GRUPPO B: Nelle pazienti ad alto rischio, la prevenzione con antiaromatasici riduce il rischio di sviluppo di carcinoma mammario invasivo?

Valutazione delle evidenze:

STUDI PUBBLICATI FINO AL 2013

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HYPOTHESIS GENERATION

The IES trial

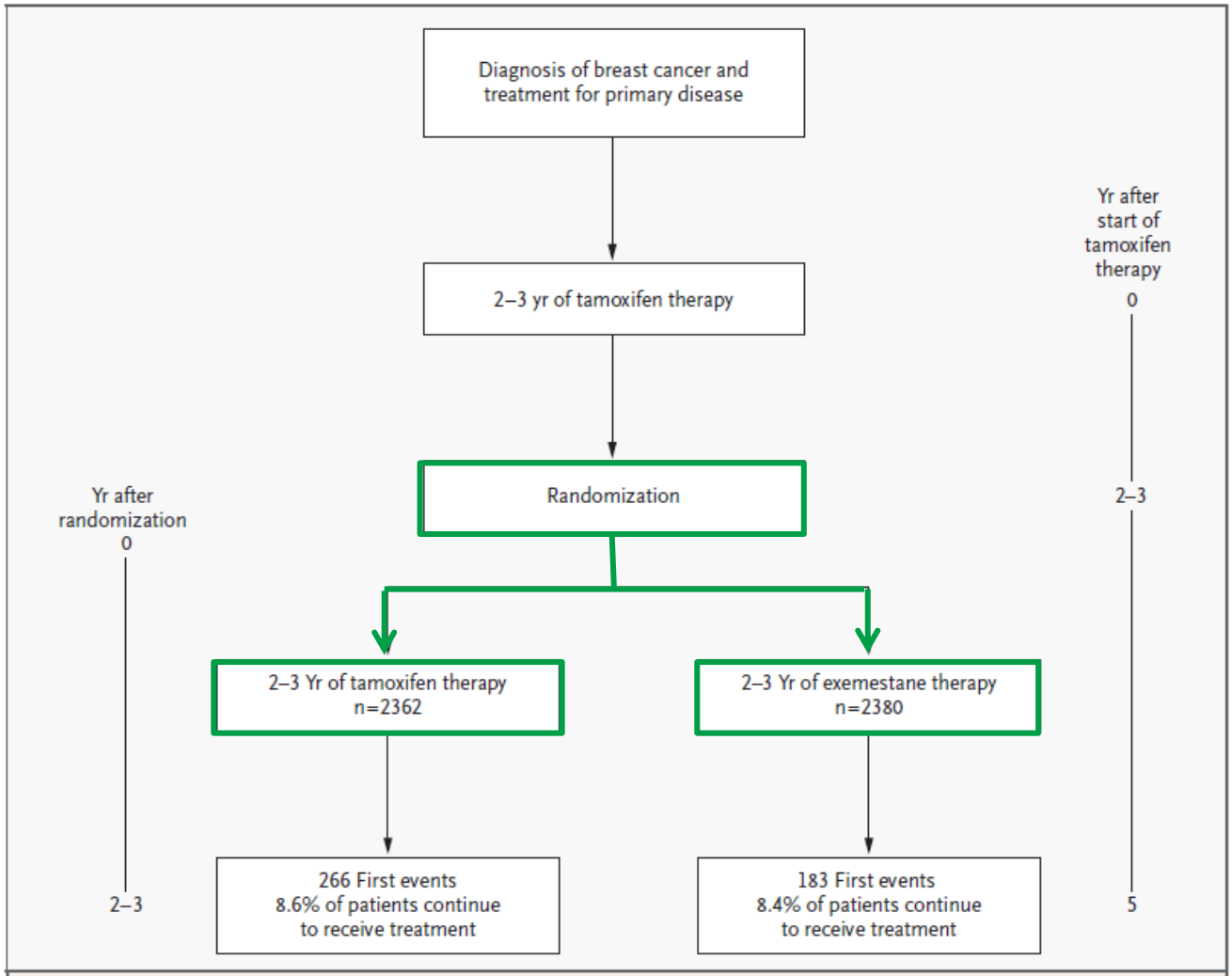


Figure 1. Trial Schema.

