliac disease	Prof. Cellier			€110,000	€110,000					€110,000
	Henri Mondor Hospital	Lymphomas	Prof. Gaulard	€165,000	€45,000						€115,000	€325,000
Midi-Pyrénées	Toulouse University Hospital – Purpan	Lymphomas	Prof. Delsol	€165,000	€45,000						€115,000	€325,000
Nord Pas de Calais	Lille Regional University Hospital	Rare skin cancers	Prof. Mortier							€250,000		€250,000
		Mesothelioma	Prof. Scherpereel					€110,850	€130 500			€110 850
PACA	Marseille University Hospital	Neuroendocrine tumours	Prof. Niccoli	€250,000								€250,000
Pays de la Loire	Nantes University Hospital	Osteosarcomas	Prof. Gouin							€150,000		€150,000
Rhône Alpes	Lyon University Hospital	Anapath Neuroendocrine tumours	Prof. Scoazec	€150,000								€150,000
		Gestational trophoblastic disease	Prof. Raudrant	€150,000								€150,000
		Rare peritoneal tumours	Prof. Gilly	€150,000								€150,000
	Centre Léon Bérard, Lyon	Rare ovarian cancers	Dr Ray-Coquard			€200,000	€200,000					€200,000
		Soft tissue sarcomas	Prof. Blay	€400,000								€400,000
	Total			**€2,630,000**	**€440,000**	**€1,250,000**	**€1,300,000**	**€302,850**	**€130,500**	**€1,200,000**	**€816,000**	**€6,688,850**

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