



**ETOILE**

Etude prospective du PHRC 2011  
PHRC-ETOILE



**France  
HADRON**

**fondazione CNAO**  
Centro Nazionale di Adroterapia Oncologica per il trattamento dei tumori



# PHRC-ETOILE

## First Transnational Randomized Prospective Trial Comparing Carbon Therapy versus Non-Carbon Therapy for Radioresistant Tumors: PHRC-ETOILE

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**Promotor:** Hospices civils de Lyon

**Coordinator :** Pr Jacques Balosso

**Principal investigator:** Dr Pascal Pommier

**Associated particle therapy centers:** CNAO, IMPT/CK (Nice), and CFB (Caen)



# TITLE

- Etude randomisée comparant l'hadronthérapie par ions carbone à la radiothérapie conventionnelle - y compris protonthérapie - pour le traitement de tumeurs radiorésistantes
- **Randomized** comparison of carbon ions therapy vs. photon or protontherapy for radioresistant tumors.
- PHRC ETOILE

## JUSTIFICATION / CONTEXTE

- Innovative treatment
- Enhanced efficacy awaited toward radioresistant tumors
- Could be useful to 1200 to 4500 patients in France
- Several centers of carbontherapy are operating (Japan 6, Germany 1, Italy 1 and Austria 1, China 2...)
- Since the opening of HIT in 2009 a rising demand of patient appeared in France, asking for the reimbursement of carbontherapy to health insurance
- This urged **the Ministry of health and the Health insurance to ask for a scientific assessment of carbontherapy**
- ***This has been specifically asked to the GCS-ETOILE in 2010***
- Thus the National Health Insurance made the commitment to support the cost of the treatments in this study
- beside the support of the scientific part of the study by the PHRC (Programme Hospitalier de Recherche Clinique)

# PRINCIPLE OF THE STUDY

- This study has a pragmatic goal **to compare two different care paths**:
  - One with the best possible available radiotherapy in France
  - vs
  - One with the use of carbontherapy
- The point of view is the one of health insurance:  
**“do we have to support this care and ultimately to provide it or not”**
- It is neither a tumor oriented trial, nor a dose comparison trial, even not a pure treatment comparison trial.

# MAIN OBJECTIVE

- To demonstrate a **20% improvement** of the **progression free survival** (about 70% vs 50%) at 5 years
- For a set of **radioresistant tumors** including: Adenoid Cystic Carcinoma, Chordoma, Sarcoma.
- Unresectable or after definitive R2 resection

## SECONDARY OBJECTIVES

- **Medical assessment:**
  - Overall survival
  - Specific survival
  - Local control rate
  - Early and late toxicity
  - Quality of life
- **Medico-economics** (associated study I)
  - Full cost
  - Cost / effectiveness (related to survival)
  - Cost / utility (related to QALY)
- **Biology** (associated study II)
  - Prospective analysis of molecular markers of radioresistance
  - Retrospective correlation to medical outcome

## METHOD AND RESEARCH ORGANIZATION

- Phase III multicentric (**transnational**) randomized trial
- **The exp. arm (carbon ions) will be exclusively carried out by the carbontherapy centers (only CNAO for the moment)**
- The reference arm (**photons or protons or both**) will be multicentric and carried out by the French investigating centers
- **Photon radiotherapy** will have to be the best possible by IMRT whatever the technique except hypofractionated stereotactic radiotherapy.
- **Protontherapy** will be carried out in one of the two French protontherapy centers (ICPO and IMPT/CK at Nice)
- **Quality insurance** In the frame of this study we will attempt to provide guidelines for photon and protontherapy (not done yet) and a dummy run will be proposed to the investigating centers.



