Management of breast cancer in France

4th International Congress of Breast Disease Centers

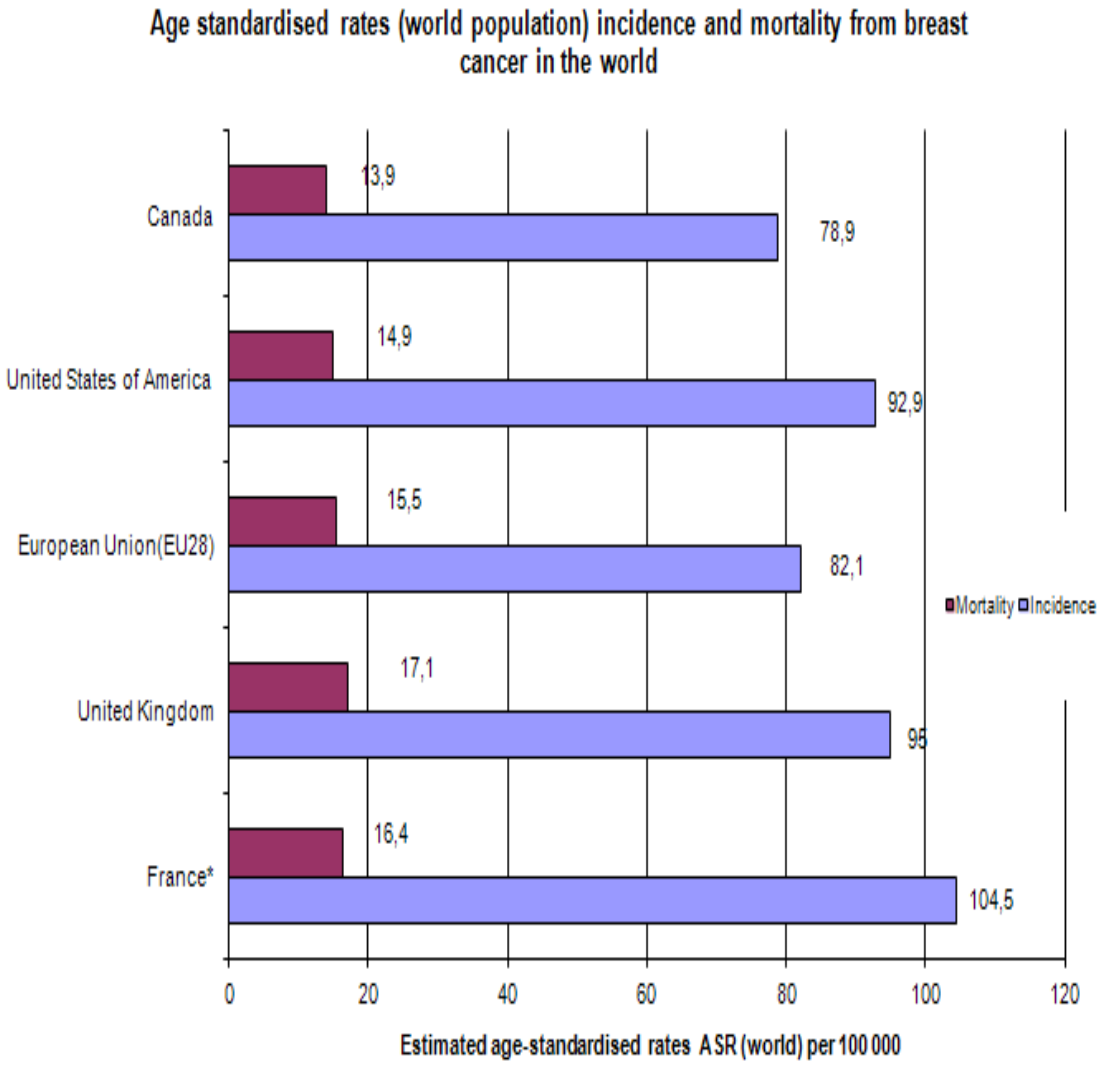
February 5, 2014

Pr Agnès Buzyn
French National Cancer Institute

Worldwide situation

- **Incidence** : France is amongst European countries with the highest rate of breast cancer such as Belgium, Denmark, UK…

