Breast Cancer Debate of the Year

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BSMO

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What treatment in residual disease following neoadjuvant chemotherapy for stage III poorly differentiated luminal breast cancer?

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27th January 2023

Financial disclosures

- My institution has received payments from the following pharmaceutical companies on my behalf:
  - Amgen
  - AstraZeneca
  - Daiichi Sankyo
  - Eli Lilly
  - Gilead
  - MSD
  - Mundi Pharma
  - Novartis
  - Pfizer
  - Pierre Fabre
  - Roche
  - Teva

Patient case

- Female patient, 31 y.o.

- October 2021 :
  - grade 3 NST cancer of the left breast
  - ER 8/8, PgR 7/8, Ki67 35%, CerbB2 2+ (SISH negative)
  - cT3 cN1 cM0 (stage IIIA)

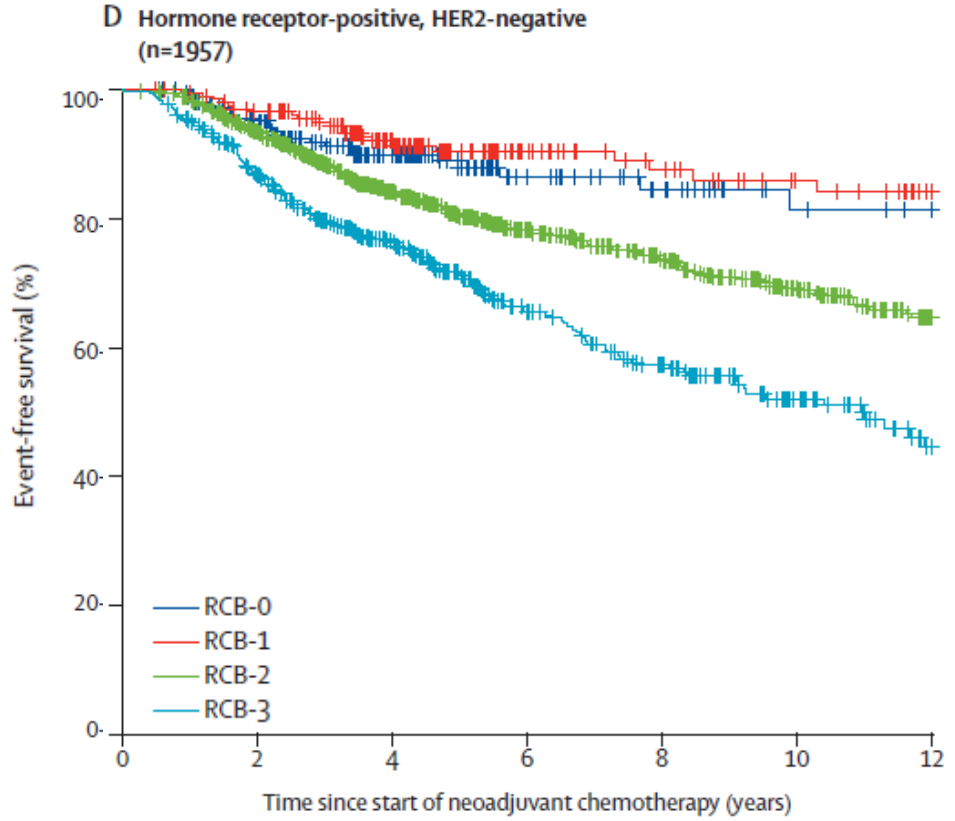
- Neoadjuvant chemotherapy :
  - 4 dose-dense EC
  - followed by 12 weekly paclitaxel

- May 2022 : left mastectomy + ALND :
  - grade 2 NST
  - ER 8/8, PgR 8/8, Ki67 10%, CerbB2 2+ (SISH negative)
  - ypT1b N1a (stage IIA)
  - RCB 3

Outcomes according to RCB

Pooled analysis of patients with primary stage I–III breast cancer treated with neoadjuvant chemotherapy followed by surgery

	All participants (n=5161)	Hormone receptor-positive, HER2-negative (all patients; n=1957)
Baseline characteristics		
Age, years	49 (20–80)	49 (20–80)
T category		
0–1	466 (9·0%)	152 (7·8%)
2	3139 (60·8%)	1195 (61·1%)
3	1026 (19·9%)	406 (20·7%)
4	345 (6·7%)	124 (6·3%)
Missing	185 (3·6%)	80 (4·1%)
Node positivity	2780 (53·9%)	1115 (57%)
Histological grade		
1	130 (2·5%)	103 (5·3%)
2	1668 (32·7%)	911 (46·6%)
3	2945 (57·1%)	782 (40%)
Missing	398 (8·1%)	161 (8·2%)
Histological type		
Ductal or mixed ductal	4790 (92·8%)	1744 (89·1%)
Lobular	216 (4·2%)	159 (8·1%)
Other	100 (1·9%)	29 (1·5%)
Unknown or missing	55 (1·1%)	25 (1·3%)
Postneoadjuvant chemotherapy: RCB class		
RCB-0	1676 (32·5%)	217 (11·1%)
RCB-1	662 (12·8%)	211 (10·8%)
RCB-2	2017 (39·1%)	1036 (52·9%)
RCB-3	806 (15·6%)	493 (25·2%)
Follow-up information		
Follow-up, months	56 (0–186)	58 (0–200)
Event-free survival events	1164	465
Distant relapse-free survival events	1072	441



Number at risk (number censored)							
RCB-0	217 (0)	187 (20)	118 (80)	56 (140)	39 (155)	26 (167)	23 (170)
RCB-1	211 (0)	196 (8)	132 (64)	73 (121)	58 (134)	46 (145)	35 (155)
RCB-2	1036 (0)	916 (54)	609 (280)	373 (479)	278 (555)	187 (631)	109 (699)
RCB-3	493 (0)	403 (26)	261 (125)	151 (204)	109 (228)	61 (268)	27 (296)

Yau C et al, Lancet Oncol 2022; 23: 149–60

How to improve the outcome?

- Adjuvant abemaciclib
- Adjuvant olaparib
- Type of endocrine therapy
- Duration of endocrine therapy
- Bone-modifying agents

Adjuvant abemaciclib

monarchE Study Design (NCT03155997)

HR+, HER2-, node positive high-risk EBC
- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on **clinical pathological features**
- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on **Ki-67**
- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

Stratified for:
- Prior chemotherapy
- Menopausal status
- Region

R 1:1
N = 5637

On-study treatment period
2 years

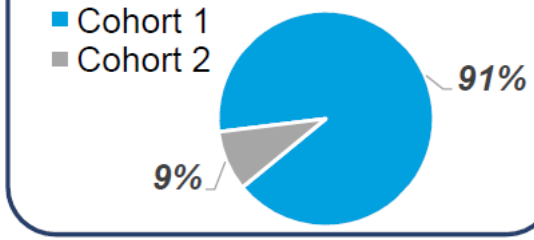
Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

