Optimizing the Management of Localized ER-Positive Breast Cancer

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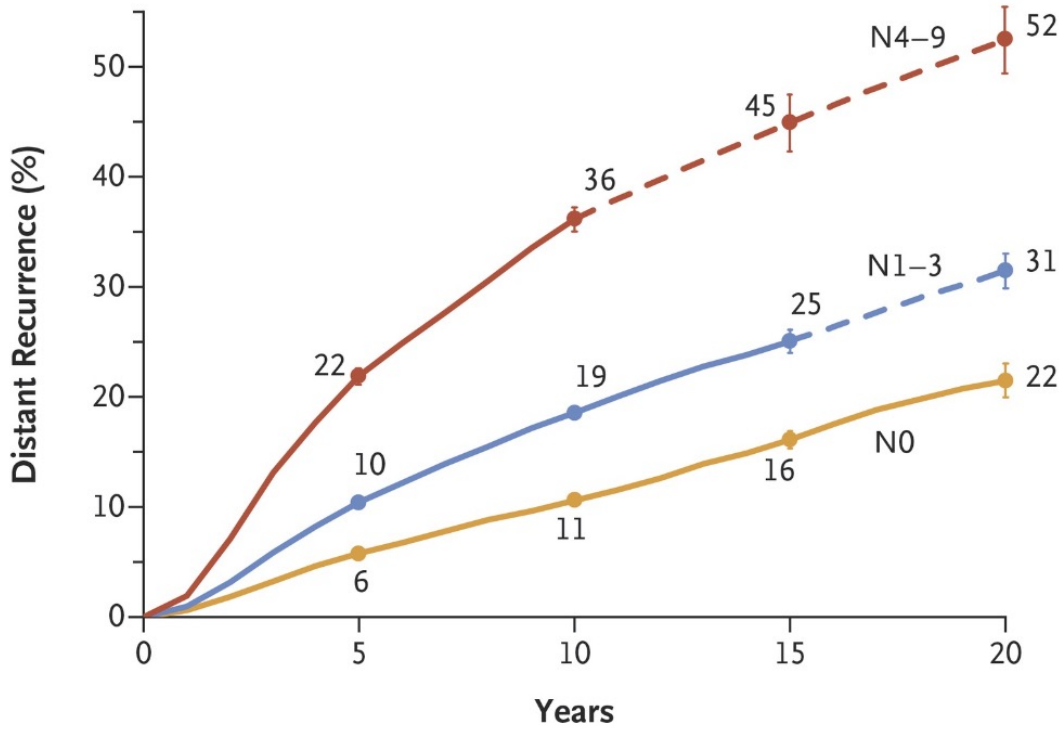
- Optimal duration of ER
- Role of OFS in preserving oncofertility and improving outcomes
- CDK4/6 inhibition in EBC
- PARPi in EBC

EBCTCG Meta-analysis of 62,923 women with ER+ BC

A Risk of Distant Recurrence



No. at Risk					
N4–9	12,333	8,116	2165	259	52
N1–3	31,936	23,576	7250	949	183
N0	29,925	24,081	8571	1982	414

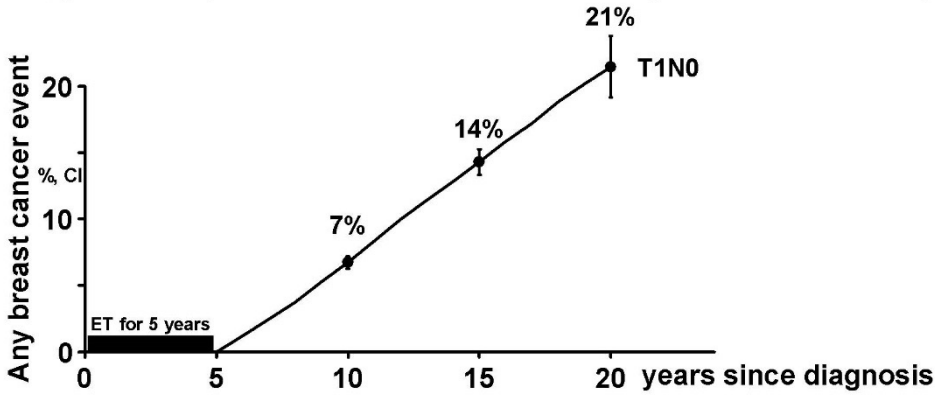
No. of Events — annual rate (%)				
N4–9	2568 (4.8)	969 (4.0)	121 (3.1)	13 (2.2)
N1–3	3126 (2.2)	1421 (1.9)	241 (1.7)	39 (1.8)
N0	1646 (1.2)	835 (1.1)	272 (1.3)	68 (1.4)

Factors associated with risk of late recurrence:

- LN status
- Tumor size
- Tumor grade
- PR and HER2 not predictive

Lowest-stage (T1N0) disease: Risk of ANY breast cancer event

21% risk, years 5-20 (14% DISTANT recurrence + 7% only local or contralateral)



Annual event rate (and no. of events), by 5-year time period

T1N0 (n=16K): **1.4%** (807) **1.7%** (309) **1.8%** (54)

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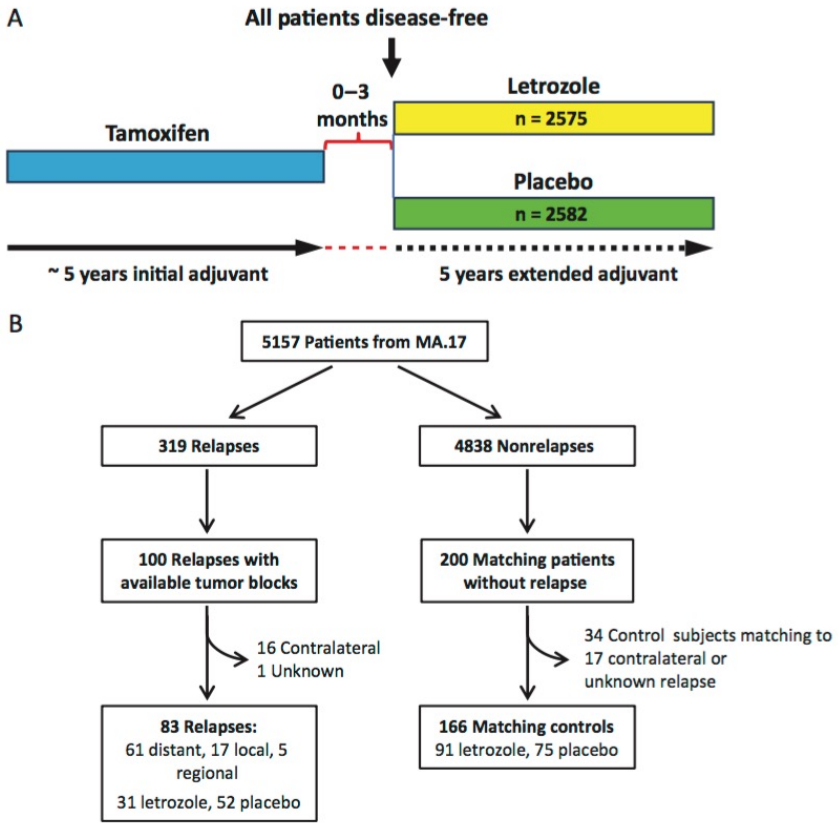
N Engl J Med 2017; 377:1836-1846

