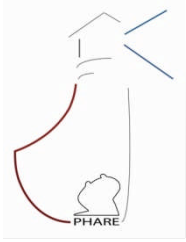


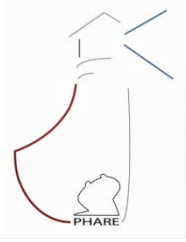
## PHARE\* Trial results comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer

**Xavier Pivot**, Gilles Romieu, Hervé Bonnefoi, 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.



# Disclosures

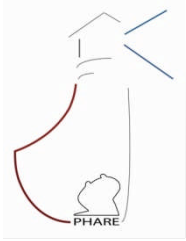
- Honoraria and Consultant for Roche, GlaxoSmithKline
- The PHARE trial is fully funded and conducted by the French National Cancer Institute



# Background

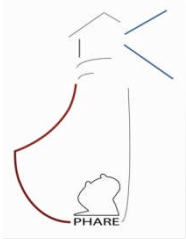
- 1 year of adjuvant trastuzumab has been improving DFS/OS<sup>(1, 2)</sup>
- 9 weeks of adjuvant trastuzumab provided similar magnitude of benefit<sup>(3)</sup>
- Concerns emerged with cardiac-toxicities following trastuzumab exposure

<sup>1</sup>Piccart 2005 ; <sup>2</sup>Romond 2005 ; <sup>3</sup>Joensuu 2006



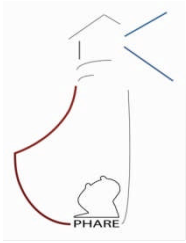
# Objectives

- **Primary objective**
  - Compare the effect of 6 months versus 12 months of treatment with trastuzumab in terms of disease-free survival
  - Disease-Free Survival (DFS) from randomization to first event
    - local, regional, or distant recurrence, contralateral breast, second non-breast malignancies, or death from any cause
- **Secondary objectives**
  - Cardiotoxicity
  - Distant metastasis Free Survival
  - Overall survival