The percentage of patients who continue to receive treatment represents the percentage who are not known to have discontinued their randomized treatment and who began initial tamoxifen therapy less than five years before December 31, 2003.

DFS (30.6 months follow-up)

- EXE vs. TAM: HR 0.68 (0.56-0.82, p<0.001)

DFS (55.7 months follow-up)

- EXE vs. TAM: HR 0.76 (0.66-0.88, p=0.001)

The IES trial - CLBC

End Point	Unadjusted		Adjusted	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Disease-free survival	0.68 (0.56–0.82)	<0.001	0.67 (0.56–0.82)	<0.001
Breast-cancer–free survival	0.63 (0.51–0.77)	<0.001	0.62 (0.50–0.76)	<0.001
Time to contralateral breast cancer	0.44 (0.20–0.98)	0.04	0.44 (0.20–0.98)	0.04
Overall survival	0.88 (0.67–1.16)	0.37	0.89 (0.67–1.17)	0.41

Variable	Exemestane Group (N=2362)	Tamoxifen Group (N=2380)	All Patients (N=4742)
	no. of patients		
Events included in analysis of disease-free survival*			
Local recurrence only	21	33	54
Distant recurrence	114	174	288
Primary cancer in contralateral breast	9	20	29
Intercurrent death (without recurrence)	39	39	78
Recurrence, contralateral breast cancer, or intercurrent death	183	266	449
Death			
Any cause	93	106	199
Breast-cancer–related	54	67	121
Intercurrent (without recurrence)	39	39	78
Second primary non-breast cancer	27	53	80

The IES trial - safety

Type of Event	Exemestane Group					Tamoxifen Group					P Value
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	
	number (percent)										
Cardiovascular disease other than myocardial infarction					984 (42.6)					913 (39.2)	0.016
Hot flashes	504	363	97	3	967 (42.0)	493	342	84	4	923 (39.6)	0.082
Pain or aches	392	305	61	8	766 (33.2)	383	242	55	4	684 (29.4)	0.001
Fatigue	336	178	31	0	545 (23.6)	352	157	36	2	547 (23.5)	0.776
Insomnia	269	143	37	0	449 (19.5)	234	140	31	1	406 (17.4)	0.151
Sweating	222	153	51	3	429 (18.6)	215	145	57	1	418 (17.9)	0.702
Headaches	272	129	26	1	428 (18.6)	243	116	17	2	378 (16.2)	0.035
Dizziness	206	73	9	0	288 (12.5)	192	74	13	0	279 (12.0)	0.904
Nausea	177	57	14	0	248 (10.8)	189	53	16	0	258 (11.1)	0.835
Visual disturbances	134	32	4	0	170 (7.4)	115	8	10	0	133 (5.7)	0.024
Osteoporosis					171 (7.4)					134 (5.7)	0.023
Gynecologic symptoms					135 (5.8)					211 (9.0)	<0.001
Arthralgia					124 (5.4)					85 (3.6)	0.005
Depression	68	50	2	0	120 (5.2)	51	37	5	0	93 (4.0)	0.114
Diarrhea	63	28	8	1	100 (4.3)	37	16	1	0	54 (2.3)	<0.001
Vaginal bleeding	49	33	11	0	93 (4.0)	73	50	5	1	129 (5.5)	0.087
Cramps	45	16	3	0	64 (2.8)	60	37	3	2	102 (4.4)	0.002
Thromboembolic disease Including ungraded serious adverse events	11	4	8	1	24 (1.0) 30 (1.3)	11	13	15	6	45 (1.9) 55 (2.4)	0.005 0.007

