HITRI plus
Heavy Ion Therapy Research Integration

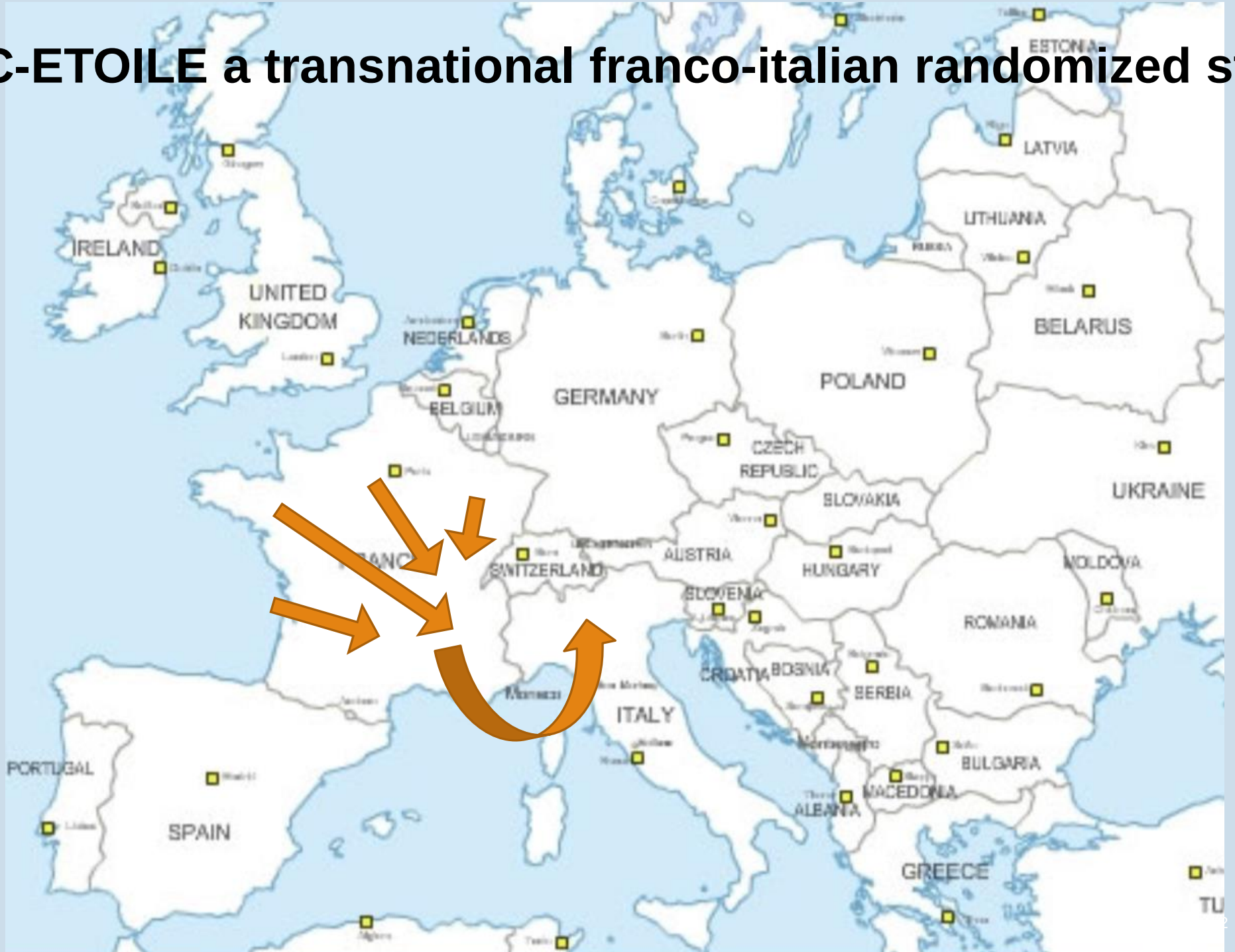
The French – Italian trial : PHRC-ETOILE

A randomized trial comparing carbon ions therapy vs. photon or protontherapy for radioresistant tumors.