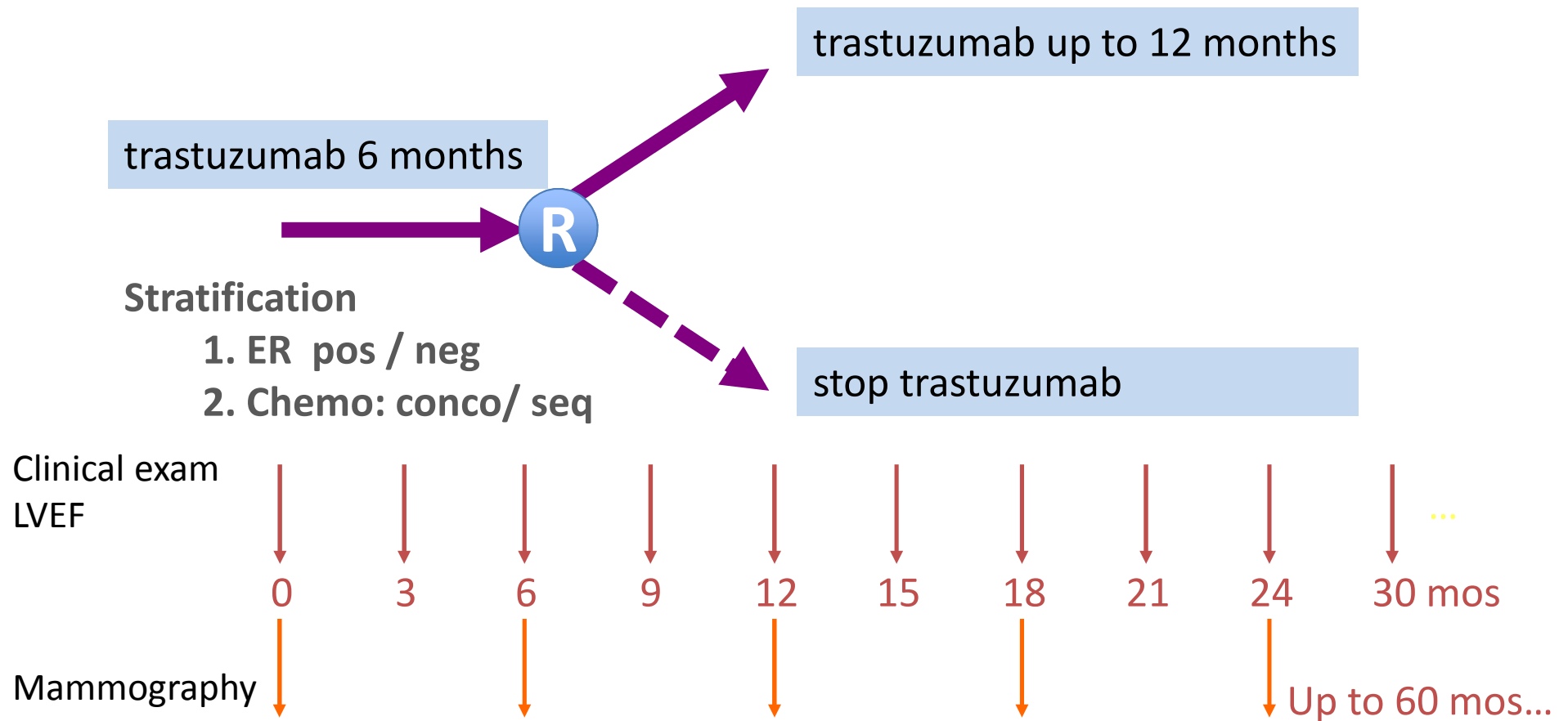


# Eligibility

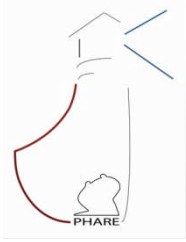
- Non metastatic operable, histologically confirmed adenocarcinoma of the breast
- Axillary nodes positive or negative and tumor size  $\geq 10$  mm
- At least four cycles of a chemotherapy for this breast cancer
- Patients for whom a 12-month adjuvant treatment with trastuzumab has been initiated
- Baseline LVEF value 3 months after initiation of treatment with trastuzumab allowing to pursue treatment
- Overexpression of HER2 in invasive component of primary tumor
- Signed informed consent
- Patients with history of other cancer eligible



# Study design



R: Randomization after informed consent



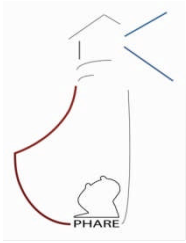
# Statistical Methods

- **Non inferiority randomized trial**
  - 2% variation in terms of absolute difference of recurrence
  - The 95% CI HR margins should not cross the 1.15 boundary
  - 1040 DFS events required for 80% power at 5% level

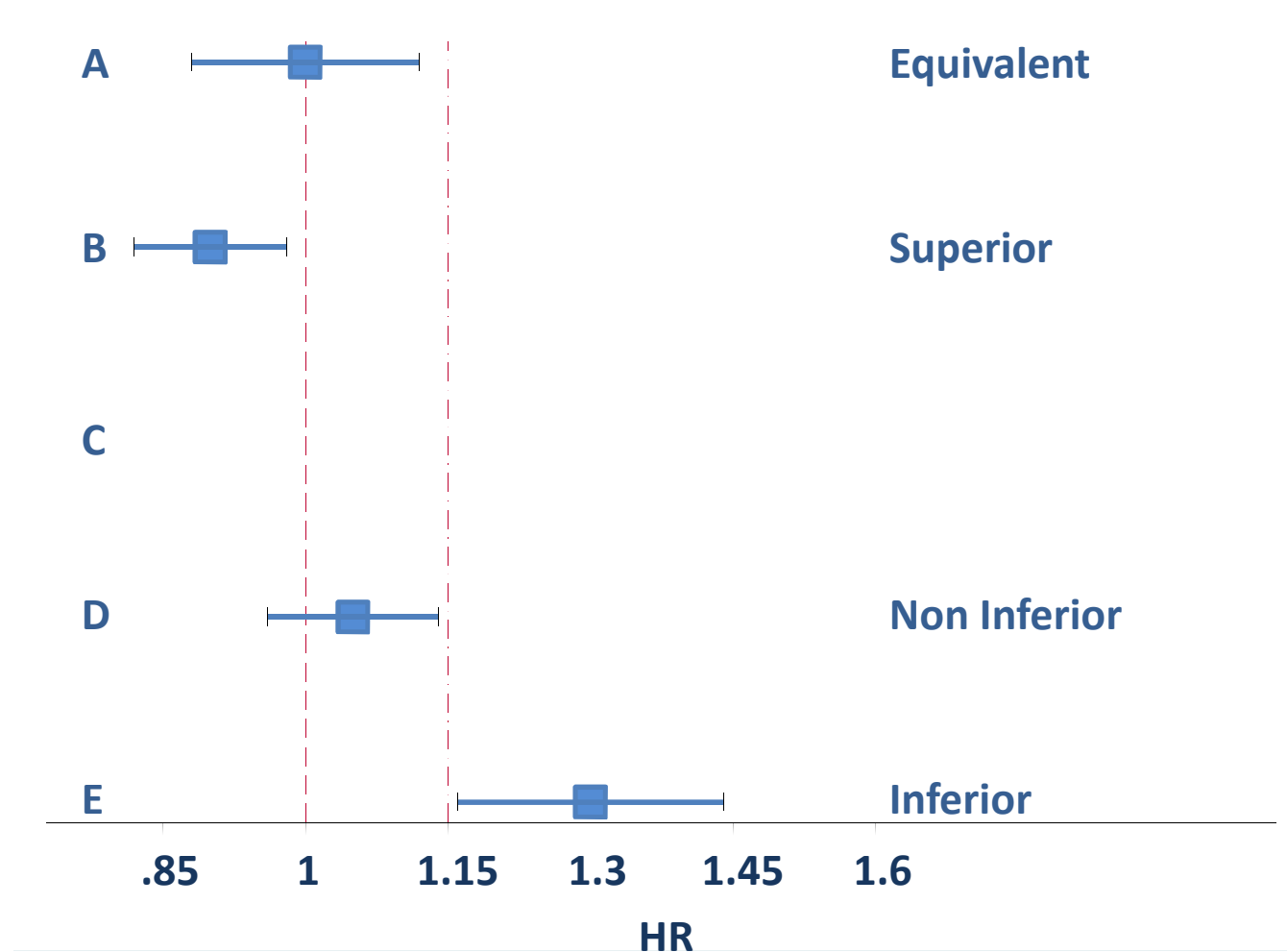
**or**

- 4 years of accrual and at least 2 years of follow-up
- HR were estimated from the stratified Cox model