Clinical trials of Extended Endocrine Therapy

Trial	Therapy	n	Absolute Benefit in DFS
ATLAS	Tam x 5 yr	6846	3%*
aTTom	Tam x 5 yr	6953	3%*
MA.17	AI x 5 yr	5187	4.6%*
MA.17R	AI x 5 yr	1918	4%*
B14	Tam x 5 yr	1172	6%*
B33	AI x 5 yr	1598	2%
B42	AI x 5 yr	3966	3%
DATA	AI x 3 yr	1912	4%
IDEAL	AI x 2.5 yr	1824	3%
ABCSG-6a	AI x 3 yr	856	4.7%
ABCSG16	AI x 3 yr	3484	-0.8%
SOLE	AI cont vs intermittent	4884	1.7%

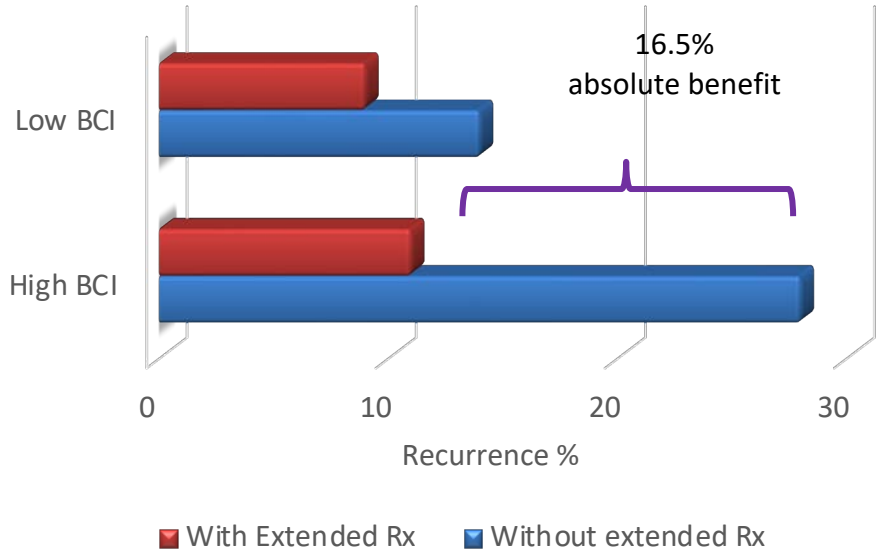
Prediction of Late Disease Recurrence and Extended Adjuvant Letrozole Benefit by the HOXB13/IL17BR Biomarker

Dennis C. Sgroi, Erin Carney, Elizabeth Zarrella, Lauren Steffel, Shemeica N. Binns, Dianne M. Finkelstein, Jackie Szymonifka, Atul K. Bhan, Lois E. Shepherd, Yi Zhang, Catherine A. Schnabel, Mark G. Erlander, James N. Ingle, Peggy Porter, Hyman B. Muss, Katherine I. Pritchard, Dongsheng Tu, David L. Rimm, Paul E. Goss



High H/I significantly associated with decreased recurrence in letrozole arm
OR=0.35, p=0.007

Interaction between H/I and letrozole, p=0.03



Lancet Oncol. 2013,14:1067-76.

