

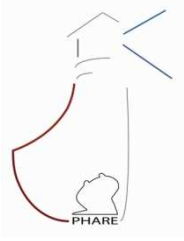
Protocol of
Herceptin®
Adjuvant with
Reduced
Exposure

PHARE

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

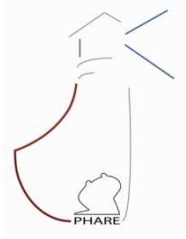
Xavier Pivot, Gilles Romieu, Marc Debled, Jean-Yves Pierga, Pierre Kerbrat, Thomas Bachelot, Alain Lortholary, Marc Espié, Pierre Fumoleau, Daniel Serin, Jean-Philippe Jacquin, Christelle Jouannaud, Maria Rios, Sophie Abadie-Lacourtoisie, Nicole Tubiana-Mathieu, Laurent Cany, Stéphanie Catala, David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

*lighthouse in French



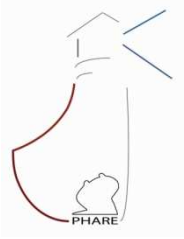
Disclosures

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

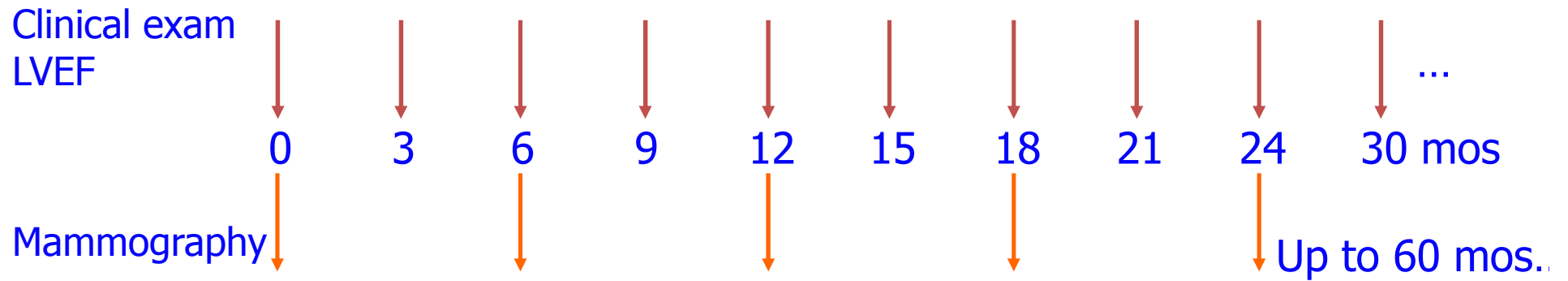
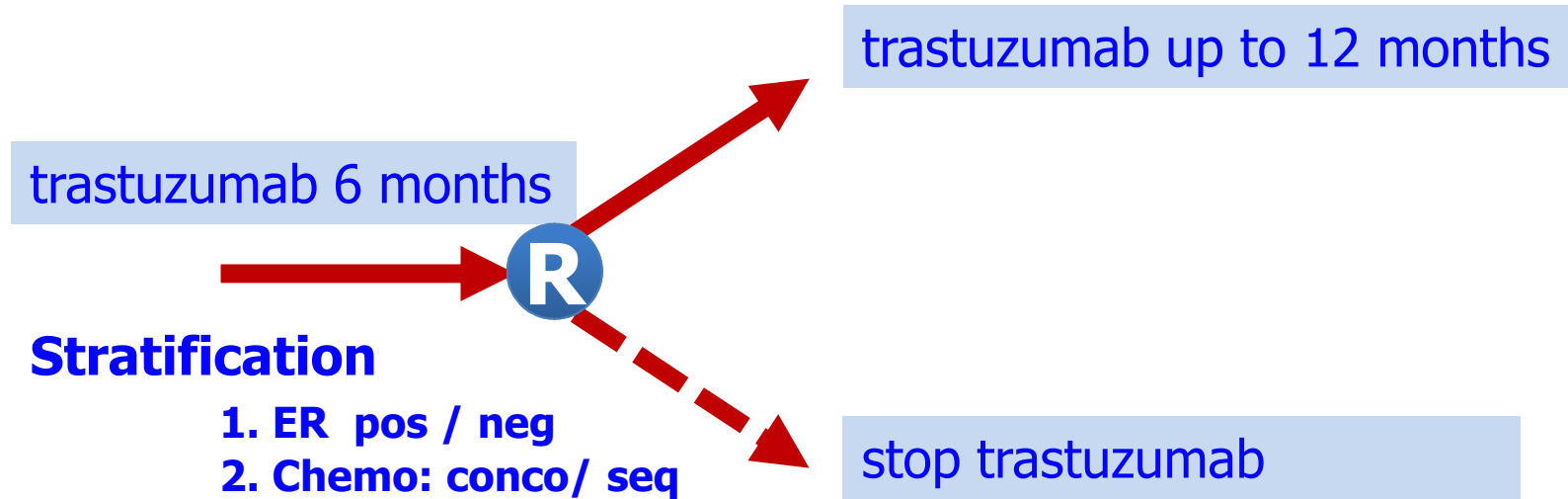


Eligibility

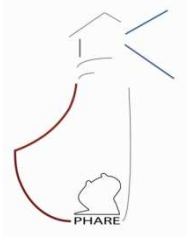
- Non metastatic operable, histologically confirmed adenocarcinoma of the breast
- Axillary nodes positive or negative and tumor size ≥ 10 mm
- At least four cycles of a chemotherapy for this breast cancer
- Patients for whom a 12-month adjuvant treatment with trastuzumab has been initiated
- Baseline 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



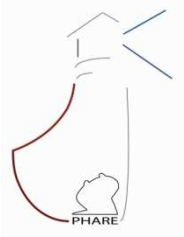
Statistical Methods

- **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

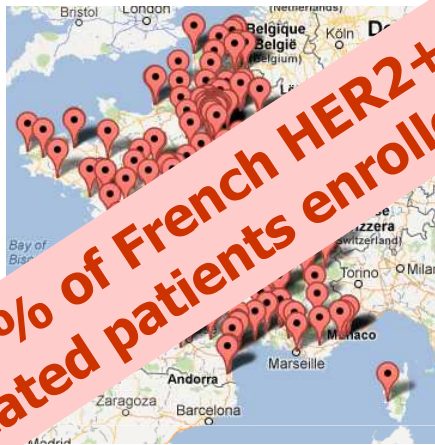
- **Accrual target: 3400 patients**



Study information

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

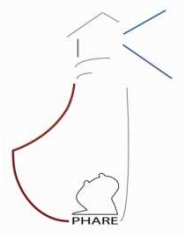
Trastuzumab 6 months
1690 patients

- May 28th 2010 – IDMC meeting

"After careful thought and lengthy debate we recommend that entry to the trial be suspended.