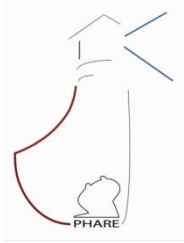
- **Accrual target: 3400 patients**



# Primary endpoint scenarii

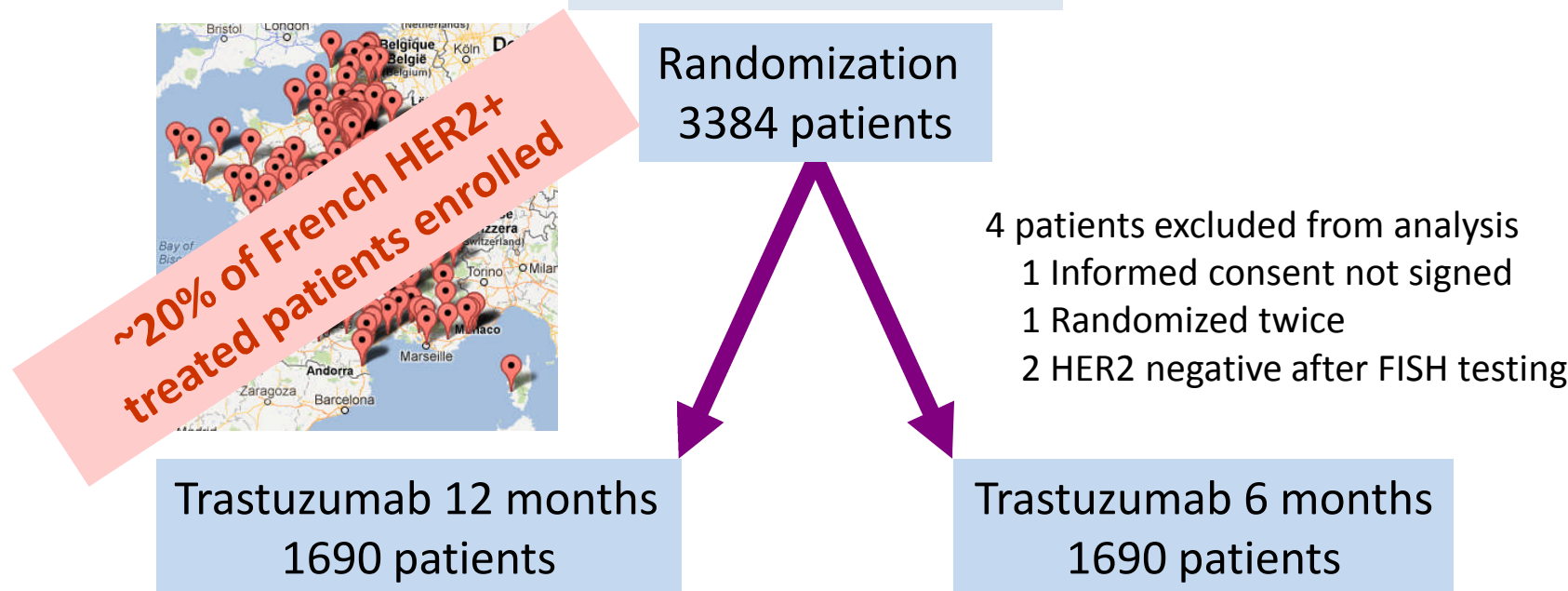






# Study information

Activated: 30/05/2006



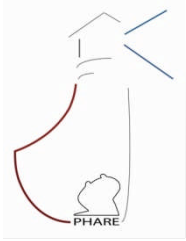
• May 28<sup>th</sup> 2010 – IDMC meeting

*“After careful thought and lengthy debate we recommend that entry to the trial be suspended. We do not recommend, at this time, a crossover to a longer duration of intervention for the 6 month group but would reserve the option of such a recommendation for the future, dependent on how the data develop”*



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

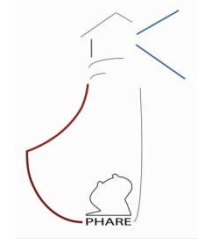
[www.esmo2012.org](http://www.esmo2012.org)



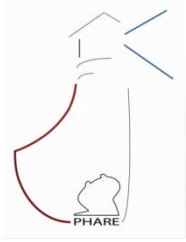
# Patient Characteristics

	12 months n=1690	6 months n=1690
Age, median (range)	54 (21 – 86)	55 (23 – 85)
Tumor : 0 – 2 cm	54.7%	52.4%
2 – 5 cm	38.5%	39.8%
>5 cm	6.8%	7.8%
Nodes: negative	55.4%	54.7%
1 – 3 nodes	30.0%	30.2%
≥4 nodes	14.6%	15.1%
Positive Estrogen receptor	57.6%	58.8%
Inflammatory disease	3.5%	3.4%
SBR: I	3.1%	3.3%
II	41.0%	40.9%
III	55.6%	55.8%