- **Mortality** : a slight variation is observed between European countries

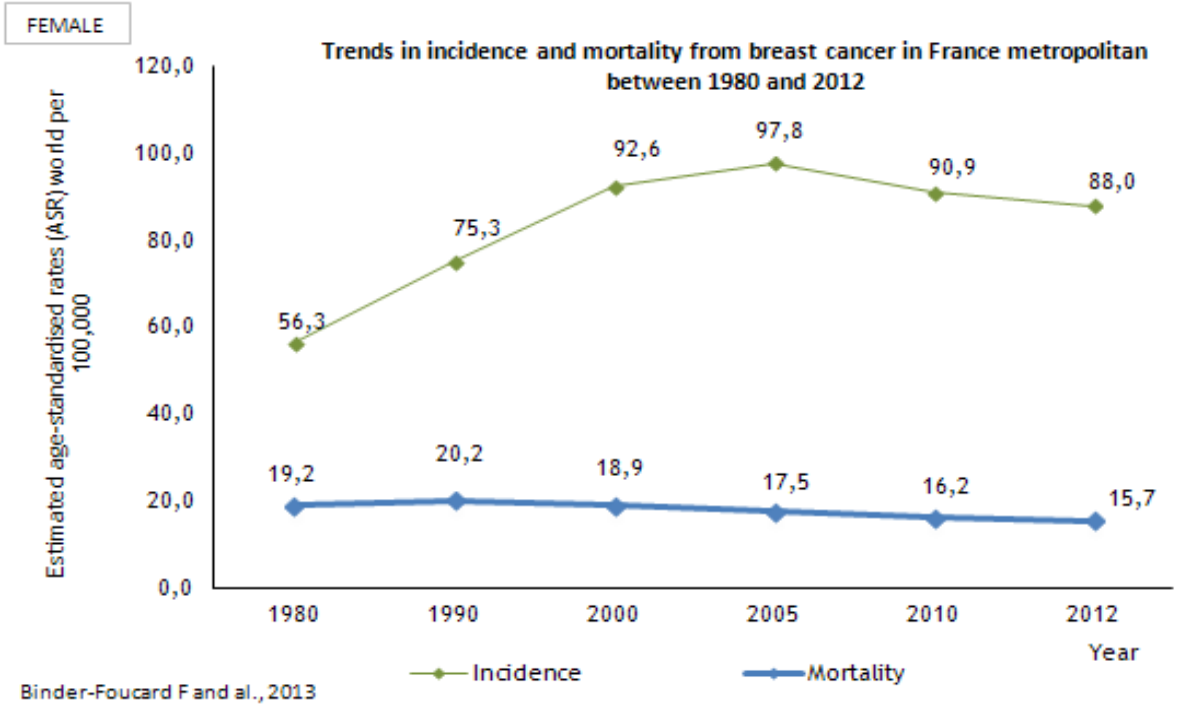


Globocan 2012; * projected rates from 2011

Incidence and mortality in France

Incidence in 2012

- ✓ ≈ 48 800 estimated cases
- ✓ ASR (world) : 88 per 100 000 women
- ✓ Median age at Dg: 63 years old
- ✓ The most frequent cancer in women, ≈ 32% of all female cancers
- ✓ 50% cases occurred in women 50-74 years old



Binder-Foucard F and al., 2013

- **Mortality in 2012**

- ≈ 11 900 estimated deaths
- ASR (world) : 15,7 per 100 000 women
- Median age at death : 73 years old
- First cause of mortality cancer in women
- 70% of deaths occurred in women > 65 years

Breast cancer survival and prevalence

- **Trend in incidence and mortality**

  - Strong increase in incidence rates between 1980 and 2000,
  - Decrease since 2005

  - Stability of mortality rates until 1995
  - Decrease of mortality rates since 2012

- **5 and 10-year net survival of cancer patients diagnosed in 1989-2004**

  - 86% at 5-years and improving with time
  - 76% at 10-years (83% for women 45-54 years old vs 65% for women ≥ 75 years)

- **Total prevalence**

  ≈ 650 000 women with breast cancer (present or past) and still alive in 2008

Survival : Worldwide situation

EUROCARE-5

- Survival in 29 European countries for patients (> 15 yr) with cancer diagnosed between 2000 and 2007 :
- In most countries, except eastern Europe (73.7%), 5-yr relative survival is close to European mean (81.8%)
- 5-yr relative survival varies from 66.7% (Lithuania) to 87.2% (Iceland); UK and Ireland (79.2%)
- France is one of the countries with the highest **5-yr relative survival rate (86.1%)** such as Iceland (87.2%) and Sweden (86.0%)

- **The French breast cancer screening program**

  - Organized by the public authorities
  - Generalized since 2004
  - Use of Digital Mammography authorised since 2008

