

Lo studio GIM4

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Disclosure Information

Relationship Relevant to this Session

Poggio, Francesca:

No relevant relationship to disclose.

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

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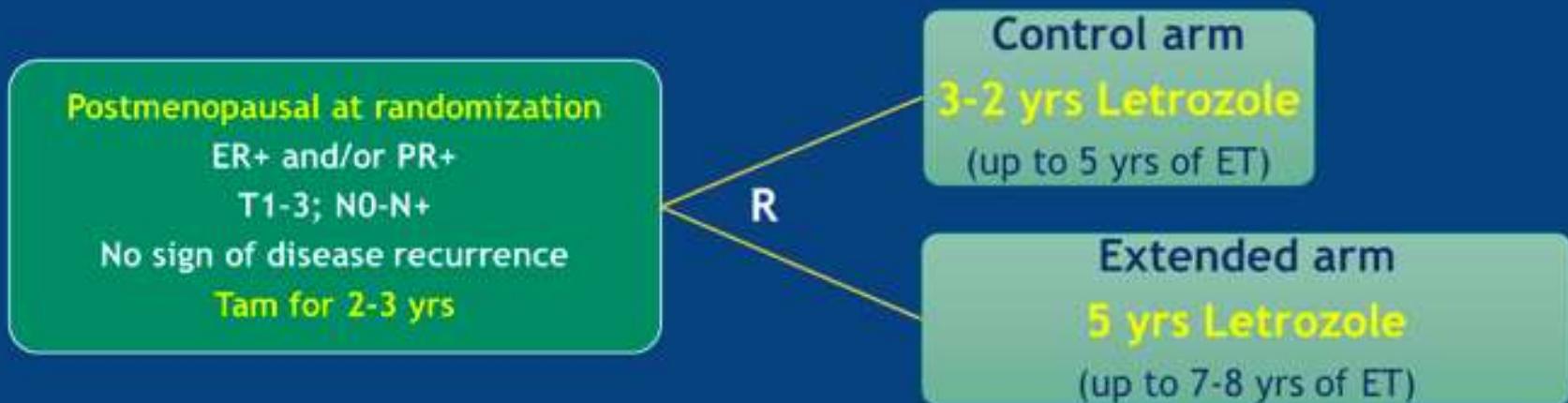
Background (2005)

- 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 diagnosis¹
- **Extended endocrine therapy** with an aromatase inhibitor (**AI**), after initial 5 years of tamoxifen, improves DFS^{2,3,4}
- **Als 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;

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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

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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%)

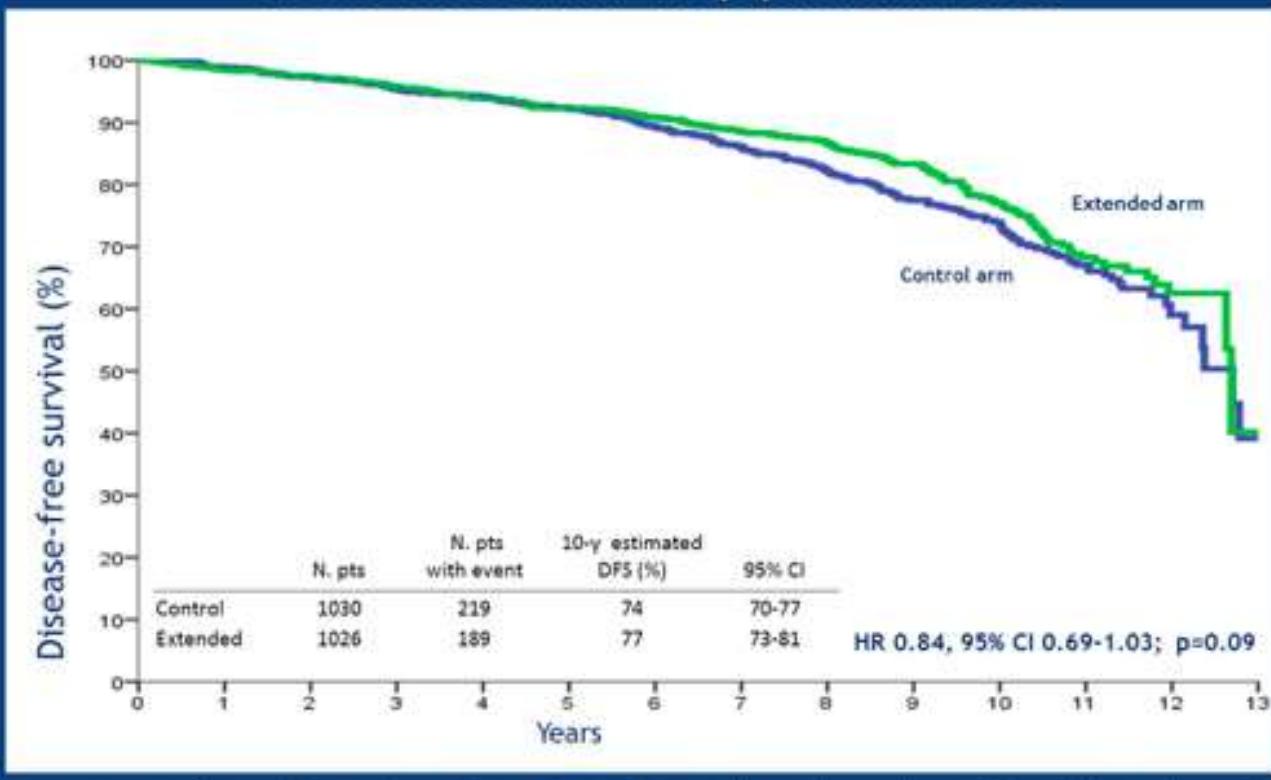
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Baseline characteristics