Endocrine Therapy: AI or tamoxifen

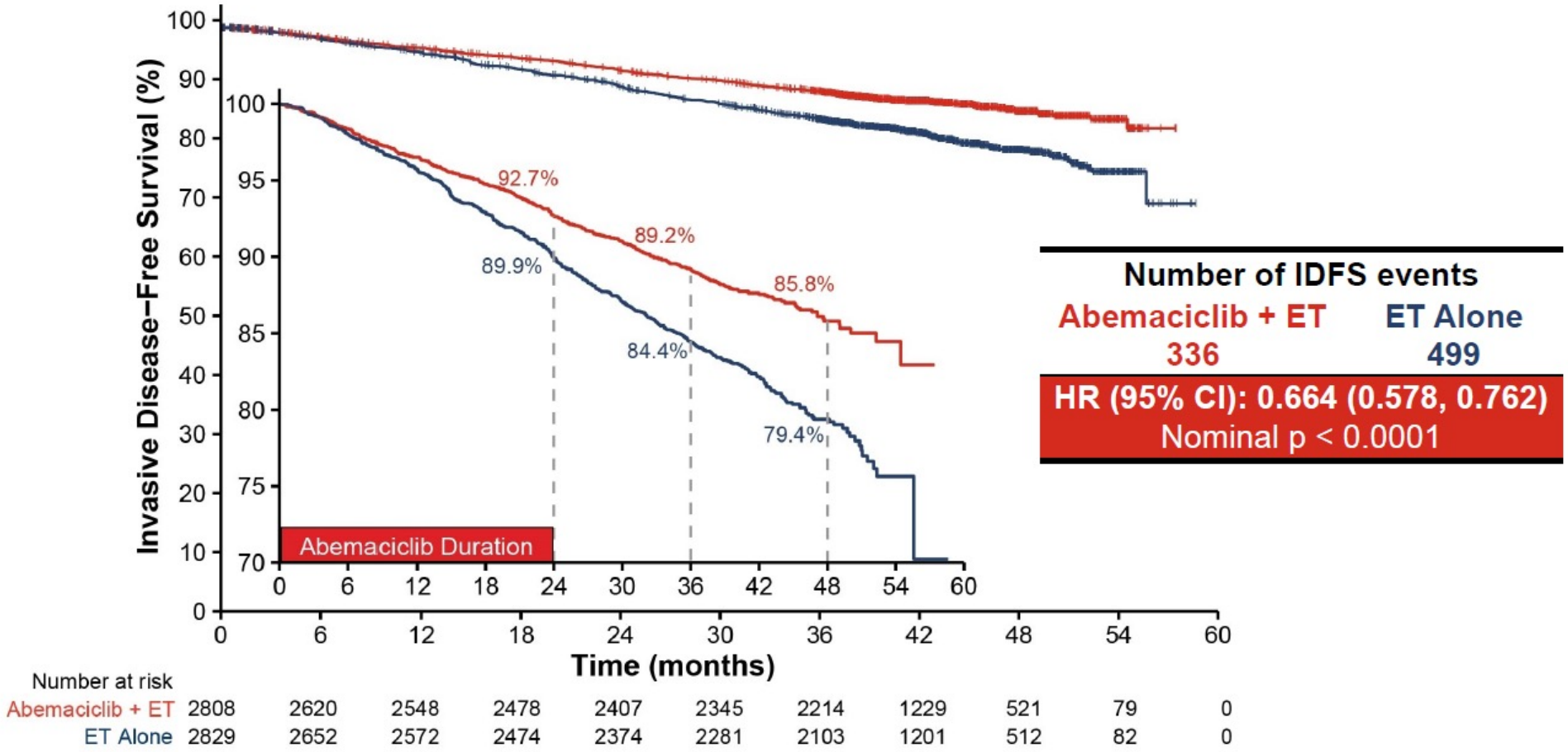
Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

Primary Objective: IDFS
Secondary Objectives: IDFS in high Ki-67 populations, DRFS, OS, Safety, PK, PRO

ITT Population



IDFS benefit in ITT population



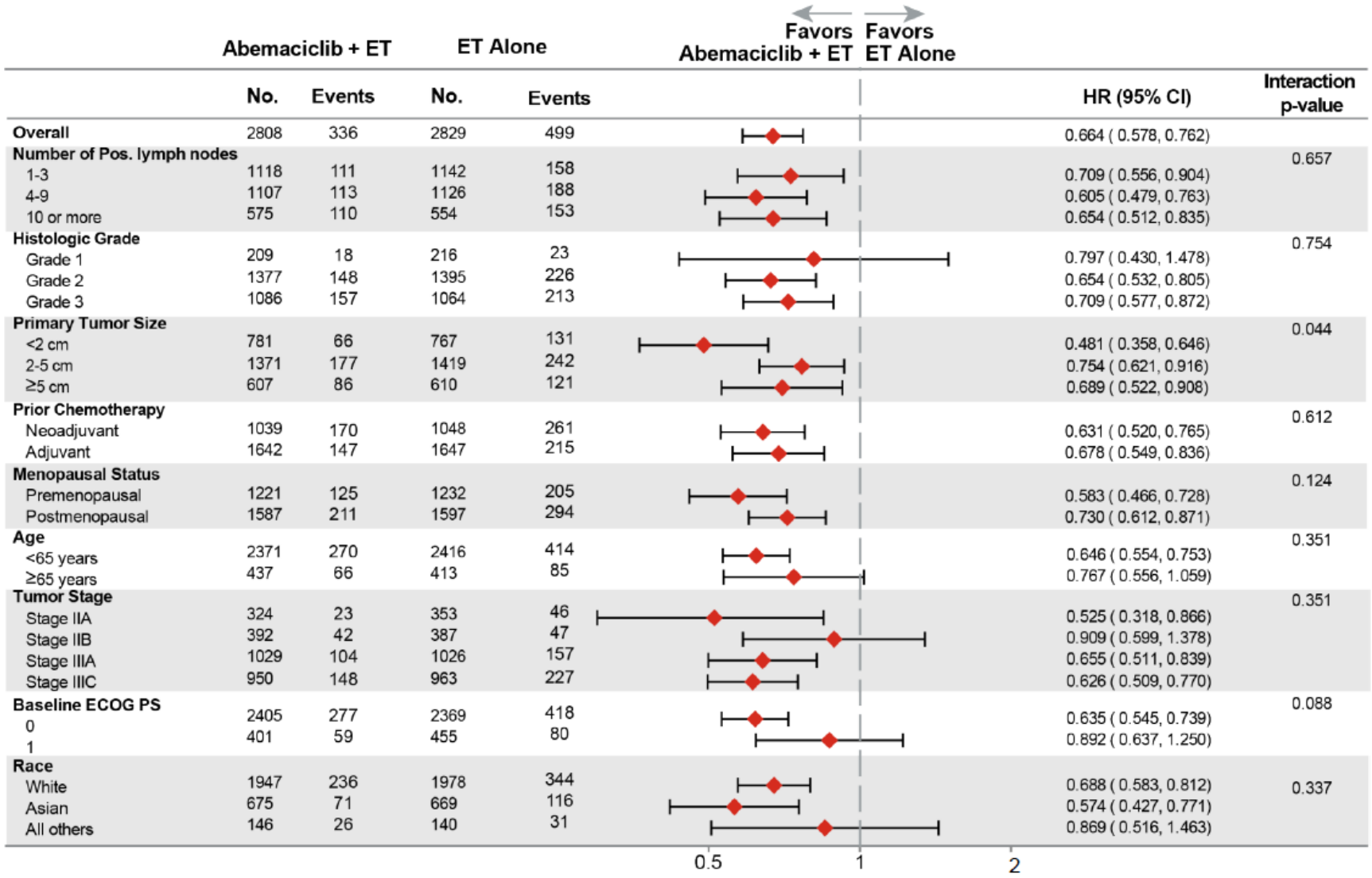
Number of IDFS events

Abemaciclib + ET	ET Alone
336	499

HR (95% CI): 0.664 (0.578, 0.762)
Nominal p < 0.0001

33.6% reduction in the risk of developing an IDFS event with an increase in absolute benefit in IDFS 4-year rates (6.4%) compared to 2-and 3-year IDFS rates (2.8% and 4.8% respectively)