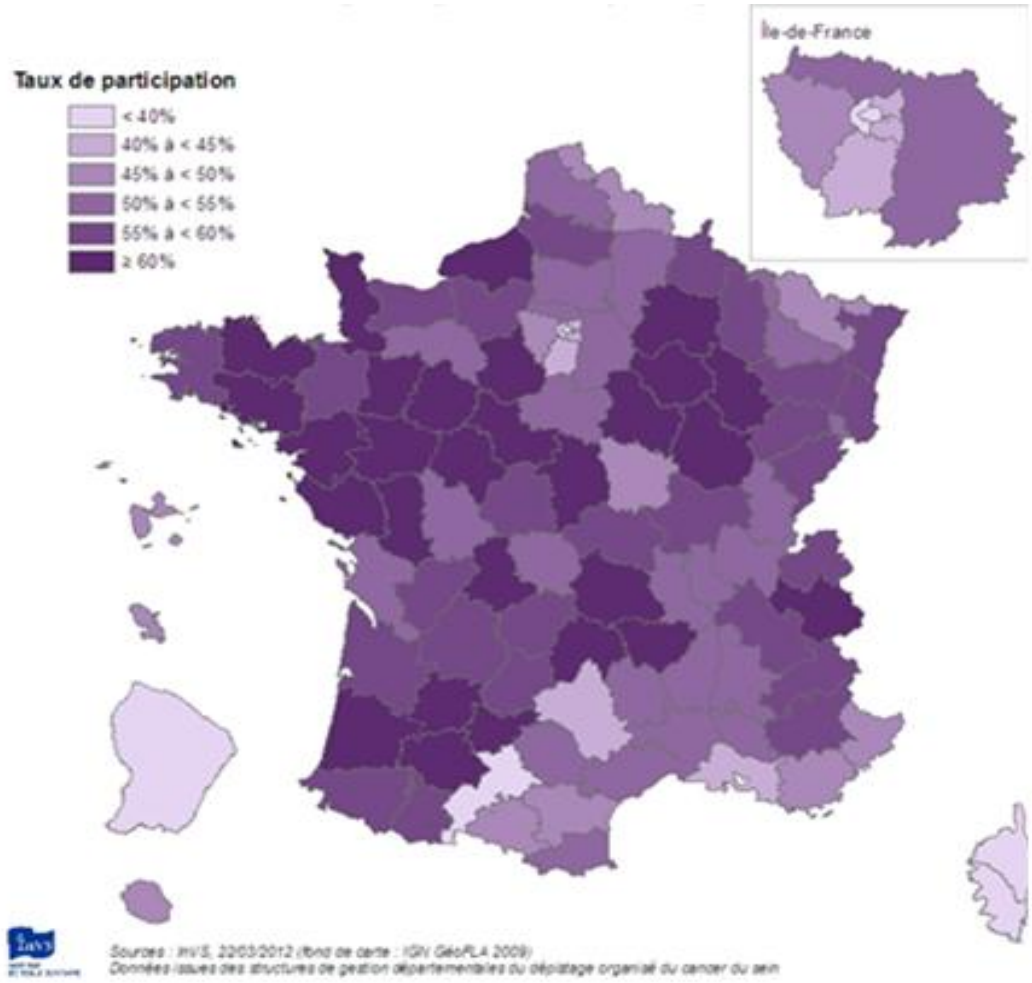
- **Modalities**

  - Target age group : 50-74 years old (size : 9 million women)
  - Invitation every 2 years
  - Screening test : clinical exam + 2-views mammography (free of charge)
  - 2nd reading centralized for negative mammography

- **Coexistence of organized screening and opportunistic screening**

Breast cancer screening : participation rates
to the french breast cancer screening program

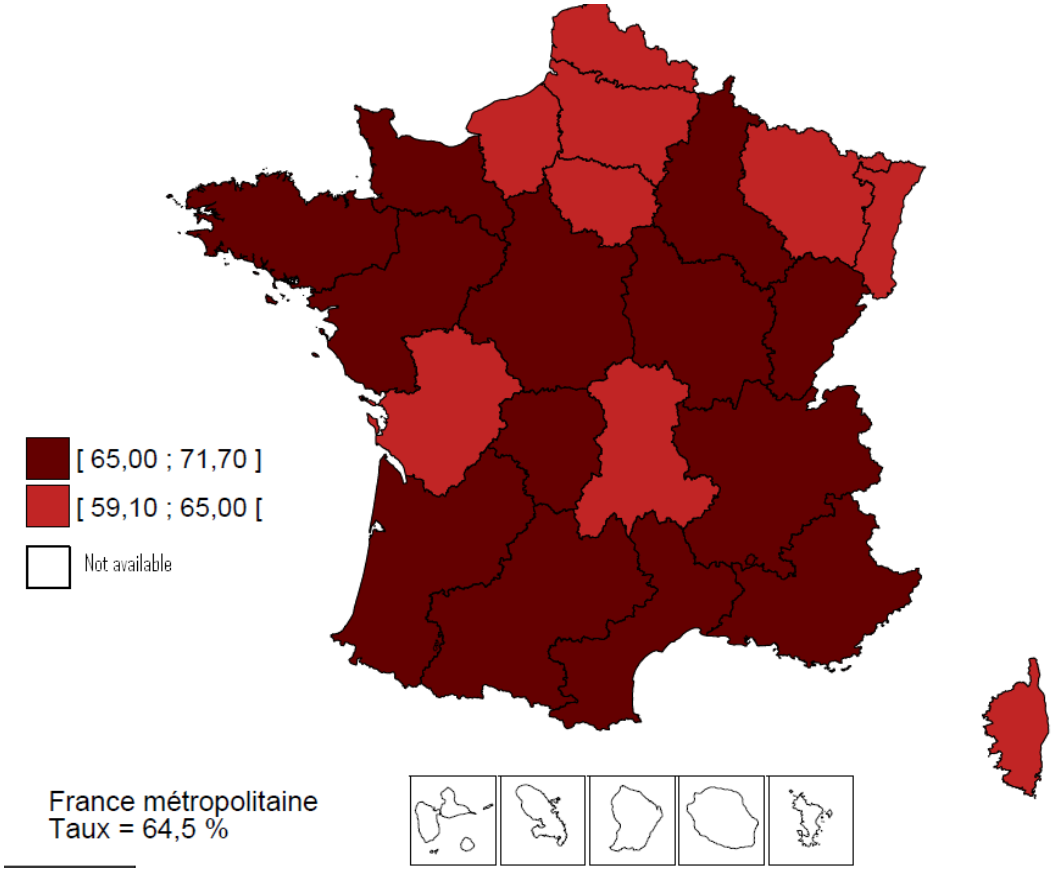
- **Breast cancer screening participation rate (2012) : 53%** (2,4 million women)



Heterogeneity in départemental participation rates : 27 % to 67 %

Organized screening and opportunistic screening – estimated coverage (50-74 years old)

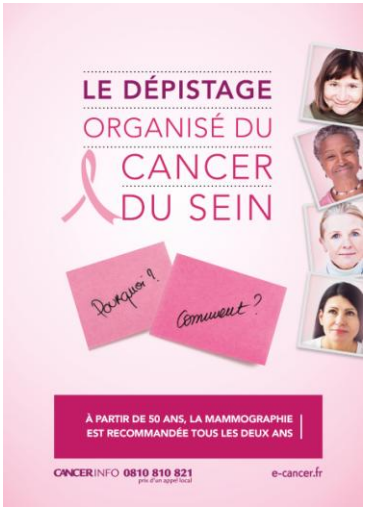
- Exploitation of Senolog, a national database for organized and opportunistic mammography screening
- National estimated coverage of organized and opportunistic screening **65 %**



Homogeneity in regional rates (organized and opportunistic screening) :
The regions with the lowest organized participation rates have the highest level of opportunistic screening.