Jacques Balosso , Olivia Febvey-Combes, Annie Iung, Helene Lozano, Abdoulkader Soumai Alloh, Catherine Cornu, Magali Herve, Zohra Akkal, Michel Lievre, Valerie Plattner, Francesca Valvo, Cristina Bono, Maria Rosaria Fiore, Viviana Vitolo, Barbara Vischioni, Stephanie Patin, Hubert Allemand, Francois Gueyffier, Jennifer Margier, Pascale Guerre, Sylvie Chabaud, Roberto Orecchia and Pascal Pommier

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

PHRC-ETOILE a transnational franco-italian randomized study



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Objective and history of the PHRC-ETOILE

- Since the opening of HIT in 2009 a rising demand of patients appeared in France, asking for the reimbursement by the French health insurance of carbontherapy proceeded in Germany.
- This urged **the Ministry of health and the Health insurance to ask for a scientific assessment of carbontherapy.**
- This mission has been given to the ETOILE-project group by the minister of health in October 2010.
- Thus an application for funding in the frame of the PHRC (Programme Hospitalier de Recherche Clinique) has been deposit in 2011.

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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

<u>According to the point of view of the health insurance</u>: “do we have to support this care and ultimately to provide it or not in France ?”

- Phase III multicentric – **transnational** – randomized trial
- The exp. arm (carbon ions) is exclusively carried out by the **CNAO** in Italy
- The reference arm (**photons or protons or both**) will be multicentric and carried out by the French investigating centers

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Main and secondary objectives

Main objective: to demonstrate a **20% improvement** of the **progression free survival** at 5 years

For a set of unresectable or after definitive R2 resection **radioresistant tumors** including: Adenoid Cystic Carcinoma, Chordoma, Sarcoma.

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)

- Analysis of molecular markers of radioresistance ***for sarcoma***

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Inclusion criteria (1/2)

Age ≥ 18 years

No severe comorbidities allowing a life expectancy > 10 years

Non resectable **or** non operable **or** definitive R2 resection of the tumor

Presumably radioresistant cancers according to the limited following list:

- **Adenoid Cystic Carcinoma (ACC) of head and neck** (laryngial and tracheal being excluded)
- **Soft tissues sarcoma including rhabdomyosarcoma (only pleiomorphic) and angiosarcoma**
- **Retroperitoneal sarcoma** unless technical limitations (over sized, moving…)
- **Osteosarcoma** of any location and grade except Ewing sarcoma
- **Chondrosarcoma** (skull base excluded) of grade WHO ≥ 2
- **Chordoma of the spine and the pelvic** (skull base excluded)

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Inclusion criteria (2/2)

No skin involment

Performance Status (PS) ECOG ≤ 2 or IK ≥ 60

Patient physically and psychologically able to follow treatments far from home

For women to rule out any pregnancy risk

Social security affiliation of the patient

Signed informed consent

To fulfill the **randomization criteria** :

- A radiotherapy proposal by the local specialized tumor board
- Validation of this proposal by the carbon ions center medical team (CNAO)
- Ability, by the carbon ions center, to initiate the treatment into the two coming months

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Exclusion criteria

R0 or R1 surgery

Previous irradiation of the same anatomic site

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 the vicinity

Previous cancer having less than 5 years of remission

Conditions making follow-up impossible.