# Treatment Characteristics



	12 months n=1690	6 months n=1690
Type of Chemotherapy :		
No Anthracyclines	10.2%	11.8%
Anthracyclines no Taxanes	15.9%	15.5%
Anthracyclines and Taxanes	73.9%	72.7%
Concomitant Chemotherapy	57.8%	57.7%
Sequential Chemotherapy	42.2%	42.3%
Radiotherapy	87.7%	88.2%
Hormonotherapy	50.6%	50.2%
Trastuzumab duration, mean (sd)	11.8 (6.3)	6.3 (1.46)

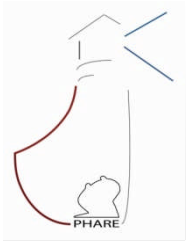


# Cardiac toxicity

	12 months (n=1690)	6 months (n=1690)	P
Cardiac events*	5.7%	1.9%	<0.0001
LVEF** < 50%	6.3%	4.7%	0.04
LVEF** < 50% and ↓ > 10%	4.8%	3.6%	0.071
LVEF** > 50% and ↓ > 15%	7.4%	7.0%	NS

\* Investigator reported events (composite with clinical and LFEV finding)

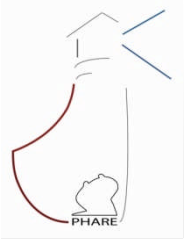
\*\* Based on more than > 25,000 assessments



