GIM - riunione annuale.
Le sfide della ricerca sul carcinoma mammario

ALL'ASCO.
Azzurri

Trieste, 24-25 Settembre 2019

Relatrice: Prof. Lucia Del Mastro

Gruppo Italiano Mammella GIM

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

AGENDA

1) Role of anthracycline in neoadjuvant anti-Her2 regimen (Pelizzari G)

2) Low-dose tamoxifene in pre-invasive disease (De Censi A)

3) Safety of pregnancy following breast cancer in BRCA mutated patients (Lambertini M)

4) GIM-4 TRIAL (Del Mastro L)

Role of anthracyclines in neoadjuvant anti-HER2 regimens for HER2+ breast cancer (BC): A network meta-analysis (NMA)

Pelizzari G[1,2], Gerratana L[1,2], Basile D[1,2], Bartoletti M[1,2], Lisanti C[1,2], Garattini SK[1,2], Bortot L[1,2], Corvaja C[1,2], Buriolla S[1,2], Curtolo G[1,2], Garutti M[2,3], Di Nardo P[2], Torrisi E[2], Da Ros L[2], Freschi A[2], Saracchini S[2], Bolzonello S[2], Miolo G[2], Spazzapan S[2], Puglisi F[1,2]

[1]Department of Medicine (DAME), University of Udine, Udine, Italy; [2]Dipartimento di Oncologia Medica, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy; [3]UOC Oncologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy

Background

It is a matter of current debate which would be the best chemotherapy backbone of neoadjuvant HER2-targeted therapy for HER2-positive BC

The TRAIN 2 trial showed no significant difference in terms of pathological complete response (pCR) when anthracycline–based (CTA) or anthracycline–free regimens (CT) were combined with dual HER2 blockade[1]

It remains unclear how anthracyclines may influence the relative benefit across different anti-HER2 treatments

Methods

A systematic review was conducted which included all phase II/III randomized clinical trials (RCTs) comparing different neoadjuvant regimens for HER2-positive BC

pCR (yT0/isN0) was the outcome of interest

Indirect comparisons of all combination of anti-HER2 agents with CTA or CT were estimated with a random-effects frequentist NMA[2]

Estimated pCR rates were inferred adopting a Bayesian NMA[3]

Results

17 RCTs (3933 patients) were included (Table 1)

Overall, 8 arms were identified, comprising all possible combinations of CTA and CT with trastuzumab (H), lapatinib (L) and dual HER2 blockade (D) but also CTA and D only (Figure 1)

Odds ratios (OR) for pCR and 95% confidence interval (CI) of all NMA comparisons are shown in Figure 2 and Figure 3

Estimated rates of pCR for each treatment and 95% credible interval (CrI) are reported in Figure 4

Conclusions

- Through indirect comparisons, no significant pCR gain was found for CTA vs CT when combined to D, H and L
- Considering double vs single-agent anti-HER2 regimens, D-CT remains superior to H-CTA, supporting a possible omission of anthracyclines when dual anti-HER2 block is used
- Our pooled estimate suggests a more relevant role for anthracyclines when comparing both H-CT and H-CTA vs CTA. Moreover, we estimated a 4% pCR gain for D-CTA vs D-CT, and an 8% higher pCR rate for H-CTA vs H-CT

Effect modifiers in a randomized phase III trial of low-dose tamoxifen in breast preinvasive disease. Abstract # 1500

Andrea DeCensi, Matteo Puntoni, Aliana Guerrieri Gonzaga, Silvia Caviglia, Franca Avino, Laura Cortesi, Antonio Ponti, Maria Grazia Pacquola, Fabio Falcini, Marcella Gulisano, Maria Digennaro, Anna Carriello, Katia Cagossi, Graziella Pinotti, Harriet Johansson, Matteo Lazzeroni, Tania Buttiron Webber, Davide Corradengo, Luca Boni, and Bernardo Bonanni.

Ente Ospedaliero Ospedali Galliera Genova
Ospedale di rilievo nazionale e di alta specializzazione

IEO Istituto Europeo di Oncologia

Queen Mary University of London

EudraCT Number 2007-007740-10
ClinicalTrials.gov NCT01357772

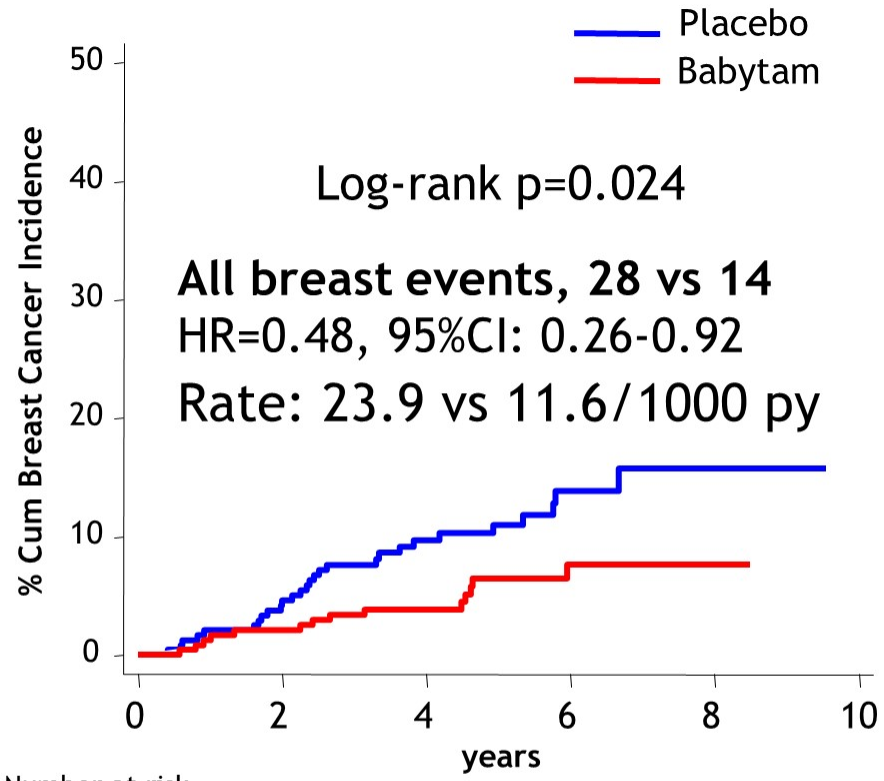
Presented By Andrea De Censi at 2019 ASCO Annual Meeting