		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%)
	Unknown	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%)
	Unknown	18 (2%)	11 (1%)
Prior duration of tamoxifen, years		2.4 (1.9-3.3)	2.5 (1.9-3.3)
Median (IQR)			

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Disease-Free Survival - ITT population. N=2056

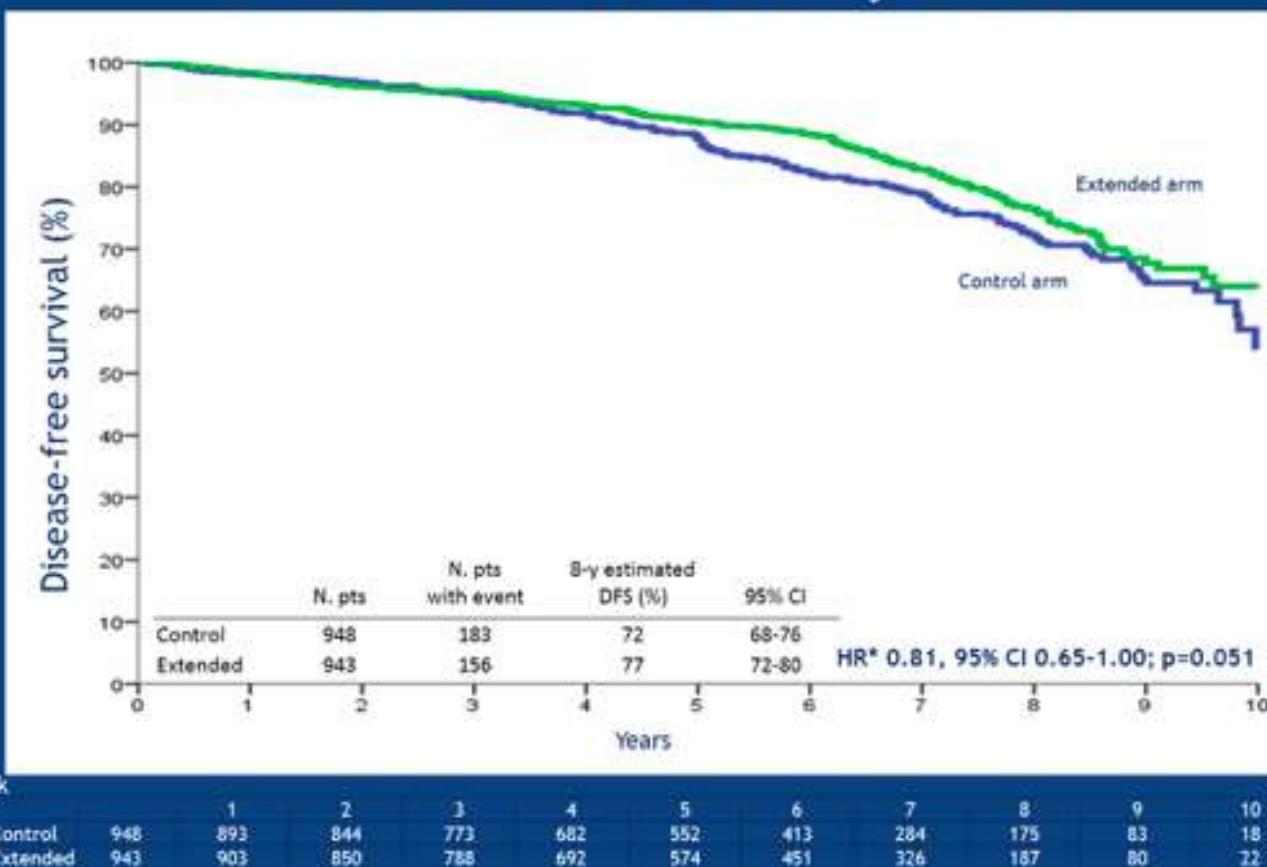