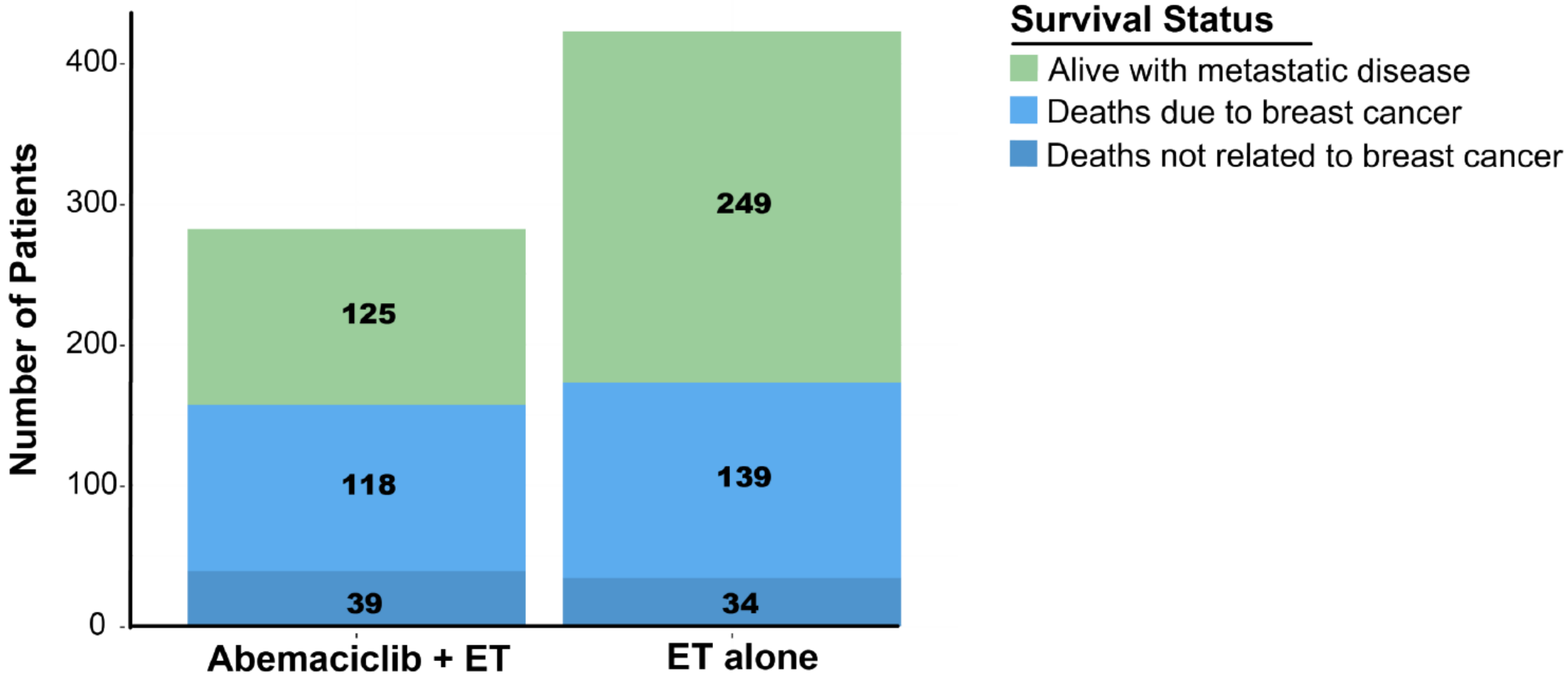
IDFS benefit in prespecified subgroups



	Abemaciclib + ET No.	Abemaciclib + ET Events	ET Alone No.	ET Alone Events	HR (95% CI)	Interaction p-value
Overall	2808	336	2829	499	0.664 (0.578, 0.762)	
Number of Pos. lymph nodes						0.657
1-3	1118	111	1142	158	0.709 (0.556, 0.904)	
4-9	1107	113	1126	188	0.605 (0.479, 0.763)	
10 or more	575	110	554	153	0.654 (0.512, 0.835)	
Histologic Grade						0.754
Grade 1	209	18	216	23	0.797 (0.430, 1.478)	
Grade 2	1377	148	1395	226	0.654 (0.532, 0.805)	
Grade 3	1086	157	1064	213	0.709 (0.577, 0.872)	
Primary Tumor Size						0.044
<2 cm	781	66	767	131	0.481 (0.358, 0.646)	
2-5 cm	1371	177	1419	242	0.754 (0.621, 0.916)	
≥5 cm	607	86	610	121	0.689 (0.522, 0.908)	
Prior Chemotherapy						0.612
Neoadjuvant	1039	170	1048	261	0.631 (0.520, 0.765)	
Adjuvant	1642	147	1647	215	0.678 (0.549, 0.836)	
Menopausal Status						0.124
Premenopausal	1221	125	1232	205	0.583 (0.466, 0.728)	
Postmenopausal	1587	211	1597	294	0.730 (0.612, 0.871)	
Age						0.351
<65 years	2371	270	2416	414	0.646 (0.554, 0.753)	
≥65 years	437	66	413	85	0.767 (0.556, 1.059)	
Tumor Stage						0.351
Stage IIA	324	23	353	46	0.525 (0.318, 0.866)	
Stage IIB	392	42	387	47	0.909 (0.599, 1.378)	
Stage IIIA	1029	104	1026	157	0.655 (0.511, 0.839)	
Stage IIIC	950	148	963	227	0.626 (0.509, 0.770)	
Baseline ECOG PS						0.088
0	2405	277	2369	418	0.635 (0.545, 0.739)	
1	401	59	455	80	0.892 (0.637, 1.250)	
Race						0.337
White	1947	236	1978	344	0.688 (0.583, 0.812)	
Asian	675	71	669	116	0.574 (0.427, 0.771)	
All others	146	26	140	31	0.869 (0.516, 1.463)	

Johnston S et al, SABCS 2022

Patients with metastatic disease



How to improve the outcome?

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- Adjuvant olaparib
- Type of endocrine therapy
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Adjuvant olaparib

Clinical stage	Score	Pathologic stage	Score	Tumor Marker	Score
Stage I	0	Stage 0	0	ER Negative	1
Stage IIA	0	Stage I	0	Nuclear Grade 3	1
Stage IIB	1	Stage IIA	1		
Stage IIIA	1	Stage IIB	1		
Stage IIIB	2	Stage IIIA	1		
Stage IIIC	2	Stage IIIB	1		
		Stage IIIC	2		

OLYMPIA: TRIAL SCHEMA

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III breast cancer or lack of PathCR to NACT

Neoadjuvant group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant chemotherapy → **Surgery** → **+/- Radiotherapy**

Adjuvant group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

Surgery → **≥ 6 cycles Adjuvant chemotherapy** → **+/- Radiotherapy**

Olaparib
300 mg twice daily for 1 year

1:1 randomisation N = 1836

Placebo
twice daily for 1 year

Presented at ASCO 2021
Presented at SABCS 2021
Primary endpoint
- Invasive disease-free survival (IDFS) by STEEP system[1]

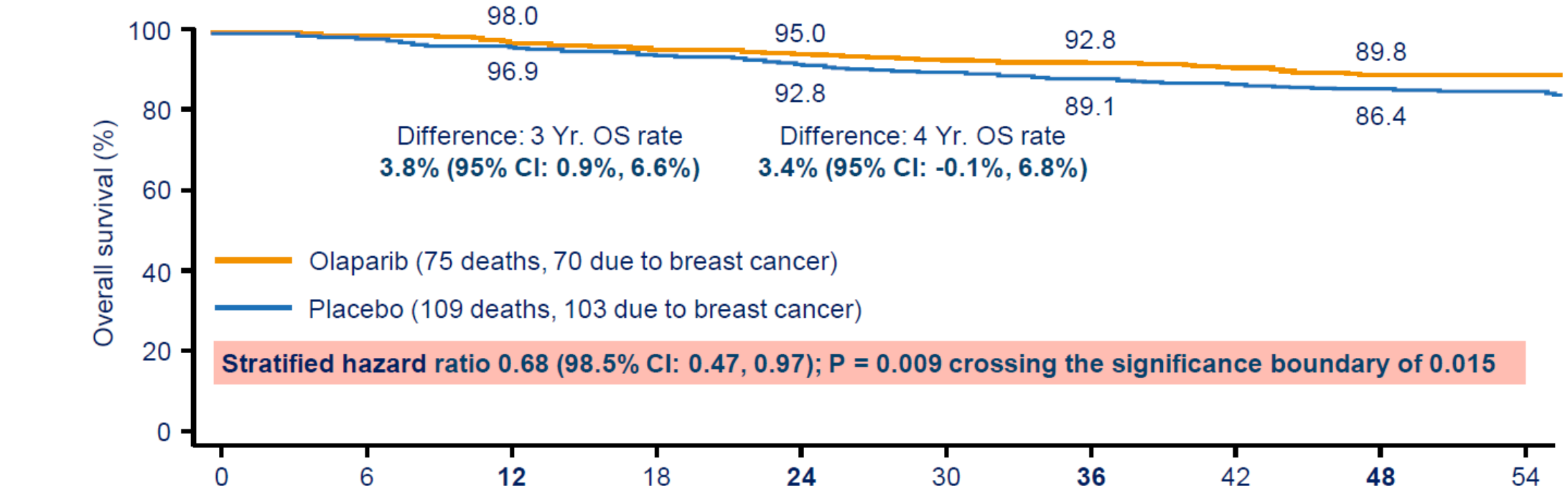
Secondary endpoints
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health-related QoL
- Safety