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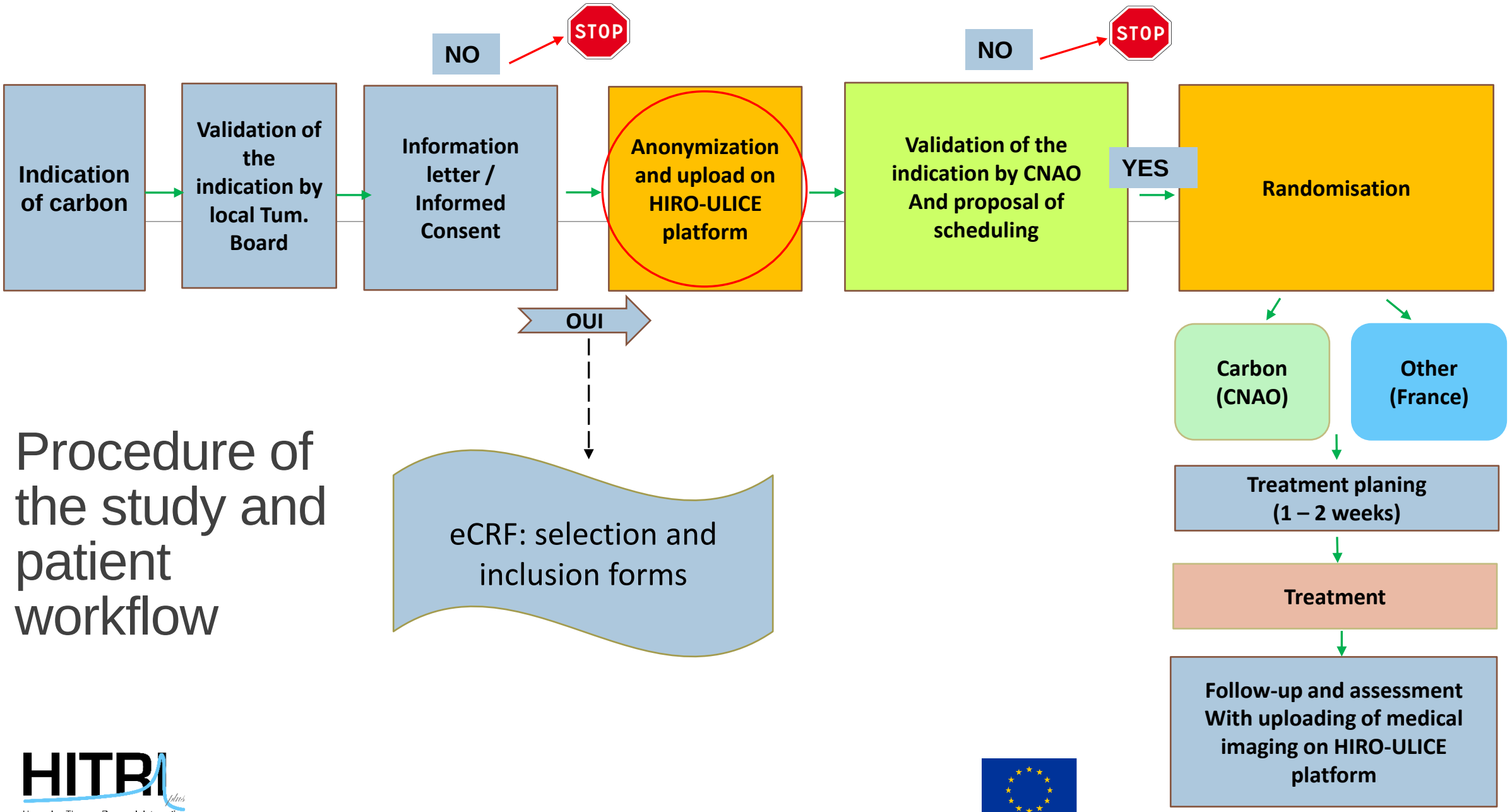
Procedure of the study and patient workflow