Balanced and accessible information about breast cancer screening

- **Promote informed choice in cancer screening :**
  - Recommendations on ethical issues by an independent board
  - Benchmark of communications developed in countries with organized screening program
  - Qualitative study to investigate women knowledge of benefits and harms and questions about screening



- Development of a complete and clear information with the collaboration of a **stakeholders working group**

- **Three levels of information** : the leaflet with the invitation letter / a 20 pages document / the web site

- Annual **radio campaign**

High quality healthcare promotion : Guidelines for clinical practices

- **Guidelines/expertise production and implementation to set standards for high quality clinical practices**
  - Targeting topics where "**loss of chance**" risks are identified
  - Involving **French learned societies**
  - With a **reliable methodology** : based on the best evidence, transparent, rigorous in its development process and independent

- **Breast cancer :**
  - **Earlier stages at diagnosis** (screening expansion policy, diagnosis techniques performances improvement..)
  - And **better knowledge/level of evidence** to promote less aggressive approaches

Make sure treatment delivery is adapted to cancer's stage and aggressivity as one major stake

High quality healthcare promotion : Guidelines for General practioners

- **Clinical practice guidelines for General practitioners :**

In order to ensure optimal patient referral and coordination between hospital and primary care teams

Guides on 25 locations of cancers, including breast cancer, with highlights on the role of GPs in :

- Diagnosis strategy and initial referral of patients ,
- Care strategy and side effects management in coordination with specialists,
- Shared follow-up between specialists and GPs,
- Quality of life management.

An evaluation of the needs of GPs (survey on 400 professionals)

- 2/3 are looking for information at least once a month for one of their patients;
- their needs: diagnosis of cancer (74%), care strategy and side (95%), ongoing follow-up (74%), screening (74%), practical information(referral, social aspects).

- **Developing patients information :**

- **“Cancer info” is an information platform (helpline, brochures collection and an internet session on the Institute’s website) for patients and close relatives** which provides valuable, reference and up-to-date medical and social information on cancers and life with cancer. It is meant to be :
  - a communication tool to serve patients-professionals relations;
  - a reference point in a large offer of information.

- The French National League Against Cancer (LNCC) is our privileged partner, along with a panel of associations involved in patients information.

high quality and security healthcare : scheme for authorisations of cancer treatment

- **Authorizations for cancer treatment :**

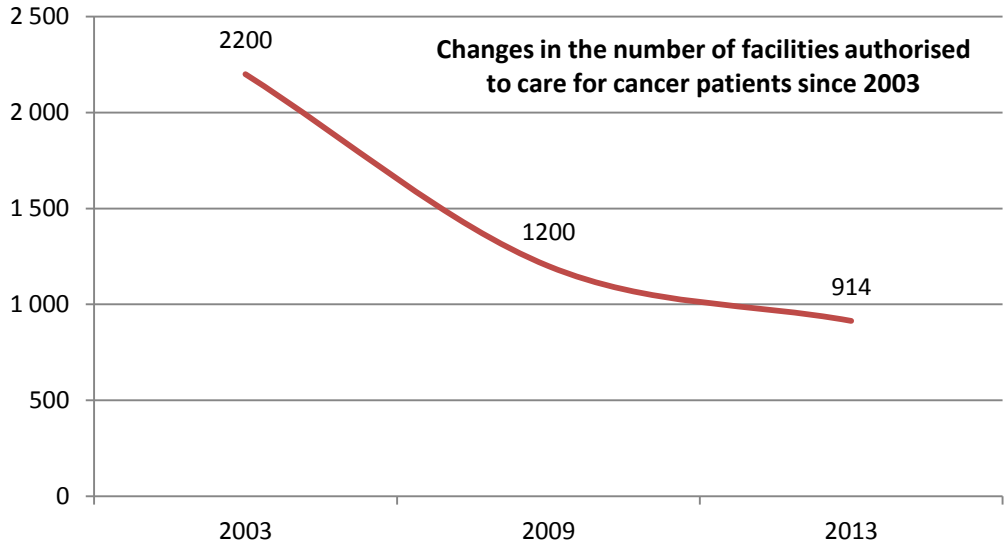
  to guarantee a minimum level of quality and safety of care, consistent for all patients.

  - cross-disciplinary measures for quality,
  - specific accreditation criteria
  - minimum activity threshold for 3 medical specialties (chemotherapy, radiotherapy and surgery).

- **At the end of the first 5 years, authorizations issued by the Regional Health Agency to healthcare institutions :**