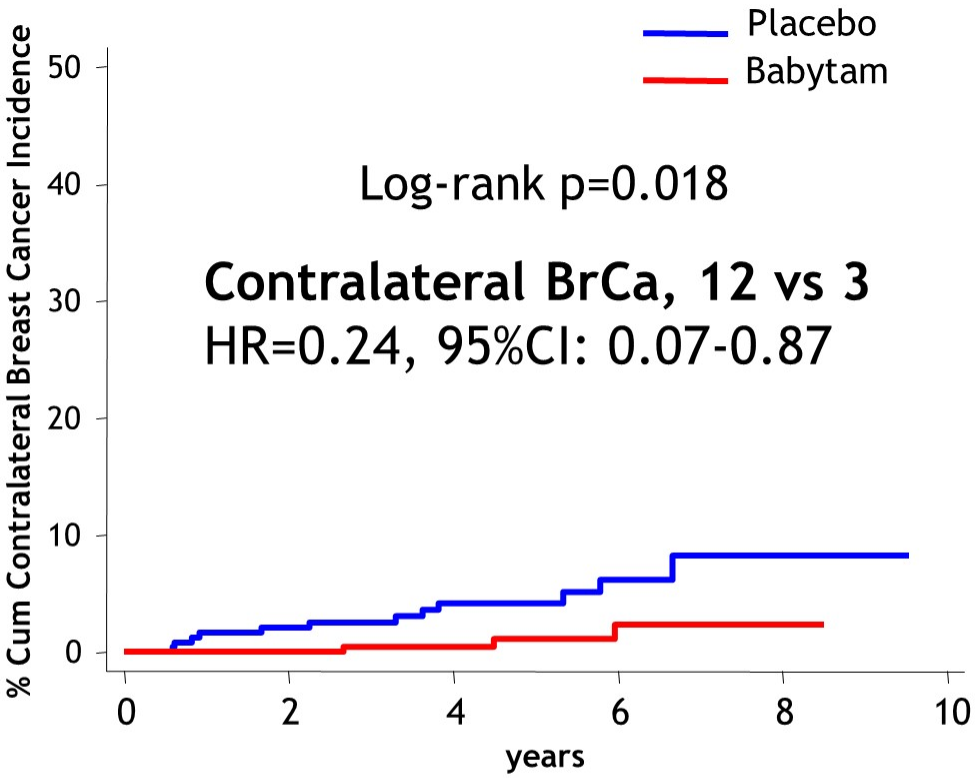
Randomized placebo controlled trial of low dose tamoxifen ("Babytam") - Study Tam01

Primary endpoint: Incidence of invasive breast cancer or DCIS

- 500 participants enrolled from 14 centers in Italy
- Median follow up = 5.1 years (IQR 3.9-6.3)
- Primary events: 42

DeCensi et al. JCO 37; 2019





Number at risk

Pla	247	225	161	78	4	0
Tam	253	234	172	76	3	0

247	225	161	78	4	0
253	234	172	76	3	0

DeCensi et al. JCO 37; 2019

Conclusions-1

- Babytam given for 3 years is effective and safe in women with pre-invasive disease.
- Possible greater benefit on ipsilateral recurrence in postmenopausal women but an opposite trend on contralateral breast cancer in premenopausal women.
- Correlative studies on CYP2D6, endoxifen and circulating hormones are underway to elucidate these complex findings.

Presented By Andrea De Censi at 2019 ASCO Annual Meeting

Safety of Pregnancy Following Breast Cancer in Patients Carrying a *BRCA* Mutation: Results of an International Cohort Study

Matteo Lambertini[1,2], Lieveke Ameye[3], Anne-Sophie Hamy[4], Anna Zingarello[5], Philip D. Poorvu[6], Estela Carrasco[7], Albert Grinshpun[8], Sileny Han[9], Christine Rousset-Jablonski[10], Alberta Ferrari[11], Shani Paluch-Shimon[12], Laura Cortesi[13], Claire Senechal[14], Gianmaria Miolo[15], Katarzyna Pogoda[16], Alejandro Pérez-Fidalgo[17], Laura De Marchis[18], Lucia Del Mastro[1,2], Fedro A. Peccatori[19], Hatem A. Azim Jr.[20]

[1]IRCCS Ospedale Policlinico San Martino, Genova, Italy; [2]University of Genova, Genova, Italy; [3]Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.), Brussels, Belgium; [4]Institut Curie, Paris, France; [5]Institut Gustave Roussy, Université Paris-Saclay, Villejuif, France; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]Vall Hebron Institute of Oncology, Barcelona, Spain; [8]Sharett Institute of Oncology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; [9]University Hospitals Leuven, KU Leuven, Leuven, Belgium; [10]Leon Berard Cancer Center, Lyon, France; [11]Fondazione IRCCS Policlinico San Matteo, University of Pavia, aBRCAdaBRA onlus, Pavia, Italy; [12]Shaare Zedek Medical Centre, Jerusalem, Israel; [13]AOU Policlinico di Modena, Italy; [14]Bergonie Institute, Bordeaux, France; [15]Centro di Riferimento Oncologico di Avano (CRO) IRCCS, Aviano, Italy; [16]Maria Sklodowska-Curie Institute, Oncology Center, Warsaw, Poland; [17]INCLIVA University Hospital of Valencia, Valencia, CIBERONC, Spain; [18]La Sapienza University of Rome, Rome, Italy; [19]European Institute of Oncology (IEO), Milan, Italy; [20]Tecnologico de Monterrey, Monterrey, Mexico

Presented By Matteo Lambertini at 2019 ASCO Annual Meeting

Pregnancy Issues in *BRCA*-mutated Breast Cancer

- Family planning is a priority area of concern for many young women with newly diagnosed breast cancer[1]
- Additional challenges exist for women with germline *BRCA* mutations[2]:
  - Indication to risk-reducing bilateral salpingo-oophorectomy by their 40's[3]
  - Possible reduced ovarian reserve and fertility potential[4,5]
- Very limited data are available on reproductive outcomes and safety of pregnancy following breast cancer in *BRCA*-mutated patients[6]

1. Paluch-Shimon S et al, *Breast* 2017;35:203-217
2. Lambertini M et al, *Cancer Treat Rev* 2017;59:61-70
3. Paluch-Shimon S et al, *Ann Oncol* 2016;27(suppl 5):v103-v110
4. Lambertini M et al, *Ann Oncol* 2018;29(1):237-243
5. Turan V et al, *Reprod Sci* 2018;25(1):26-32
6. Valentini A et al, *Breast Cancer Res Treat* 2013;142(1):177-185

Presented By Matteo Lambertini at 2019 ASCO Annual Meeting

Study Design and Participants

- International, multicenter, hospital-based, retrospective cohort study

Key inclusion criteria

- Stage I - III invasive breast cancer
- Diagnosis between January 2000 and December 2012
- Age ≤ 40 years
- Deleterious germline *BRCA1* and/or *BRCA2* mutation

Key exclusion criteria

- Stage IV *de novo* breast cancer
- No follow-up nor information on post-treatment pregnancies
- Ovarian cancer or other malignancies without breast cancer
- *BRCA* variants of unknown significance
- *BRCA* healthy carriers

ClinicalTrials.gov Identifier: NCT03673306

Statistical Analysis

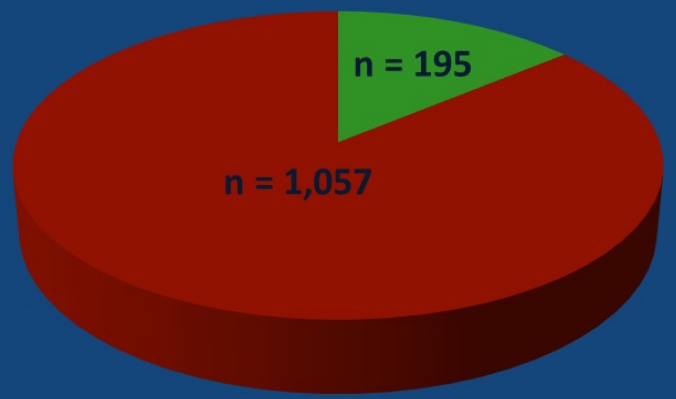
- To account for guarantee-time bias, two analyses were performed:
  1. **Case-control approach**[1,2] matching (1:3) according to: disease-free interval, year at diagnosis (± 2.5 years), nodal status (negative vs. positive), hormone receptor status (positive vs. negative), type of *BRCA* mutation (*BRCA1* vs. *BRCA2*)
  2. **Extended Cox model with occurrence of pregnancy as time-varying covariate**[3]
- This study aimed to include a minimum of 200 patients with a pregnancy following breast cancer (estimated pregnancy rate = 10%) in order to have a power of 0.83 to detect a HR of 0.75 in favor of the pregnancy cohort, at a 2-sided significance level of 0.05

