Ministère des affaires sociales et de la santé

Appel à projets national en cancérologie 2013

Lettre d'intention / *Letter of intent*

La lettre d'intention est à rédiger en anglais pour permettre l'évaluation internationale

PHRC-K T **PRME-K** £

Veuillez cocher l'appel pour lequel vous soumettez votre projet

Date limite de soumission en ligne : 7 mai 2013 avant Minuit

Si soumission PHRC-K :
http://www.e-cancer.fr/aap/recherche/phrc2013

Si soumission PRME-K :
http://www.e-cancer.fr/aap/recherche/prmek2013

Responsable: Ghizlane Delaval - tel 01 41 10 14 87

In the frame of DGOS calls for proposals:

First submission T Previous submission £ (fill in section dedicated to previous submission in the last page):

Titre de l'étude envisagée, précédé par son acronyme[1]
ACRONYME TRANSMET Chimiothérapie et Transplantation hépatique vs Chimiothérapie seule dans le traitement des métastases hépatiques de cancer colorectal (MCR) définitivement non résécables : étude prospective randomisée multicentrique
Project title
Chemotherapy and Liver Transplantation versus Chemotherapy alone in the treatment of definitively unresectable liver metastases from colorectal cancer (MCR): a prospective multicentric randomized trial.

GENERAL INFORMATION

First name and name of coordinator :	**René ADAM**
Previous grants in the frame of DGOS calls (List with: year, ref number, state.):	
Specialty	Professor of Surgery
Service ou département - Unit or department	Head of Hepato-Biliary Surgery, Cancer and Transplantation Unit
Name and adress of the hospital	Centre hépato biliaire Hôpital Paul Brousse Villejuif
Phone number	+33 1 4559 3049
E-mail	rene.adam@pbr.aphp.fr
Physician, dental practitioner / Biologist / Nurse, other paramedical :	Physician, surgeon
Affiliated institution responsible for the budget from ministry of health	Assistance Publique-Hôpitaux de Paris

[1] L'acronyme sera formé d'un nombre de lettres inférieur à 15, suivi de 2 chiffres (01 le plus souvent, ou 02 s'il s'agit du 2ème projet dans la continuation d'un 1er projet portant le même titre, etc...

Research domain :	
Organ, tumor location :	Liver Cancer; Liver metastases ; Colorectal cancer ;
Others :	Chemotherapy ; Liver transplantation ; Long time survival; Oncology;
Keywords :	
Coordinator domain	Oncologic liver surgery ; Liver transplantation
Whished reviewer domain	Oncologic liver surgery; Liver transplantation

Anticipated number of recruiting centers (NC)	12 French centers and 8 European centers

Approximate level of funding required (K euros):	

First name and name of the methodologist :	**Hélène AGOSTINI**
Name and adress of the hospital	Unité de Recherche Clinique Paris Sud Hôpitaux Universitaires Paris-Sud (APHP) - Hôpital Bicêtre 78 rue du Général Leclerc, 94275 Le Kremlin Bicêtre Cedex France.
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First name and name of the economist (if any)	NA
Name and address of the establishment:	NA
Phone number	NA
E-mail	NA

Organization responsible for project management:	Assistance Publique – Hôpitaux de Paris : Clinical Research and Development Department (DRCD), Saint Louis Hospital, Paris, and Paris-Sud clinical research unit (URC), Bicêtre Hospital, Le Kremlin Bicêtre
Organization responsible for quality assurance:	Assistance Publique – Hôpitaux de Paris : Clinical Research and Development Department (DRCD), Saint Louis Hospital, Paris, and Paris-Sud clinical research unit (URC), Bicêtre Hospital, Le Kremlin Bicêtre
Organization responsible for data management and statistics :	Paris-Sud clinical research unit (URC), Bicêtre Hospital, Le Kremlin Bicêtre