# INCLUSION CRITERIA (1)

- Age  $\geq 18$  years
- No severe comorbidities allowing a life expectancy above 10 years
- Non resectable or non operable or definitive R2 resection of the tumor
- Assumed radioresistant cancers as quoted in the limiting following list taking account of the exclusion criteria:
  - **Adenoid Cystic Carcinoma (ACC) of head and neck (laryngial and tracheal being excluded)**
  - **Soft tissues sarcoma including rhabdomyosarcoma and angiosarcoma**
  - **Retroperitoneal sarcoma unless technical limitations (over sized, moving, ...)**
  - **Ostéosarcoma of any location and grade except Ewing sarcoma**
  - **Chondrosarcoma (skull base excluded)**
  - **Chordoma of the spine and the pelvic (skull base excluded)**

## INCLUSION CRITERIA (2)

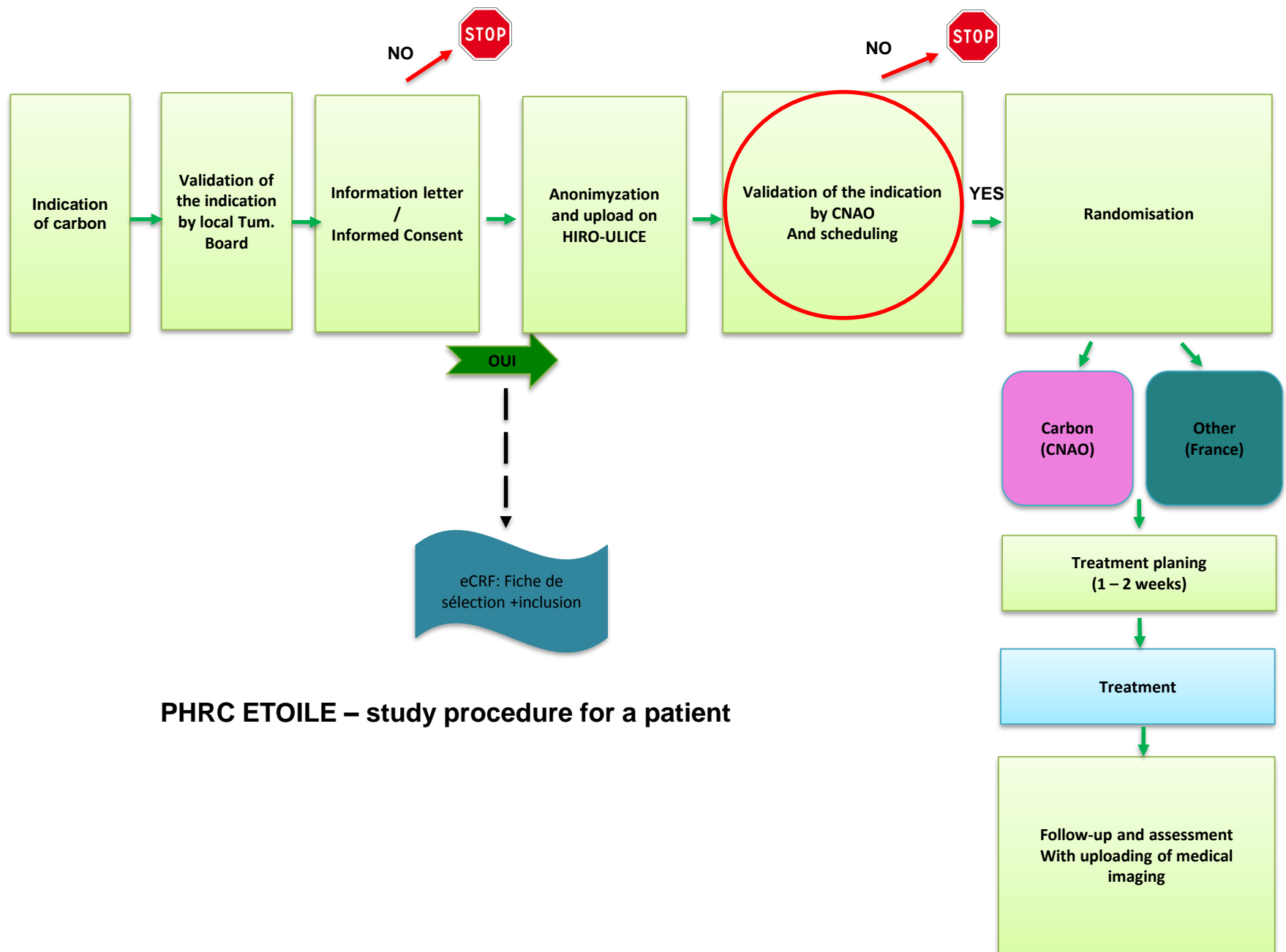
- **No skin** involvement
- Performance Status (PS) ECOG  $\leq 2$  or Karnofsky  $\geq 60$
- Patient physically and psychologically able to follow treatments far from his / her home and even abroad
- For women to rule out any pregnancy risk
- Social security affiliation of the patient
- Signed informed consent