1. Azim HA Jr et al, *J Clin Oncol* 2013;31(1):73-79
2. Lambertini M et al, *J Natl Cancer Inst* 2018;110(4):426-429
3. Lambertini M et al, *Cancer* 2019;125(2):307-316

ClinicalTrials.gov Identifier: NCT03673306

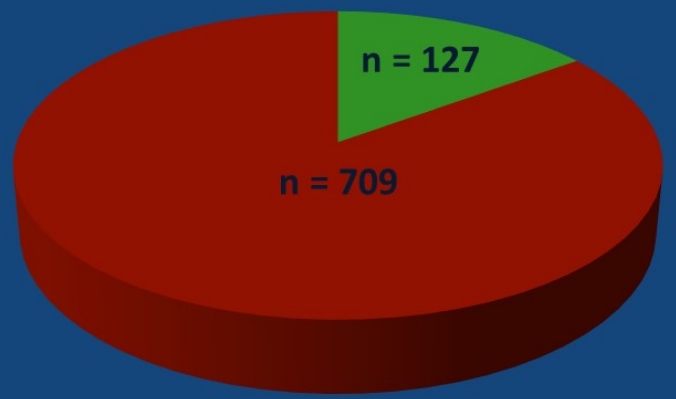
Pregnancy Rate

Overall study population
n = 1,252



16% (95% CI, 14% - 18%)

Centers with ≥ 50 patients
n = 836



15% (95% CI, 13% - 18%)

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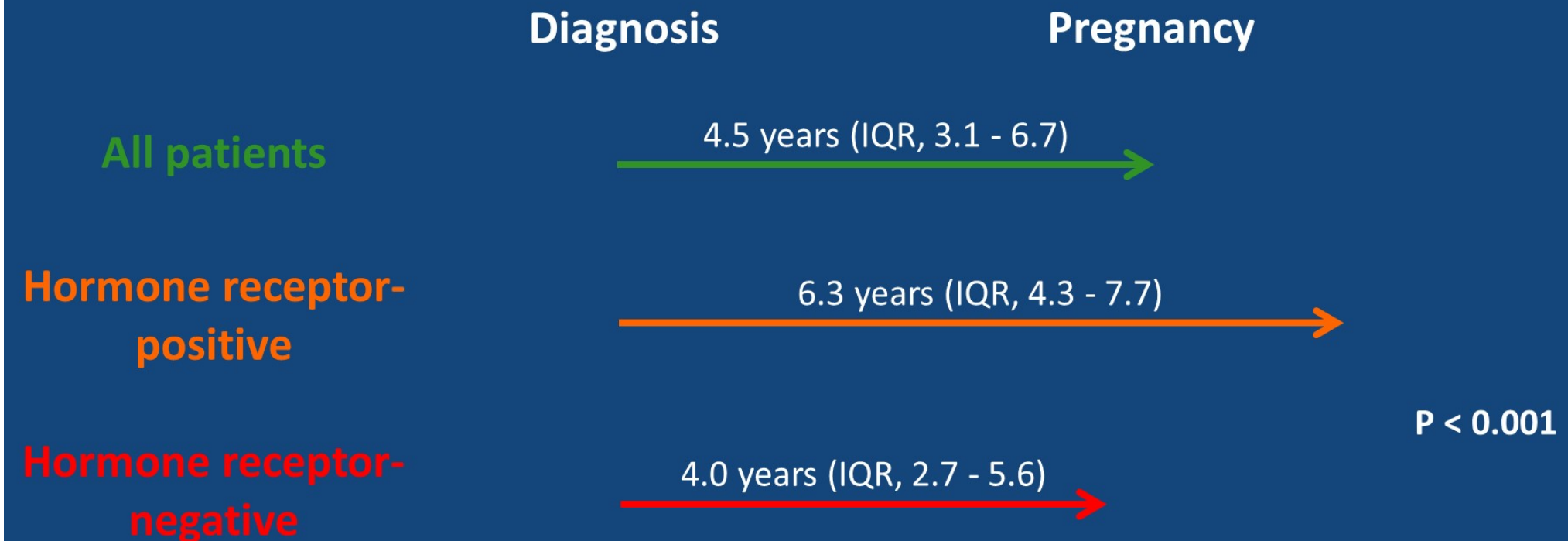
Pregnancy, Fetal and Obstetrical Outcomes

Median age at the time of pregnancy = 35.7 years (IQR, 32.9 - 38.6)



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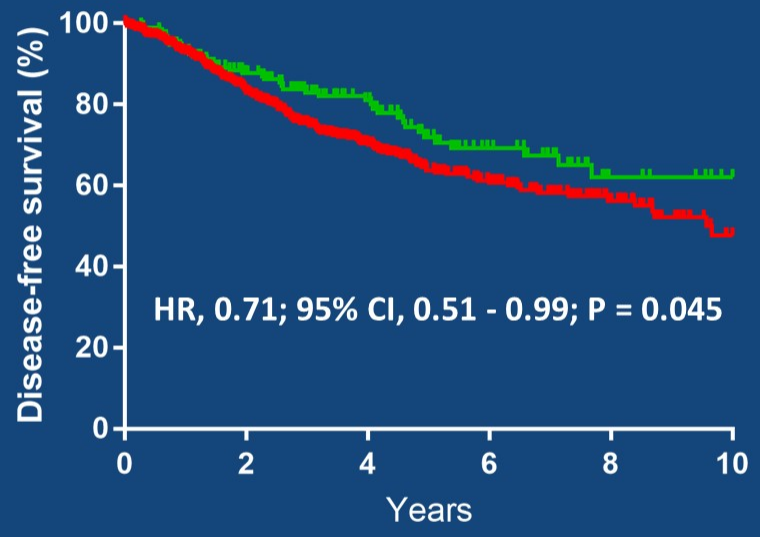
Disease-Free Survival

Median follow-up = 8.3 years (IQR, 8.1 - 8.7)



No. at risk						
non-pregnancy cohort	528	336	198	114	53	19
pregnancy cohort	176	119	80	41	17	10

Extended Cox model with occurrence of pregnancy as time-varying covariate

Unadjusted HR, 0.96; 95% CI, 0.70 - 1.33; P = 0.83

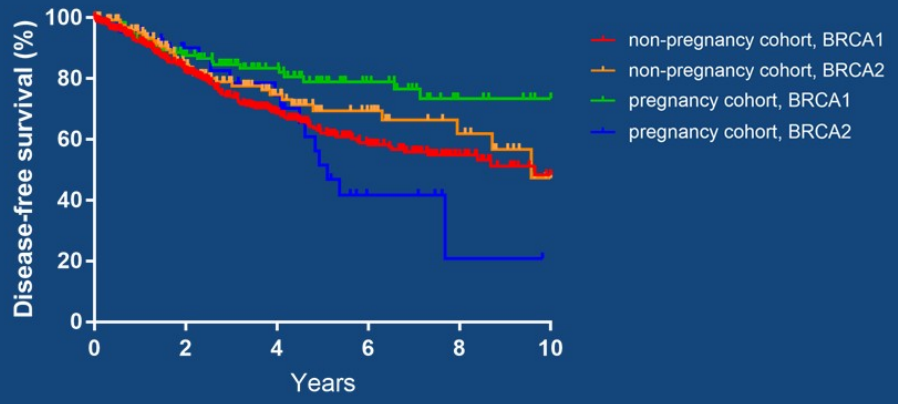
Adjusted* HR, 0.87; 95% CI, 0.61 - 1.23; P = 0.41