	Co-investigators (1 à n)							
N°	Name	Firstname	Town	Country	Hospital	E-mail	Tel	Speciality
1	René	ADAM	Villejuif	France	Hôpital Paul Brousse	rene.adam@pbr.aphp.fr	01 45 59 30 49	Liver surgery andTransplantation
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18	Markus	Buechler	Heidelberg	Germany	Universitätsklinikum Heidelberg	peter.schemmer@med.uni-heidelberg.de	+49 62 21 56 4821	Liver surgery andTransplantation
19	Paolo	Muiesan	Birmingham	UK	The Queen Elizabeth Hospital	Paolo.Muiesan@uhb.nhs.uk	+44 (0) 121 627 2418	Liver surgery andTransplantation
20	Aksel	Foss	Oslo	Norway	Rikshospitalet	aksel.foss@rikshospitalet.no	+47 90 83 35 29	Liver surgery andTransplantation

References

List of the main publications (5 maximum) justifying the project in the national and international context

1- **Adam R,** Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F, Ghemard O, Levi F, Bismuth H. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Annals of Surgery* 2004 Oct;240(4):644-57; discussion 657-8..

2- **Adam R,** Pascal G, Castaing D, Azoulay D, Delvart V, Paule B, Levi F, Bismuth H. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Annals of Surgery* 2004 Dec;240(6):1052-61; discussion 1061-4.

3- Hoti E, **Adam R.**Liver transplantation for primary and metastatic liver cancers. *Transplant International* 2008; 21(12):1107-17.

4- Foss A, **Adam R,** Dueland S. Liver transplantation for colorectal liver metastases: revisiting the concept. *Transplant International* 2010 Jul;23(7):679-85.

5- **Adam R,** Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, Castaing D, Neuhaus P, Jamieson N, Salizzoni M, Pollard S, Lerut J, Paul A, Garcia-Valdecasas JC, Rodríguez FS, Burroughs A; All contributing centers (www.eltr.org); European Liver and Intestine Transplant Association (ELITA). Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *Journal of Hepatology* 2012 Sep;57(3):675-88.

6- Hagness M, **Foss A**, Line D, Scholz T, Jørgensen F, Fosby B, Muri Boberg K, Mathisen O, Gladhaug IP, Skatvedt Egge T, Solberg S, Hausken J and Dueland S. Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer. Ann Surg 2013;257: 800–806.

RESEARCH PROJECT

RATIONAL (Context and hypothesis, max 320 words)

Despite the tremendous progress in the efficacy of chemotherapy, the prognosis of patients with unresectable liver metastases from colorectal cancer (LMCR) remains poor, with anecdotal long-term survivors. Resection when tumor downsizing is obtained by chemotherapy, offers a 33% 5-year survival and currently represents the main objective of the treatment strategy. However, when resectability could not be achieved, no other therapeutic option than palliative chemotherapy could be offered, with a dismal prognosis and almost no chance of long term survival. In this situation, liver transplantation (LT) is an attractive option that may offer a curative approach to patients with liver-limited disease. The results obtained up to the nineties in 50 patients transplanted in european centers, however demonstrated a 5-year survival of only 18%. These poor results lead to consider LMCR as a relative contraindication to LT. However, almost 50% of deaths were related to non tumoral causes, in a period when LT was still in a learning curve process. As survival post-LT has improved by 30% in the last 20 year-period, as imaging techniques could now detect extrahepatic tumor with better accuracy, and as immunosuppressive therapy could be tailored to decrease the tumor recurrence rate post-LT, we have proposed to revisit the indication of LT for CRLM with the hypothesis that a 5-year survival of 50% could now be achieved. This hypothesis has recently been validated in a Norway study reporting a 60% estimated survival at 5 years. However, the disease free survival (DFS) in this preliminary study has still been poor with 19/21 patients who recurred after LT. The objective of our study is to validate on a larger multicentric scale these results, to propose a more strict policy of patient selection, excluding patients with tumor progression while on chemotherapy and/or having received more than 2 lines of chemotherapy, to plan in advance a real strategy combining perioperative chemotherapy with LT and to compare the results of this strategy to the standard approach represented by modern chemotherapy.