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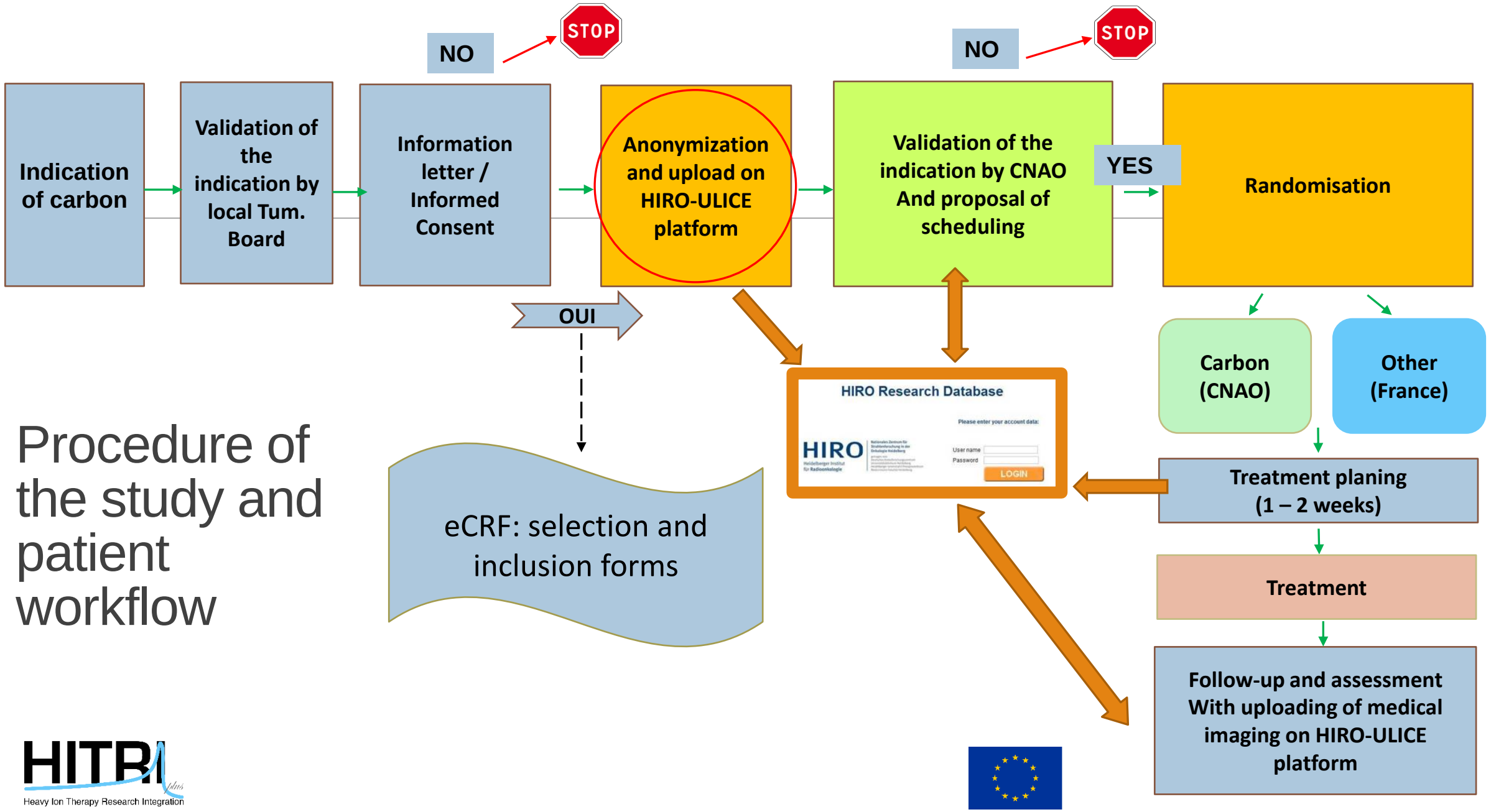

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Number of patients and duration of study

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.

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**

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Funding of the study

Sponsoring by the Univ. Hospit. of Lyon (HCL)

Financial support have been obtained

- PHRC 2011 (French government) about 500 k€ at the beginning
- CNAM all treatments and travels of patients (estimated 7 M€ for the whole study)
- Complementary support of the health ministry has been obtained later on (housing, etc.)

Data management is organized

- Access to the data exchange platform of Heidelberg (HIRO)
- Data management by Laennec Medical school in Lyon
- Statistics by the anti-cancer Centre Léon Bérard in Lyon

Carbontherapy by CNAO

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Treatment recommendations

Adenoid cystic carcinoma

- Photons 54 to 66 Gy / 30 fr; protons 50 and 70 Gy (RBE) / 35 fr
- Carbon ions 60,8 to 64.0 Gy (RBE) in 16 fractions 4 per week.

Chordoma

- Photons 66 to 74 Gy; protons 78 Gy (RBE) / 39 fr
- Carbon ions 70,4 à 73.6 Gy (RBE) in 16 fractions 4 per week.

Sarcoma

- Photons or protons 64 to 70 Gy
- Carbon ions 70,4 à 73,6 Gy (RBE) in 16 fractions 4 per week.