***Adjusted for age, tumor size, nodal status, hormone receptor status, type of endocrine therapy, breast surgery and *BRCA* mutation**

Disease-Free Survival: Subgroup Analysis

Median follow-up = 8.3 years (IQR, 8.1 - 8.7)

Type of *BRCA* mutation



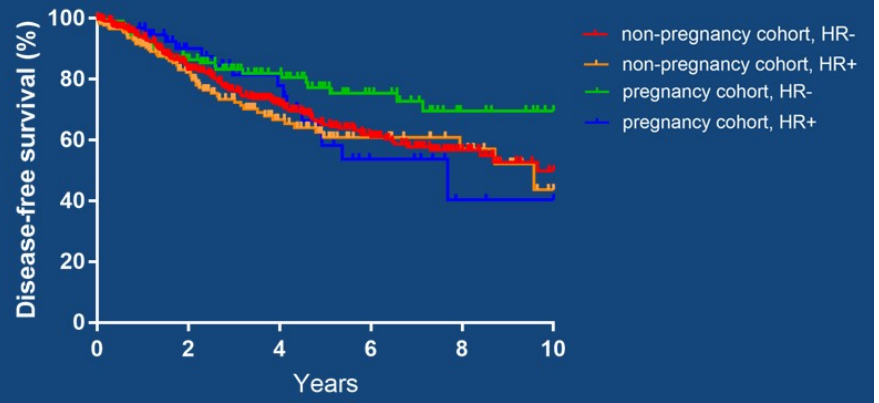
No. at risk						
Non pregnant, BRCA1	393	256	150	87	39	16
Non pregnant, BRCA2	134	80	48	27	14	3
Pregnant, BRCA1	130	93	61	35	16	10
Pregnant, BRCA2	44	25	18	5	1	0

P for interaction < 0.01

***BRCA1*: HR, 0.53; 95% CI, 0.35 - 0.81**

***BRCA2*: HR, 1.60; 95% CI, 0.86 - 2.89**

Hormone receptor status



No. at risk						
Non pregnant, HR-	348	235	146	88	38	16
Non pregnant, HR+	180	101	52	26	15	3
Pregnant, HR-	116	86	58	32	15	9
Pregnant, HR+	60	33	22	9	2	1

P for interaction = 0.28

Hormone receptor-positive: HR, 0.91; 95% CI, 0.52 - 1.60

Hormone receptor-negative: HR, 0.62; 95% CI, 0.40 - 0.95

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Conclusions

- In this large cohort of young *BRCA*-mutated patients, 16% of women had a pregnancy following breast cancer
- No detrimental effect of pregnancy on disease-free survival and overall survival was observed, particularly in *BRCA1*-mutated patients
- Fetal and pregnancy complications appeared similar to those of the general population
- These findings provide reassurance for counseling young *BRCA*-mutated breast cancer patients inquiring about the feasibility and safety of future conception

Benefit from letrozole as extended adjuvant therapy after sequential endocrine therapy: A randomized, phase III study of the Gruppo Italiano Mammella (GIM)

Lucia Del Mastro[1,2], Mauro Mansutti[3], Giancarlo Bisagni[4], Riccardo Ponzone[5], Antonio Durando[6], Laura Amaducci[7], Alessandra Fabi[8], Antonio Fassoldati[9], Andrea Michelotti[10], Antonio Pazzola[11], Enrichetta Valle[12], Giovanni Sanna[13], Stefania Gori[14], Sabino De Placido[15], Ornella Garrone[16], Michela Donadio[6], Paolo Bruzzi[2], Claudia Bighin[2], Matteo Lambertini[1,2], Francesca Poggio[2] **on behalf of the Gruppo Italiano Mammella (GIM)**

1. DIMI, University of Genova; 2. Ospedale Policlinico San Martino, Genova; 3. ASIU Udine University Hospital; 4. Azienda USL/IRCCS Reggio Emilia; 5. Candiolo Cancer Institute, Torino; 6. Città della Salute e della Scienza ASO S. Anna, Torino; 7. Dipartimento oncologico Ospedale Faenza; 8. Regina Elena National Cancer Institute, Roma; 9. Ferrara University Hospital, Ferrara; 10. Ospedale S. Chiara, Pisa; 11. Ospedale Civile SS Annunziata; Sassari; 12. Ospedale Oncologico A. Businco, Cagliari; 13. Azienda Ospedaliera Universitaria; Sassari; 14. Ospedale Sacro Cuore Don Calabria, Negrar; 15. Università Federico II, Napoli; 16. S. Croce e Carlo Teaching Hospital, Cuneo

Breast Cancer

Capsule Summary Slidesets

GIM4 LEAD: Phase III Trial of Extended Adjuvant Therapy With Letrozole After Sequential Endocrine Therapy in Patients With HR+ Early Breast Cancer

VIEW SLIDESET

VIEW MORE

SOPHIA: Phase III Trial of Margetuximab + CT vs Trastuzumab + CT in Patients With HER2+ Metastatic Breast Cancer After Standard Anti-HER2 Therapies

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Phase III NALA: Neratinib + Capecitabine vs Lapatinib + Capecitabine in HER2+ MBC Previously Treated With HER2-Targeted Therapies

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Atezolizumab + nab-Paclitaxel in Previously Untreated Advanced Metastatic TNBC: Updated OS Analysis of Phase III IMpassion130

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Young-PEARL Phase II Study of Palbociclib, Exemestane, and Leuprolide vs Capecitabine in Premenopausal Women With HR+/HER2- MBC

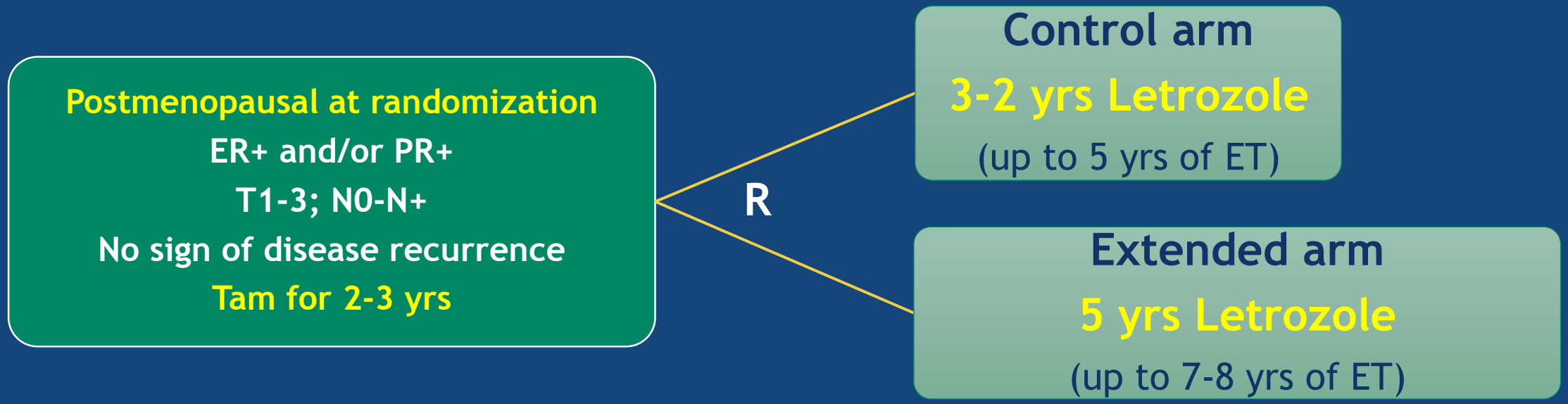
Phase III MONALEESA-7: OS Analysis of Ribociclib + ET vs Placebo + ET in Pre/Perimenopausal Women With HR+/HER2- Advanced Breast Cancer

Background (2005)

- Hormone receptor-positive tumors are at high risk of late recurrence: there are more recurrences after 5 years than in the first 5 years after diagnosis[1]
- Extended endocrine therapy with an aromatase inhibitor (AI), after initial 5 years of tamoxifen, improves DFS [2,3,4]
- AIs are a routine component of early endocrine therapy, either instead of tamoxifen or in sequence with tamoxifen
- Unresolved question: In women who had received AI-based therapy as part of their initial 5 years of adjuvant treatment, does extended therapy with ongoing AI treatment reduce the risk of recurrence?