  - Radiotherapy : 171
  - Chemotherapy : 503
  - breast surgery* : 430

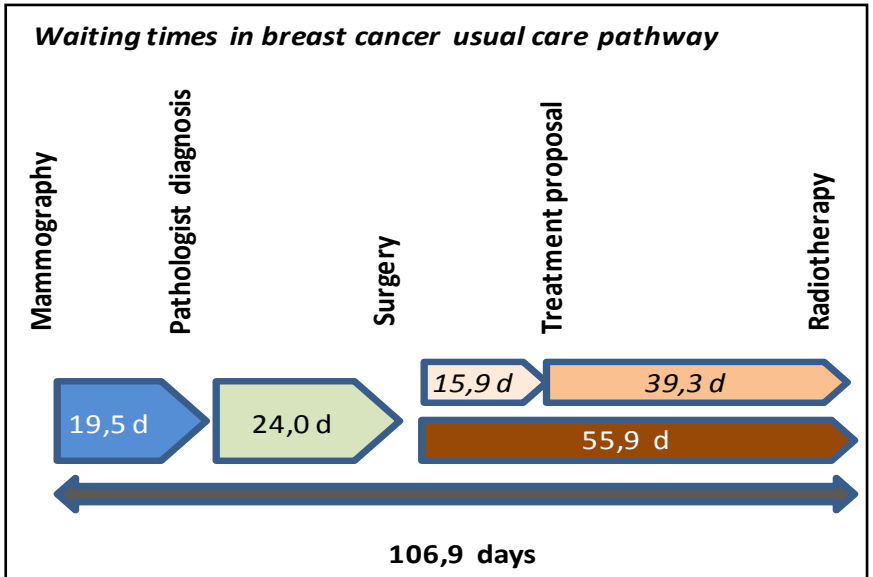
* Minimum threshold = 30 ops/year (one missing region)



Measuring waiting times in breast cancer care

Study in several French regions in 2011 *

To determine the most representative waiting times in breast cancer care in several regions of France



To analyze the influence of individual, medical or health care system factors on those waiting times

- Age, circumstance of diagnosis, tumor stage, category of care center had an influence
- Important differences between regions that could be explained by organizational factors or individual factors (social vulnerability, category of employment,…)

Waiting time is one indicator of quality of cancer care and could reveal inequalities in cancer care access.

**:Waiting times for cancer care in four most frequent cancers in several French regions in 2011 and 2012, Bull Cancer , December 2013*

Targeted intraoperative radiotherapy (IORT)
call for applications initiated in 2011

- **Context :**

  - Progressive increase of advanced mode of high-precision radiotherapy

  - Patient cares : development of a more refined and personalized approach, new treatment protocols with a reduced number of fractions (SHARE, TARGIT, ELIOT, etc.)

- **Objectives :**

  regarding intermediate positive results of international trials on IORT, INCa intended to run an economical assessment in order to anticipate prerequisites to national deployment

  - Run the medico-economic assessment of IORT versus fractionated external beam radiotherapy (standard treatment)

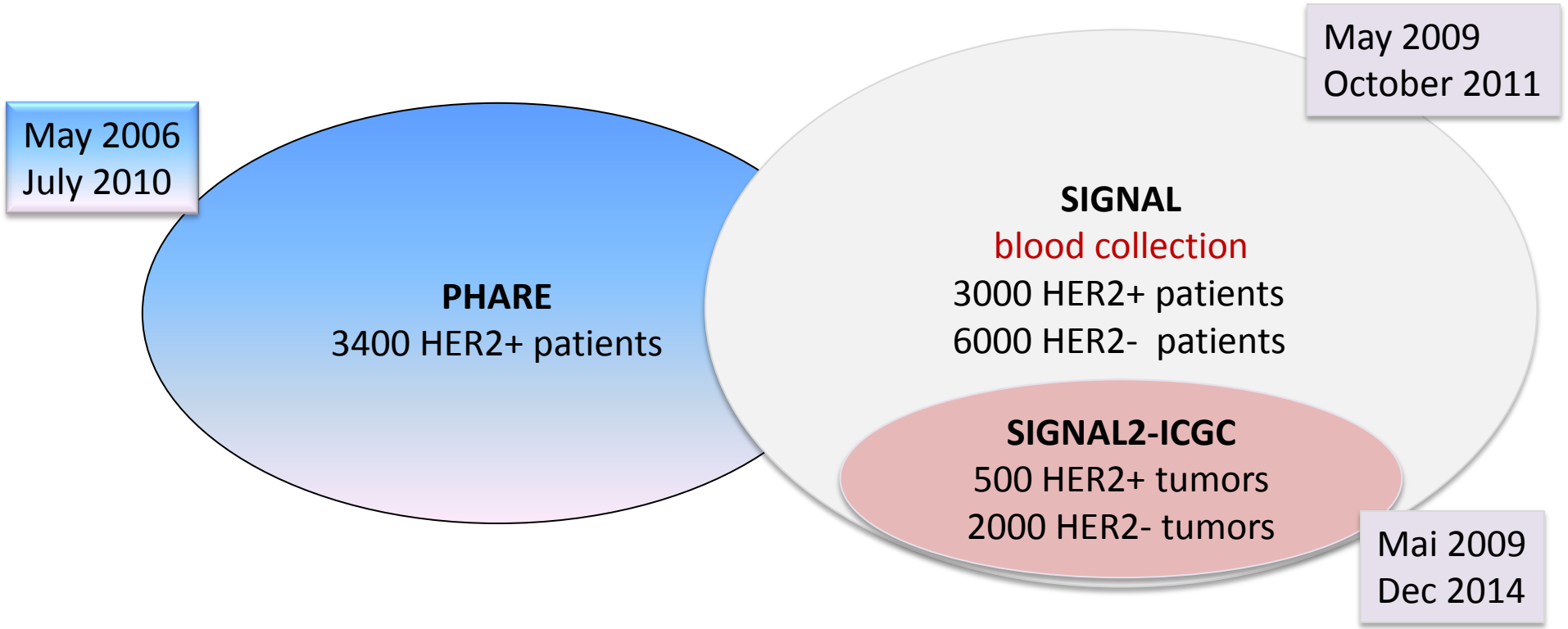
  - Define, implement and validate organisational procedures, radiation protection conditions, treatment protocols, etc.