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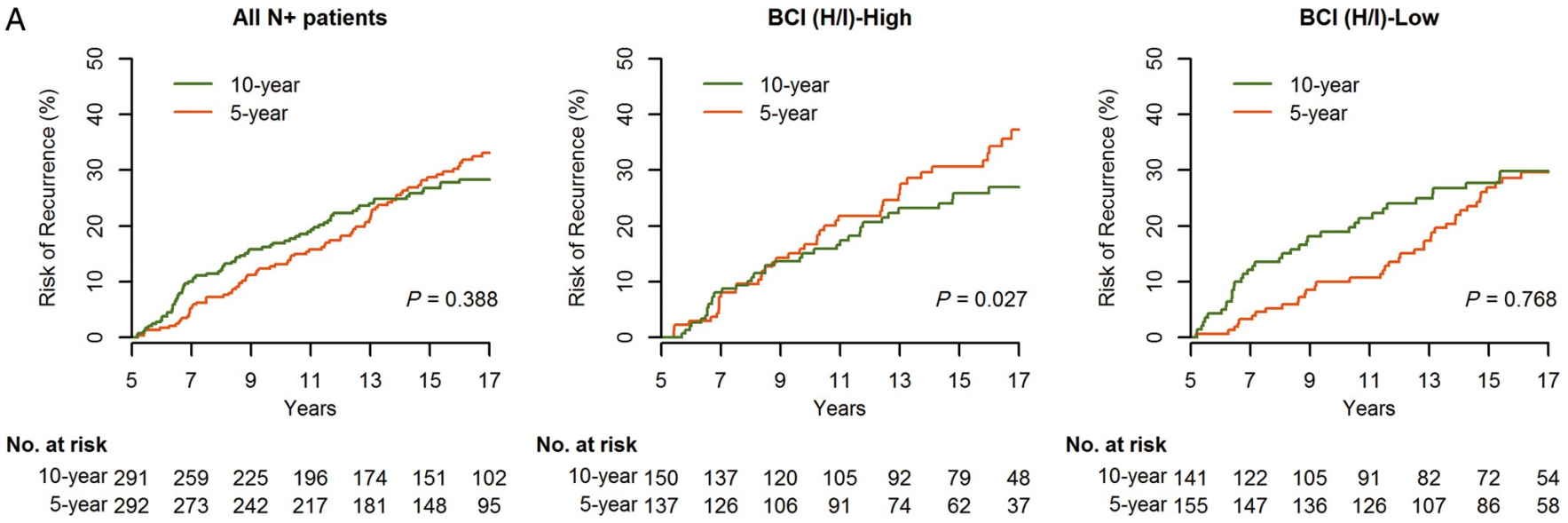
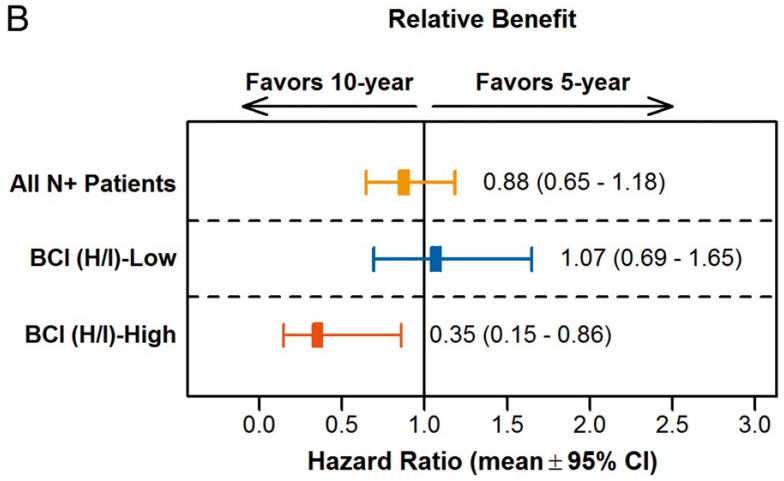
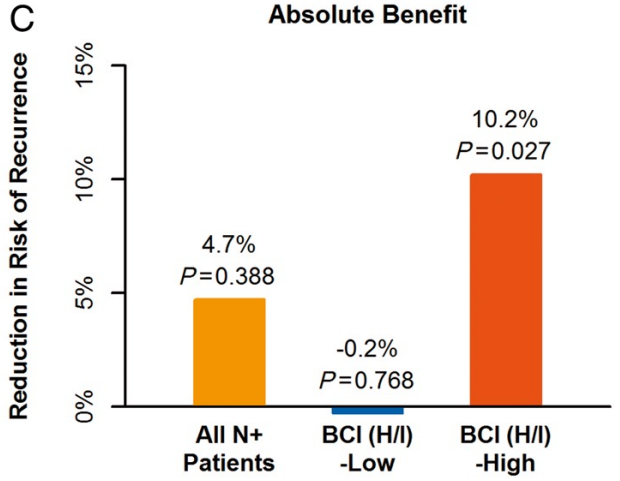
aTTom: Predictive performance by BCI (H/I) groups based on RFI in HR+ N+ patients (n = 583).







51% of patients identified as low

Annals of Oncology, mdz289, https://doi.org/10.1093/annonc/mdz289

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Factors Affecting Late Recurrence and Benefit from Extended Endocrine Therapy

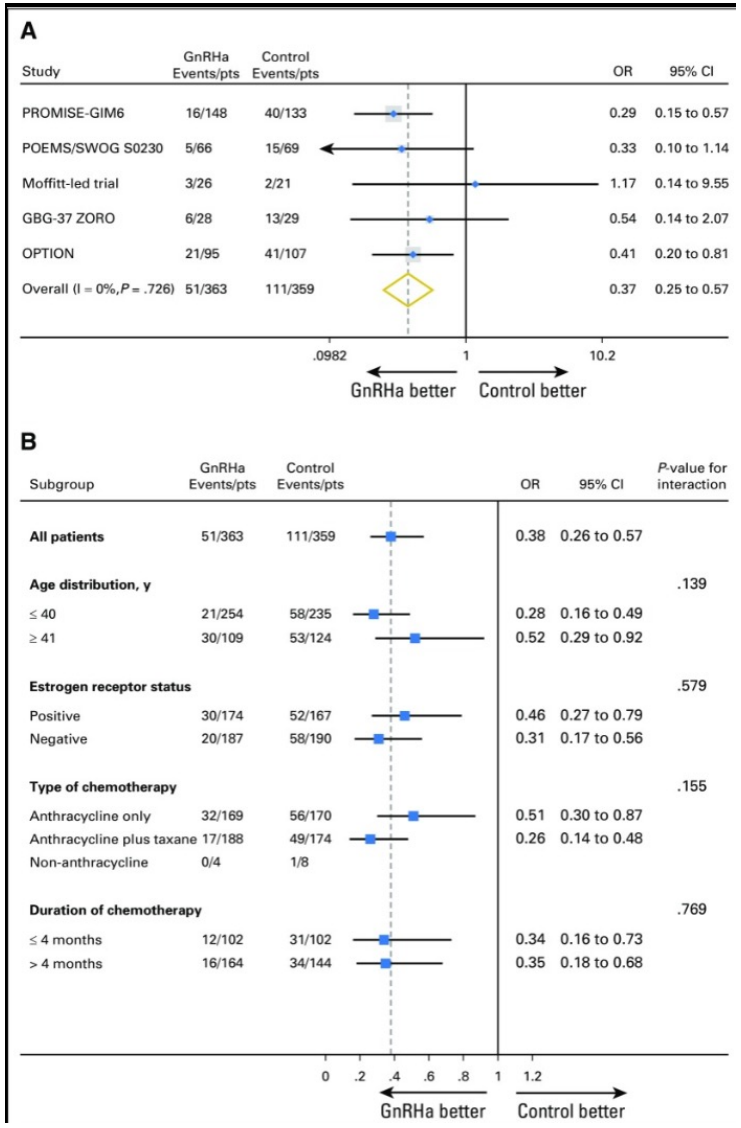
- LN status
- Tumor Size
- Tumor Grade
- Prior Chemotherapy
- Switching from TAM to AI
- Genomic Assays