Stratification factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent adjuvant therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd adjuvant chemotherapy

Hormone receptor-positive defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

Overall survival (IA2 – ITT)

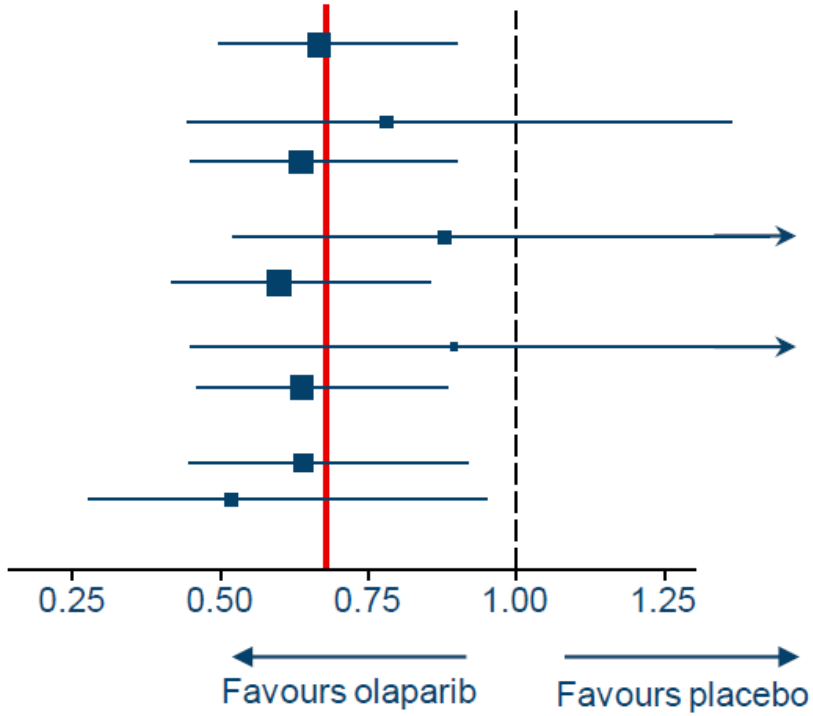


No. at risk									
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

98.5% confidence intervals are shown for the hazard ratio because P < 0.015 is required for statistical significance

OS subgroup analysis

Subgroup	Olaparib	Placebo	Stratified hazard ratio for overall survival (95% CI)	P value for heterogeneity
	No. of patients who died /total no.			
All patients	75 / 921	109 / 915	0.678 (0.503, 0.907)	NA
Prior chemo				0.543
Adjuvant	22 / 461	28 / 455	0.783 (0.444, 1.365)	
Neoadjuvant	53 / 460	81 / 460	0.638 (0.449, 0.900)	
Prior platinum				0.236
Yes	27 / 247	29 / 238	0.882 (0.520, 1.491)	
No	48 / 674	80 / 677	0.601 (0.417, 0.855)	
HR status				0.381
HR+/HER2-	16 / 168	17 / 157	0.897 (0.449, 1.784)	
TNBC	59 / 751	92 / 758	0.640 (0.459, 0.884)	
BRCA				0.845
BRCA1	49 / 579	75 / 588	0.643 (0.446, 0.918)	
BRCA2	16 / 235	28 / 216	0.521 (0.276, 0.951)	
BRCA1/2 both	0 / 2	0 / 3	NC	



All subgroup hazard ratio point estimates are < 1 and confidence intervals include the hazard ratio for olaparib treatment effect in the overall ITT population

How to improve the outcome?

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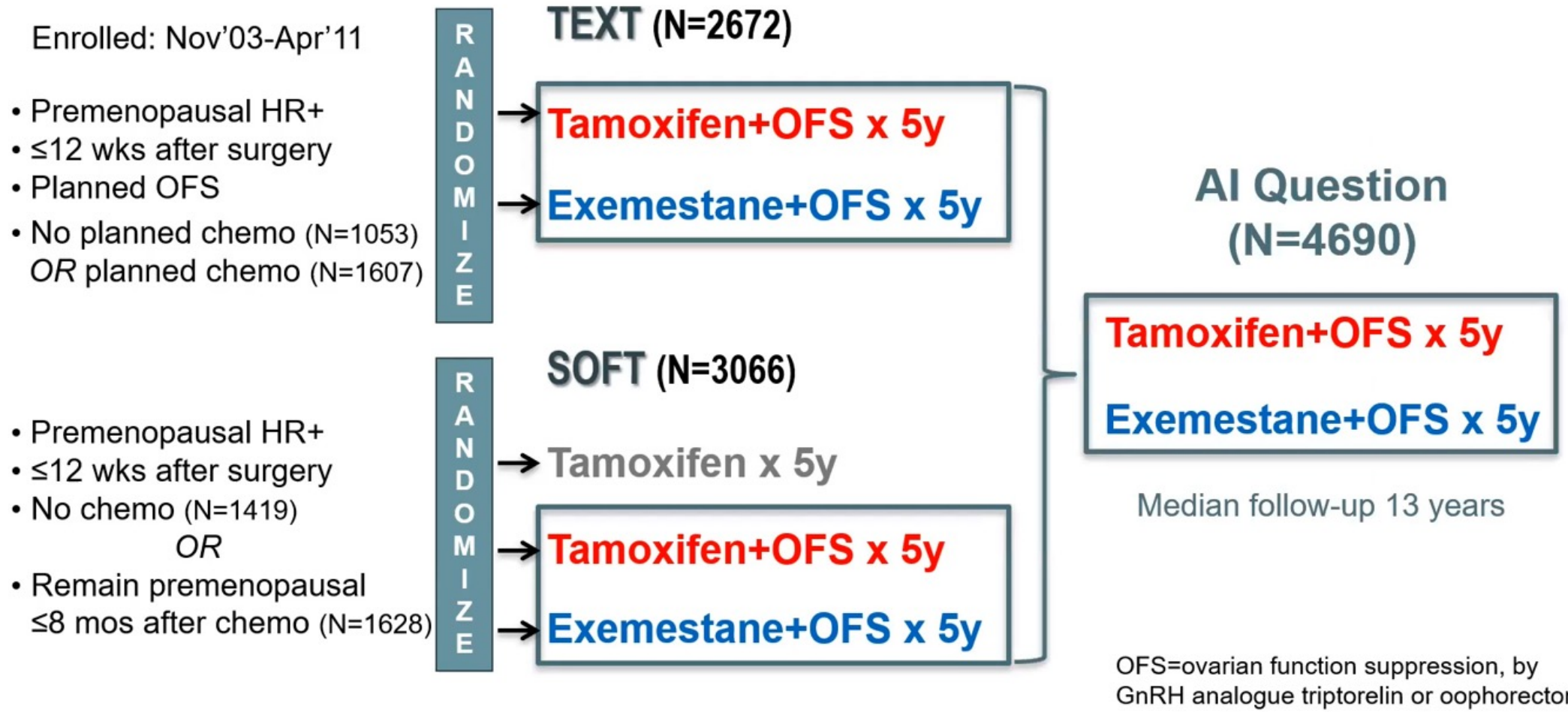
Tamoxifen or AI ?