Targeted intraoperative radiotherapy (IORT)
call for applications initiated in 2011

- **Rational : IORT advantages**
  - One-off radiation treatment at the time of surgery versus standard treatment (25 to 33 fractions)
  - Better consideration for patients with limited access to radiotherapy (clinical dilemma for patients suitable for breast conserving surgery but unable to attend daily for up to 6 weeks for postoperative radiotherapy, that will face mastectomy)
  - Optimized accuracy for surgical banks irradiation
  - No additional ambulance required

- **Assessment (in progress) :**
- **2M€ budget, prospective randomized assessment, 203 menopausal women aged 55 and older with invasive ductal carcinoma enrolled so far in 8 centers. Final conclusions expected for February 2014.**

INCa-sponsored BC research program



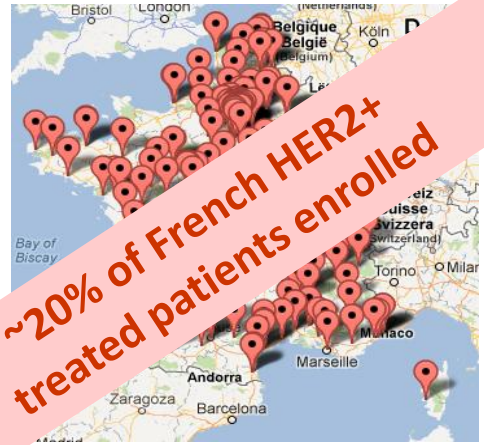
- PHARE : Clinical trial comparing 6 mo vs 12 mo of trastuzumab
- 10 years follow-up

- SIGNAL : genetics study → SNP predictive for toxicity/relapse
- 5 years follow-up
- Epidemiological data & blood collection

- SIGNAL2-ICGC : somatic mutations catalog
- All above & tumor collection

PHARE trial design

Activated: 30/05/2006



~20% of French HER2+ treated patients enrolled

Randomization
3384 patients

4 patients excluded from analysis
- 1 Informed consent not signed
- 1 Randomized twice
- 2 HER2 negative after FISH testing

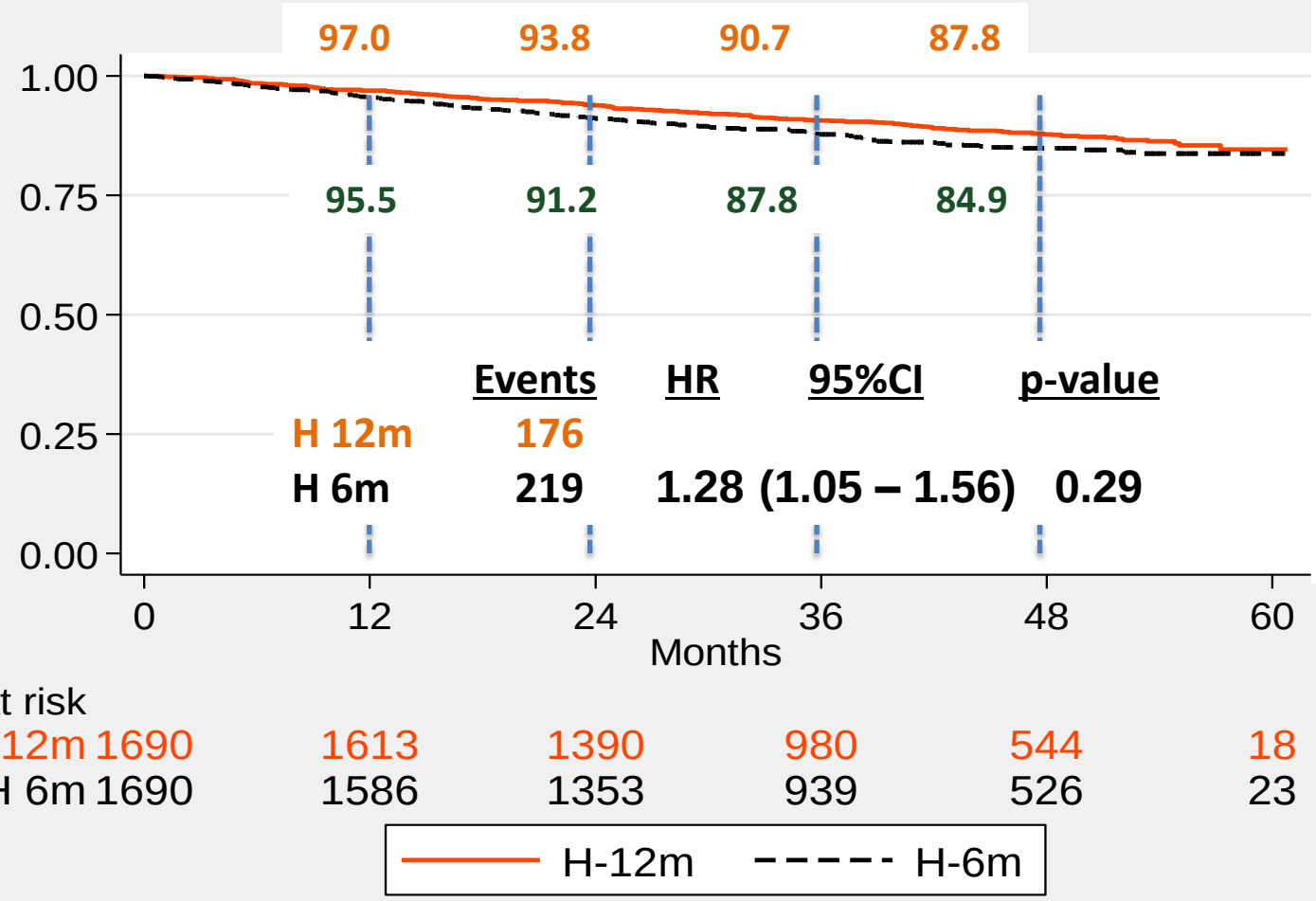
Trastuzumab 12 months
1690 patients

Trastuzumab 6 months
1690 patients

Closed: 09/07/2010
Database locked: 31/07/2012

- 156 investigation sites
- 350 investigators
- 100 study nurses

PHARE trial results (DFS)