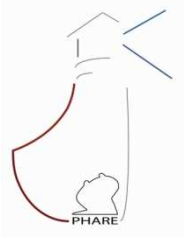
We do not recommend, at this time, a crossover to a longer duration of intervention for the 6 month group but would reserve the option of such a recommendation for the future, dependent on how the data develop"

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



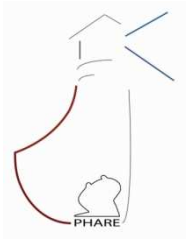
Patient Characteristics

	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

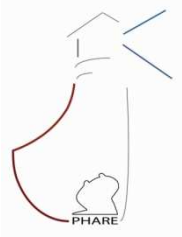
	12 months n=1690	6 months n=1690
Type of Chemotherapy		
No Anthracyclines	10.2%	11.8%
Anthracyclines no taxanes	15.9%	15.5%
Anthracyclines and Taxanes	73.9%	72.7%
Concomitant Chemotherapy	57.8%	57.7%
Sequential Chemotherapy	42.2%	42.3%
Radiotherapy	87.7%	88.2%
Hormonotherapy	50.6%	50.2%
Trastuzumab duration, mean (sd)	11.8 (2.03)	6.3 (1.46)



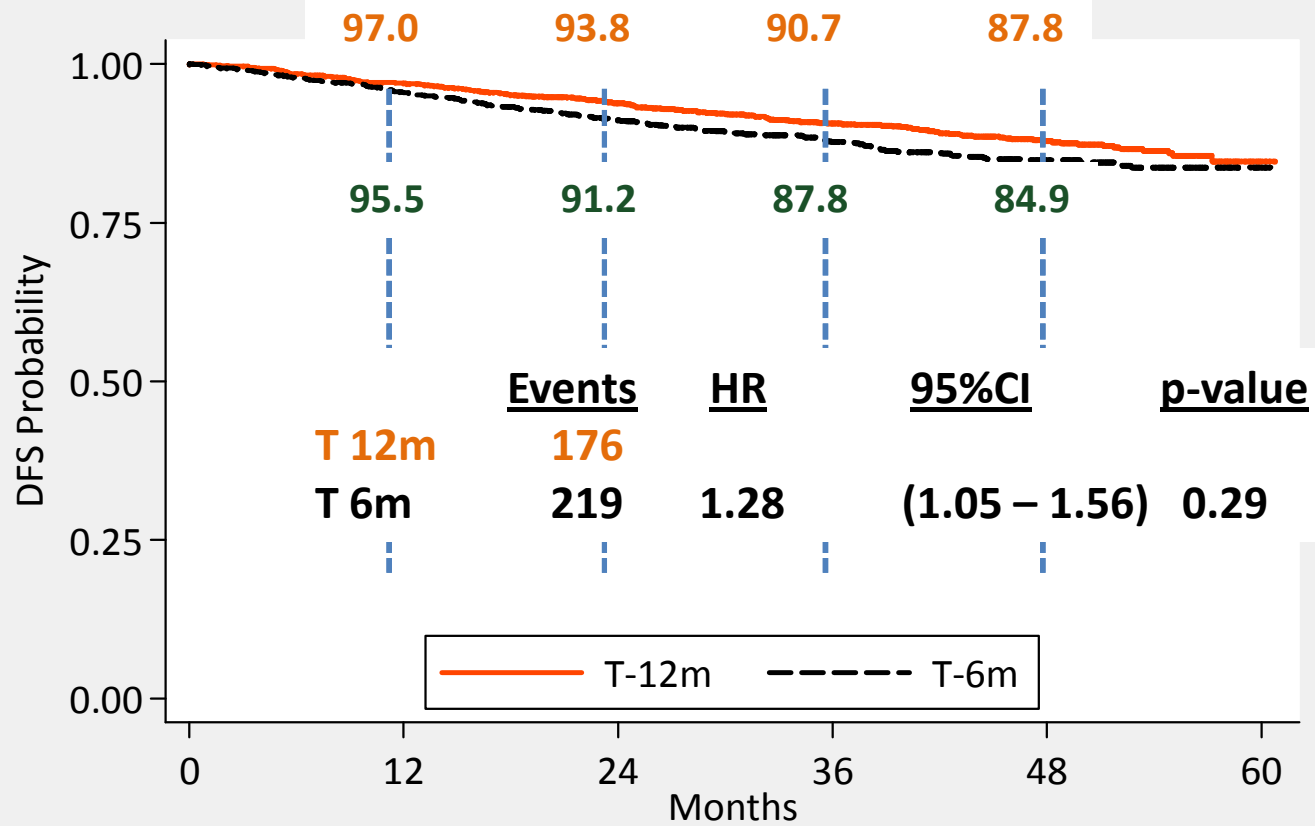
DFS Events

42.5mos. median Follow-up

	12 mos (n=1690)	6 mos (n=1690)
DFS Events (n=394)	10.4%	13.0%
Local Recurrence	1.1%	1.4%
Regional Recurrence	0.6%	0.5%
Distant Recurrence	6.4%	8.3%
Controlateral Breast Cancer	0.4%	0.7%
2 nd Primary Malignancy	1.5%	1.5%
Death	0.4%	0.5%