## INCLUSION CRITERIA (3)

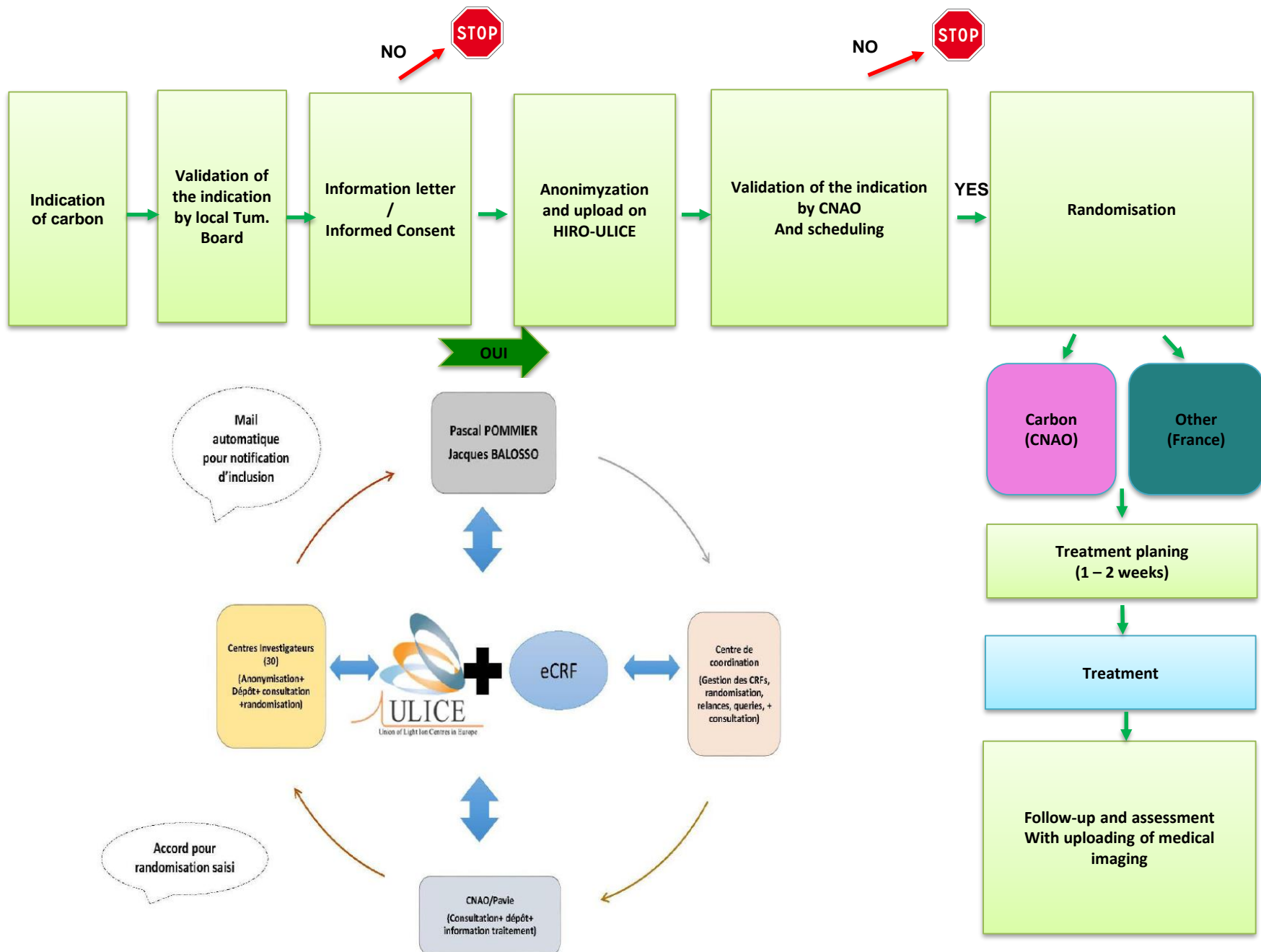
- To fulfill the **randomisation criteria** :
  - A radiotherapy proposal by the local specialized tumor board in the frame of the indications listed above;
  - Validation of this proposal by the carbone ions center medical team (CNAO)
  - Ability, by the carbon ions center, to initiate the treatment into the two coming months