Tolerability

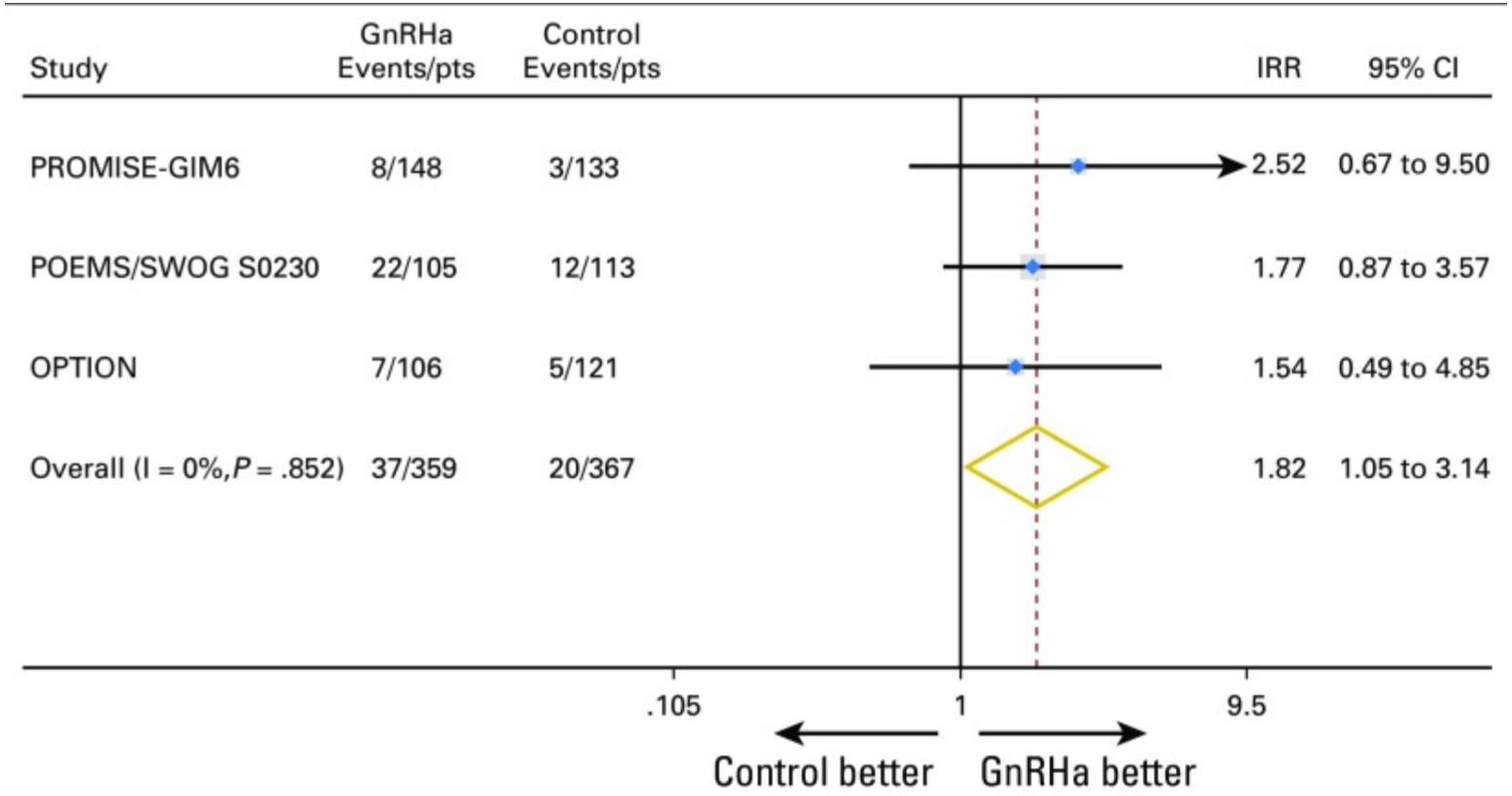
- Bone Fractures
- Osteoporosis
- Bone Pain
- Uterine ca
- VTEs

Meta-analysis of GnRHa during chemotherapy

Premature ovarian insufficiency



Pregnancies



Similar outcomes in all groups

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J Clin Oncol. 2018 Jul 1;36(19):1981-1990.

SOFT and TEXT Designs

Enrolled: Nov03-Apr11

- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo (40%)
  OR planned chemo (60%)

RANDOMIZE

TEXT (n=2672)

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

Current Follow-up

Median follow-up 9 years

- Premenopausal HR+
- ≤12 wks after surgery
- No chemo (47%)

OR

- Remain premenopausal
  ≤ 8 mos after chemo (53%)

RANDOMIZE

SOFT (n=3066)