1. EBCTCG Lancet 2005;365:1687-717; 2. Goss, N Engl J Med 2003;349:1793-802; 3. Mamounas, J Clin Oncol 2008;26:1965-1971;
4. Jakesz, J Natl Cancer Inst 2007;99:1845-53;

GIM4 Study Design



N= 2056
Recruitment in 64 centres in Italy (GIM group), 2005-2010
Median follow-up: 10.4 years (IQR 8.8-11.4)

ClinicalTrials.gov: NCT01064635; EudraCT: 2005-001212-44

GIM4 end-points and study populations

- **Primary study end-point**
  - Invasive Disease Free Survival (DFS)[1] (local recurrence, distant metastases, contralateral or ipsilateral breast tumour, excluding ductal carcinoma in situ, second primary malignancy, death from any cause, and loss to follow-up or end of study)
    - **Intention-To-Treat population**: DFS was computed from the date of randomization to the date of the event (or last follow-up) in the overall patient population
    - **Landmark analysis:** patients with a DFS event or lost to follow up before treatment divergence (2 to 3.3 years after randomization, depending on the duration of pre-random HT) were excluded. DFS was computed from the time of treatment divergence to the date of the event
- **Secondary end-points**
  - Overall survival
  - Adverse events

1. Hudis, J Clin Oncol 2007; 25: 2127-32

GIM4 statistics and sample size

- Minimum therapeutic effect worth detecting with the extended arm was a 23% relative reduction of the risk of recurrence (hazard ratio, HR=0.77), corresponding to a 4% absolute increase in 8-year Disease-Free Survival, from 78% to 82%
- HR 0.77 with power 80% and a two-sided alpha 0.05:
  - 2000 patients to be included
  - Minimum follow-up ≥ 6 years after randomization

Trial profile

2056 patients randomized

1030 assigned to **Control arm**

1026 assigned to **Extended arm**

1030 eligible for ITT analyses

1026 eligible for ITT analyses

82 had a DFS event or were lost to follow up before divergence

83 had a DFS event or were lost to follow up before divergence

948 eligible for Landmark analyses

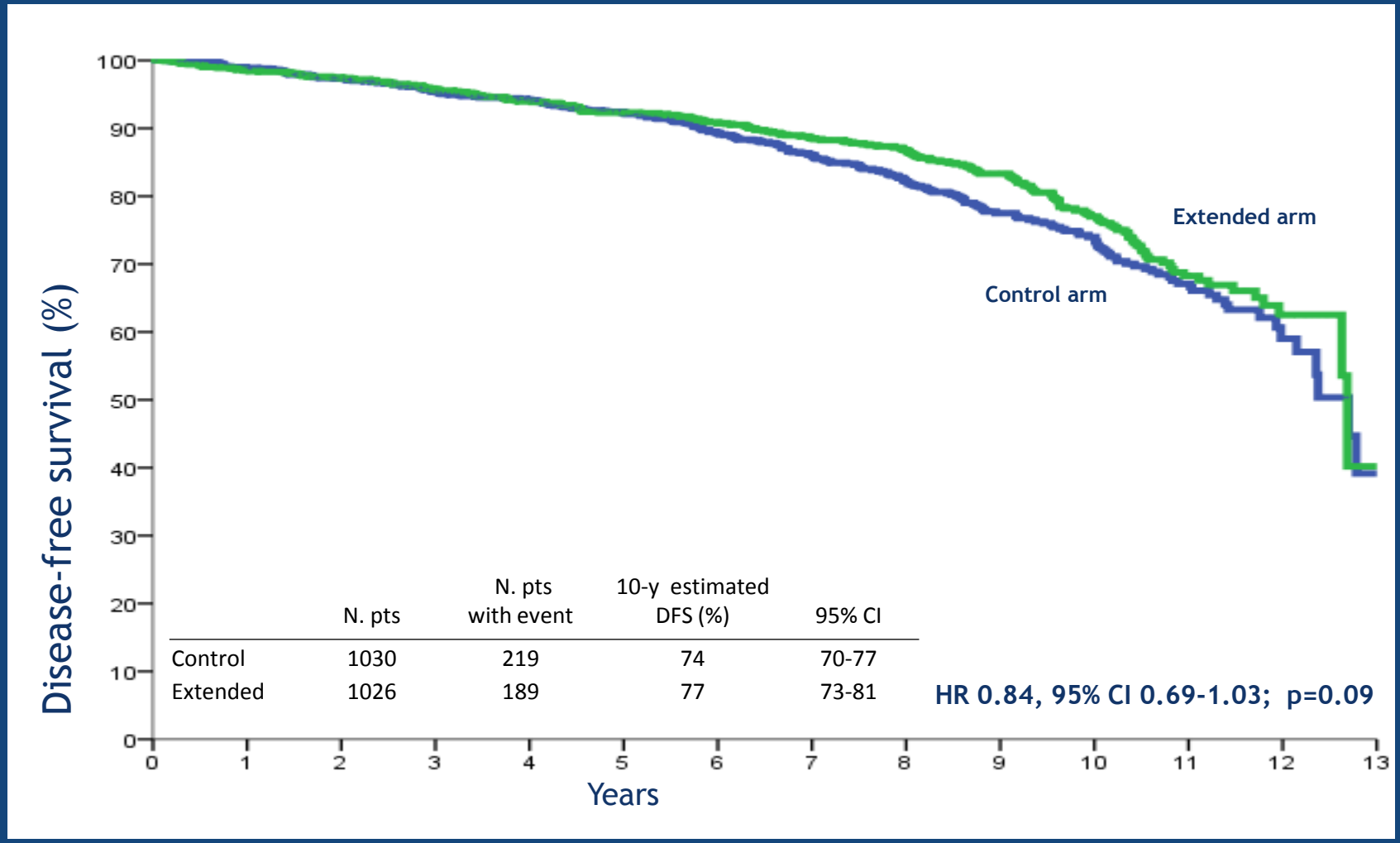
943 eligible for Landmark analyses

Characteristic		Control arm 2-3 year letrozole (n=1030)	Extended arm 5-year letrozole (n=1026)
Age, median (range)		60 (34-86)	61 (41-89)
Tumor size	pT1	704 (68%)	703 (68%)
	pT2	261 (25%)	252 (25%)
	pT3-4	34 (3%)	43 (4%)
	Unknown	31 (3%)	28 (3%)
Nodal status	pN0	581 (56%)	568 (55%)
	pN1-2-3	411 (40%)	428 (42%)
	Unknown	38 (4%)	30 (3%)
Histological grade	G1	156 (15%)	161 (16%)
	G2	564 (55%)	589 (57%)
	G3	221 (21%)	213 (21%)
	Unknown	89 (9%)	63 (6%)
HR status	ER+ and PR+	855 (83%)	866 (84%)
	ER+ or PR+	153 (15%)	146 (14%)
	Uknown	22 (2%)	14 (1%)
HER2 status	Positive	63 (6%)	60 (6%)
	Negative	851 (83%)	833 (81%)
	Unknown	116 (11%)	133 (13%)
Prior (neo)adjuvant CT	No	455 (44%)	450 (44%)
	Yes	557 (54%)	565 (55%)
	nknown	18 (2%)	11 (1%)
Prior duration of tamoxifen, years Median (IQR)		2.4 (1.9-3.3)	2.5 (1.9-3.3)