# EXCLUSION CRITERIA

- R0 or R1 surgery
- Previous irradiation in the location to treat
- **Metastasis**
- Contra-indication to carry out a radiotherapy:
  - Impossible immobilization in decubitus
  - Severe acute physiological breakdown
  - Active infection in the treating volume or portals; etc.
- **Planned surgery or chemotherapy after the radiotherapy**
- **Metallic device** impossible to remove from the target volume or in the volume to image for planification procedure
- History of invasive cancer having less than 5 years of remission
- Pregnant woman or fertile woman refusing effective contraception during the treatment
- Conditions of impossible follow-up.



**PHRC ETOILE – study procedure for a patient**



## NUMBER OF PATIENTS

- To demonstrate a PFS of 50% in the control arm vs 70% in the experimental one (equivalent to an HR = 0.515)
- With a recruitment period of 2 years and a minimum follow-up of 5 years, a bilateral test with alpha risk of 5% and a power of 90%, 108 patients per group are necessary (for security **250 as total**).
- The number of events awaited at the time of analysis is 92.

# FEASIBILITY

- Promotion by the HCL
- Financial support have been obtained
  - **PHRC 2011** about 500 k€
  - **CNAMTS** all treatments and travels of patients which is about 7M€
  - Complementary support of the health ministry is possible
- Data management is organized
  - Access to the data exchange platform of Heidelberg
  - Data management by Laennec Medical school
  - Statistics by Centre Léon Bérard
- Carbontherapy by CNAO
- Rate of accrual...



## DURATION OF THE STUDY

- Inclusion phase: 2 years (!!!!??)
- Participation of each patient : **from 5 to 7** years according to their inclusion date
- Total duration of the study : 7 years (??)
- Starting of inclusions : December 2017