6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial

*Xavier Pivot, Gilles Romieu, Marc Debled, Jean-Yves Pierga, Pierre Kerbrat, Thomas Bachelot, Alain Lortholary, Marc Espié, Pierre Fumoleau, Daniel Serin, Jean-Philippe Jacquin, Christelle Jouannaud, Maria Rios, Sophie Abadie-Lacourtoisie, Nicole Tubiana-Mathieu, Laurent Cany, Stéphanie Catala, David Khayat, Iris Pauporté, Andrew Kramar, and the PHARE trial investigators**

Summary

Background Since 2005, 12 months of adjuvant trastuzumab has been the standard treatment for patients with HER2-positive early-stage breast cancer. However, the optimum duration of treatment has been debated. We did a non-inferiority trial of a shorter exposure of 6 months versus the standard 12 months of trastuzumab for patients with early breast cancer.

Methods We did an open-label, randomised, phase 3 trial in 156 centres in France. Patients with HER2-positive early breast cancer who had received at least four cycles of chemotherapy, had breast-axillary surgery, and had received up to 6 months of trastuzumab (administered by intravenous infusions over 30–90 min every 3 weeks; initial loading dose 8 mg/kg; 6 mg/kg thereafter) before randomisation were eligible. Patients were randomly assigned via central randomisation procedure with web-based software to continue trastuzumab for another 6 months (12 months total duration; control group) or to discontinue trastuzumab at 6 months (6 months total duration; experimental group). Randomisation was stratified by concomitant or sequential administration of trastuzumab with chemotherapy, oestrogen-receptor status, and centre using a minimisation algorithm. The primary endpoint was disease-free survival, with a prespecified non-inferiority margin of 1·15. Analyses were done in the intention-to-treat population. This study is registered at ClinicalTrials.gov, number NCT00381901.

Findings 1691 patients were randomly assigned to receive 12 months of trastuzumab and 1693 to receive 6 months of trastuzumab; 1690 patients in each group were included in the intention-to-treat analyses. After a median follow-up of 42·5 months (IQR 30·1–51·6), 175 disease-free survival events were noted in the 12-month group and 219 in the 6-month group. 2-year disease-free survival was 93·8% (95% CI 92·6–94·9) in the 12-month group and 91·1% (89·7–92·4) in the 6-month group (hazard ratio 1·28, 95% CI 1·05–1·56; p=0·29). 119 (93%) of the 128 cardiac events (clinical or based on assessment of left ventricular ejection fraction) occurred while patients were receiving trastuzumab. Significantly more patients in the 12-month group experienced a cardiac event than did those in the 6-month group (96 [5·7%] of 1690 patients *vs* 32 [1·9%] of 1690 patients, p<0·0001).

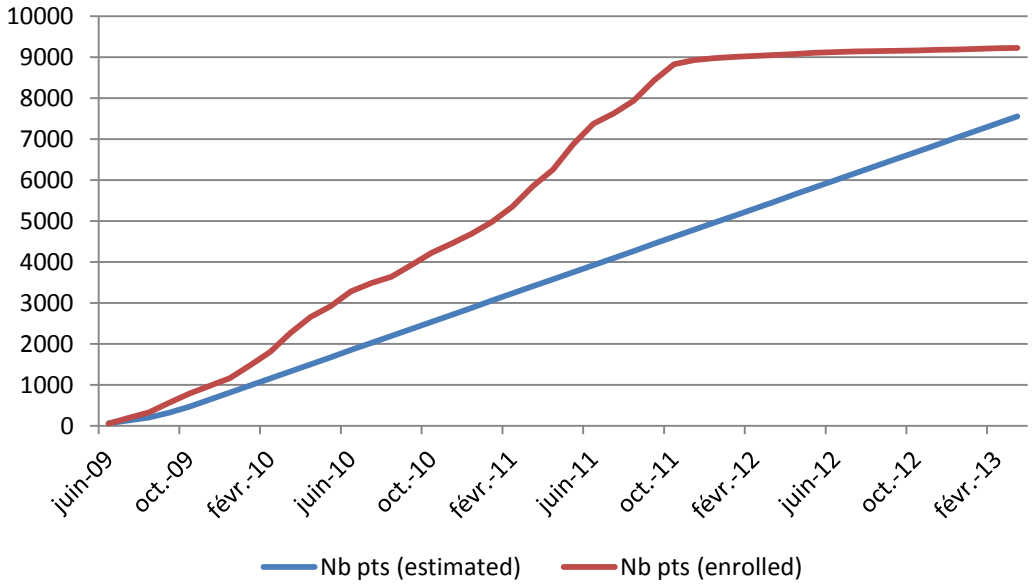
Interpretation After 3·5 years follow-up, we failed to show that 6 months of treatment with trastuzumab was non-inferior to 12 months of trastuzumab. Despite the higher rates of cardiac events, 12 months of adjuvant trastuzumab should remain the standard of care.