Treatment compliance

	Control arm 2-3 year letrozole (n=1030)	Extended arm 5-year letrozole (n=1026)
Treatment completed	779 (76%)	582 (57%)
Median duration of letrozole (IQR), years	2.4 (1.9 -2.8)	5.0 (2.4-5)
Early treatment discontinuation	**251 (24%)**	**444 (43%)**
Toxicity	87 (8%)	133 (13%)
Patient refusal	37 (4%)	96 (9%)
Primary disease event	35 (3%)	65 (6%)
Not begun	27 (3%)	35 (3%)
Other	65 (6%)	115 (11%)

Disease-Free Survival - ITT population. N=2056



	N. pts	N. pts with event	10-y estimated DFS (%)	95% CI
Control	1030	219	74	70-77
Extended	1026	189	77	73-81

HR 0.84, 95% CI 0.69-1.03; p=0.09

Number at risk

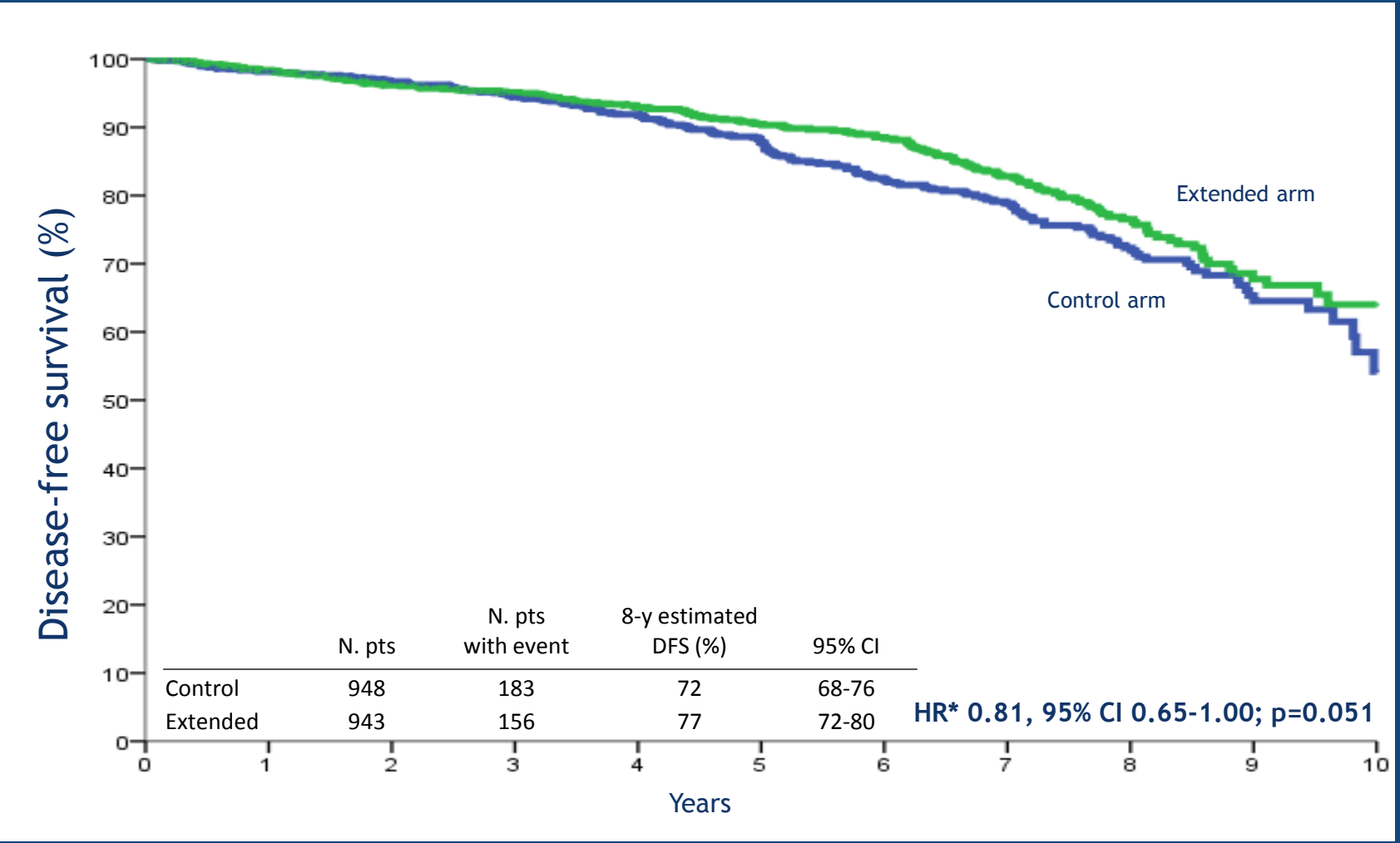
		1	2	3	4	5	6	7	8	9	10	11	12	13
Control	1030	999	967	919	873	805	731	611	485	332	236	135	35	5
Extended	1026	990	963	917	875	814	739	636	512	397	254	120	38	3

Median follow up: 10.4 years

GIM4 study: DFS first events by treatment

	Control arm 2-3-year letrozole (n=1030)		Extended arm 5-year letrozole (n=1026)	
First event	n.	%	n.	%
Distant recurrence	77	7.5	69	6.7
Local recurrence	28	2.7	21	2.0
Second primary cancer	65	6.3	57	5.5
Breast	36	3.5	31	3.0
Non –breast	29	2.8	26	2.5
Death without recurrence	49	4.8	42	4.1
Total first event	219	21.2	189	18.4