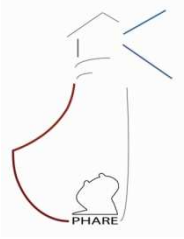
Disease Free Survival



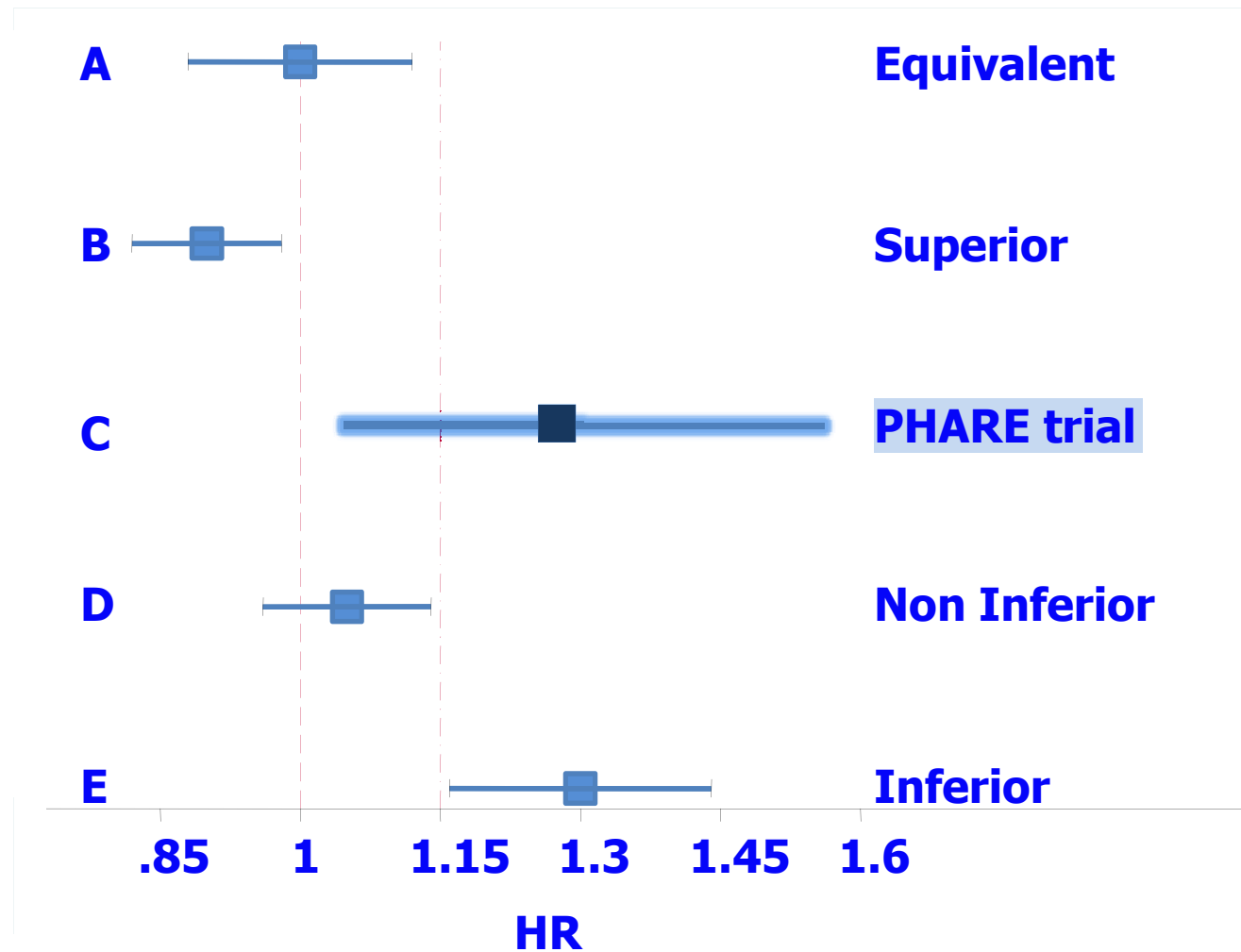
Trastuzumab

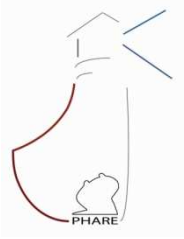
T-12m	1690	1613	1390	980	544	18
T-6m	1690	1586	1353	939	526	23