Originality and innovative aspects (max 160 words)

The new anticipated insights of the study will be :

1- To validate LT as a recognized treatment option in very well selected patients suffering from confirmed unresectable liver metastases from colorectal cancer
2- To base the selection process not only on a surgical consideration but on a multidisciplinary decision involving medical oncologists, radiologists, pathologists and surgeons
3- To reach a 5-year survival of at least 50% by restricting the candidates to patients younger than 60 yrs, with metastases responding to ≤ 2 lines of chemotherapy while remaining unresectable (as assessed by another independent expert team), with CEA / CA19-9 levels < 100 ng/ml and a previous high standard carcinological resection of the primary. Finally to combine routinely LT with perioperative chemotherapy
4- To precise the real survival benefit provided by this approach compared to modern chemotherapy treatment in a constantly evolving field of progress.

Focus of research

Health technology (tick and then detail):

Drugs **£** Devices **£**

Procedures and organizational systems used in health care (including Health services[2]) **T**

If relevant: date of CE mark / market authorization

Keywords (5):

Liver metastases ; Colorectal cancer ; Chemotherapy ; Liver transplantation ; Long term survival

Main objective (Detail, max 48 words)

To increase significantly the long term survival of very selected patients with non resectable liver metastases of colorectal cancer by adding LT to chemotherapy and comparing the 5-year survival obtained with this strategy to that of chemotherapy alone.

[2] http://htaglossary.net

Tick one:		
Hypothesis £	Description feasibility £	Tolerance efficacy
Safety efficience £	Budget impact £	Organization of care T

Tick one:		
Etiology Causality[3] £	Diagnosis £	Prognosis T
Therapeutics (impact on clinical end-points[4]) T		
Therapeutics (impact on intermediate end-point[5]) £		
Compliance £	Effective Practice £	Research methodology £
Qualitative Research £	Others £	

[3] Studies designed to determine the causes of a disease, the risk of being exposed to a drug, a pollutant etc
[4] Example : reduction of myocardial infarction incidence, of mortality
[5] Example : reduction of serum cholesterol, improvement of a pain scale

Secondary objectives (detail, max 160 words)

- To refine the selection of patients with non resectable LMCR for offering them a survival close to that obtained by LT for recognized malignant liver tumors (Hepatocellular carcinoma, Neuroendocrine liver metastases...)
- To assess the potential of Cure with this multimodal strategy
- To improve the quality of life by reducing the need for continuous chemotherapy

Primary end point (linked with the main objective)

Overall survival at 5 years

Secondary end points (linked with the secondary objectives)

To compare between the two groups of patients :

- The 3-year overall survival
- The disease free survival (DFS) at 3 and 5 years
- The progression free survival (PFS) at 3 and 5 years
- The rate of recurrence at 3 and 5 years
- The Quality of life (QOL) of patients at Baseline, 1, 3 and 5 years

Study population

Main inclusion and exclusion criteria

At least 18 years old patients, both genders, with the following criteria:

- ≤ 60 years
- Confirmed non resectable liver metastases of colorectal cancer,
- High standard carcinological resection of the primary
- Treatment by at least 6 months of optimal chemotherapy
- With stable or partial response while on ≤ 2 lines of chemotherapy
- Serum CEA and CA 19-9 levels < 100 ng/ml
- without extrahepatic tumor localisation
- eligible for both treatments groups

These selection criteria will be validated by a local multidisciplinary Tumor Board meeting and confirmed by the independant scientific committee of the study including oncologists, radiologists and hepatic / Transplant surgeons

Patients will be excluded in case of:

- Participation refusal
- No social security or health insurance
- LT contraindication
- Pregnancy
- ...

Design (tick + detail max 320 words)

Meta analysis **£** Randomized clinical trial **T** if yes : Open **T** Single blind **£** Double blind **£**

Systematic reviews **£** Pragmatic studies **£**

Quasi-experimental studies (non randomized cohorts ...) **£** Prospective cohort study **£**

Case-control study **£** Cross-sectional study **£**

Retrospective cohort **£** Administrative / hospital inpatient database research **£**

Modelisation **£** Case series **£** Qualitative studies **£** Others **£**

To minimize the biais risk the treatment will be allocated randomizely.
To improve the power without too increase costs, the sample size will be calculated focusing 66% of patients in C-group and 33% of patients in C-LT-group.
Because of the nature of the compared treatments (C versus C-LT), the blind will be impossible to maintain.