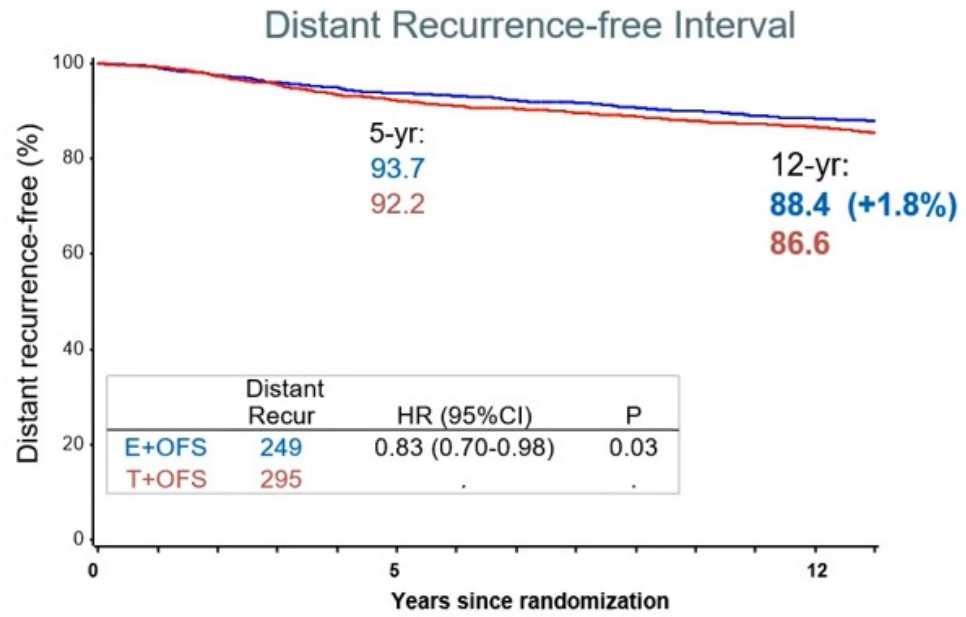
TEXT and SOFT Designs



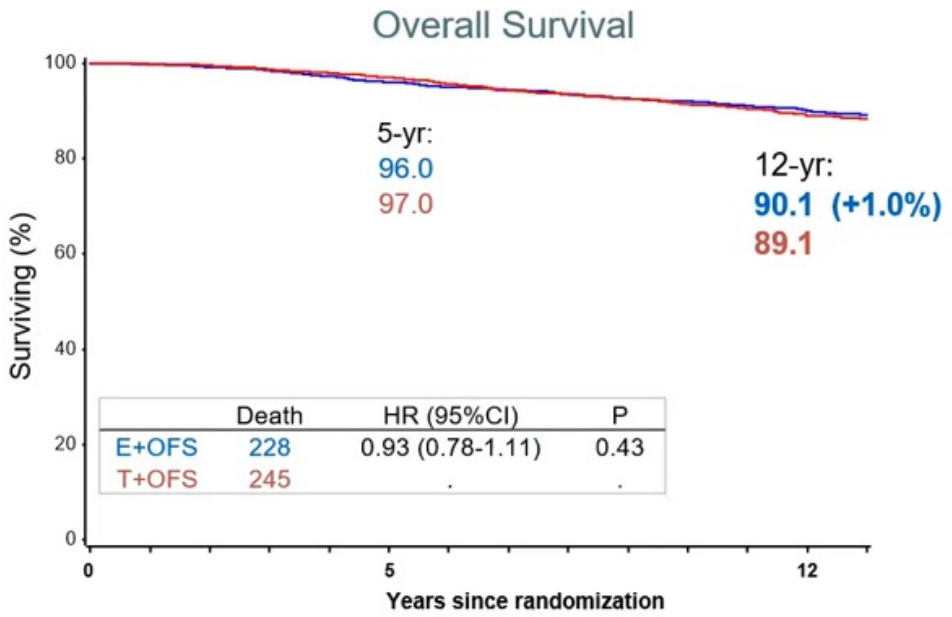
OFS=ovarian function suppression, by GnRH analogue triptorelin or oophorectomy

SOFT + TEXT overall population

42% LN+; 13 years median follow-up



	0-5 years		>5 years	
	Recur	HR (95% CI)	Recur	HR (95% CI)
E+OFS:	139	0.78 (0.63-0.98)	110	0.90 (0.70-1.17)
T+OFS:	175	.	120	.
At risk:	**4690** pts	21535 pyfu	3947 pts	26891 pyfu

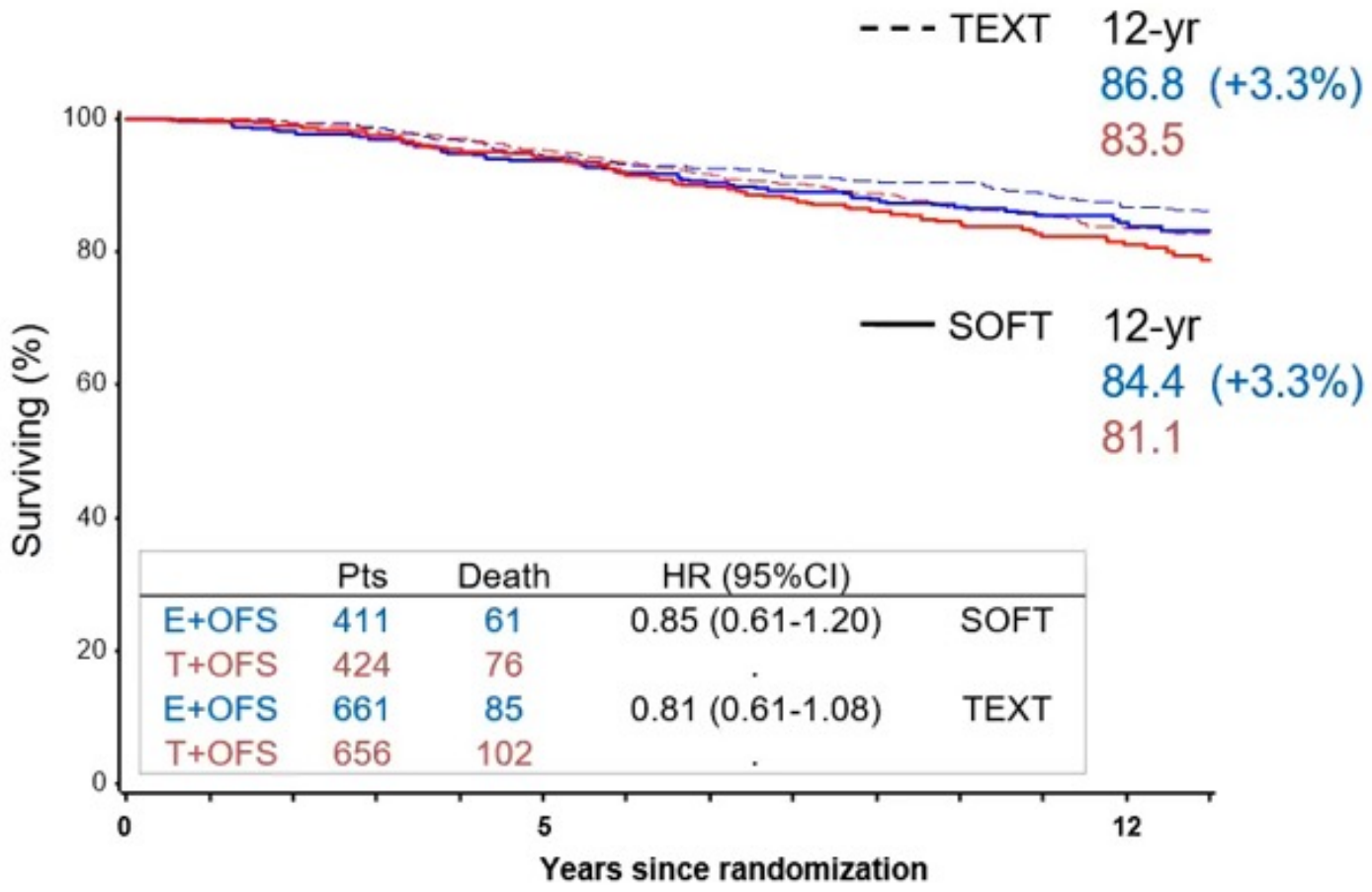


	0-5 years		>5 years	
	Deaths	HR (95% CI)	Deaths	HR (95% CI)
E+OFS:	91	1.34 (0.98-1.84)	137	0.77 (0.62-0.97)
T+OFS:	68	.	177	.
At risk:	**4690** pts	22467 pyfu	4283 pts	30294 pyfu

E+OFS vs T+OFS: absolute reduction in distant recurrence, 1.8% at 12 years
absolute reduction in death, 1.0% at 12 years

SOFT + TEXT HER2- chemo cohorts

86% of the population is HER2-; 13 years median follow-up



How to improve the outcome?