→ **Tamoxifen x 5y**

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

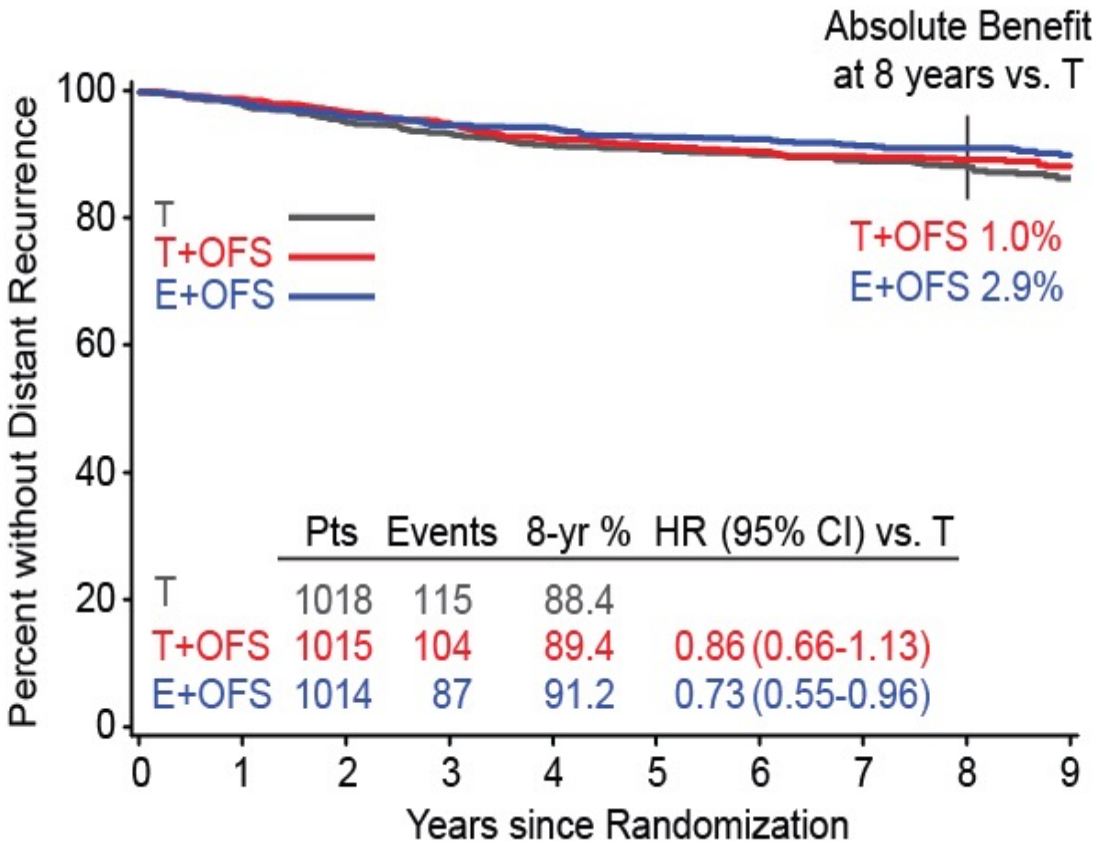
→

Median follow-up 8 years

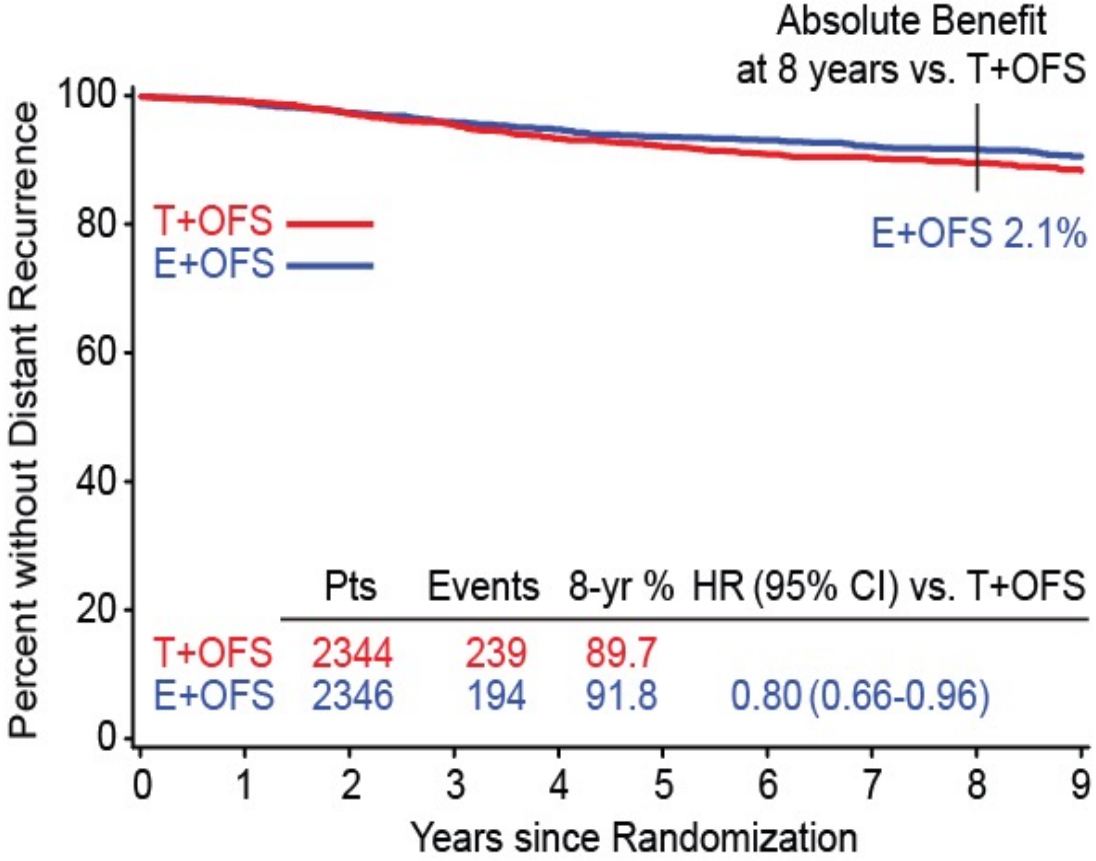
OFS=ovarian function suppression

Distant Recurrence-free Interval

SOFT



SOFT+TEXT

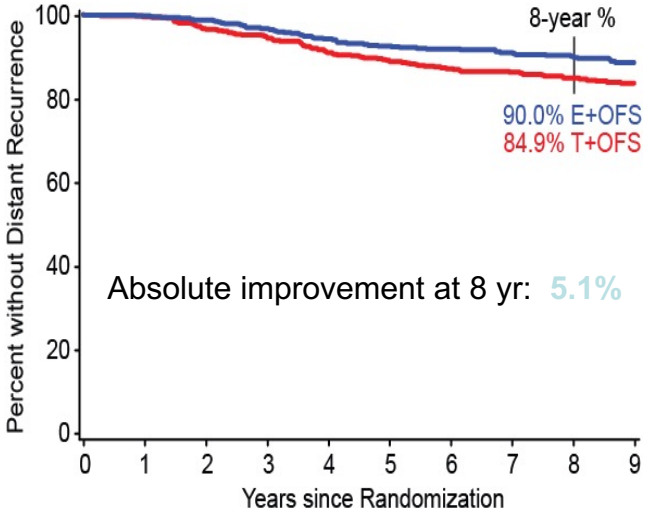


Combined SOFT+TEXT, use of E+OFS vs T+OFS improved 8-yr freedom from distant recurrence by 2.1%

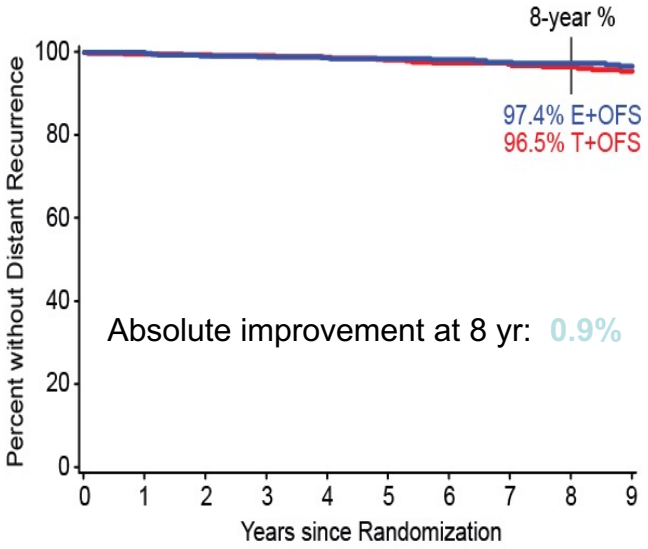
Distant Recurrence-free Interval by Cohort (HR+/HER2-)