Number at risk	1	2	3	4	5	6	7	8	9	10	11	12	13
Control	1030	999	967	919	873	805	731	611	485	332	236	135	35
Extended	1026	990	963	917	875	814	739	636	512	397	254	120	38

Median follow up: 10.4 years

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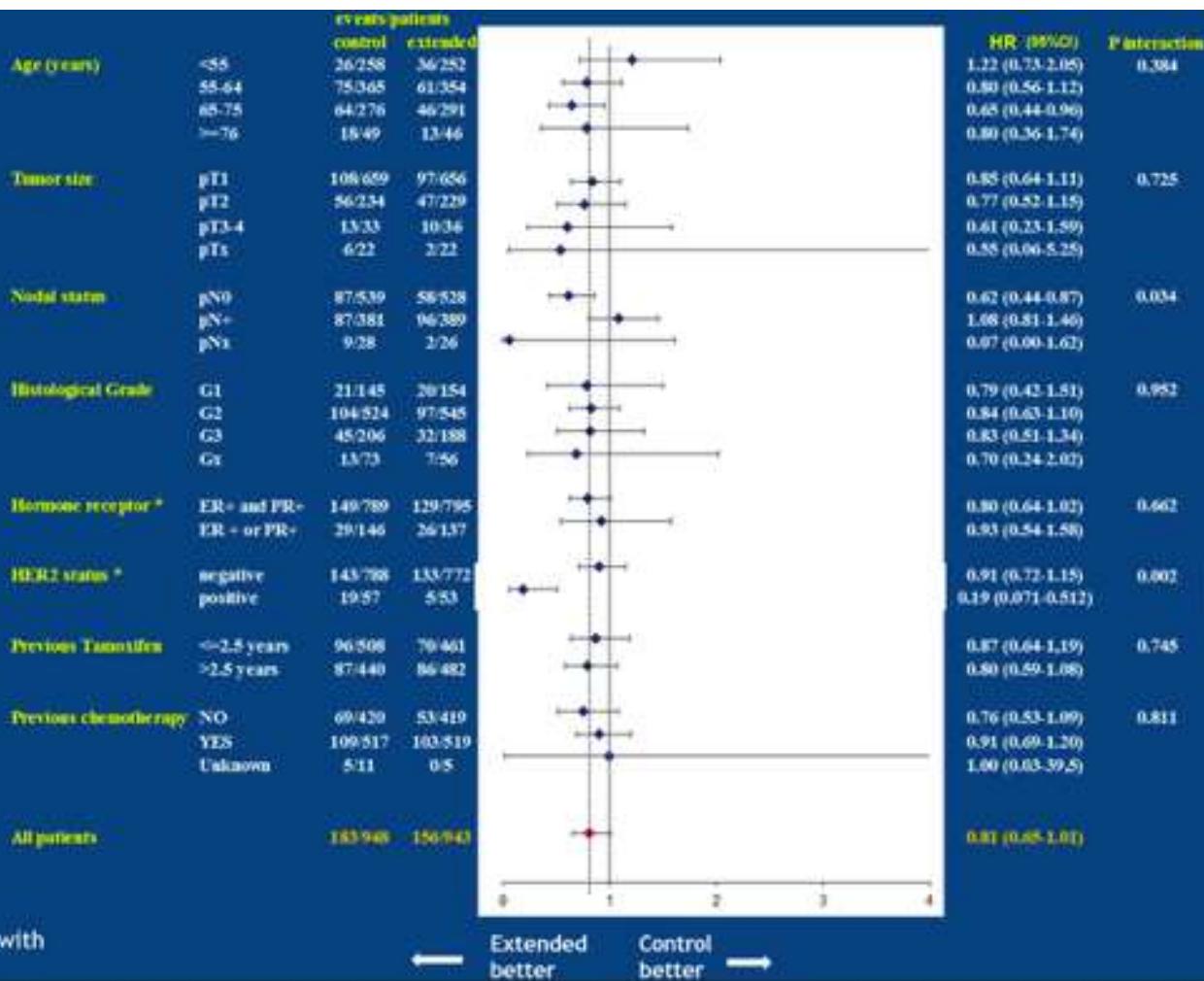
Disease-free Survival - Landmark analysis. N=1891