Disease-free Survival - Landmark analysis. N=1891



	N. pts	N. pts with event	8-y estimated DFS (%)	95% CI
Control	948	183	72	68-76
Extended	943	156	77	72-80

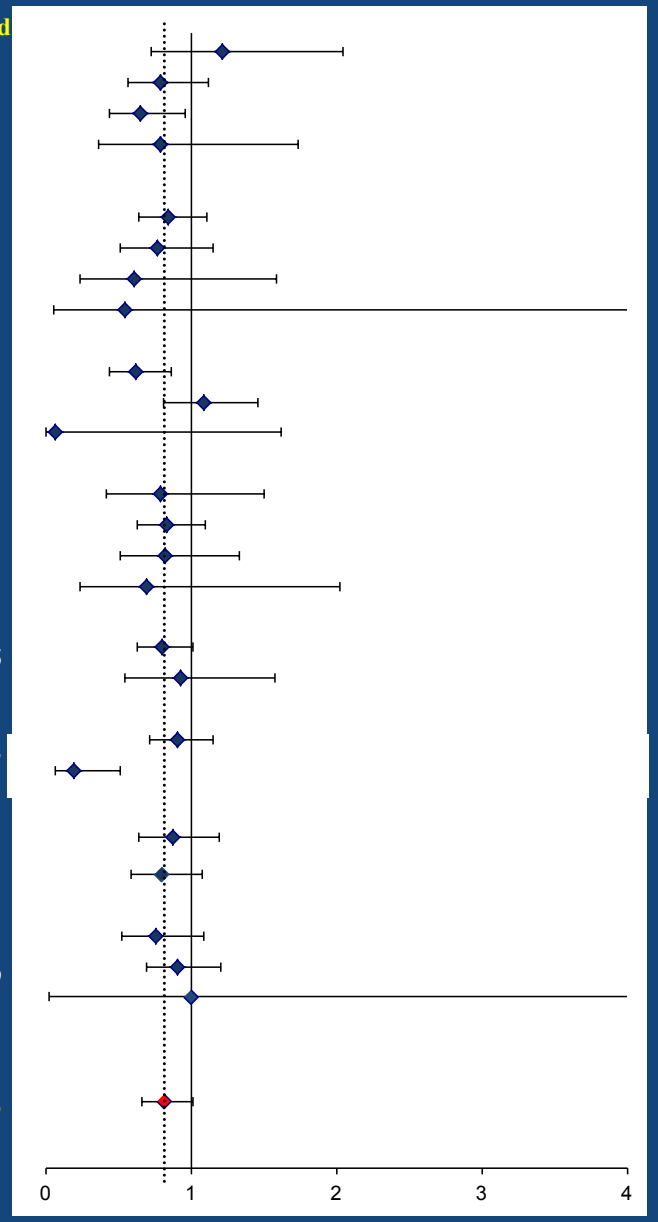
Number at risk

		1	2	3	4	5	6	7	8	9	10
Control	948	893	844	773	682	552	413	284	175	83	18
Extended	943	903	850	788	692	574	451	326	187	80	22

Time 0 is time when treatment diverged in the two arms (i.e. 2-3 yrs after randomization); * Adjusted HR 0.815, 95% CI 0.66-1.01

DFS
Subgroup analysis

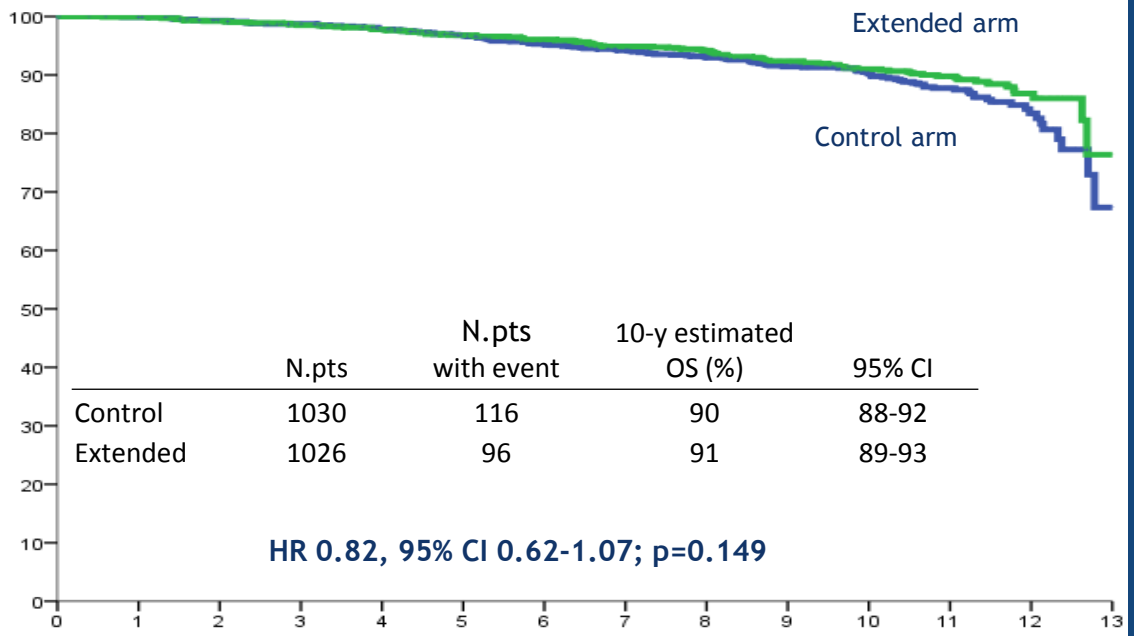
		events/patients control	events/patients extended	HR (95%CI)	P interaction
Age (years)	<55	26/258	36/252	1.22 (0.73-2.05)	0.384
	55-64	75/365	61/354	0.80 (0.56-1.12)	
	65-75	64/276	46/291	0.65 (0.44-0.96)	
	>=76	18/49	13/46	0.80 (0.36-1.74)	
Tumor size	pT1	108/659	97/656	0.85 (0.64-1.11)	0.725
	pT2	56/234	47/229	0.77 (0.52-1.15)	
	pT3-4	13/33	10/36	0.61 (0.23-1.59)	
	pTx	6/22	2/22	0.55 (0.06-5.25)	
Nodal status	pN0	87/539	58/528	0.62 (0.44-0.87)	0.034
	pN+	87/381	96/389	1.08 (0.81-1.46)	
	pNx	9/28	2/26	0.07 (0.00-1.62)	
Histological Grade	G1	21/145	20/154	0.79 (0.42-1.51)	0.952
	G2	104/524	97/545	0.84 (0.63-1.10)	
	G3	45/206	32/188	0.83 (0.51-1.34)	
	Gx	13/73	7/56	0.70 (0.24-2.02)	
Hormone receptor *	ER+ and PR+	149/789	129/795	0.80 (0.64-1.02)	0.662
	ER + or PR+	29/146	26/137	0.93 (0.54-1.58)	
HER2 status *	negative	143/788	133/772	0.91 (0.72-1.15)	0.002
	positive	19/57	5/53	0.19 (0.071-0.512)	
Previous Tamoxifen	<=2.5 years	96/508	70/461	0.87 (0.64-1,19)	0.745
	>2.5 years	87/440	86/482	0.80 (0.59-1.08)	
Previous chemotherapy	NO	69/420	53/419	0.76 (0.53-1.09)	0.811
	YES	109/517	103/519	0.91 (0.69-1.20)	
	Unknown	5/11	0/5	1.00 (0.03-39,5)	
All patients		183/948	156/943	0.81 (0.65-1.01)	



*24 pts with missing HR and 221 pts with missing HER2 status excluded

Overall Survival

ITT population N=2056

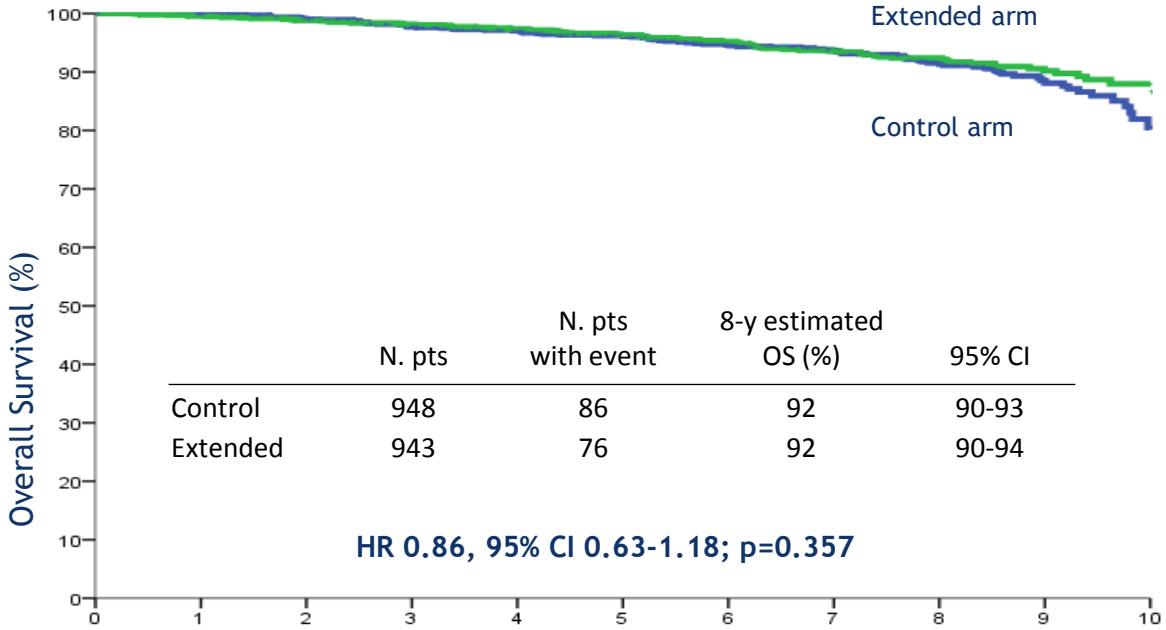


	N.pts	N.pts with event	10-y estimated OS (%)	95% CI
Control	1030	116	90	88-92
Extended	1026	96	91	89-93