* Cox model stratified by ER status and concomitant chemotherapy

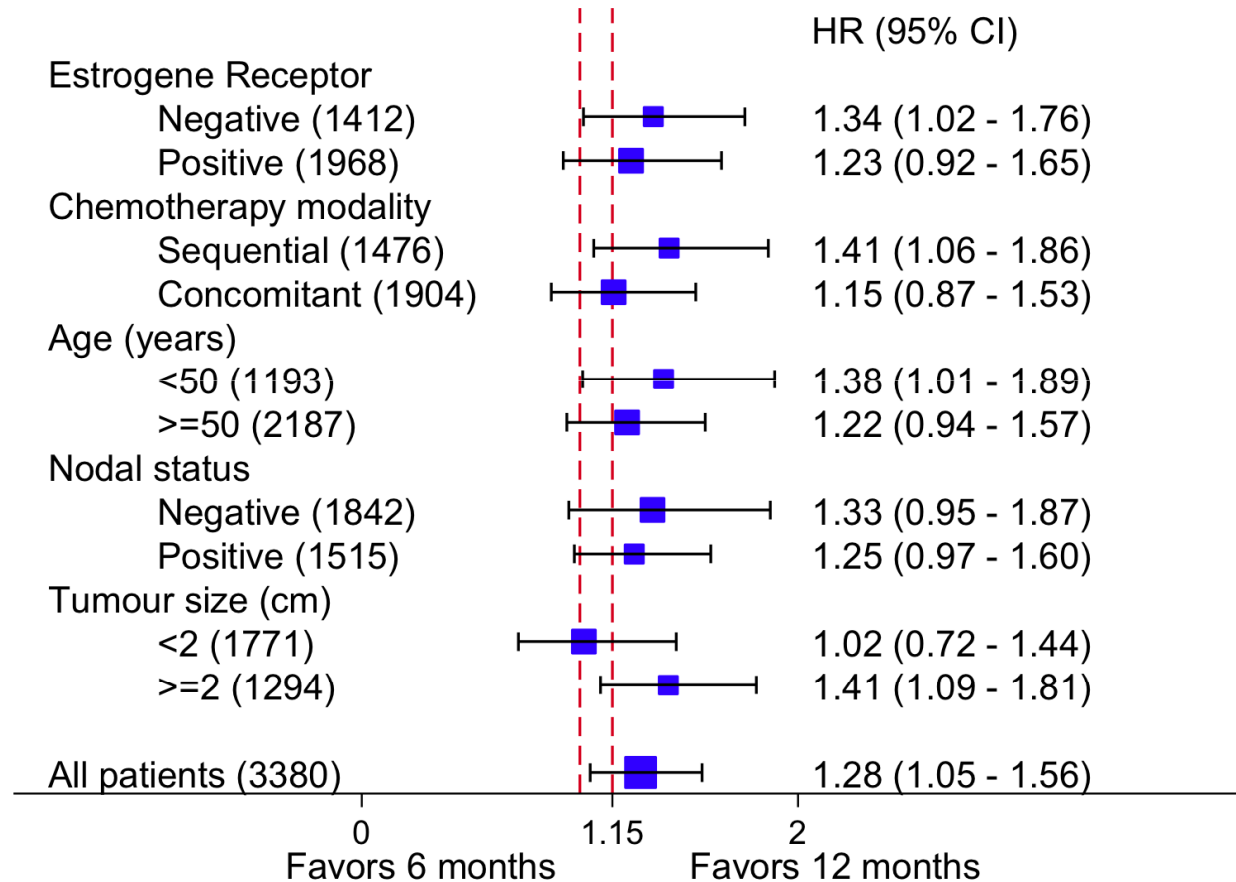


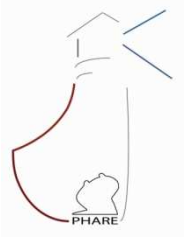
Primary endpoint scenarios





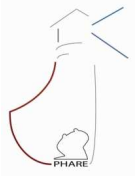
Subgroup effects





Objective and strategy of subgroup analysis

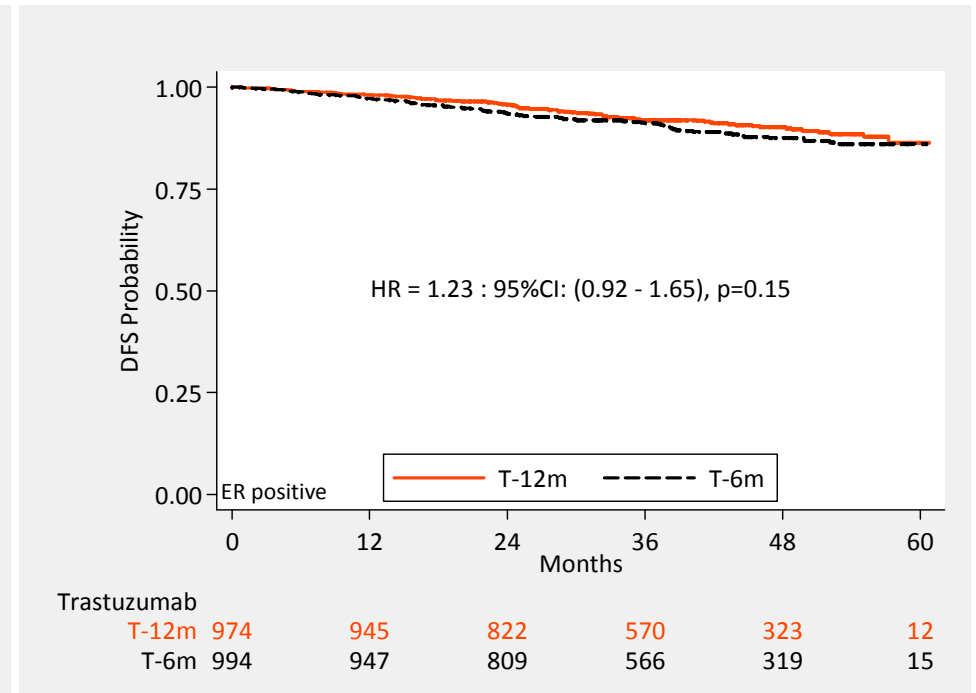
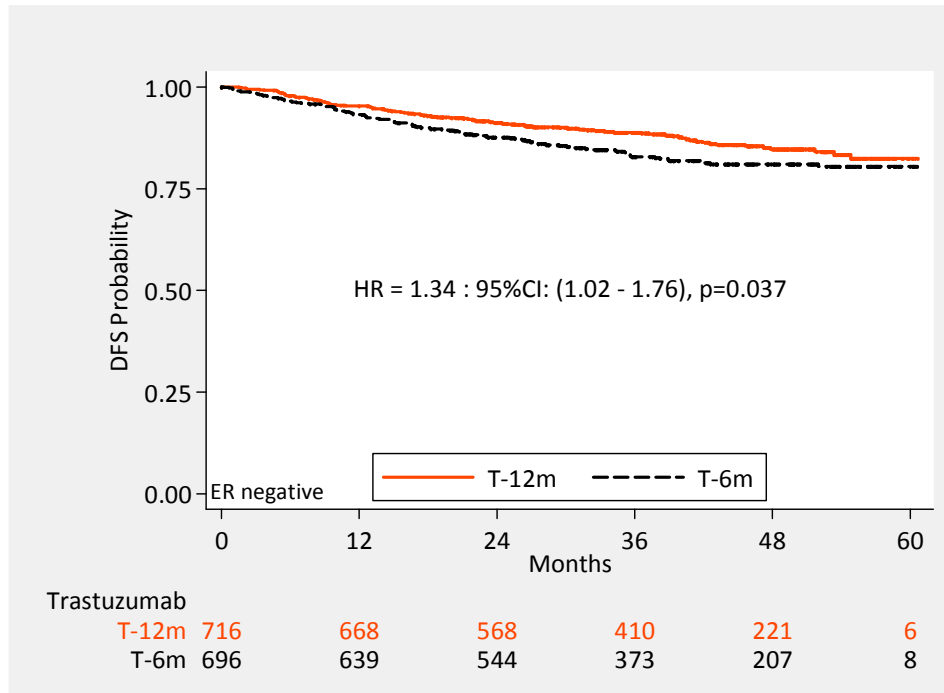
- The aim of this analysis was to assess the trastuzumab duration effects for specific subgroups
 - Identified by pre-defined stratification factors
 - Estrogen receptor status
 - Sequential or concomitant administration of trastuzumab with chemotherapy
- Assess heterogeneity by interaction tests
 - 0.10 significance level



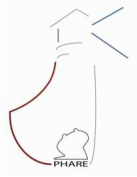
Trastuzumab duration effect: according to ER

ER negative

ER positive

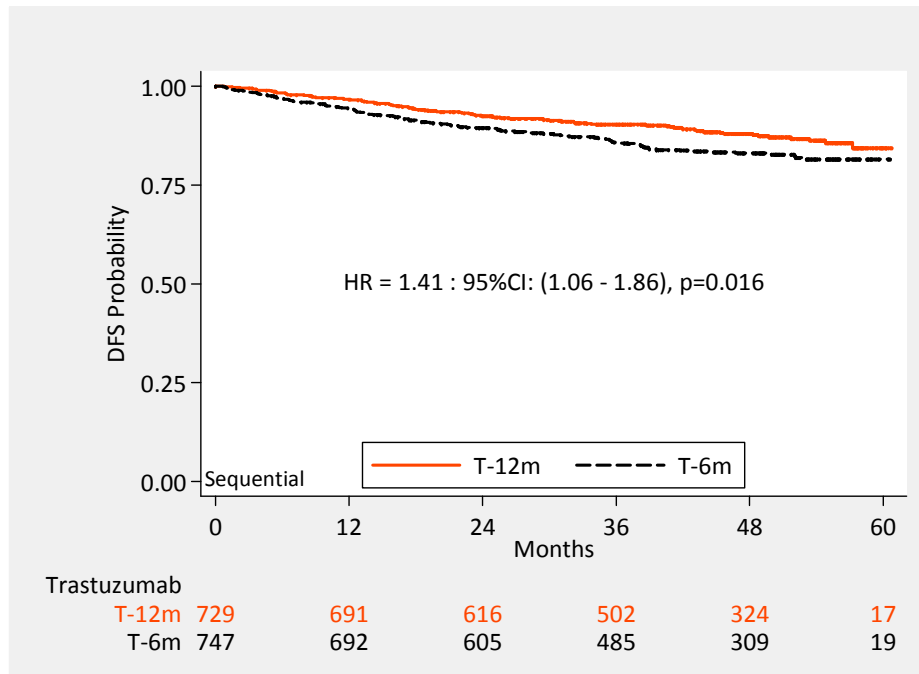


	Trastuzumab 12 months			Trastuzumab 6 months		
	Events	N	DFS-3	Events	N	DFS-3
ER negative	92	716	0.888	117	696	0.829
ER positive	83	974	0.920	102	994	0.912