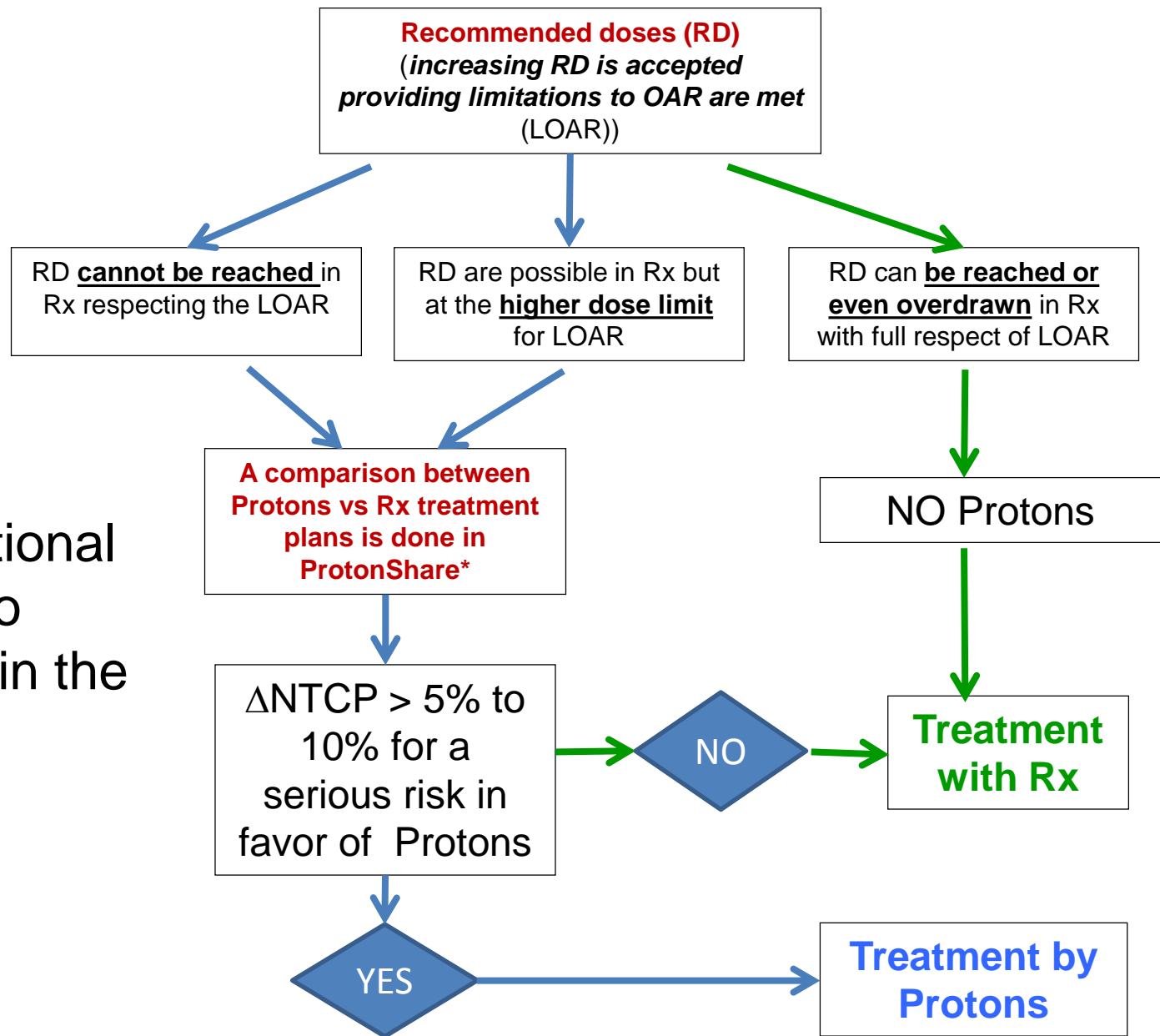
## PRESENT STATE OF INCLUSIONS

- **20 inclusions and 12 randomizations**

# TREATMENT RECOMMENDATIONS (Rx 2 Gy / fr)

- Adenoid cystic carcinoma
  - Photons 54 to 60 Gy; protons 50 and 70 Gy (RBE)
  - Carbon ions 60,8 to 64.0 Gy (RBE) in 16 fractions 4 per week.
- Chordoma
  - Photons 64 to 70; protons 74 Gy (RBE)
  - Carbon ions 70,4 à 73.6 Gy (RBE) in 16 fractions 4 per week.
- Sarcoma
  - Photons 64 to 70 Gy
  - Carbon ions 70,4 à 73,6 Gy (RBE) in 16 fractions 4 per week.

If necessary a quantitative rational can give way to protontherapy in the reference arm.