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

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DFS Subgroup analysis

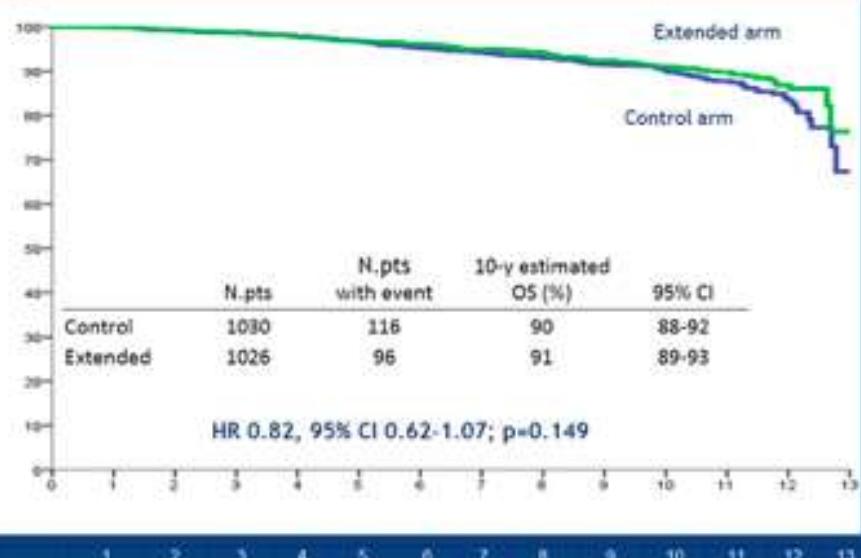


*24 pts with missing HR, and 221 pts with missing HER2 status excluded

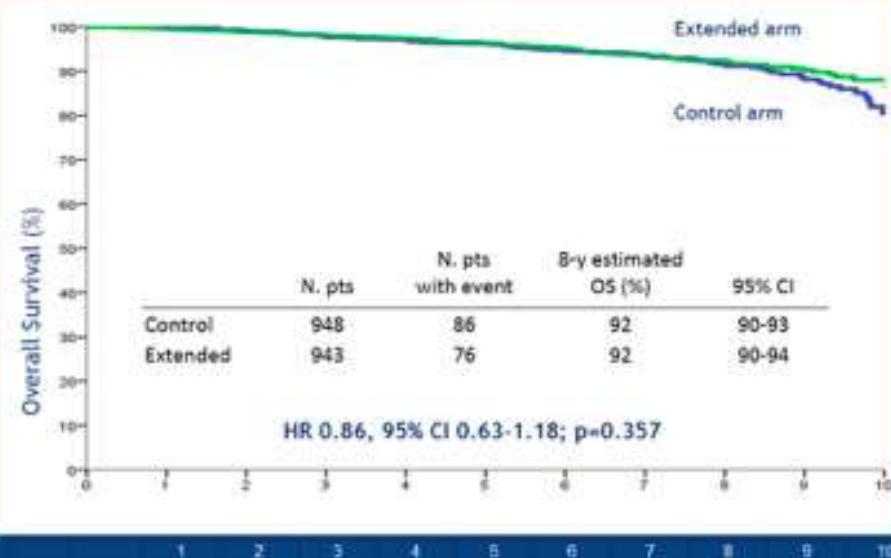
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Overall Survival

ITT population N=2056



Landmark analysis N=1891



	1	2	3	4	5	6	7	8	9	10	11	12	13
Control	1030	1020	1004	988	966	927	880	853	788	665	523	335	107
Extended	1026	1018	1004	988	966	942	913	881	801	693	545	339	111