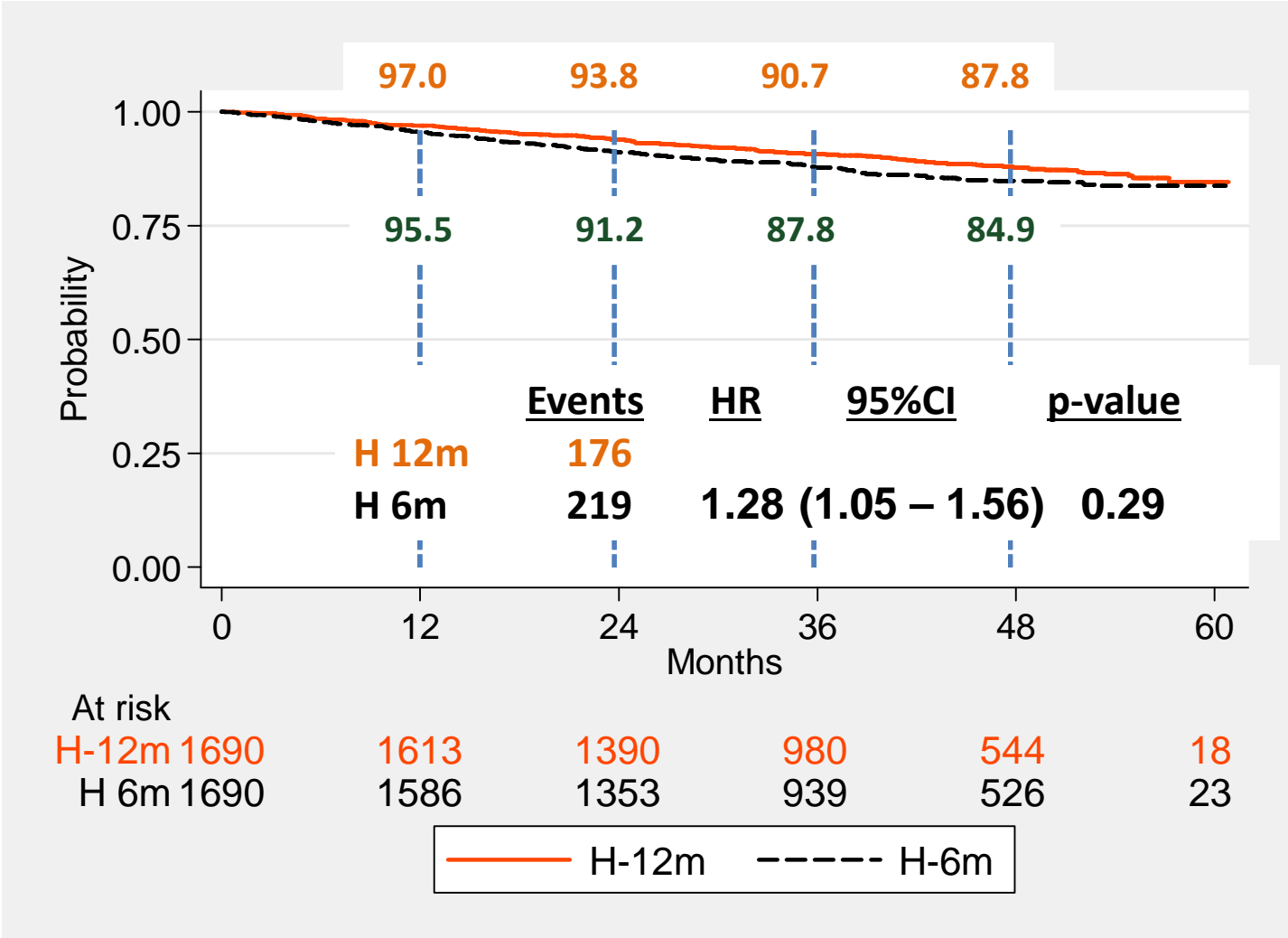
# DFS Events

42.5mos. median Follow-up

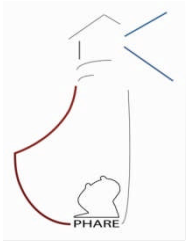
	12 mos (n=1690)	6 mos (n=1690)
<b>DFS Events (n=395)</b>	<b>10.4%</b>	<b>13.0%</b>
<b>Local Recurrence</b>	<b>1.1%</b>	<b>1.4%</b>
<b>Regional Recurrence</b>	<b>0.6%</b>	<b>0.5%</b>
<b>Distant Recurrence</b>	<b>6.4%</b>	<b>8.3%</b>
<b>Controlateral Breast Cancer</b>	<b>0.4%</b>	<b>0.7%</b>
<b>2<sup>nd</sup> Primary Malignancy</b>	<b>1.5%</b>	<b>1.5%</b>
<b>Death</b>	<b>0.4%</b>	<b>0.5%</b>