\* If the Rx dosimetry is fulfilling high quality criteria as IMRT calculated by a class at least (b) TPS

## Presently open centres

- |                                 |                      |
|---------------------------------|----------------------|
| 1. Lyon                         | 9. Bordeaux (CHU)    |
| 2. Grenoble                     | 10. Reims            |
| 3. Saint-Etienne                | 11. Lille            |
| 4. Nancy                        | 12. Strasbourg       |
| 5. Montpellier                  | 13. Clermont-Ferrand |
| 6. Nice                         | 14. Amiens           |
| 7. Pitié-Salpêtrière<br>(Paris) | 15. Toulouse         |
| 8. Caen                         | 16. Dijon            |
|                                 | 17. Nantes           |
|                                 | 18. IGR              |



1. Pavia CNAO

# **Two associated studies are carried out with the PHRC-ETOILE**

## **A biological study**

A retrospective evaluation of proteins and genomic radioresistance markers of the prospective population of the PHRC-ETOILE. Pr Claire Rodriguez-Lafrasse

## **A medico-economical study**

Comparison of full cost of each arm at long termes to assess the medical and societal utility (cost efficiency) of carbon ions. Christell Ganne and the French Health Insurance

# Specific difficulties of such type of trial

- To prepare and organise the trial took 6 years
- The lack of « experimental treatment » funding... (no corporation obligation and interest)
- The difficulties of any trial needing to refer patients to another centre... (loss of doctors' benefit!!!)
- The need of a higher commitment of patients
- The lack of investigators' refunding
- The long, long time course of this kind of research...
- Complementary collaborations in EU are necessary and would be welcomed!