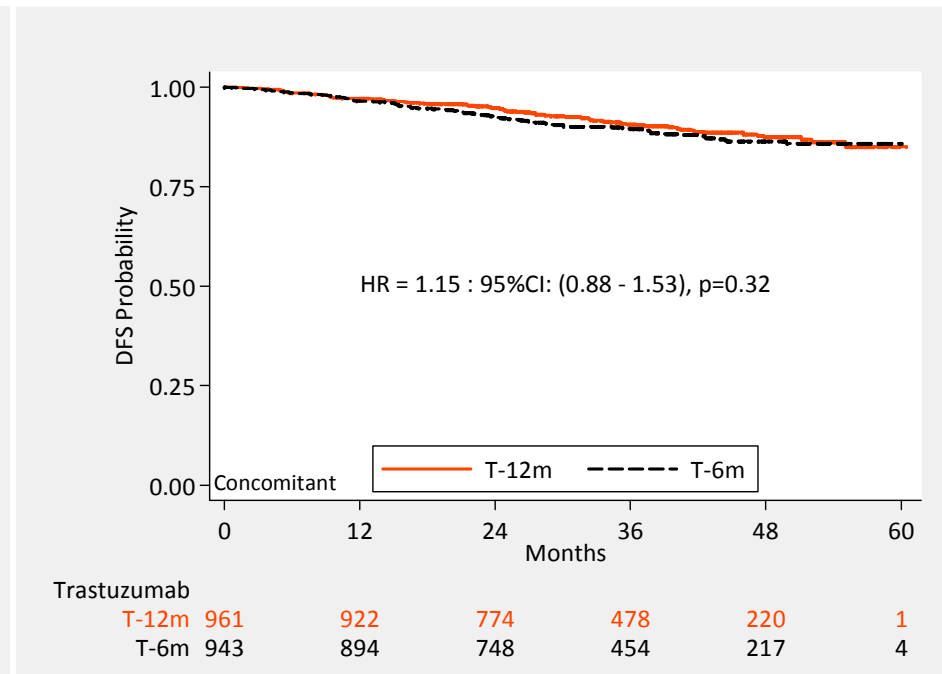


Trastuzumab duration effect: Treatment modalities

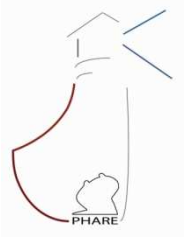
Sequential



Concomitant



	Trastuzumab 12 months			Trastuzumab 6 months		
	Events	N	DFS-3	Events	N	DFS-3
Sequential	84	729	0.904	117	747	0.857
Concomitant	91	961	0.907	102	943	0.896



Estrogen Receptor and Chemo-trastuzumab modalities

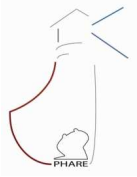
DFS	Main effects model			Nested Interaction model		
	HR	95% CI	P	HR	95% CI	P
N=3380						
ER +	0.61	(0.50 – 0.75)	<0.0001	0.52	(0.39–0.68)	<0.0001
Conc	0.83	(0.68 – 1.01)	0.065	0.71	(0.54–0.93)	0.013
ER* Conc	---			1.41	(0.95–2.09)	0.093
LR test	-3077.38			-3075.96		0.092

- **Significant interaction**

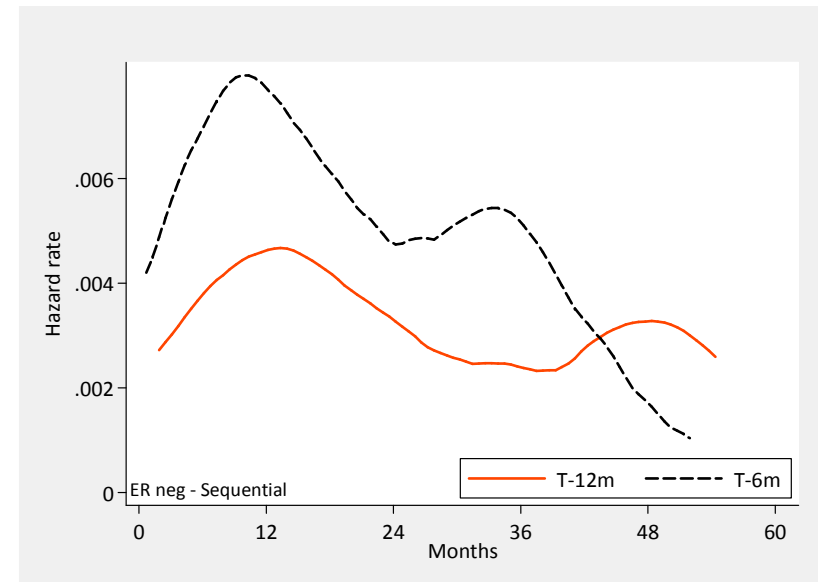
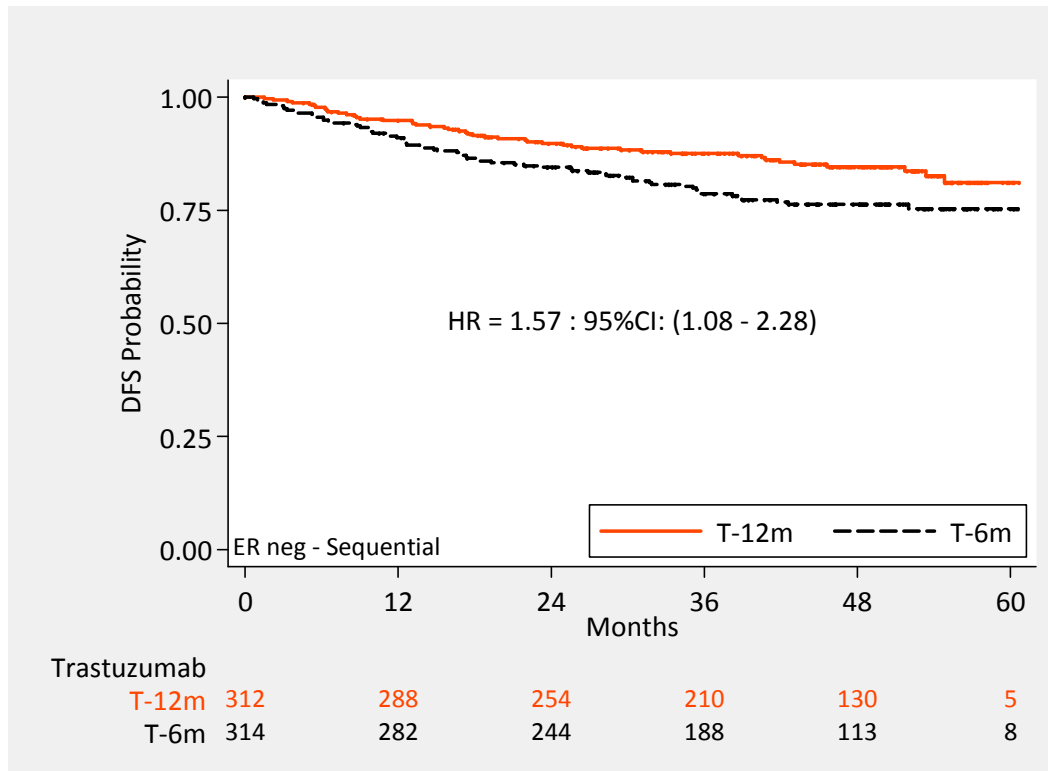
- * Reference category