OAR protection according to current recommendations

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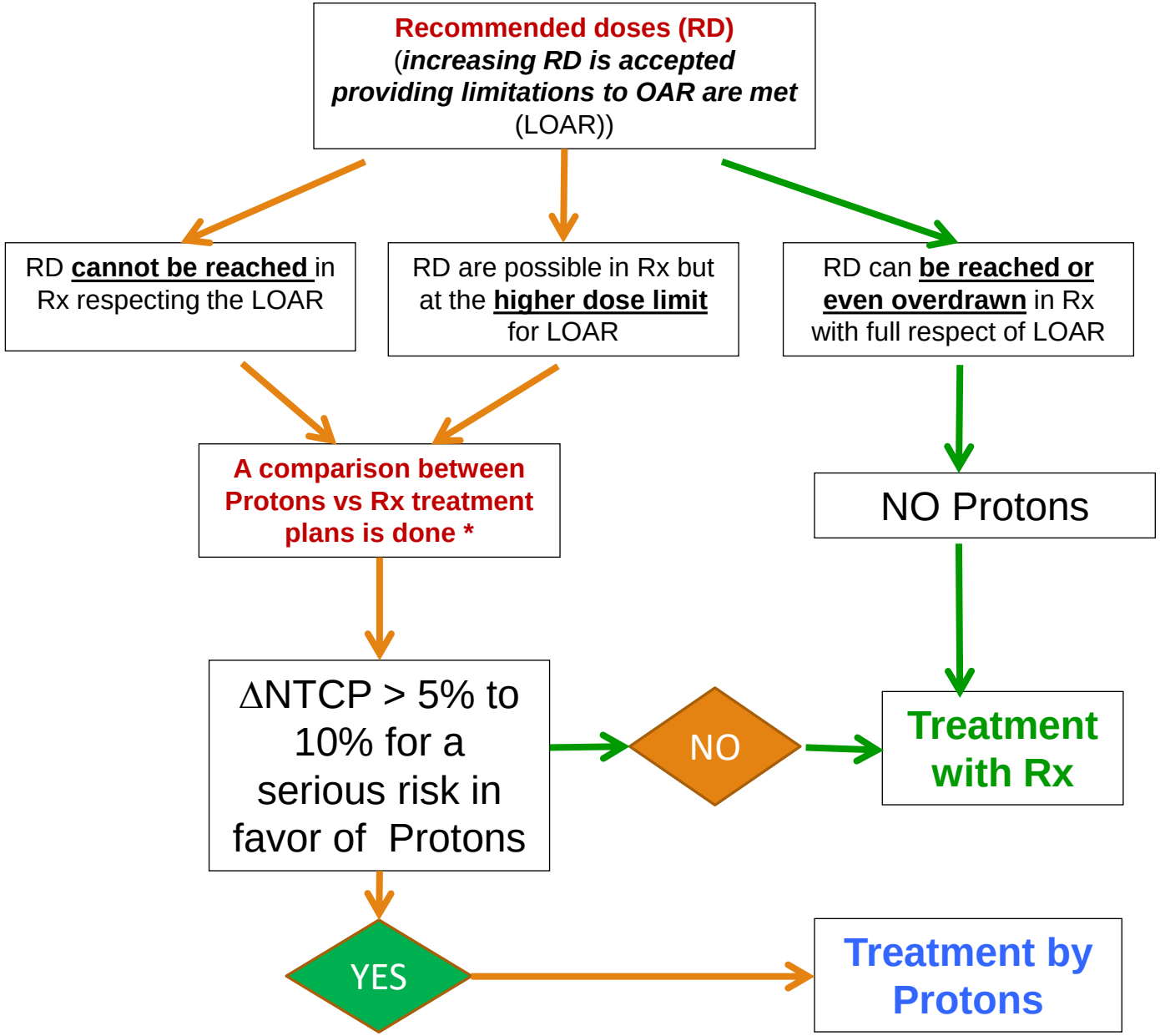
If necessary a quantitative rational can give way to protontherapy in the reference arm.



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

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Advance and the present state of the study

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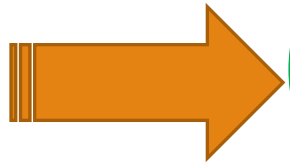
Presently open centres