TEXT

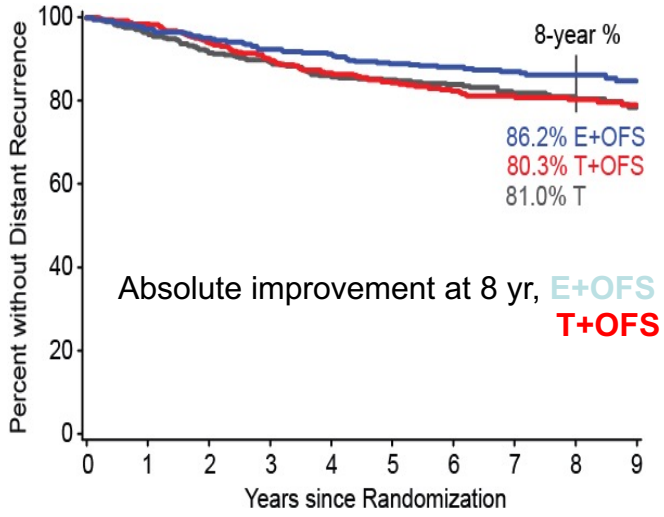
Chemo-therapy

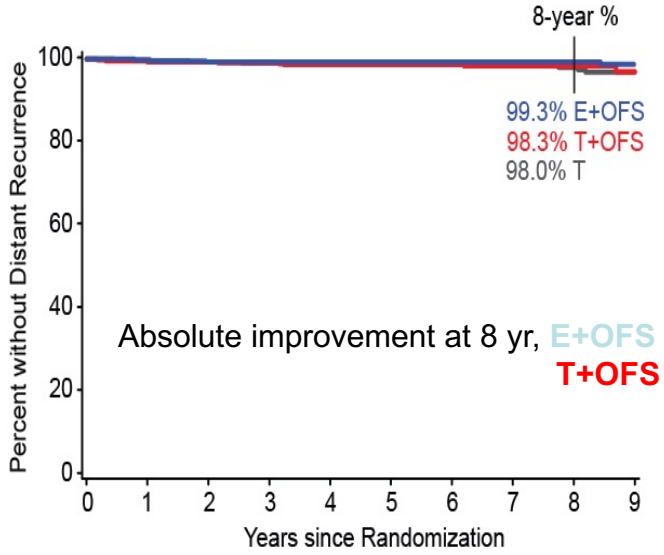


No Chemo-therapy



SOFT



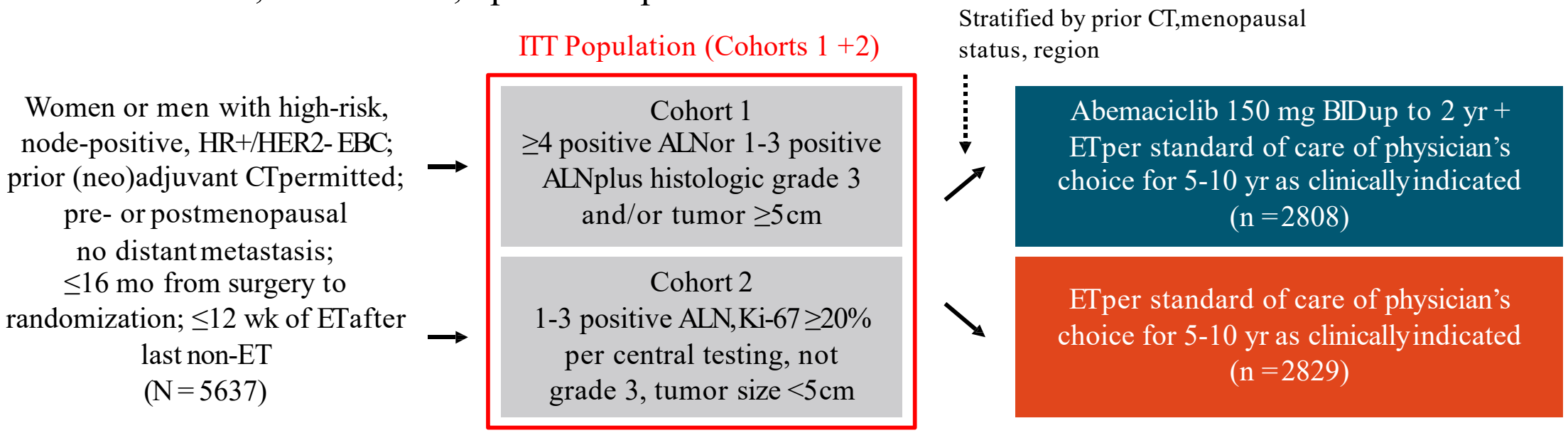


Guidelines for OFS

- ASCO:
  - Offer in women receiving chemotherapy
  - Offer to higher risk women: larger tumors, younger age, higher grade, pos LN
- St Gallen:
  - Offer in women who are less than 35yo, received chemotherapy, have 4+LN