When a patient will fullfill the inclusion criteria for the local tumor board, the chart will be submitted to another expert center to confirm the unresectability of LMCR. The indication will be further validated by the scientific committee of the study. Once the indication validated, the patient will be submitted to a pre-transplant evaluation. A complete work up including Ct Scan and PET CT and Colonoscopy will exclude any extrahepatic tumor or any local recurrence. If potentially transplantable, the patient will be randomized for one of the two treatment arms. During all these assessments, the optimal chemotherapy regimen determined by the team in charge of the patient will be continued to control the tumoral disease.
- If the patient is randomized for the transplant arm, he will be registered in the waiting list of a transplant center and this registration will be linked to a requirement to the Organ Sharing Organization of a priority for a transplant being performed between 1-2 months from the last chemotherapy course. After LT, the patient will receive an immunosuppressive therapy based on a mTOR inhibitor - sirolimus or everolimus – with reduced dose of tacrolimus. and corticosteroids. Initial dose of Tacrolimus will be delivered for trough levels between 6 and 10 ng/ml during the first 14 days and therefore reduced to between 3-5 ng/ml after the introduction of m-TOR inhibitors. Sirolimus or Everolimus will be introduced on postoperative day 14, aiming for a trough level of 6 to 10 ng/mL. Corticosteroids will be tapered to 0 or 5 mg daily at 1 month post–liver transplantation. Mycophenolate mofetil will be allowed during the first 14 days according to center practice and will be withdrawn at the time of initiation of m-TOR inhibitors.
After 3-4 days in the intensive care unit and 2-3 weeks on conventional hospitalization unit, the follow up will be weekly during 1 month, then biweekly during 2 months and monthly thereafter during 6 months. Post transplant chemotherapy will be envisaged as soon as the patient will recover, but at least one month from LT, for a maximum period of 6 months (in the absence of recurrence). A post transplant imaging check up will be performed at 1 month and then every 3 months with tumor markers (CEA, CA 19-9), thoracic and abdominal CT Scan. Liver MRI will be performed at 6 months and then every year to better detect any small liver recurrence. This strict follow up will be extended up to 2 years from LT. Thereafter the follow up will be extended to every 6 months for a period of 3 years. PET CT will be performed every 6 months for the 1st year and then every year up to a complete follow up to 5 years post LT.
- If the patient is randomized for the Chemotherapy arm, the type, duration and modalities of administration of this chemotherapy will be at the discretion of the team in charge of the patient with an evaluation every 4 courses (2-3 months). The surveillance will consist mainly on tumor markers (CEA, CA 19-9, thoracic and abdominal CT with MRI as an option in doubdtful cases. The management of these patients will be the same as all patients with unresectable LMCR treated by the local team.

The data will be recorded prospectively by an e-CRF and validated by the monitor according to the procedures of the promoter.
The primary end point, 5-years overall survival will be calculated in each group with the Logrank method and compared between both group by logrank test. An univariate analysys will be search the prognostic value of many factors using adjusted logrank tests.

If health-economics analysis (tick + detail max 320 words) :

Cost-utility analysis £ Cost-effectiveness analysis £ Cost-benefit analysis £

Budget impact analysis £ Cost-minimization analysis £ Cost-consequence analysis £

Cost of illness analysis £ Others £

In the case of a drug trial:

Phase: I £ phase: II £ phase: I/II £ phase: III £ phase: IV £

If comparison groups :

Experimental group (detail max 48 words)

Chemotherapy is the usually recommended treatment in these patients (2).
Experimental group patients will be treated with chemotherapy and LT (C-LT)

Control group (detail max 48 words)

Chemotherapy is the usually recommended treatment in these patients (2).
Control group patients will be treated with chemotherapy alone (C)

INCLUSIONS

Duration of participation of each patient (days/months/years):

At least 5 years

Anticipated duration of recruitment (DUR) (in months):

36 months

Total number of scheduled patients / observations to be recruited (NP) (3 digits + Justification of sample size max 80 words):

90
A two-sided log rank test with an overall sample size of 48 patients (of which 24 are in group C and 24 are in group C-LT) achieves 90% power at a 5% significance level to detect a difference of 40% between 10% and 50%--the proportions surviving in groups C and C-LT after 5 years. Patients entered the study during an accrual period of 3 years. Approximately 50% of the enrollment was complete when 50% of the accrual time had past. A follow-up period of 5 years had a 2% loss from group 1 and a 10% loss from group 2.
An overall sample size of 90 included patients will be definitively enrolled to obtain 80 evaluable patients and increase the power, to adjust the two-sided log rank tests with one covariable.