France

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



Italy

1. Pavia CNAO

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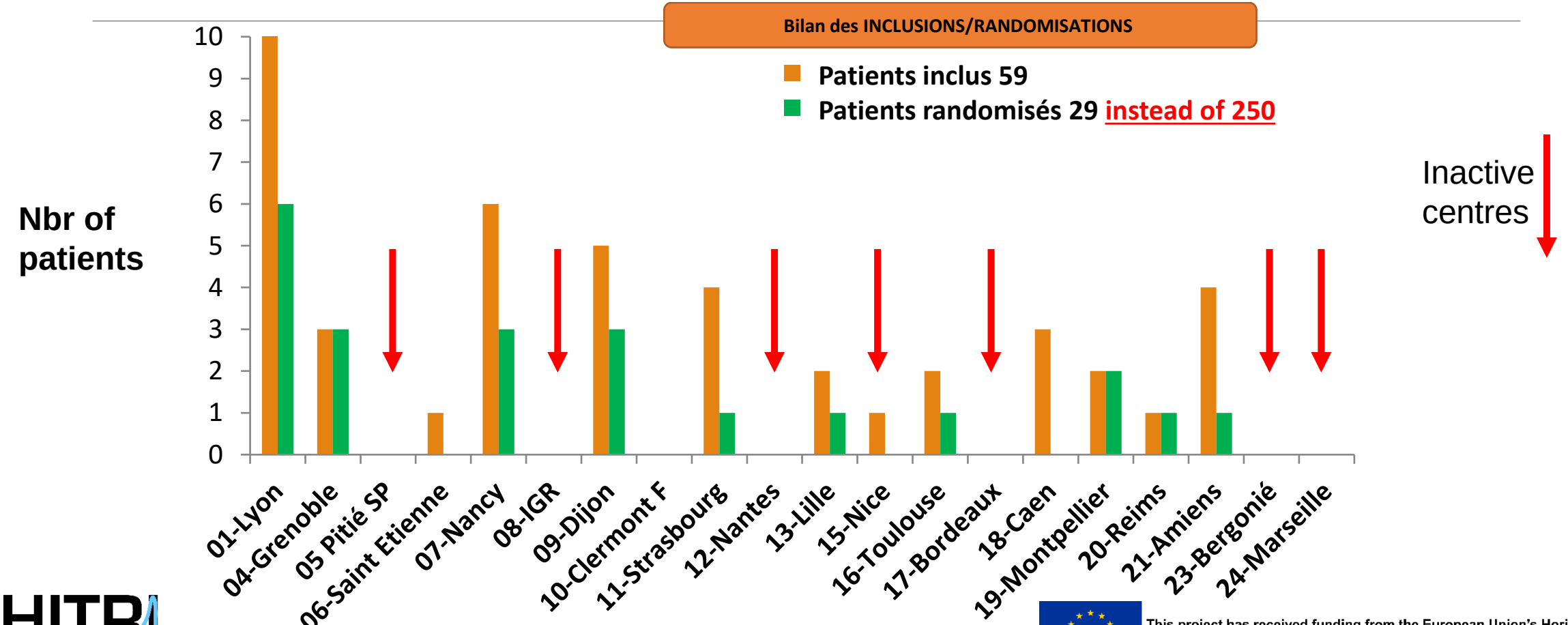
The recruitment status after 5 years of recruitment : 10% at end of June 2023 instead of … 100%



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Advancement and present state of the study

Inclusion rate per year and per centers in may 2022 (n=50)

Centres	2017	2018	2019	2020	2021	2022	
C01	0	4	2	3	2	3	**14**
C04	0	2	0	1	0	1	**4**
C06	0	0	0	1	0	0	**1**
C07	1	3	2	0	0	0	**6**
C09	0	2	2	0	0	1	**5**
C13	0	2	0	0	0	0	**2**
C11	0	0	1	1	2	0	**4**
C15	0	1	0	0	0	0	**1**
C16	0	0	2	0	0	0	**2**
C18	0	0	2	0	1	0	**3**
C19	0	0	0	2	0	0	**2**
C20	0	1	0	0	0	0	**1**
C21	0	2	0	2	0	1	**5**
	1	**17**	**11**	**10**	**5**	**6**	**50**
cumulated		18	29	39	44	50	

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Advancement and present state of the study

Types of tumours included

Adenoid Cystic Carcinomas (n=9)

Soft tissue sarcomas (n=5)

Osteosarcomas (n=5)

Chordomas (n=4)

Chondrosarcomas (n=2)

Total (n=25)

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Advancement and present state of the study

Raisons of non randomization of the recruited patients

50% of the recruited patients are not randomized for several reasons.