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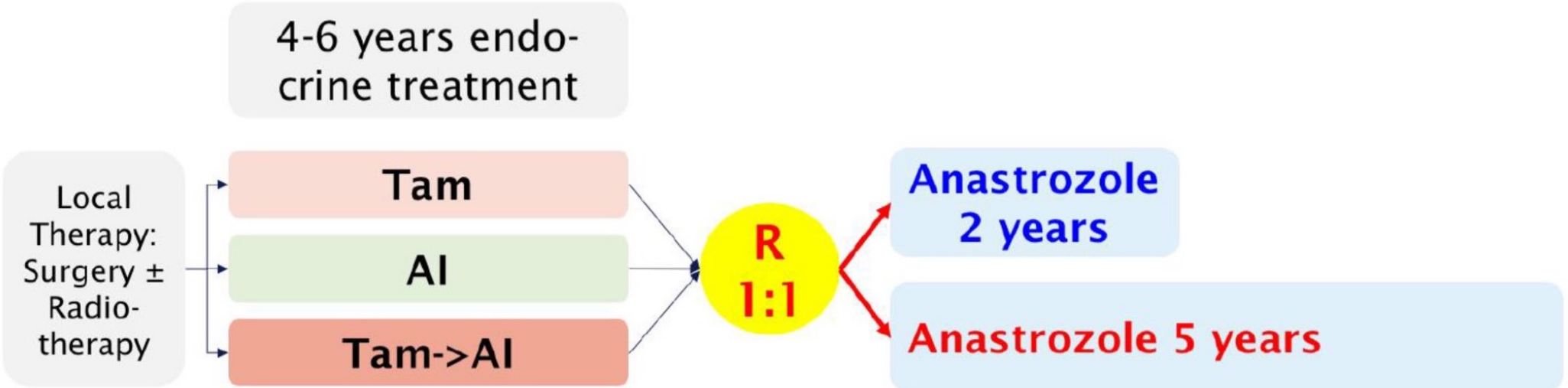
Duration of endocrine therapy

ABCSG-16 Trial Design



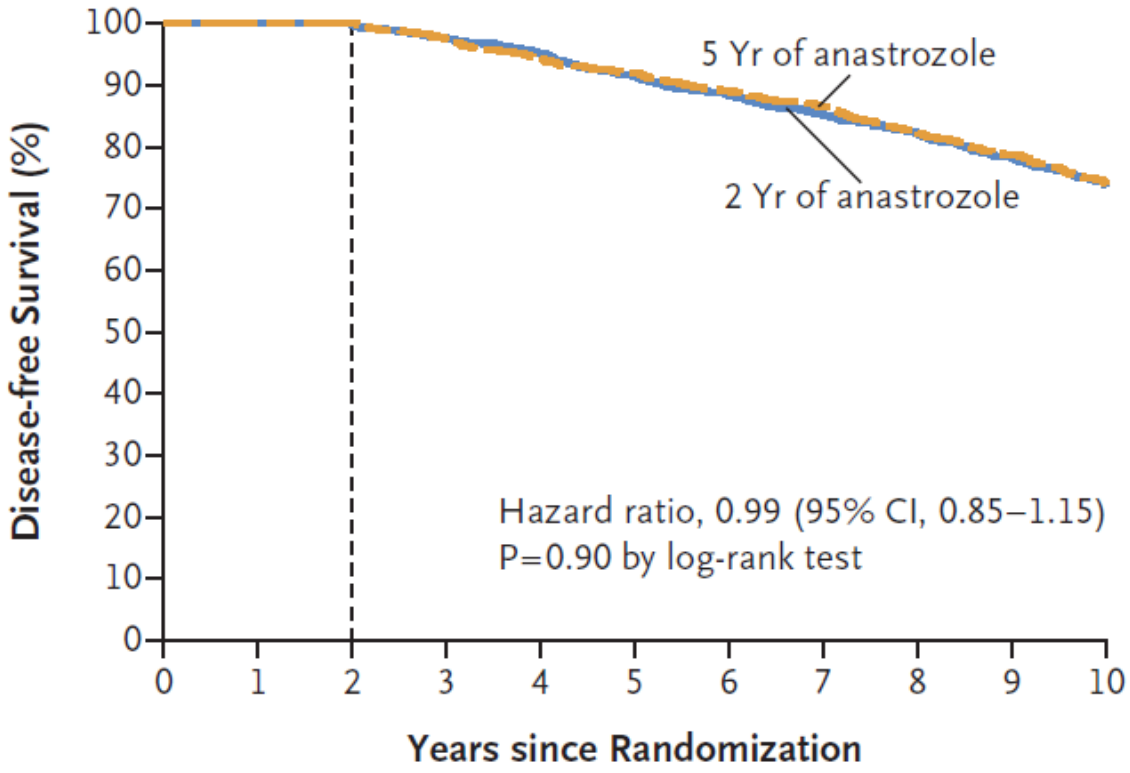
N=3,484

Postmenopausal, HR+, T1-3, N0/N+, M0

Recruitment in 75 centers in Austria, 2004-2010

ABCSG-16 - DFS

Median follow-up after randomization 118.0 months (IQR 97.8-121.1)

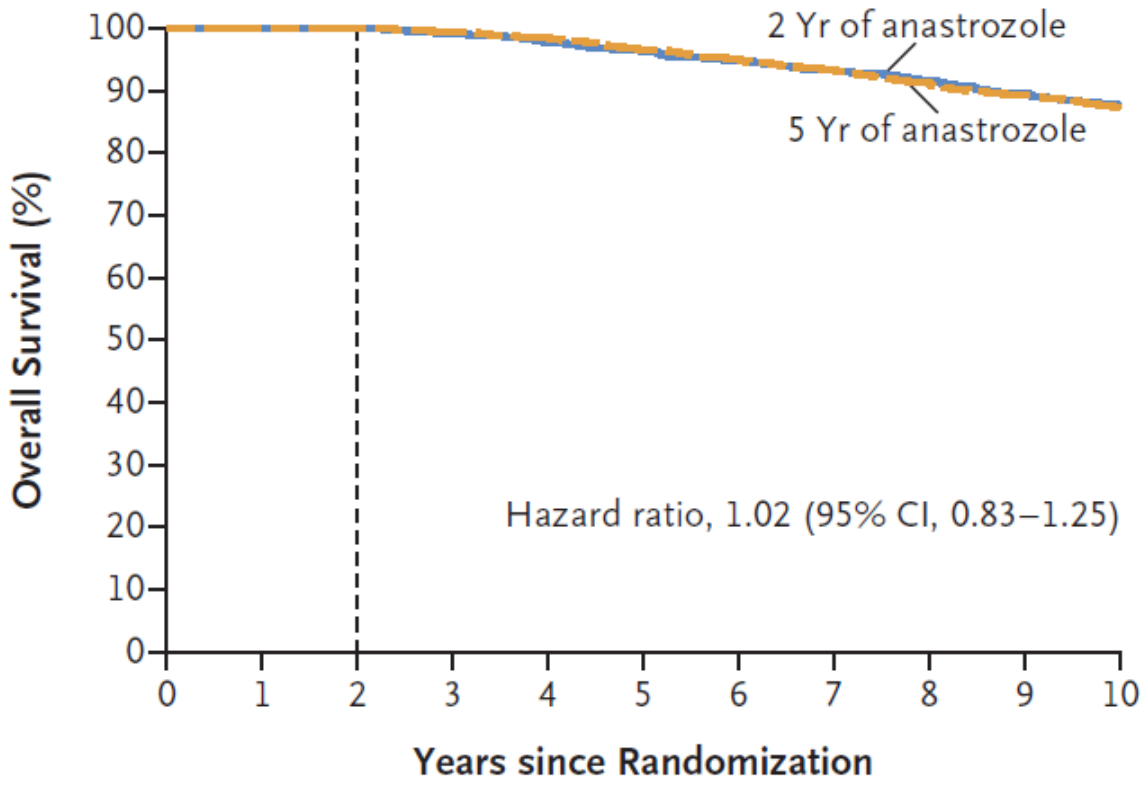


No. at Risk

2 Yr of anastrozole	1732	1603	1540	1478	1378	1267	1107	889	657	298
5 Yr of anastrozole	1738	1605	1551	1485	1402	1295	1136	913	673	300

ABCSG-16 - OS

Median follow-up after randomization 118.0 months (IQR 97.8-121.1)



No. at Risk

2 Yr of anastrozole	1732	1665	1645	1620	1588	1552	1451	1233	1000	558
5 Yr of anastrozole	1738	1670	1655	1634	1593	1558	1457	1244	986	542

CAVE : 100% postmenopausal, 72.8% T1 and 66.9% N0

Gnant M et al, NEJM 2021

How to improve the outcome?