	Sequential	Concomitant
ER –	HR* = 1.00	HR = 0.83 (0.68 – 1.01)
ER +	HR = 0.61 (0.50 – 0.75)	HR = 0.51 (0.38 – 0.67)

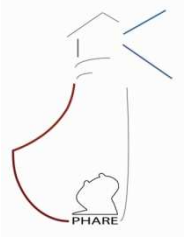
	Sequential	Concomitant
ER –	HR* = 1.00	HR = 0.71 (0.59 – 0.85)
ER +	HR = 0.52 (0.39 – 0.68)	HR = 0.51 (0.39 – 0.67)



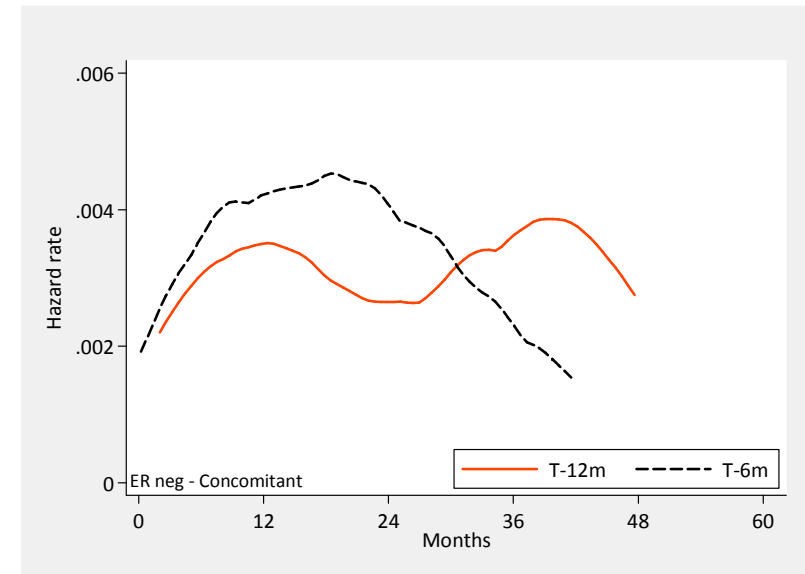
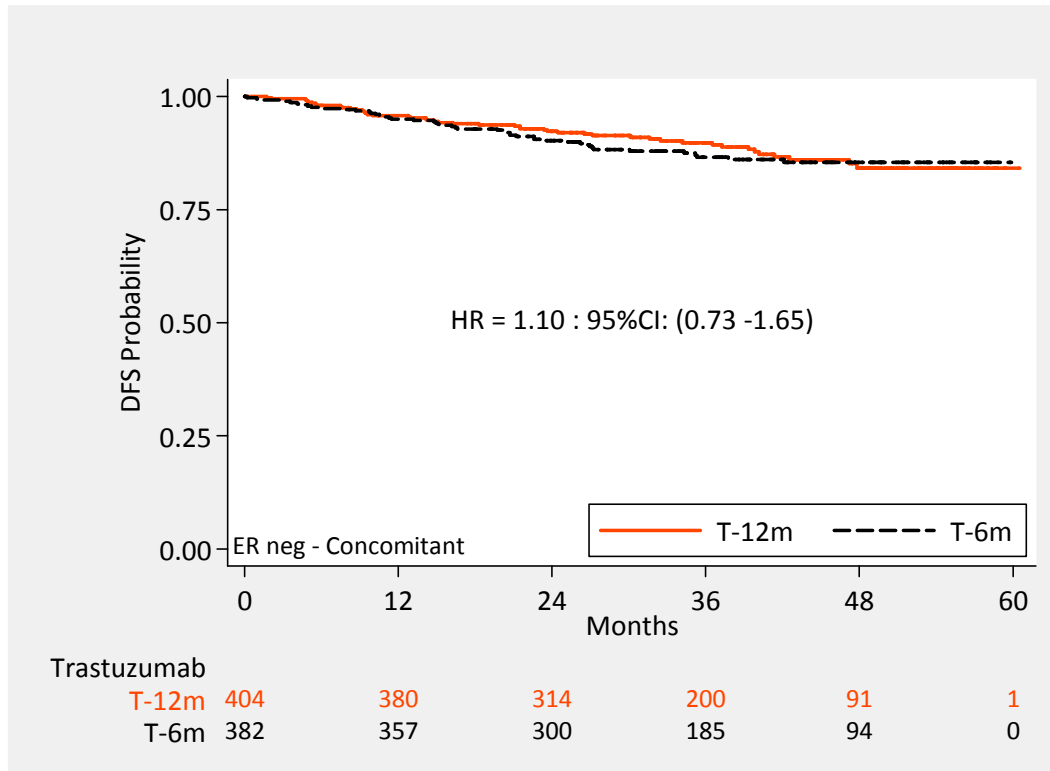
Trastuzumab duration effect: ER negative – Sequential modality



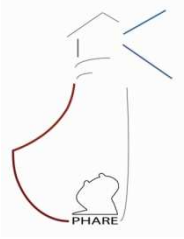
Trastuzumab 12 months			Trastuzumab 6 months		
Events	N	DFS-3	Events	N	DFS-3
46	312	0.875	69	314	0.786
			HR = 1.57	(1.08 – 2.28)	