The IES trial´s hypothesis

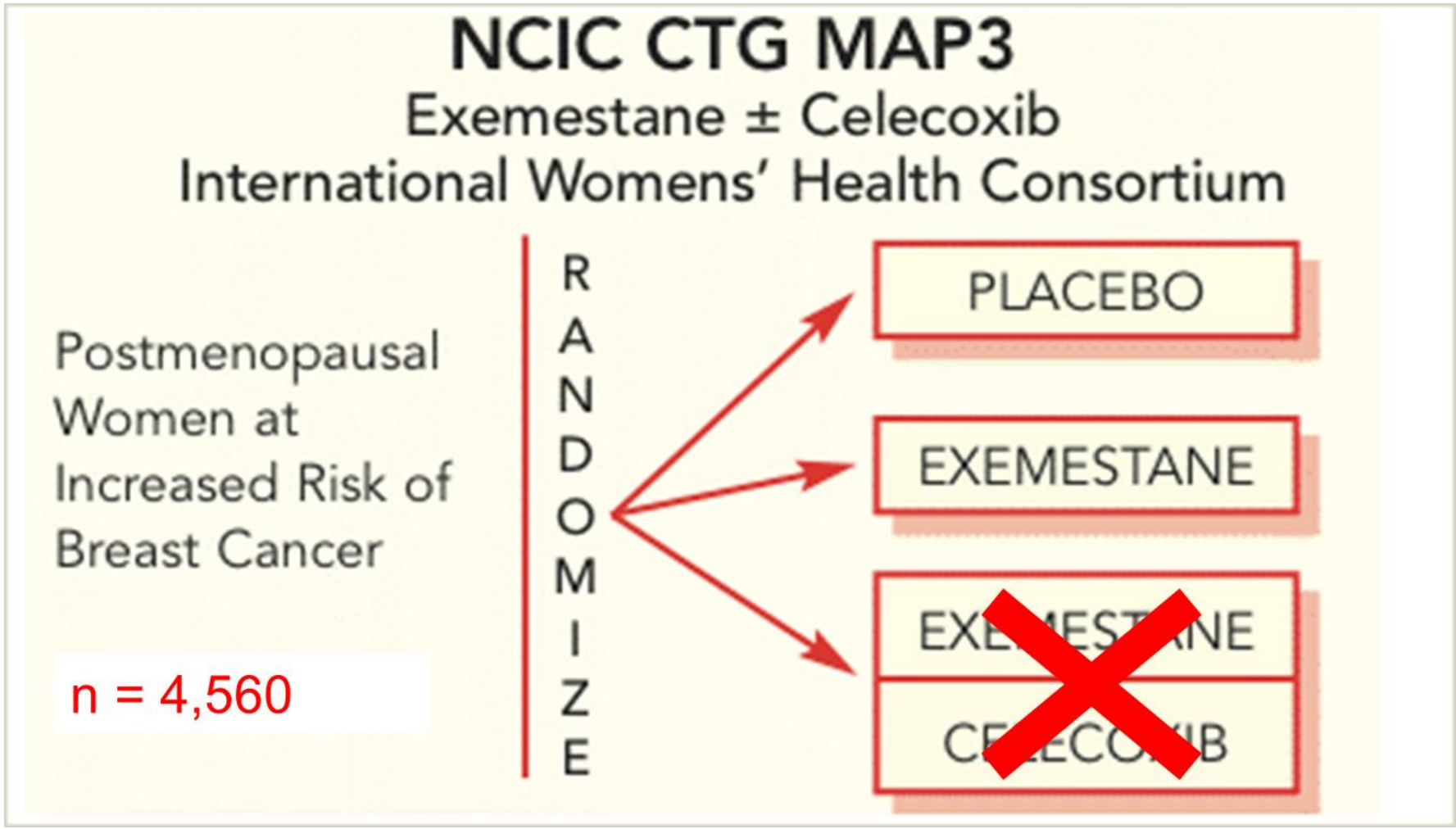
The IES trial data offer a hypothesis on which to base a primary breast cancer prevention trial testing EXEMESTANE