MONARCH-E
Adjuvant abemaciclib in high risk node positive EBC

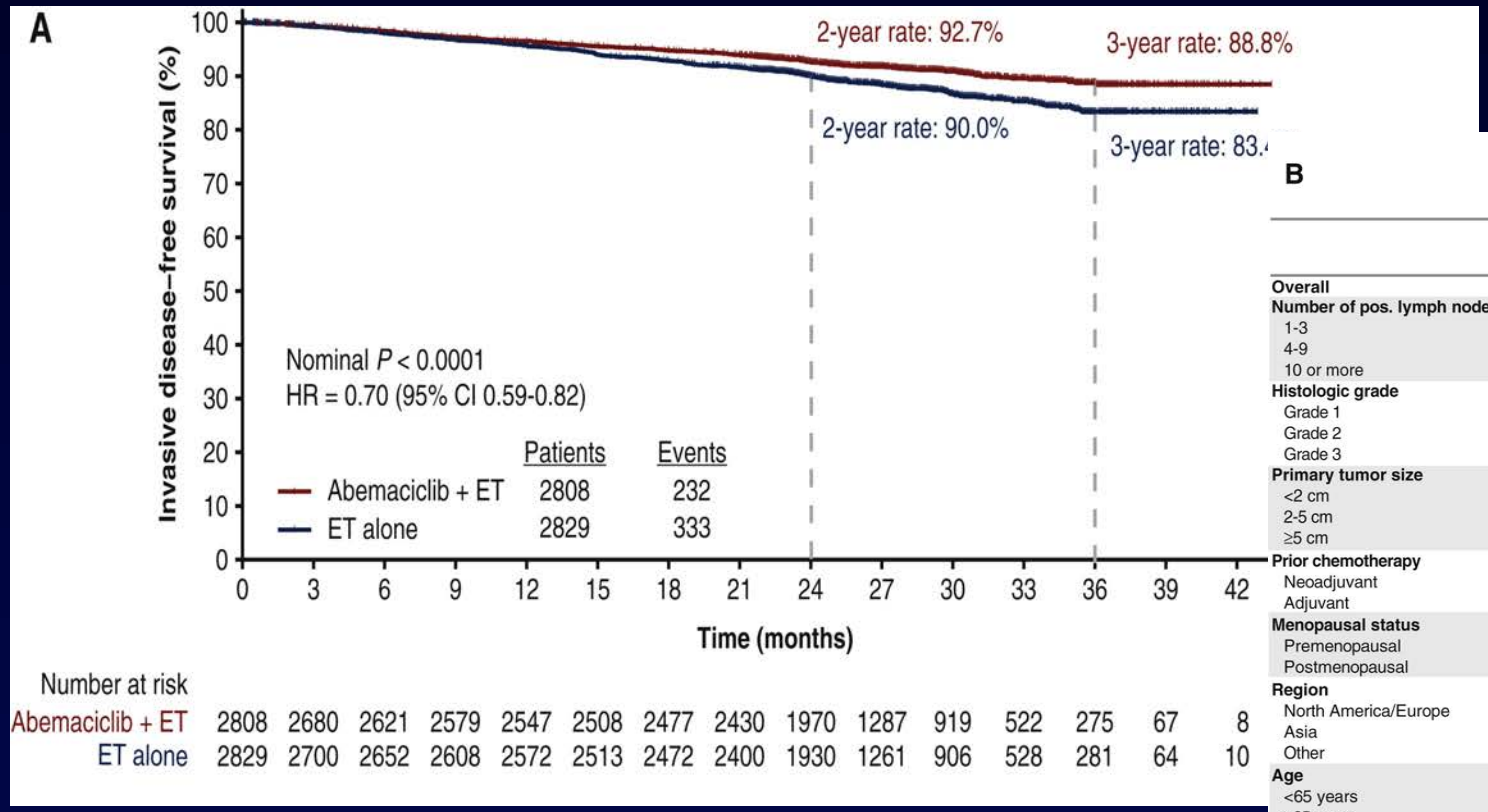
- International, randomized, open-label phase III trial