	1	2	3	4	5	6	7	8	9	10
Control	948	941	920	883	849	806	732	588	411	211
Extended	943	931	917	891	850	807	725	601	420	239

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

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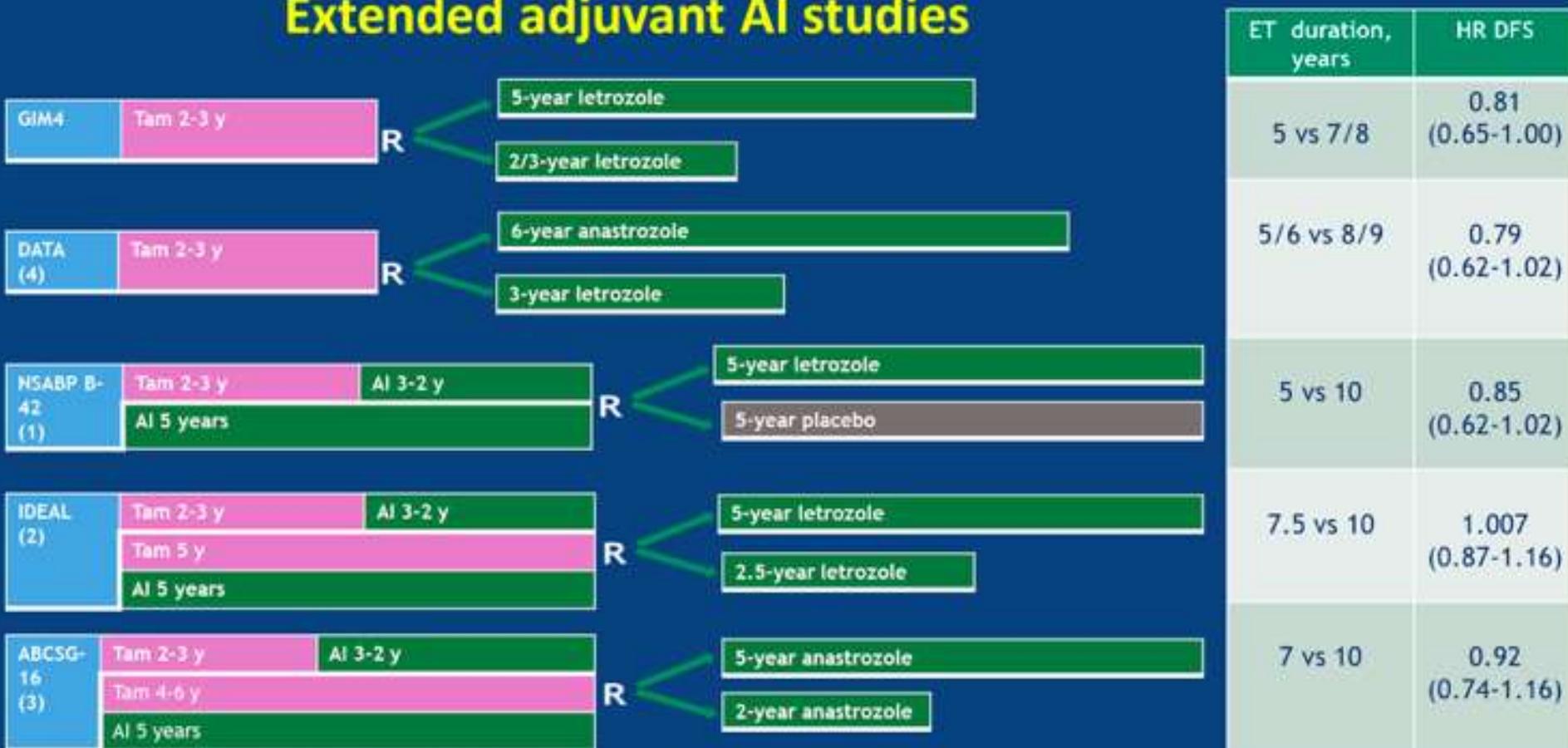
Selected side effects

	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

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Extended adjuvant AI studies



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

Conclusions

- After 2 to 3 years of tamoxifen, extended adjuvant treatment with additional 5 years of letrozole, 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 suggest that tamoxifen for 2 to 3 years followed by AI for 5 to 6 years is a strategy of extended treatment which could be considered in breast cancer patients at residual risk of BC recurrence