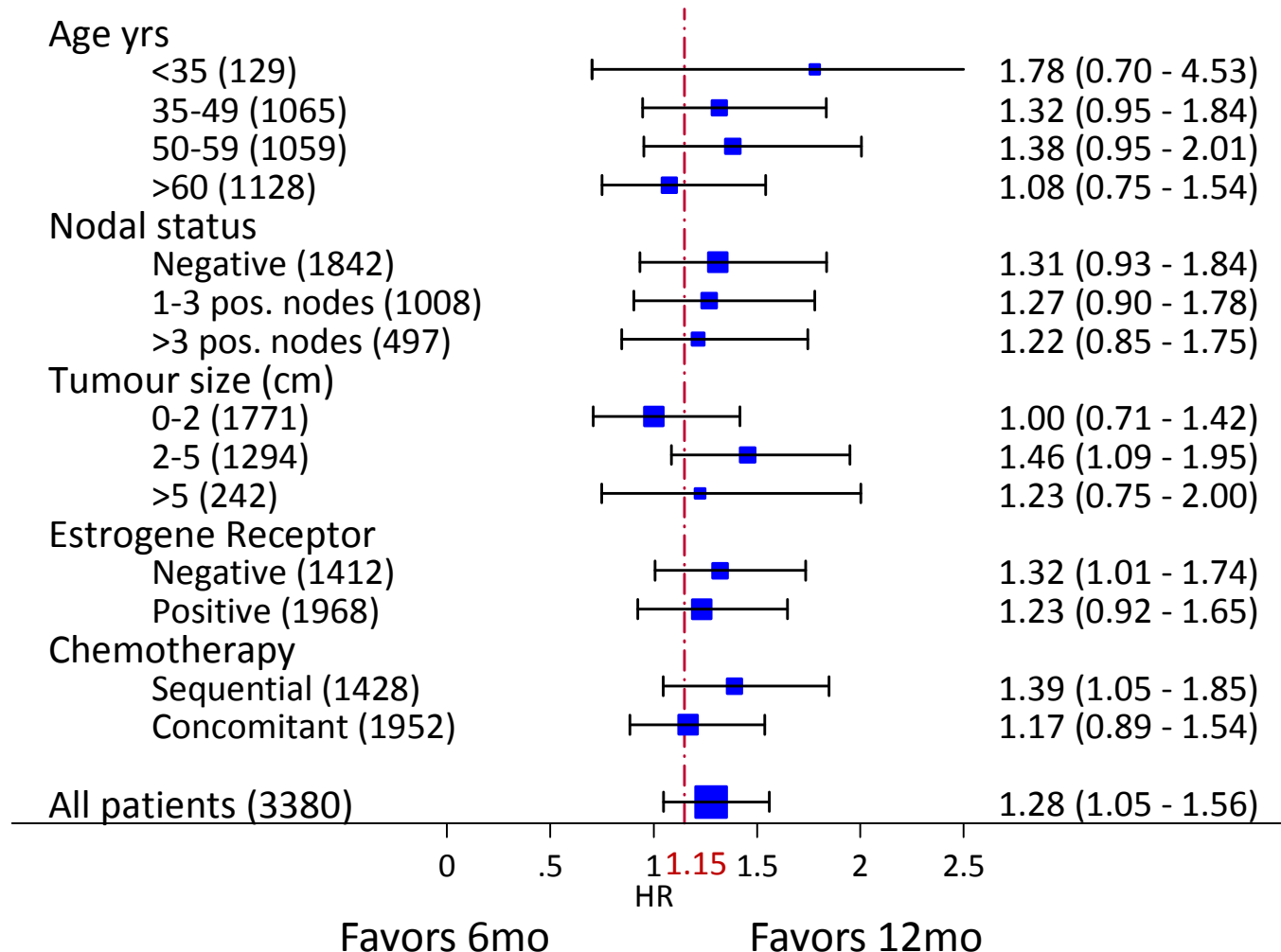
# Disease Free Survival

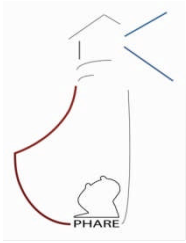


\* Cox model stratified by ER status and concomitant chemotherapy



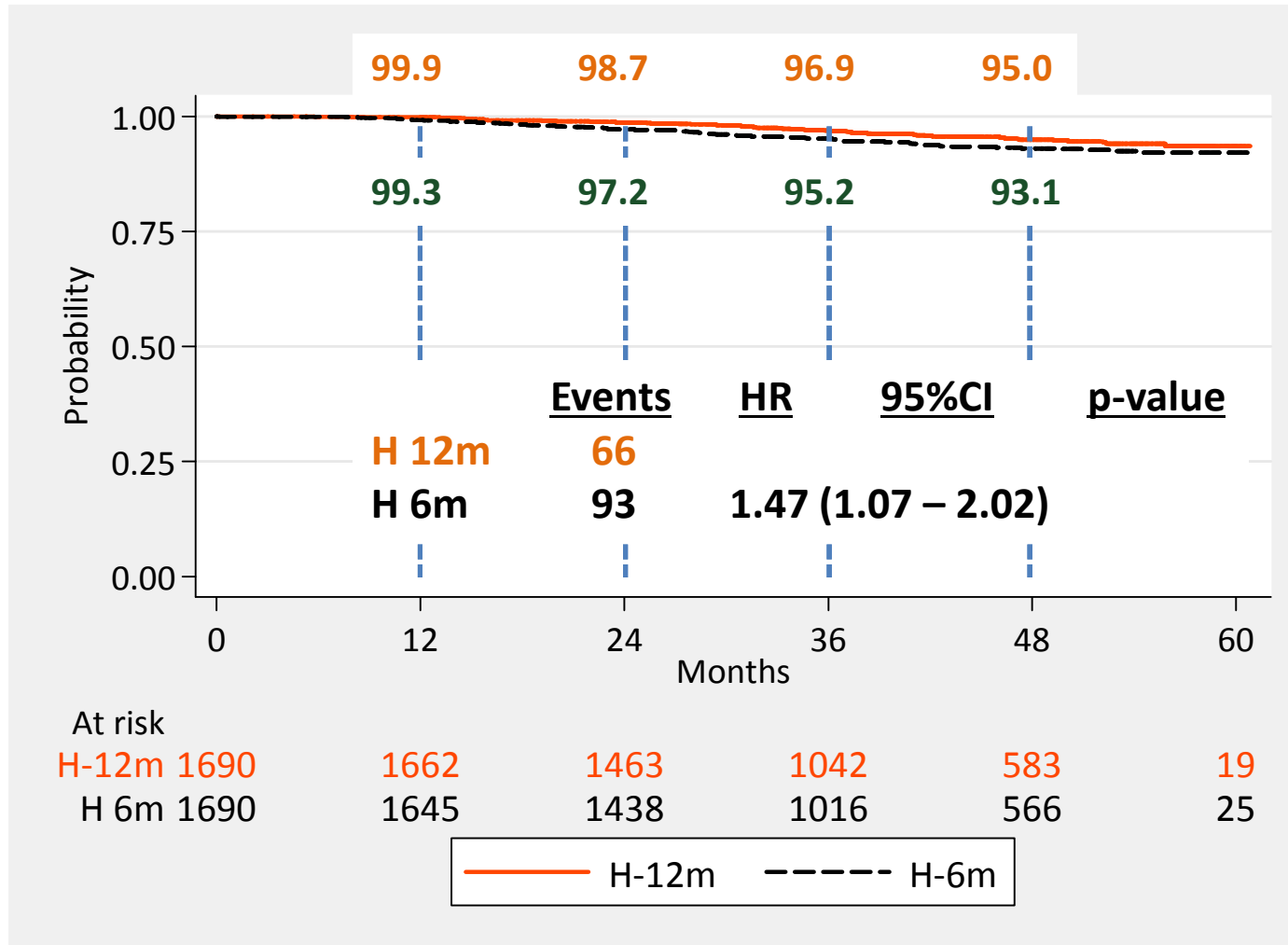
# DFS Forest plot





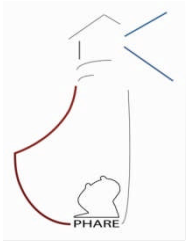
# Overall Survival

42.5mos. median FU

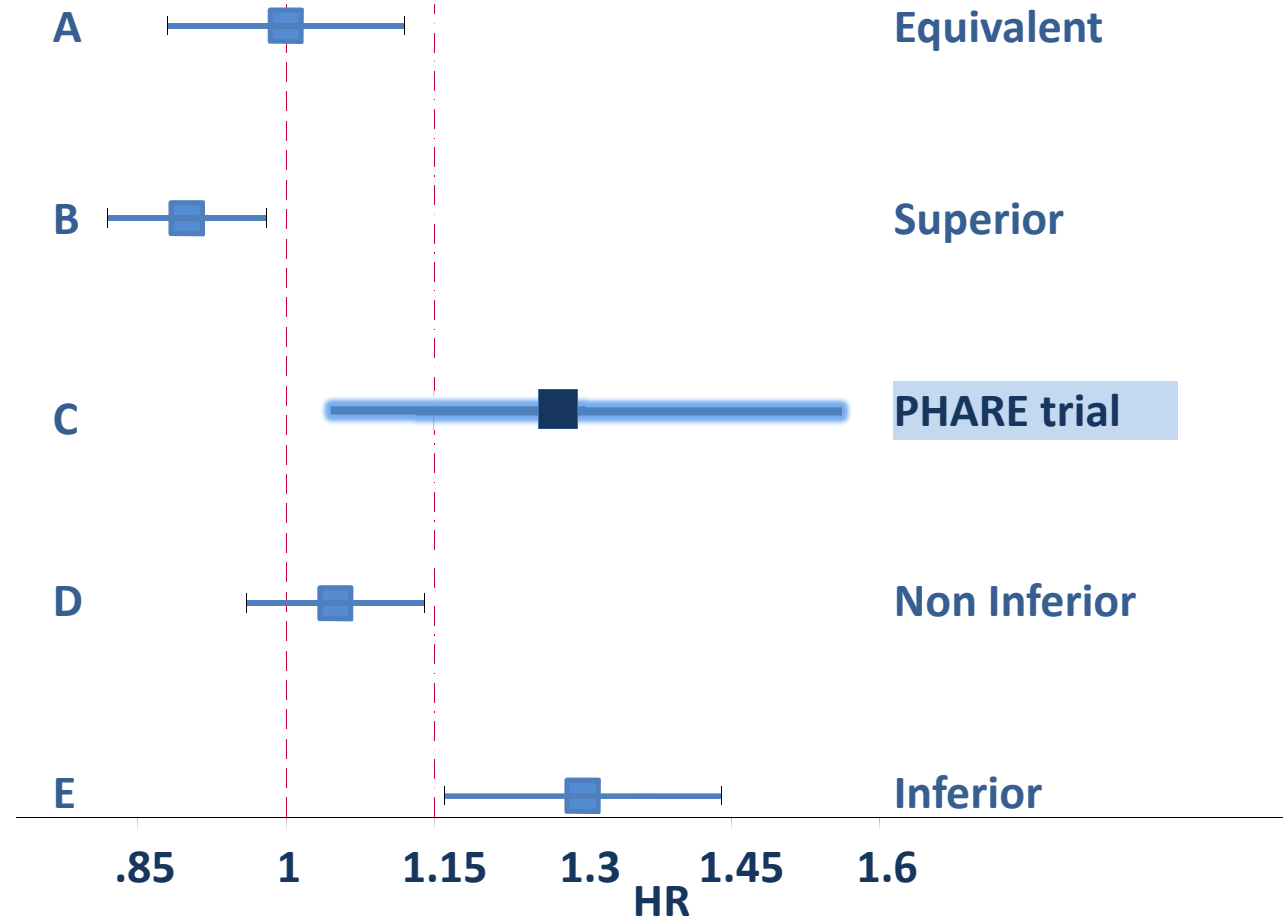


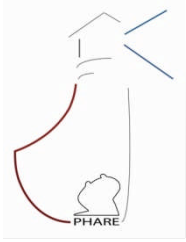
\* Cox model stratified by ER status and concomitant chemotherapy





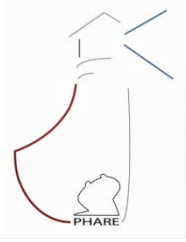
# Primary endpoint scenarii





# Conclusions

- Results were inconclusive for the non-inferiority hypothesis
- Nevertheless, there was a trend favouring the standard 12 months treatment
- There is a significant difference in cardiac events in favor of 6 months treatment
- Multivariate analysis will be presented at SABCS 2012
- PERSEPHONE, SHORTHER & SOLD trials results expected in next years
- A G-WAS ongoing to identify predictors for HER2+ BC risk and trastuzumab response/toxicity (SIGNAL, 9000 pts recruited)

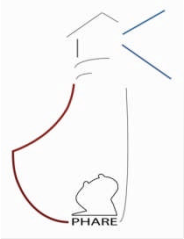


# Acknowledgments

- All patients and their families
- The IDMC members
- French National Cancer Institute staff: Céline Faure-Mercier, Nicolas Thammavong, Nadia Bachouche, Claire Verbeke
- Marc Buyse and Xavier Paoletti for their input in the original trial design