Number of patients / observations to be recruited / month / center ((NP/DUR)/NC) (2 digits + Justification if more than 2 patients/month/center)

1 to 2 /year/center

Expected number of patients eligible in the centers						
N°	Name	Surname	Town	Country	Expected recruitment/month	Total
1	René	ADAM	Villejuif	France	2/year =0.16	6
2	Jacques	BELGHITI	Clichy	France	2/an=0.16	6
3	Daniel	AZOULAY	Créteil	France	2/an=0.16	6
4	Francois René	PRUVOT	Lille	France	1/an=0.8	3
5	Karim	Boudjema	Rennes	France	2/an=0.16	6
6	Philippe	Bachelier	Strasbourg	France	2/an=0.16	6
7	Olivier	Soubrane	Paris	France	1/an=0.8	3
8	Laurence	Chiche	Bordeaux	France	1/an=0.8	3
9	Jean-Yves	Mabrut	Lyon	France	1/an=0.8	3
10	Jean Robert	Delpero	Marseille	France	1/an=0.8	3
11	Denis	Pezet	Clermont-Ferrand	France	1/an=0.8	3
12	Jean Marc	Regimbeau	Amiens	France	1/an=0.8	3
13	Gilles	Mentha	Genève	Switzerland	2/an=0.16	6
14	Pierre-Alain	Clavien	Zurich	Switzerland	2/an=0.16	6
15	Jan	Lerut	Bruxelles	Belgium	2/an=0.16	6
16	Jacques	Pirenne	Leuven	Belgium	1/an=0.8	3
17	Vincent	Donkier	Bruxelles	Belgium	1/an=0.8	3
18	Markus	Buechler	Heidelberg	Germany	2/an=0.16	6
19	Paolo	Muiesan	Birmingham	UK	2/an=0.16	6
20	Aksel	Foss	Oslo	Norway	2/an=0.16	6

Participation of a research network (Detail max 32 words)

This study will be supported by the “European Liver and Intestine Transplant Association” (ELITA), the “European Liver Transplant Registry” (ELTR) and by the French “Association de Chirurgie Hépato-Biliaire et Transplantation” (ACHBT). It is promoted by the “Assistance Publique-Hôpitaux de Paris” (AP-HP). A further support from the European Organization for Research and Treatment of Cancer (EORTC) is under submission.

Participation of industry (Detail max 64 words)

Not applicable

Others aspects to insure the feasibility of the project (Detail max 64 words)

A previous agreement with all national Organ Sharing Organizations of the European centers participating to the trial will be needed. When all the selection criteria will be fulfilled by the local center and the indication for a possible LT confirmed by the scientific committee of the study, randomization will be performed. In case of LT, a prioritization of the patient will be required to

respect an interval of 1-2 months maximum from the last chemotherapy.

Expected patient or public health benefit (Detail max 320 words)

With 1.2 millions new cases per year worldwide and 50% of patients developing liver metastases, colorectal cancer is a real problem of Public health. Among patients with LM, 80 to 90% are deemed unresectable at the time of diagnosis. A proportion of 20-30% of these unresectable patients are sufficiently downsized by chemotherapy to become resectable but still 70-80% remain unresectable and promised to a very poor outcome despite the tremendous progress achieved by chemotherapy. Offering LT to some of these patients may be associated with a real chance of long-term survival and a potential of cure. The scientific demonstration of such benefit could change the current treatment strategy of metastatic colorectal cancer. The expected patient benefit are:

- Better long term survival
- Potential of cure

The expected public health benefit are:

- The avoidance of unjustified indications of LT for LMCR
- The avoidance of a loss of organs that could be attributed to patients with other liver diseases known to have a better survival
- The validation of selection guidelines improving the cost/benefit ratio of LT for LMCR.

In the case of a previous submission, mention the additional aspects relevant to the recommendations of the scientific committee (Experts comments and corresponding answers, max 320 words)

Not applicable