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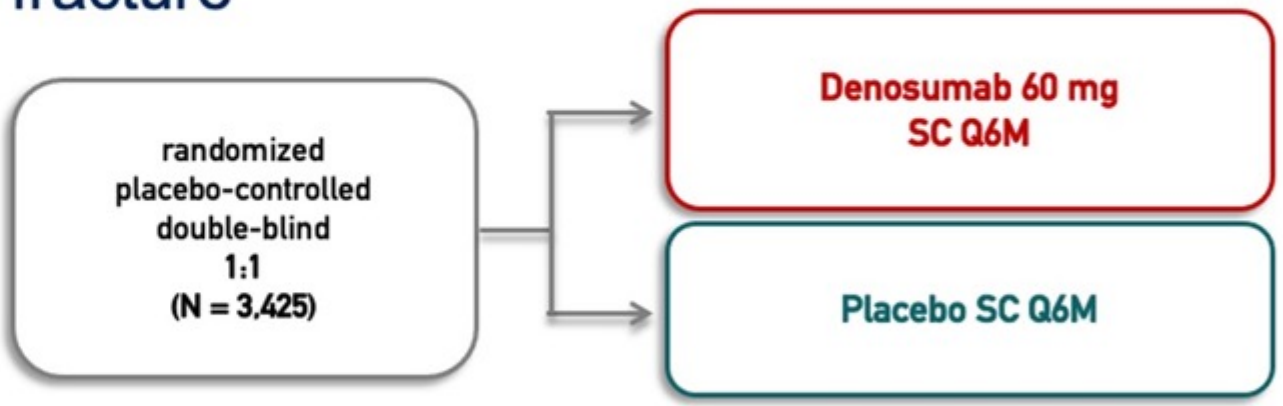
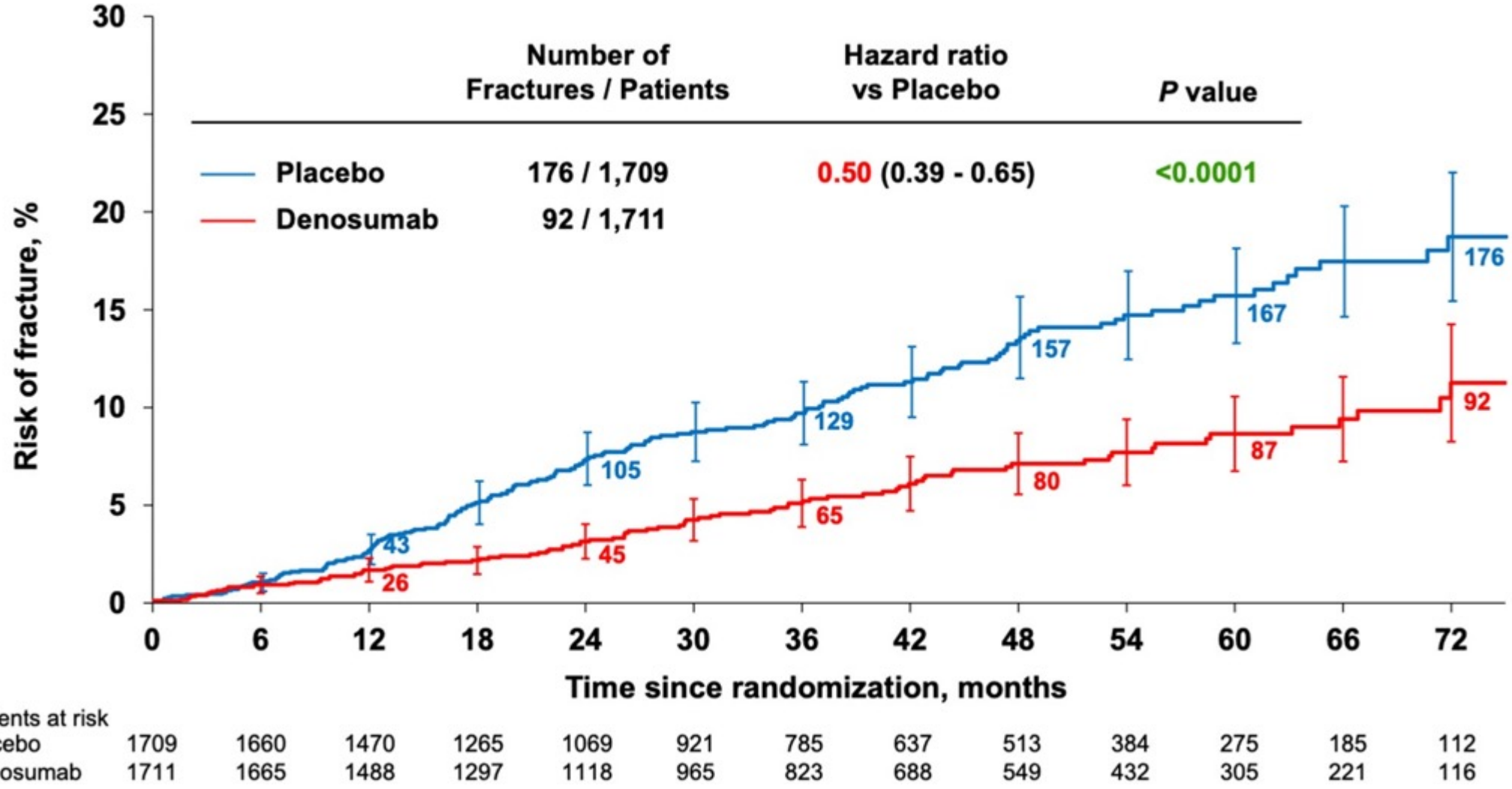
Bone-modifying agents

ABCSG-18: Trial Design

- Prospective randomized placebo-controlled double-blind multicenter phase-3 trial
- Recruitment 2006 – 2013 (3,425 postmenopausal patients)
- Primary end point: Time to first clinical fracture
- Inclusion criteria:
  - Postmenopausal women with early breast cancer
  - ER+ and/ or PR+
  - adjuvant non-steroidal aromatase inhibitor therapy
- Exclusion criteria:
  - Prior or concurrent treatment with Selective Estrogen Receptor Modulators (SERMs)
  - Current or prior IV bisphosphonate administration
  - Recent use of oral bisphosphonates
  - Known history of: Paget's disease, Cushing's disease, hyperprolactinaemia, hypercalcaemia or hypocalcaemia, other active metabolic bone disease