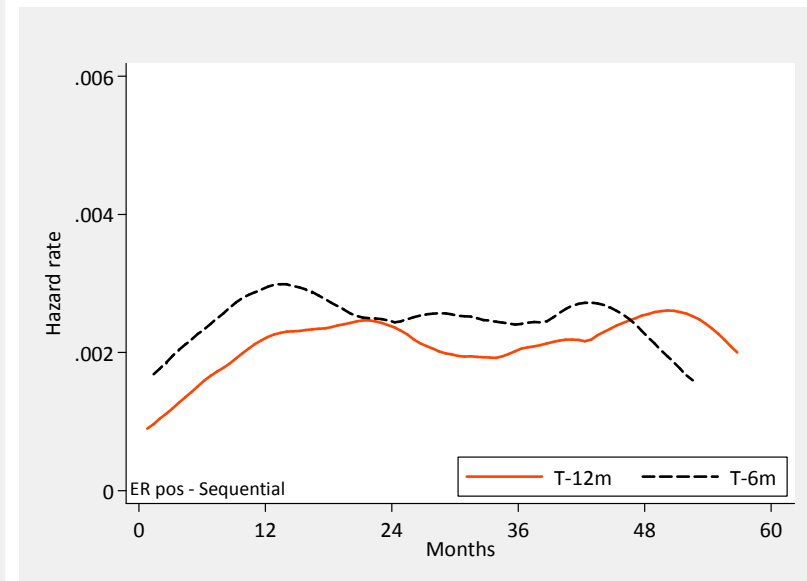
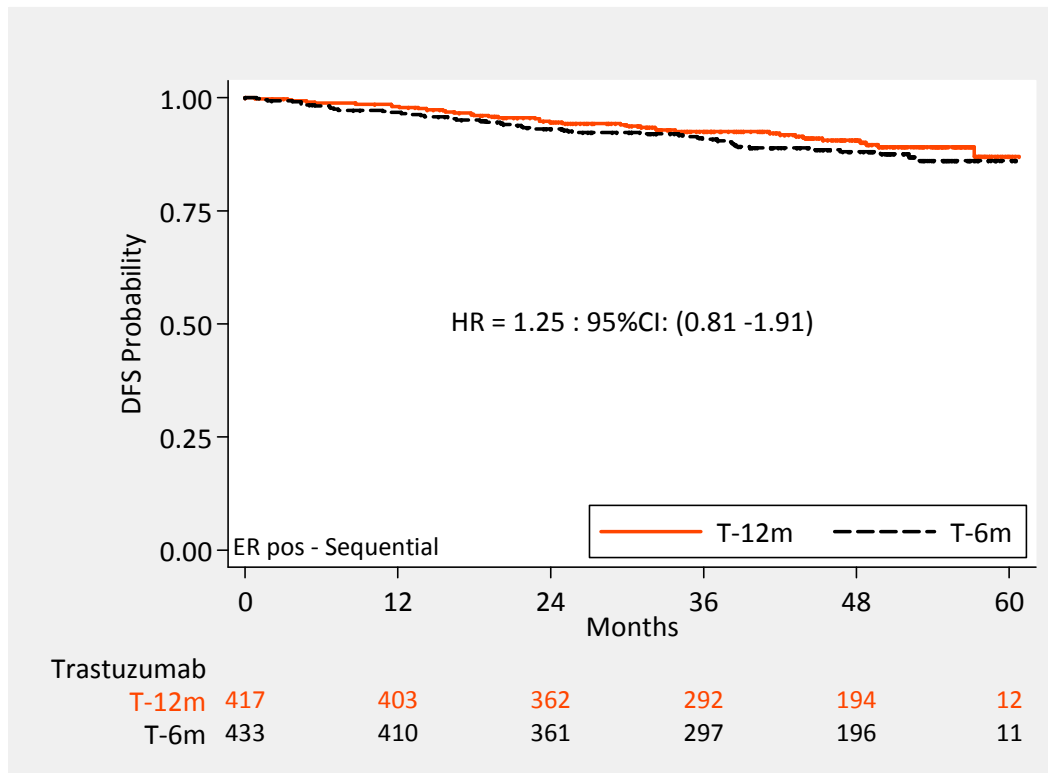
Trastuzumab duration effect: ER negative – concomitant modality



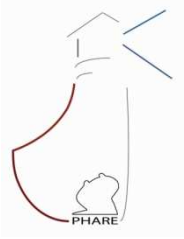
Trastuzumab 12 months			Trastuzumab 6 months		
Events	N	DFS-3	Events	N	DFS-3
46	404	0.898	48	382	0.866
			HR = 1.10	(0.73 – 1.65)	



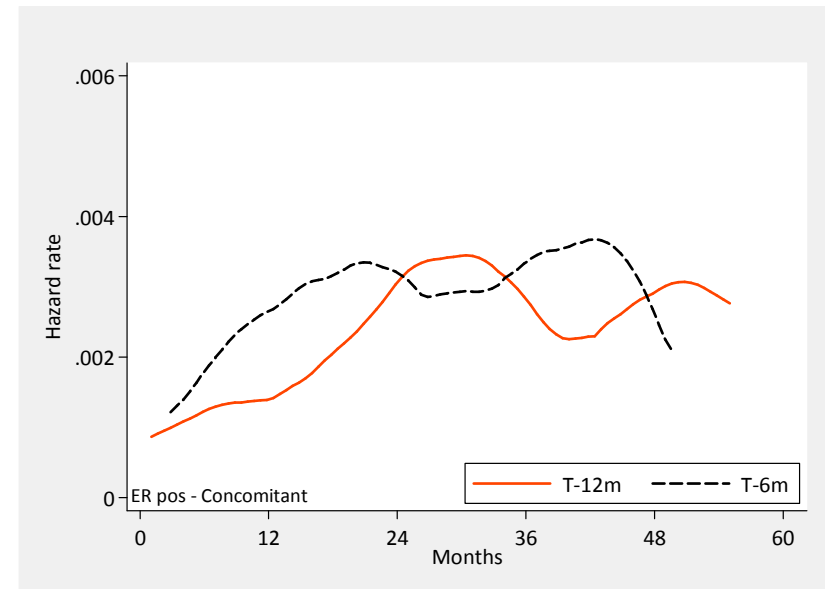
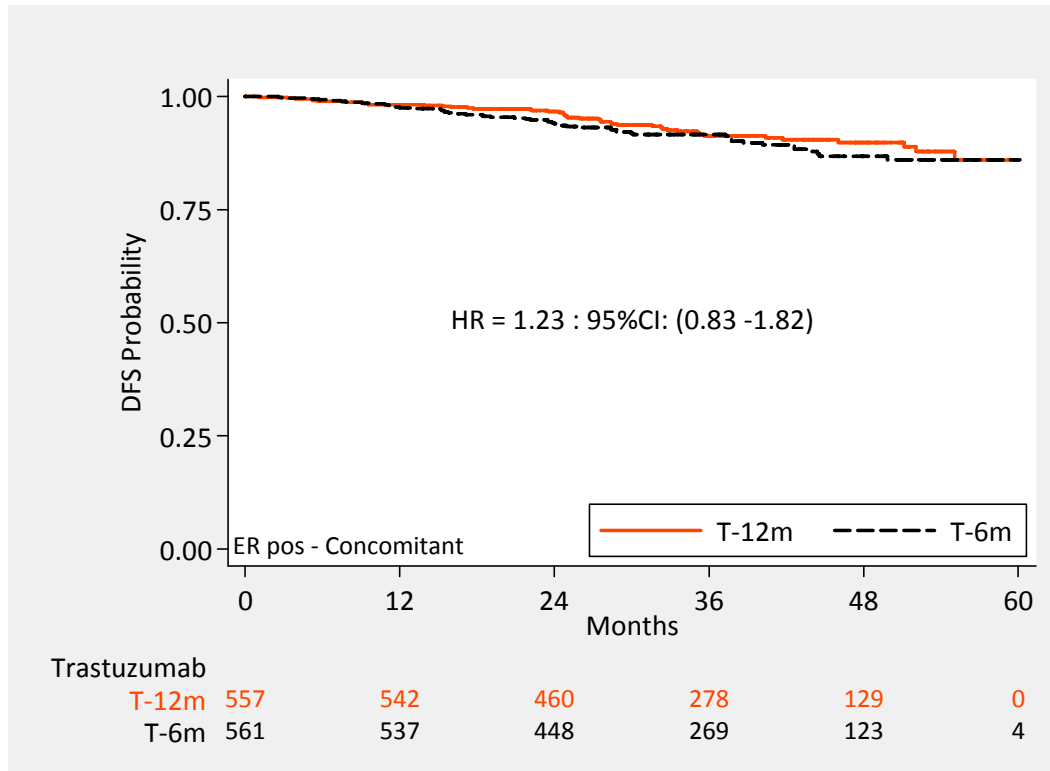
Trastuzumab duration effect: ER positive- Sequential modality