The MAP.3 trial

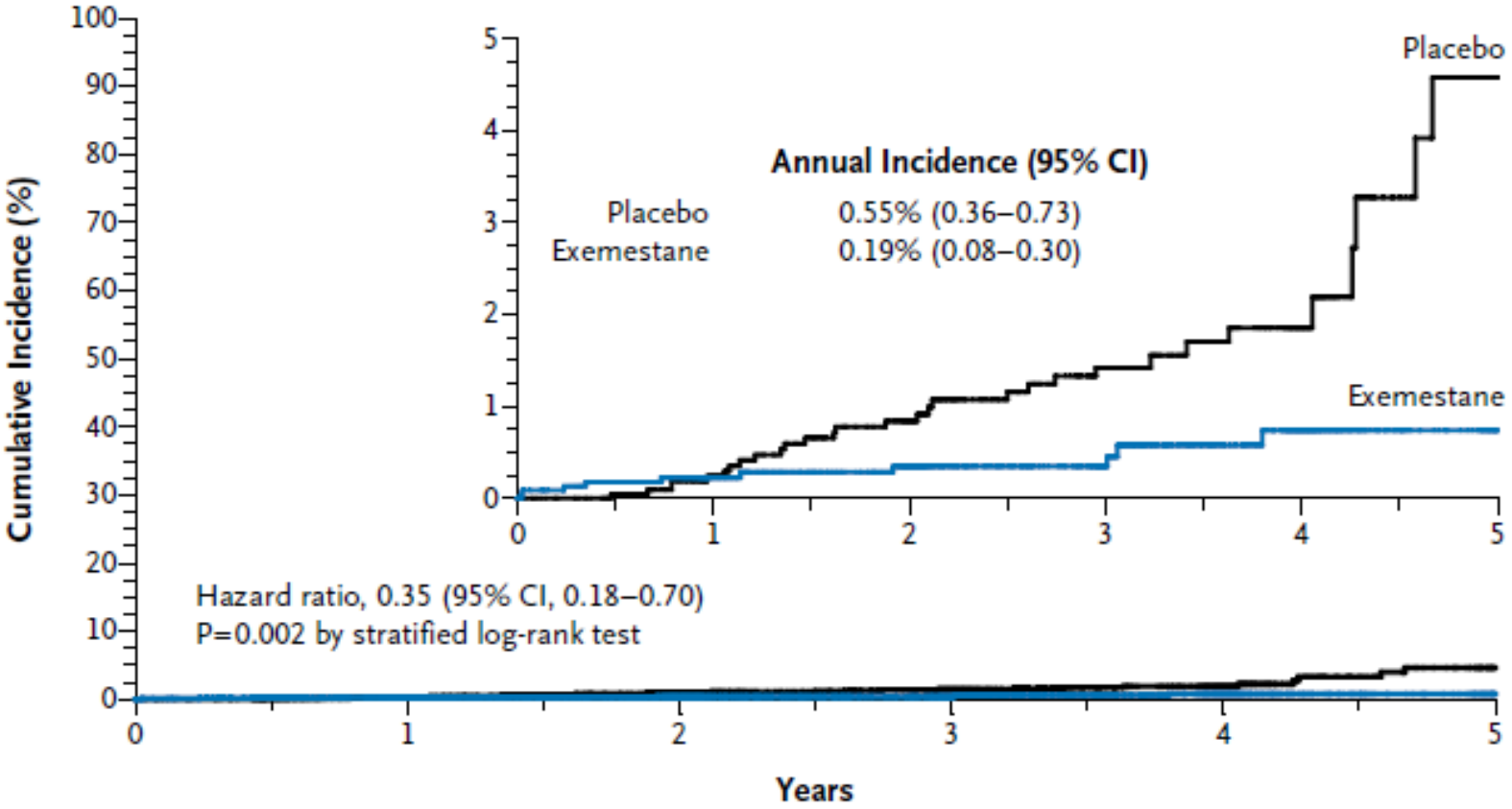
4560 postmenopausal women with a 5-year Gail score > 1.67% will be randomized to:

- Exemestane 25 mg daily x 5 years
- Placebo

The MAP.3 trial – study design [2]



The MAP.3 trial – efficacy [1]



No. at Risk						
Placebo	2275	1905	1468	986	477	82
Exemestane	2285	1902	1468	980	464	77