**Presently franco-italian**



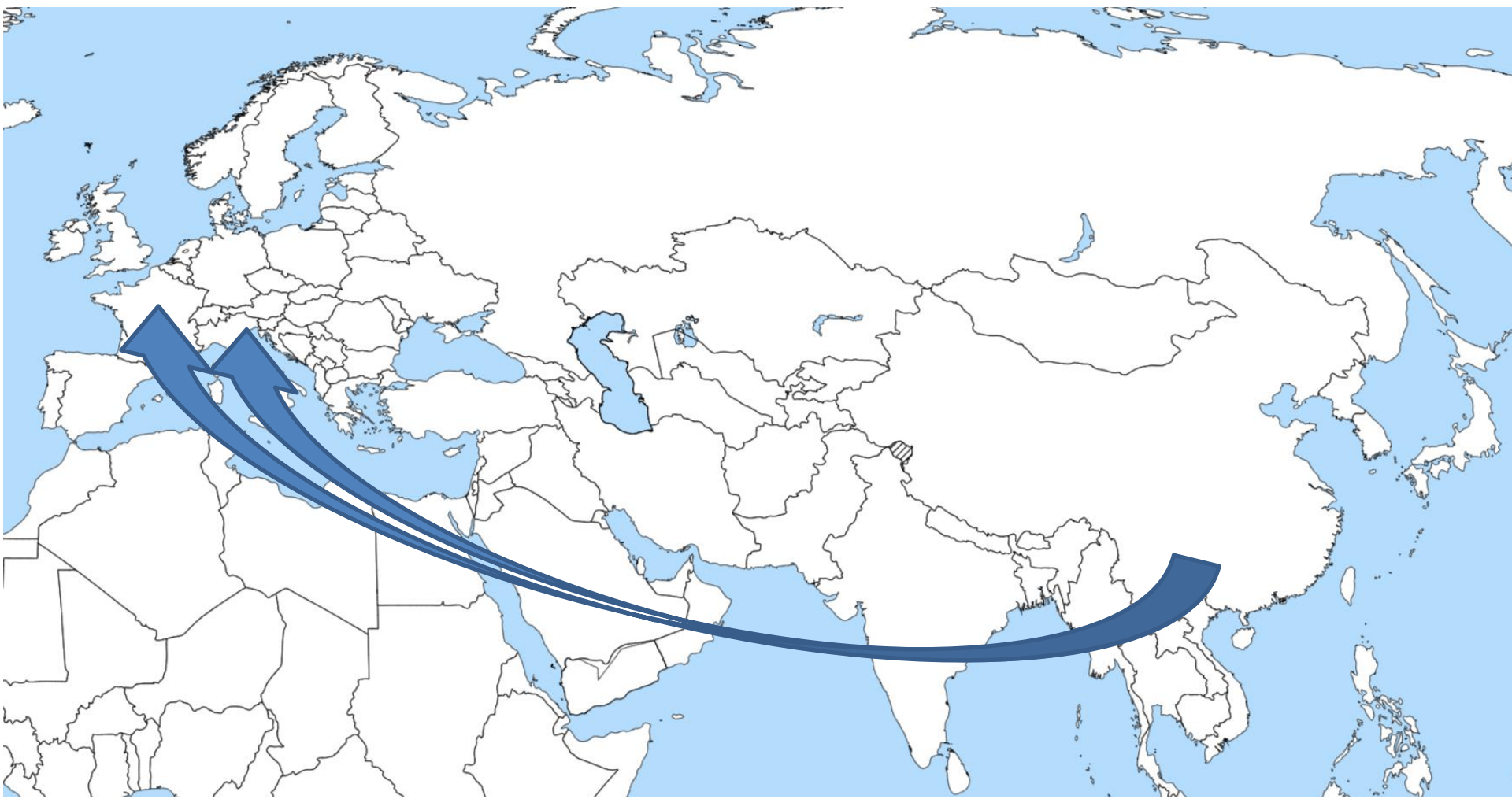
**A futur in other country ?**



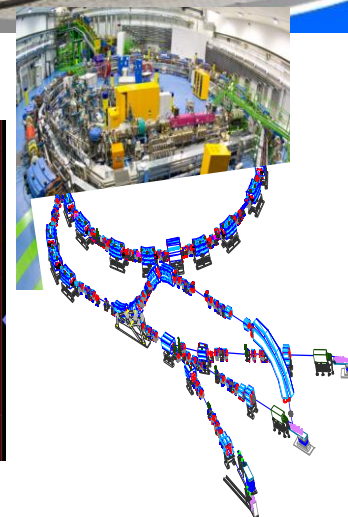
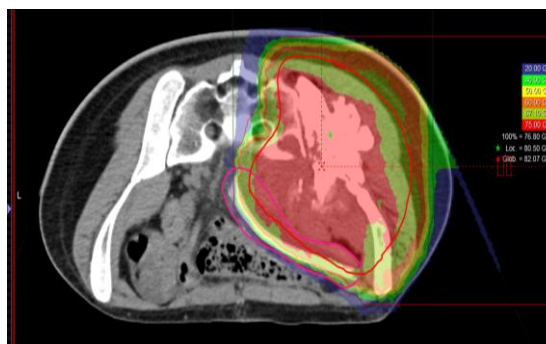
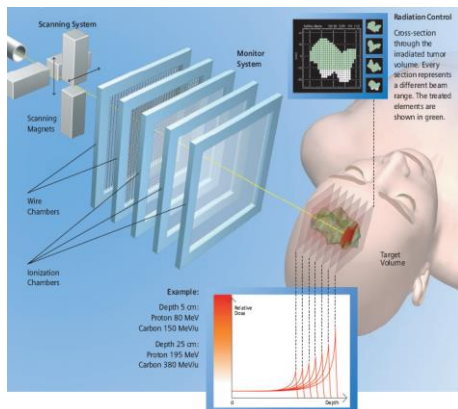
A map of Europe showing various countries. Four blue arrows point towards the Central European region, specifically towards the area between Germany, Poland, Czech Republic, Austria, and Slovakia. The arrows originate from the right side of the map and converge towards the center.



# Possibly a sino-european cooperation ?



Thanks  
CNAO



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# Thank-you, discussion...



Hospices Civils de Lyon



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