Funding French National Cancer Institute.

Pivot et al, Lancet O 2013

➢ non-inferiority was not demonstrated; subgroup analysis to be published in 2014

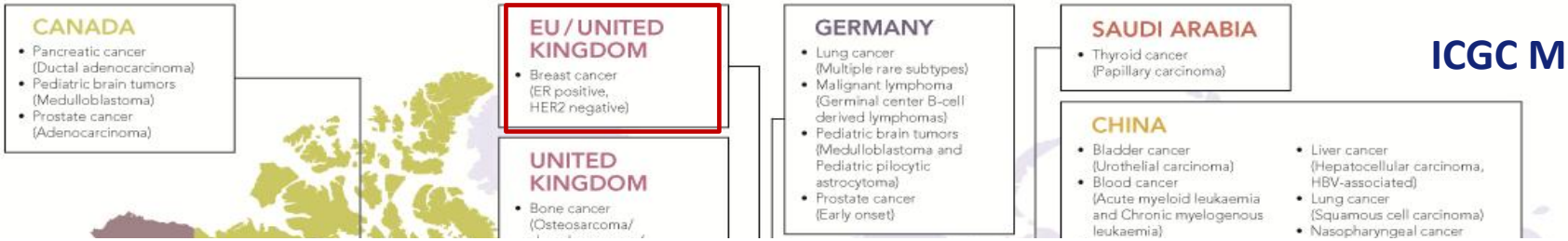
SIGNAL status



- 112 investigation sites
- > 9300 patients data & blood samples
- Genotyping started

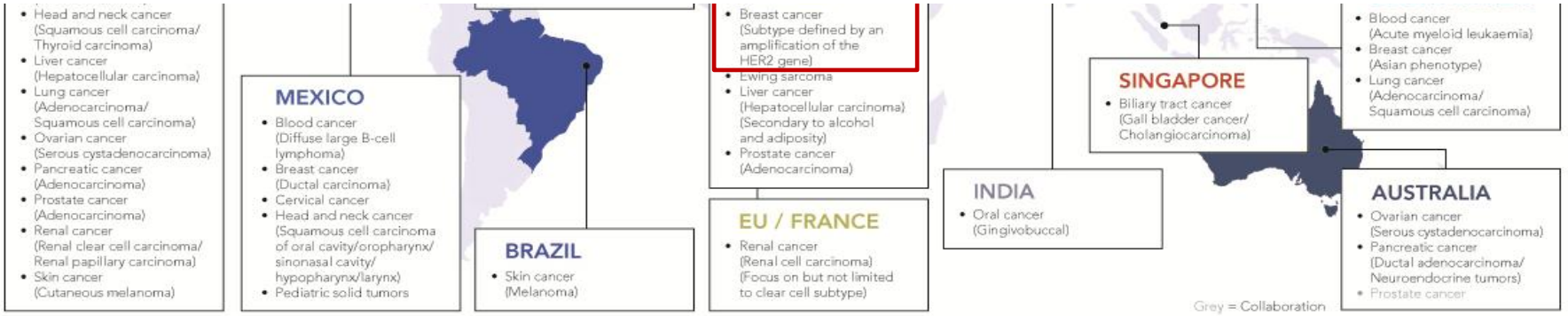
→ **First results in 2014**

INCa commitment - BC



ICGC Map - Nov 2013

- 12 French centers participate : common procedures and biobank
- 700 BC samples in the common biobank
- 200 BC samples in the sequencing pipeline
- 50 HER2+ samples analysed → **first results in 2014**



www.icgc.org

INCa-funded BC projects (2005-2012)

	Nb projects	Funding (M€)
Education	**9**	**0,71**
PhDs	3	0,28
Post-PhDs	3	0,26
Translationnal Research for MDs	3	0,17
Clinical Research	**54**	**21,59**
Early phase trials network	1	0,6
Hospital Clinical Research Projects	48	16,86
Medico-Economics	5	4,13
Translationnal Research Projects	**19**	**3,69**
Patients' Care	**15**	**3,1**
Oncogenetics	7	1,3
Other	8	1,8
Basic Research	**10**	**5,81**
Projects	8	3,21
Networks	2	2,6
Human & Social Sciences	**28**	**4,9**
Epidemiology	17	2,99
Human Sciences	11	1,91
Patients' advocacy	**7**	**0,15**
Total	**142**	**39,95**

For clinical research :

- 11% of funded projects
- 14% of total funding

- **Early stage breast cancer : program launched in 2014**

- **Improvement of the knowledge** of the natural course of the disease so as to reduce overdiagnosis and overtreatment

- **Risk levels and screening** : multidisciplinary approaches

- **De-escalation** : Biological, medical, socio-psychological and medico-economic evaluation of de-escalation of treatment using a unified multidisciplinary approach

- **Life after cancer treatment** : sociological, psychological, medical and economic aspects

→ 42 projects submitted

→ 18 retained for further evaluation

→ Final results in June 2014

Conclusion

- INCa strategy is a global approach
  - Prevention
  - Screening
  - Good clinical practice (authorization of centers/ recommendations)
  - Patients information (transparency on overdiagnosis, overtreatment, radiation risks)
  - Clinical research (chemotherapy, radiotherapy)
  - Translational research
  - Fundamental research
  - Integrated research progamme including social science

- To continue to increase the survival rate of women with breast cancer in France, to improve quality of life and decrease sequelaes

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