HR 0.82, 95% CI 0.62-1.07; p=0.149

		1	2	3	4	5	6	7	8	9	10	11	12	13
Control	1030	1020	1004	988	966	927	886	853	788	665	523	335	107	7
Extenden	1026	1018	1004	986	966	942	913	861	807	693	545	339	111	6

Landmark analysis N=1891



	N. pts	N. pts with event	8-y estimated OS (%)	95% CI
Control	948	86	92	90-93
Extended	943	76	92	90-94

HR 0.86, 95% CI 0.63-1.18; p=0.357

		1	2	3	4	5	6	7	8	9	10
Control	948	941	920	883	849	806	732	588	411	211	54
Extended	943	931	917	891	860	807	725	601	426	230	66

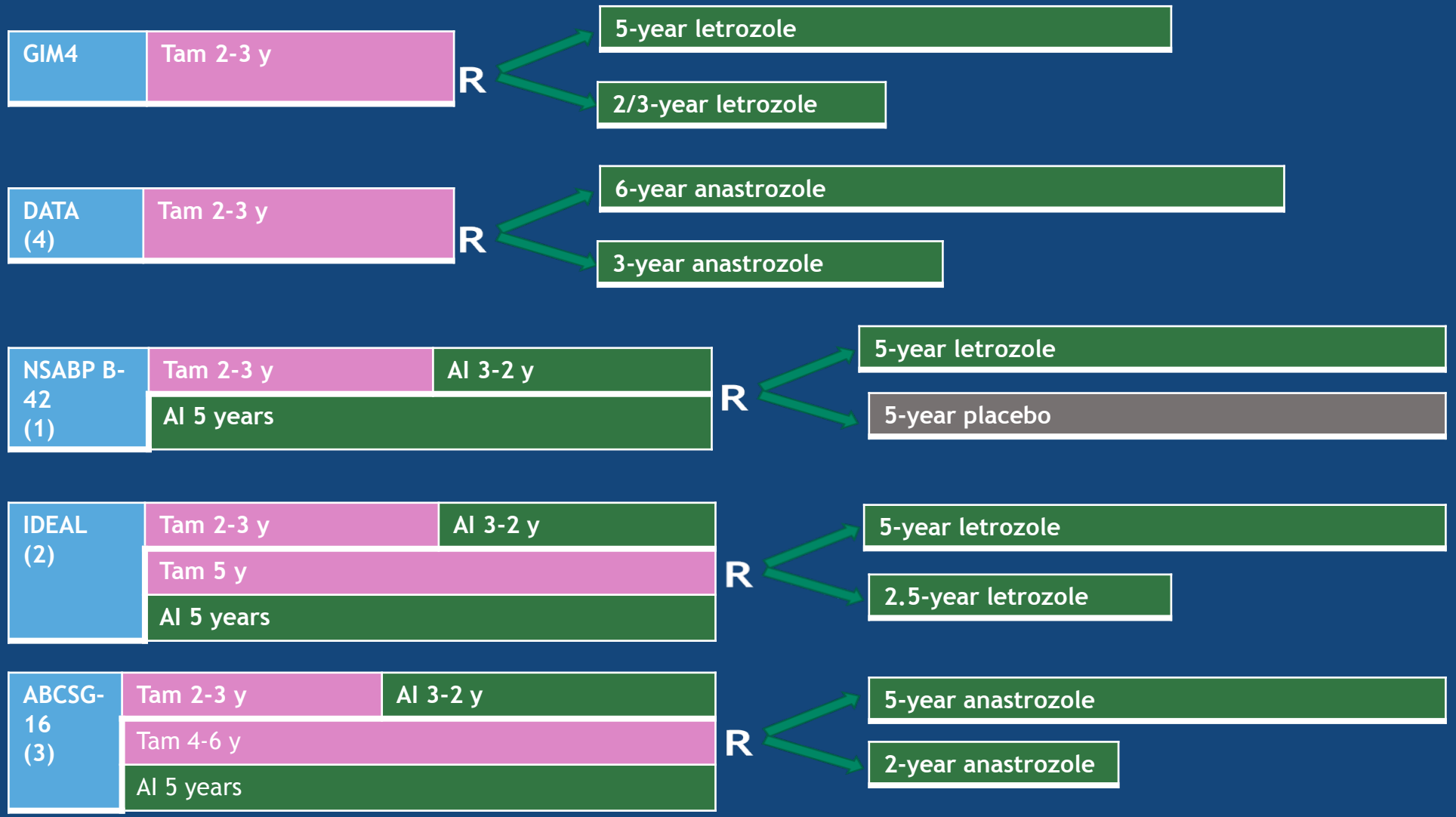
Time 0 is time when treatment diverged in the two arms (i.e. 2-3 yrs after randomization)

Selected side effects

	Control arm 2-3-year letrozole (n=983)		Extended arm 5-year letrozole (n=977)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Arthralgia	263 (27%)	22 (2%)	311 (32%)	29 (3%)
Myalgia	65 (7%)	7 (1%)	95 (10%)	9 (1%)
Hot flashes	119 (12%)		127 (13%)	
Alopecia	31 (3%)		35 (4%)	
Osteoporosis	47 (5%)[a]		81 (8%)[b]	
Bone fractures	5 (<1%)		9 (1%)	
Hypercholesterolemia	32 (3%)		22 (2%)	
Hypertension	7 (1%)		19 (2%)	
Cardiovascular event	1 (<1%)		6 (1%)	

a. 103 pts (10%) and b. 79 pts (8%) had baseline osteoporosis

Extended adjuvant AI studies



HR DFS
0.81 (0.65-1.00)
0.79 (0.62-1.02)
0.85 (0.62-1.02)
1.007 (0.87-1.16)
0.92 (0.74-1.16)

1. Mamounas; Lancet Oncol. 2019; 20:88-99; 2. Blok; J Natl Cancer Inst 2018; 110:40-48; 3. Gnant; SABCS 2017; 4. Tjan-Heijnen ; Lancet Oncol 2017; 18:1502-11

Conclusions

- Extended adjuvant Letrozole, after 5-y sequential endocrine therapy, is associated with a 19% reduction in iDFS events (HR 0.81; 0.65-1.00; p=0.051)
- These findings are consistent with the results of previous studies and support the ASCO adjuvant endocrine therapy Expert Panel recommendation: tamoxifen for 2 to 3 years followed by AI for 7 to 8 years is one of the strategies of extended treatment which could be considered in postmenopausal breast cancer patients at residual risk of BC recurrence[1]

1.Burstein, JCO 2019;37:423-38

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