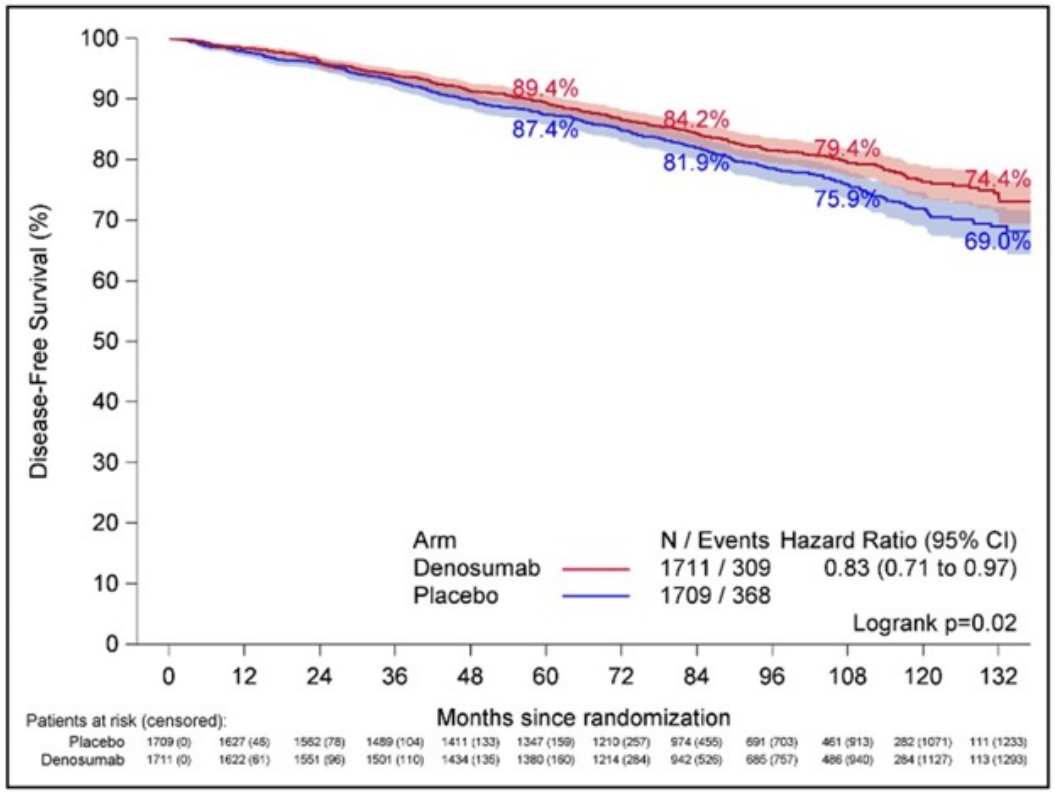


ABCSG-18 – primary endpoint

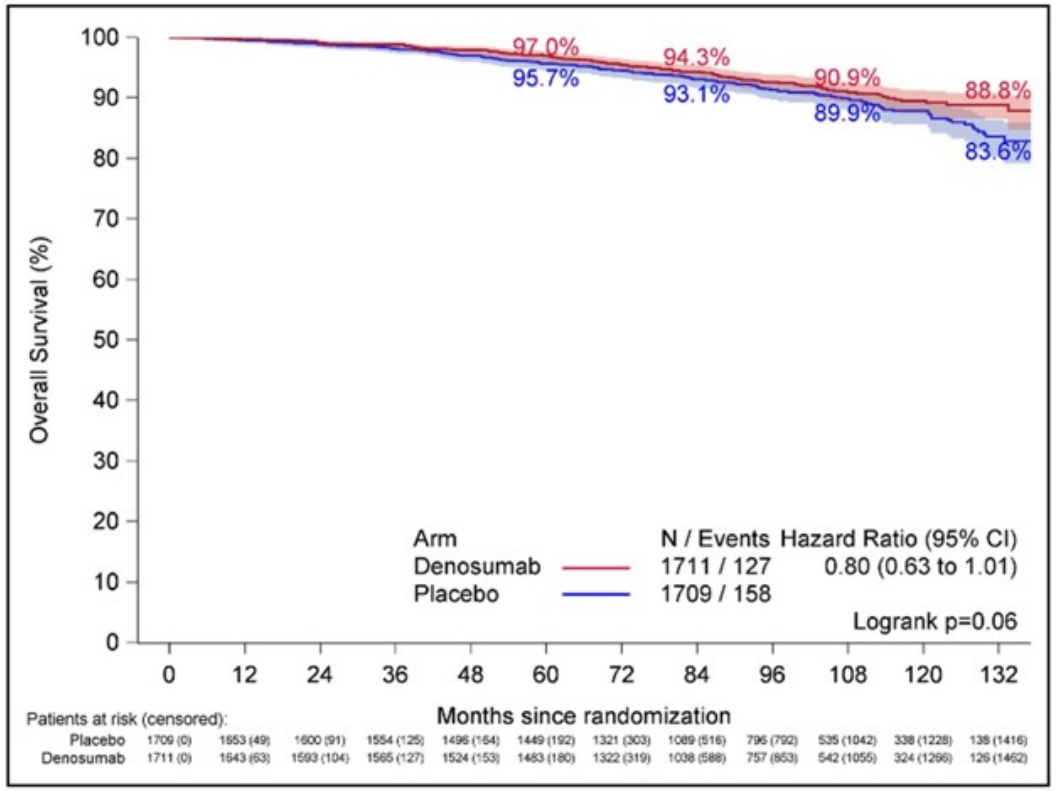


ABCSG-18 – descriptive statistics

Disease-free survival



Overall survival



Poll question : what should I do?

1) Adjuvant abemaciclib + OFS + AI for 10 years + bone-modifying agent
2) Adjuvant abemaciclib + OFS + AI for 7 years + bone-modifying agent
3) Adjuvant abemaciclib + OFS + AI for 5 years + bone-modifying agent
4) Adjuvant abemaciclib + OFS + AI for 10 years
5) Adjuvant abemaciclib + OFS + AI for 7 years
6) Adjuvant abemaciclib + OFS + AI for 5 years
7) Adjuvant abemaciclib + OFS + AI followed by TAM for 7-10 years in total

What should I do?

Adjuvant abemaciclib + OFS + AI for 10 years + bone-modifying agent

Adjuvant abemaciclib + OFS + AI for 7 years + bone-modifying agent

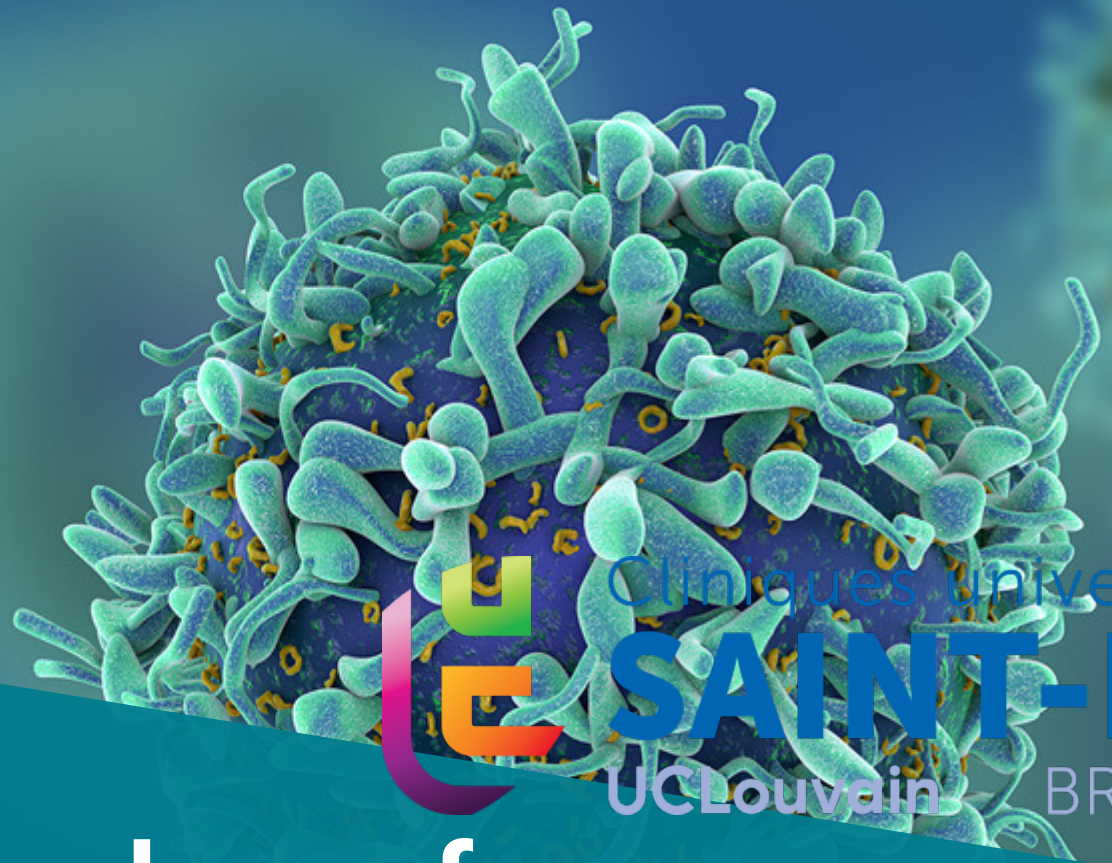
Adjuvant abemaciclib + OFS + AI for 5 years + bone-modifying agent

Adjuvant abemaciclib + OFS + AI for 10 years

Adjuvant abemaciclib + OFS + AI for 7 years

Adjuvant abemaciclib + OFS + AI for 5 years

Adjuvant abemaciclib + OFS + AI followed by TAM for 7-10 years in total



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Thank you for your attention!