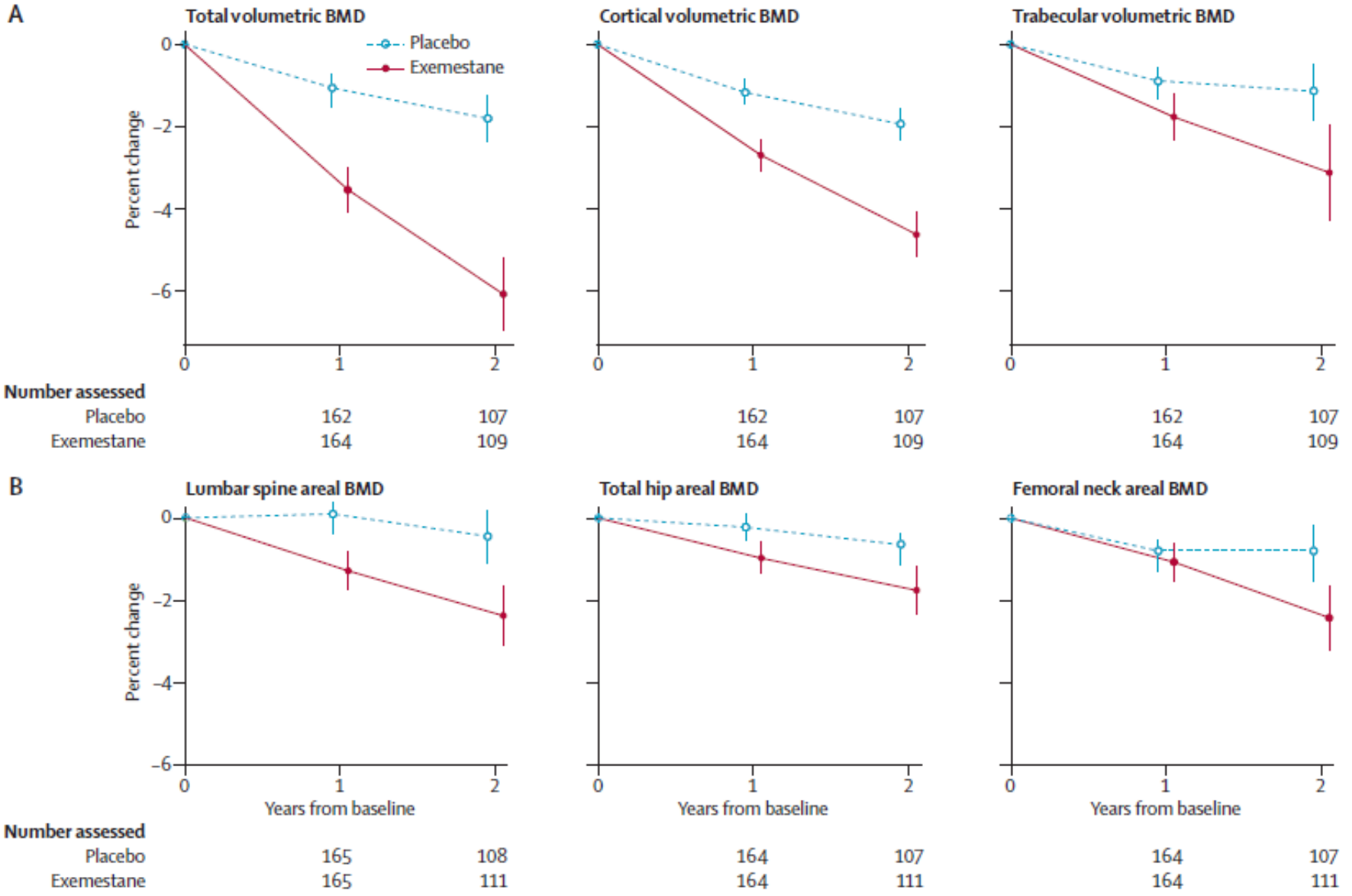
The MAP.3 trial – efficacy [2]