This rate remains stable throughout the 5 years of recruitment:

Included patients (n=50)

excluded from randomization (n=25)

- inclusion criteria not fulfilled (n=5)
- investigator decision (n=1)
- Informed consent not signed (n=1)
- **CNAO refusal (n=18)**

randomized (n=25)

- on follow-up (n=19)
- out of the study (mainly dead) (n=6)

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Advancement and present state of the study

Some reasons of refusal by the highly specialized team of the CNAO

- Tumor volume to large (CIRT field about 25 cm)
- Some image artefact due to dense materiel including cimentoplasty, osteosynthesis…
- Need of spacer sometime impossible to place
- N+ case for a ACC
- High risk of necrosis of a surgical reconstruction fatty flap
- High risk of osteoradionecrosis of skull base in ACC threatening internal carotid
- Difficult tumor location needing specific incidence angle not available without a gantry
- Palliative situation

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Discussion and recent decisions (1/3)

Specific difficulties of such type of trial

- To prepare and organise the trial took 6 years mainly due to the transnational formalities
- Eligible case are rare, thus any inclusion is a “restarting story” for investigators (difficult to gain a routine)
- Often to late referral with to advanced diseases
- The difficulties for Doctors to refer patients to another centre… (loss of doctors’ benefit)
- The patient commitment to go abroad for treatment (time, complexity, language, expenses)
- Some technical problems of complexity (S2 form demand, refunding of travel, computer compatibilities, …)
- The lack of « experimental treatment » funding… (no industrial obligation and interest)
- The lack of investigators’ attractive rewarding (compared to very attractive concurrent drug studies)
- Probably a lack of interest of most of the radiation-oncologists regarding hadrontherapy
- The long, long time course of this kind of research…

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Discussion and recent decisions (2/3)

Specific difficulties of the PHRC-ETOILE

- Difficulties to recruit patients (many large centers remained totally inactive)
  - this difficulty is similar for the recruitment for protontherapy in France
- A constant 50% rejection of recruited patients with no learning improvement has been an unexpected difficulty for investigators
- Several opportunities to extend the study have been voids :
  - no *sibling study* have been able to be set up (proposals in Lux, Italy and Austria)
  - no acceptance by the sponsor to enlarge the number of inclusion centers as «*associated (new) centers*» beside «reference (active) centers»

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Discussion and recent decisions (3/3)

- Finally the recruitment rate being to slow to make possible to fulfil the requirement of the study, the sponsor decided after several consultations of partners and investigators to stop randomization end of June 2023.

However…

- The French health authorities are keeping on demanding real comparative studies to estimate the real benefit of CIRT (and hadrontherapy in general)
- Outside randomization the definition of a unbias reference or control cohort is puzzling

  - the difficulties to *a priori* define a candidate patient for CIRT is a great concern: 50% chance of error for an investigator out of a CIRT center