[www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT00381901

[www.e-cancer.fr](http://www.e-cancer.fr): essai Phare



# All Investigators

ACHILLE, ACHOUR, AGOSTINI, AL AUKLA, ALBIN, ALCARAZ, ALLEAUME, ALLIOT, ALTWEGG, AMSALHEM, ANDRE, ANTOINE, ARDISSON, ARSENE, AUCLERC, AUDHUY, AULIARD, AVENIN, BARATS, BARBET, BATICLE, BAUMONT, BEERBLOCK, BEGUE, BEGUIER, BELLAICHE – MICCIO, BERNARD, BERTON-RIGAUD, BESSON, BICHOFFE, BIELSA, BIRON, BONICHON-LAMICHHANE, BONNETERRE, BON, BOUE, BOUGNOUX, BOULANGER, BOURBOULOUX, BOURCIER, BOURGEOIS, BOUSQUET, BOUTAN –LAROZE, BRAIN, BRAIN, BREAU, BRUNA, BURKI, CAILLEUX, CALS, CAMPONE, CAMPOS-GAZEAU, CAPITAIN, CAROLA, CARTRON, CAUVIN, CHAIGNEAU, CHANTELARD, CHEVRIER, CHIEZE, CHIRAT, CHOLLET, CHOUAHNIA, CLAVREUL, CLIPPE, CLUET, COEFFIC, COJEAN-ZELEC, COLLARD, COMBE, COSTA, COTTU, COUDERC, COUDERT, CRETIN, CURE, CUVIER, DALENC, DARLOY, DARUT-JOUVE, DAUBA, DE HARTINGH, DE SAINT HILAIRE, DEBLED, DELALOGÉ, DELBALDO, DELECROIX, DELVA, DELZENNE, DEMARCHI, DENIS, DENIZON, DIAB, DIERAS, DIETMANN, DILLIES, DION, DOHOLLOU, DOMAS, DOMONT, DRONY, DUFRESNE, DUJOLS, DUPUIS, DUPUY, DUPUY-BROUSSEAU, DURAND, DURANDO, DURIEUX, DUTEL, DUVERT, EGRETEAU, EL AMARTI, EL KOURI, ELLIS, EXTRA, EYMARD, EZENFIS, FABBRO, FACCHINI, FALANDRY, FEDERICO, FERRANT, FERRERO, FERRIERE, FICHET, FOLLANA, FREYER, FRIC, GABEZ, GALOTTE, GANEM, GARNIER, GAUTIER-FELIZOT, GEAY, GEDOUIN, GENET, GHOUL, GIACCHETTI, GIRAUD, GIRRE, GLADIEFF, GLIGOROV, GOUBELY, GOUDIER, GOUTTEBEL, GREGET, GRENIER, GROSSAT, GUASTALLA, GUARDIOLA, GUILLEMET, GUILLET, GUIMONT, GUINET, GUTIERREZ, HAJJAJI, HARDY-BESSARD, HENRY, HERVE, HOCINI, HOUYAU, IBANEZ MARTIN, IURISCI, JACQUOT, JANSSEN, JAUBERT, JOUVE, JOVENIN, KANOUI, KARA –SLIMANE, KIRSCHER, KREITMANN, LAGUERRE, LAHARIE- MINEUR, LAMY, LANCRY, LAPORTE, LARGILLIER, LAUCHE, LAURENCE, LAVAU-DENES, LE HEURTEUR, LE MAIGNAN, LE ROL, LÉBOUVIER SADOT, LEBRUN, LEDUC, LEFEUVRE, LEGOUFFE, LEGUEUL, LEHEURTEUR, LEVACHE, LEVY, LEYRONNAS, L'HELGOUALC'H, LIGEZA-POISSON, LITOR, LLORY, LOISEAU, LUPORSI, MADRANGES, MAHOUR BACHA, MAILLART, MANDET, MANGOLD, MARI, MARTI, MARTIN, MAURIAC, MAYER, MAYEUR, MEDIONI, MEFTI- LACHERAF, MERAD-BOUDIA, MEUNIER, MEUNIER, MIGNOT, MILLE, MISSET, MONTCUQUET, MORAN RIBON, MORICEAU, MORVAN, MOULLET, MOURET-REYNIER, MOUTEL-CORVIOLE, NABHOLTZ, NETTER, N'GUYEN, NOUYRIGAT, ODDOU-LAGRANIERE, ORFEUVRE, PARAISO, PAVLOVITCH, PETIT, PIPERNO-NEUMANN, PIPROT, PLANTADE, PLAT, PORTOIS, POTTIER-KYNDT, POUESSEL, POURNY, PRIOU, PROVENCAL, RABAN, RAICHON PATRU, RAMEE, RATOANINA, RAY-COQUARD, RE, REBATTU, RIGAL, RIVERA, ROCHE, ROCHE FORESTIER, ROHART DE CORDOUE, ROUSSEAU, RUCK, SAAD, SADKI-BENAOUDIA, SAINTIGNY, SALLES, SALVAT, SARDA, SARRAZIN, SCHAEFFER, SERVENT, SEVIN –ROBICHE, SLAMA, SOULIE, SOYER, SPIELMANN, STEFANI, STEIN, TADRIST, TARPIN, TARTAS, TEISSIER, TENNEVET, THEVENOT, TOCCANIER, TOURNIGAND, TRAGER-MAURY, TREDAN, TRESCA, TRILLET-LENOIR, UWER, VALENZA, VAN PRAAGH, VAN-HULST, VANICA, VANNETZEL, VANNEUVILLE, VANOLI, VAULEON, VEDRINE, VENNIN, VEYRET, VIGNOT, VIGNOUD, VILLANUEVA, VILLING, VINCENT, VOLOCH, WEBER, YAKENDJI, YAZBEK, YOUSSEF, ZYLBERAIT