Type of Event	Exemestane (N=2285)		Placebo (N=2275)		Hazard Ratio (95% CI)†	P Value‡
	No. of Cases	Annual Incidence (%)	No. of Cases	Annual Incidence (%)		
Invasive breast cancer						
All cases	11	0.19	32	0.55	0.35 (0.18–0.70)	0.002
ER-positive	7	0.12	27	0.46	0.27 (0.12–0.60)	<0.001
ER-negative	4	0.07	5	0.09	0.80 (0.21–2.98)	0.74
PR-positive	5	0.09	20	0.34	0.26 (0.10–0.69)	0.004
PR-negative	6	0.10	12	0.20	0.50 (0.19–1.33)	0.16
HER2/neu-positive	0	0.00	6	0.10	NA	NA
HER2/neu-negative	10	0.17	26	0.44	0.40 (0.19–0.82)	0.01
HER2/neu unknown	1	NA	0	NA	NA	NA
T stage 1	8	0.14	28	0.48	0.29 (0.13–0.65)	0.001
T stages 2 to 4	3	0.05	3	0.05	0.98 (0.20–4.86)	0.98
T stage X	0	NA	1	NA	NA	NA
Node-positive	3	0.05	9	0.15	0.33 (0.09–1.71)	0.08
Node-negative	7	0.12	22	0.38	0.33 (0.14–0.78)	0.008
Node unknown	1	NA	1	NA	NA	NA
M stage 0	11	0.19	30	0.51	0.38 (0.19–0.75)	0.004
M stage X1	0	NA	2	NA	NA	NA
DCIS§	9	0.16	14	0.24	0.65 (0.28–1.51)	0.31
Invasive breast cancer and DCIS§	20	0.35	44	0.77	0.47 (0.27–0.79)	0.004
ADH, ALH, and LCIS	4	0.07	11	0.20	0.36 (0.11–1.12)	0.08

The MAP.3 trial - safety

Side Effect	Exemestane (N = 2240)					Placebo (N = 2248)					P Value
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total	
		no.			*no. (%)*		*no.*			*no. (%)*	
Any	464	931	536	32	1963 (88)	557	877	437	30	1901 (85)	0.003
Cardiac: hypertension	119	109	112	1	341 (15)	124	118	109	3	354 (16)	0.65
Endocrine											
Hot flashes	489	344	67		900 (40)	450	225	43		718 (32)	<0.001
Fatigue	342	150	31	2	525 (23)	305	135	25		465 (21)	0.03
Sweating	284	201	1		486 (22)	263	169	1		433 (19)	0.046
Insomnia	117	98	15		230 (10)	127	55	7		189 (8)	0.04
Constitutional and gastrointestinal											
Diarrhea	77	32	9		118 (5)	58	16	1		75 (3)	0.002
Heartburn	223	92	17		332 (15)	200	79	10		289 (13)	0.06
Nausea	137	15	3		155 (7)	102	18	2		122 (5)	0.04
Musculoskeletal: arthritis	102	113	30	2	247 (11)	96	83	17		196 (9)	0.01
Neurologic											
Dizziness	145	35	9		189 (8)	152	48	9		209 (9)	0.32
Mood alteration or depression	123	90	19	4	236 (11)	128	98	8	1	235 (10)	0.96
Pain											
Back	106	77	21	2	306 (9)	119	80	23		222 (10)	0.45
Extremity	67	68	17	1	153 (7)	60	54	8		122 (5)	0.054
Joint	294	293	75	3	665 (30)	308	264	33	1	606 (27)	0.04
Muscle	69	62	16		147 (7)	111	67	14		192 (9)	0.01
Upper respiratory: cough	196	28	10		234 (10)	224	31	11		266 (12)	0.14
Sexual function: vaginal dryness	209	142	1		352 (16)	219	124			343 (15)	0.68
Secondary-end-point toxic effects											
Clinical skeletal fracture					149 (6.7)					143 (6.4)	0.72
New osteoporosis					37 (1.7)					30 (1.3)	0.39
Cardiovascular events					106 (4.7)					111 (4.9)	0.78
Other solid tumors or hematologic malignant lesions					43 (1.9)					38 (1.7)	0.58

The MAP.3 trial – bone safety



CONCLUSIONS – ASCO 2013

1. Exemestane is a reasonable option for reducing the risk of invasive breast cancer in postmenopausal women at increased risk of breast cancer

2. Women receiving exemestane should undergo bone monitoring and have adequate vitamin D and calcium supplementation

3. Longer-term follow-up is needed to further characterize both adverse effects and breast cancer outcomes