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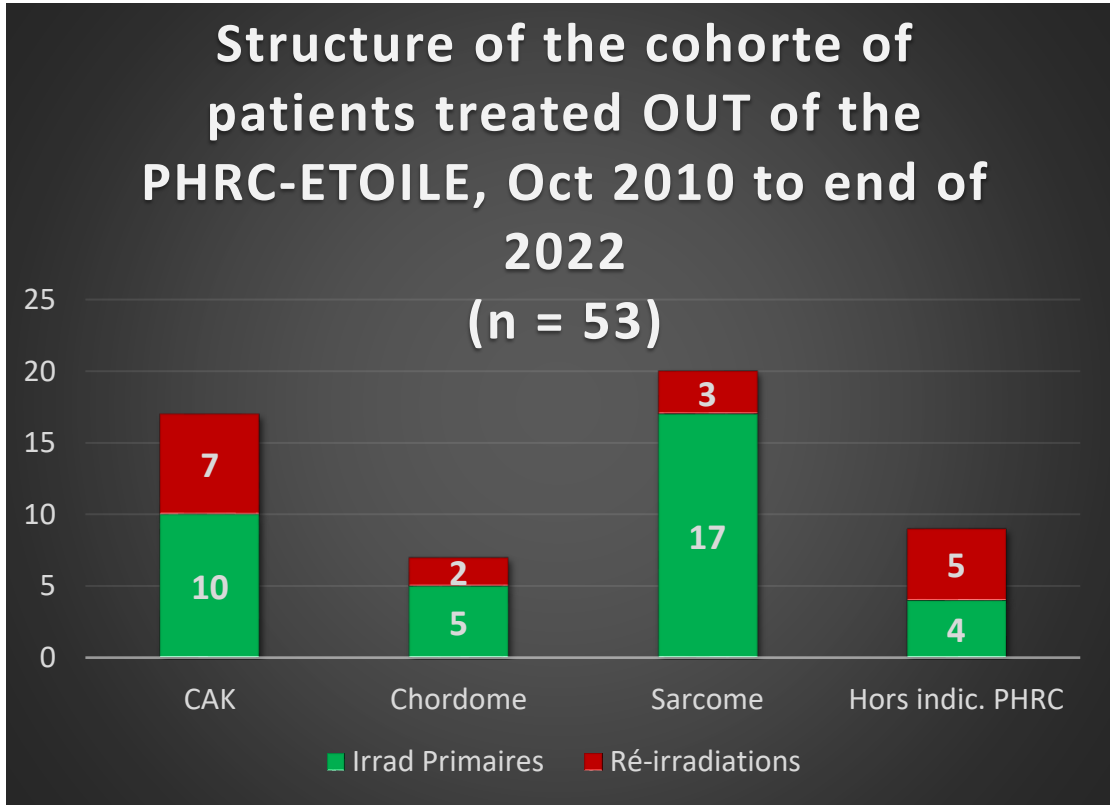
Perspective of continuation of comparative studies (1/3)

- Patients for CIRT will continue to be recruited and referred to HIT or CNAO at the expenses of the French Health Insurance (S2 European form) after case by case expert approval of the indications
- This is on-going since October 2010:

In the OUT of PHRC cohort there are 32 cases that can be cumulated with those of the carbon arm of the PHRC (n = 13): making 45 patients treated in radical intend by CIRT.



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Perspective of continuation of comparative studies (2/3)

- We can expect that a reasonable advertisement and a much simplified procedure will provide more patients than in the randomized study
- However the definition and moreover the set up of a control group is an unsolved problem as yet.
- The biological and the economics associated studies already very complex per se are objectives that must be kept in any future study.

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Perspective of continuation of comparative studies (3/3)

- We expect to developpe an **ETOILE-2** study still comparative but without randomization.

- This study will aim to fill the gap between the present time and the opening of the French CIRT center in Caen in 2027-28 for which the principles of prospective evaluation of the patients are still in discussion.

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Conclusion

1. Complex and rather expensive trials are by principle difficult in radiotherapy due to the lack of mandatory industrial sponsorship unlike for pharmaceutics
2. Everywhere MDs are reluctant to refer «their» patients to a remote center for an advanced treatment, even more in the frame of a (*complicated, time consuming, and not attractively paid*) study.
3. The lack of comparative trials is a concern and a danger for the future need of stable and adequate funding of CIRT by health insurances.
4. We should continue to make efforts to conduct and fund comparative trials and to resume randomization as soon as possible.
5. Prospective multi-center meta-analysis could also have a place in the attempt of increasing the power of several isolated (truncated) studies.

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Thank you

ETOILE

Etude prospective du PHRC 2011
PHRC-ETOILE

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https://doi.org/10.1186/s12885-022-09564-7

BMC Cancer

STUDY PROTOCOL Open Access

A randomized controlled phase III study comparing hadrontherapy with carbon ions versus conventional radiotherapy – including photon and proton therapy – for the treatment of radioresistant tumors: the ETOILE trial

Jacques Balosso[1*], Olivia Febvey-Combes[2], Annie Iung[3], Hélène Lozano[2], Abdoulkader Soumai Alloh[3], Catherine Cornu[4,5], Magali Hervé[2], Zohra Akkal[2], Michel Lièvre[4], Valérie Plattner[3], Francesca Valvo[6], Cristina Bono[6], Maria Rosaria Fiore[6], Viviana Vitolo[6], Barbara Vischioni[6], Stéphanie Patin[7], Hubert Allemand[8], François Gueyffier[2,4], Jennifer Margier[2], Pascale Guerre[2,9], Sylvie Chabaud[10], Roberto Orecchia[6,11] and Pascal Pommier[12]

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