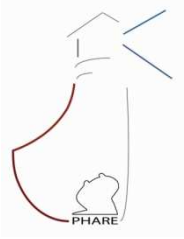
Trastuzumab 12 months			Trastuzumab 6 months		
Events	N	DFS-3	Events	N	DFS-3
38	417	0.925	48	433	0.908
			HR = 1.25	(0.81 - 1.91)	



Trastuzumab duration effect: ER positive- concomitant modality

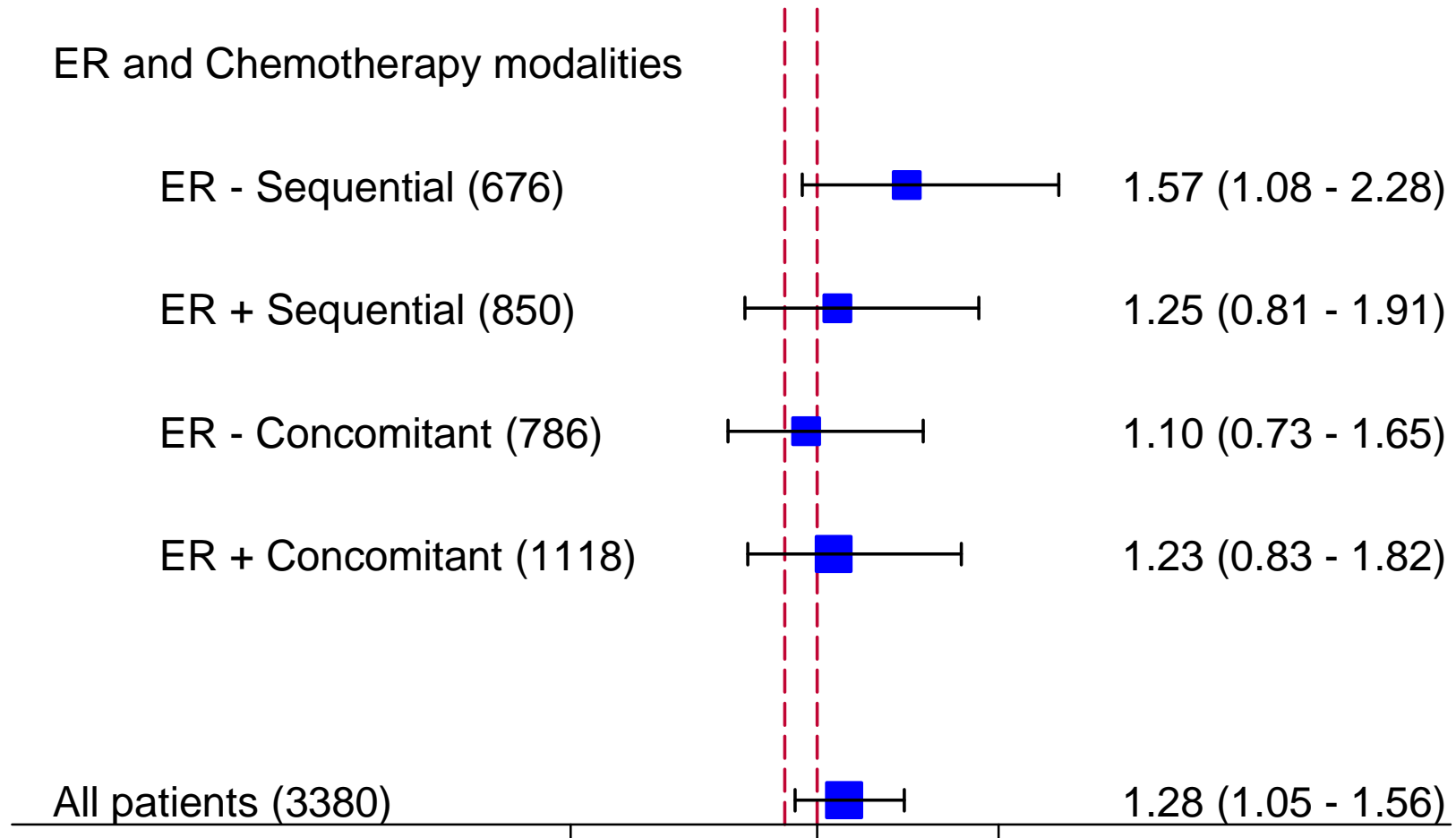


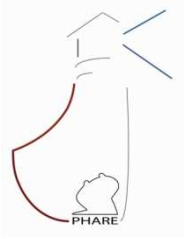
Trastuzumab 12 months			Trastuzumab 6 months		
Events	N	DFS-3	Events	N	DFS-3
45	557	0.913	54	561	0.916
			HR = 1.23	(0.83 -1.82)	



Conclusion

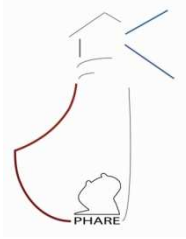
ER and Chemotherapy modalities





Conclusion

- PHARE failed to show that 6 months of trastuzumab is non inferior to 12 months
- Subgroups analysis suggested
 - Sequential modality for ER negative tumors impacted the overall results
 - Results in other groups seemed compatible with non-inferiority hypothesis
- PHARE longer FU & PERSEPHONE, SHORTHER & SOLD trial results are expected

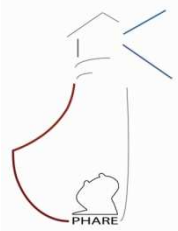


Acknowledgments

- 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: NCT00381901

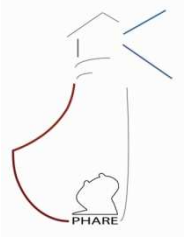
www.e-cancer.fr: essai Phare



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, BONS, 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, DELALOGUE, 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, LEBOUVIER 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, VANLEMMENS, VANNETZEL, VANNEUVILLE, VANOLI, VAULEON, VEDRINE, VENNIN, VEYRET, VIGNOT, VIGNOUD, VILLANUEVA, VILLING, VINCENT, VOLOCH, WEBER, YAKENDJI, YAZBEK, YOUSSEF, ZYLBERAIT

BACK UP



Conclusion

Trastuzumab duration effect: subgroup ER negative – Sequential modality

Trastuzumab duration effect: subgroup other patients