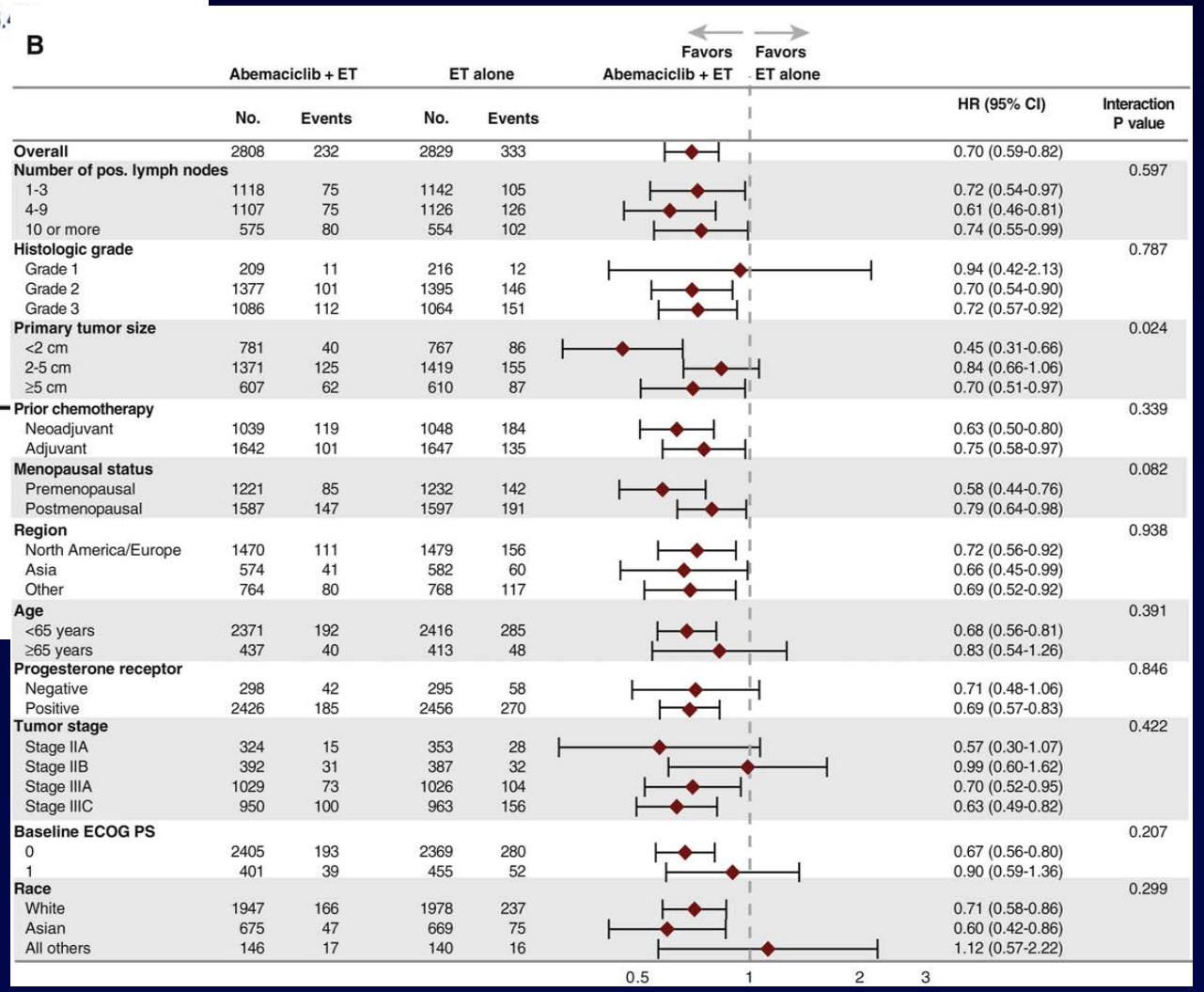


- Primary endpoint: iDFS
  - Planned for after ~390 iDFS events (~85% power, assumed iDFS hazard ratio of 0.73, cumulative 2-sided α =0.05)
  - Current primary outcome efficacy analysis occurred after 395 iDFS events in ITT population
- Key secondary endpoints: iDFS in Ki-67 high (≥20%) population, distant RFS, OS, safety, PRO, PK

Johnston. JCO. 2020;38:3987. Rastogi. SABCS 2020. Abstr GS1-01.

MONARCH-E iDFS (median f/u 27.1 mos)

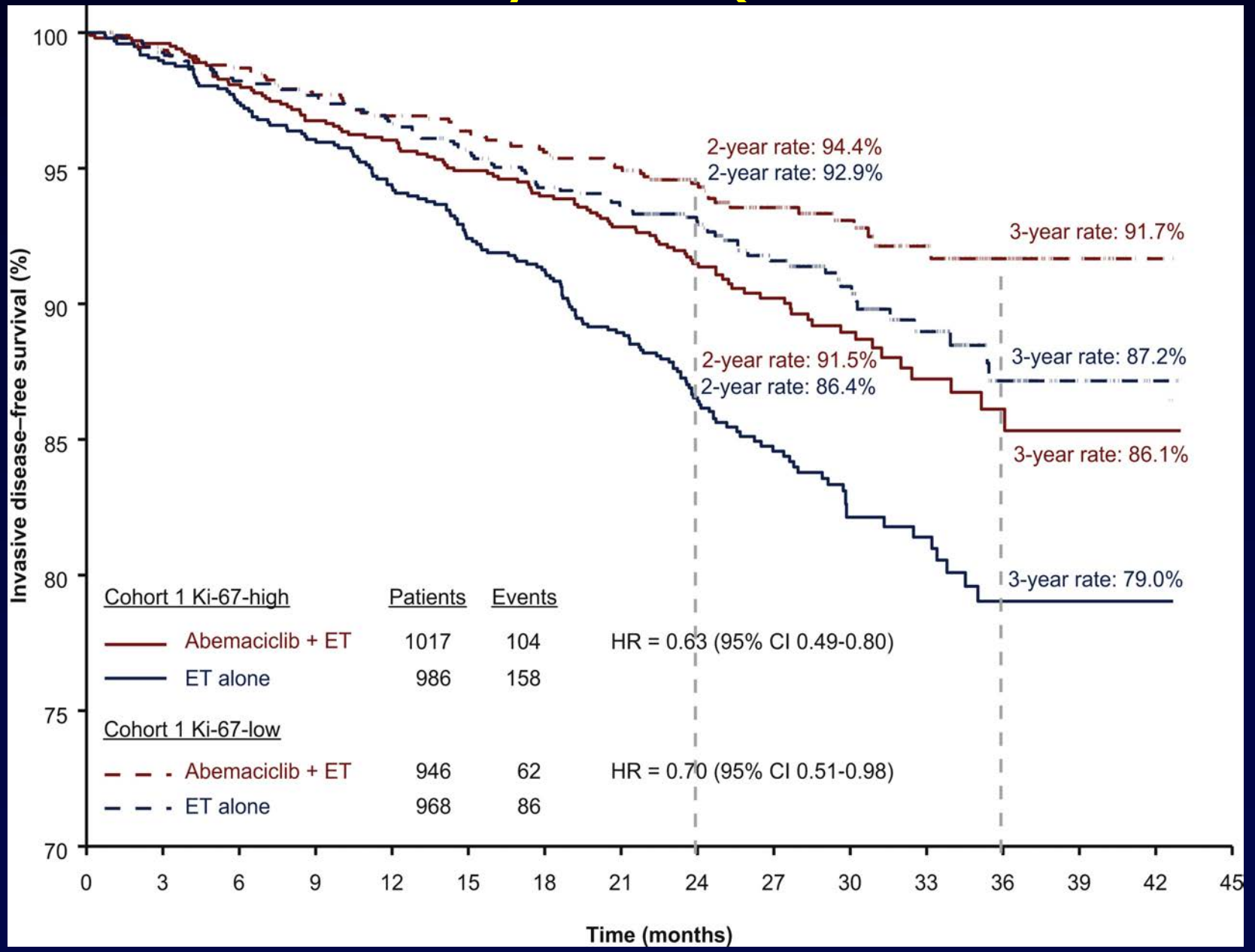




	Abemaciclib + ET No.	Abemaciclib + ET Events	ET alone No.	ET alone Events	HR (95% CI)	Interaction P value
Overall	2808	232	2829	333	0.70 (0.59-0.82)	
Number of pos. lymph nodes						0.597
1-3	1118	75	1142	105	0.72 (0.54-0.97)	
4-9	1107	75	1126	126	0.61 (0.46-0.81)	
10 or more	575	80	554	102	0.74 (0.55-0.99)	
Histologic grade						0.787
Grade 1	209	11	216	12	0.94 (0.42-2.13)	
Grade 2	1377	101	1395	146	0.70 (0.54-0.90)	
Grade 3	1086	112	1064	151	0.72 (0.57-0.92)	
Primary tumor size						0.024
<2 cm	781	40	767	86	0.45 (0.31-0.66)	
2-5 cm	1371	125	1419	155	0.84 (0.66-1.06)	
≥5 cm	607	62	610	87	0.70 (0.51-0.97)	
Prior chemotherapy						0.339
Neoadjuvant	1039	119	1048	184	0.63 (0.50-0.80)	
Adjuvant	1642	101	1647	135	0.75 (0.58-0.97)	
Menopausal status						0.082
Premenopausal	1221	85	1232	142	0.58 (0.44-0.76)	
Postmenopausal	1587	147	1597	191	0.79 (0.64-0.98)	
Region						0.938
North America/Europe	1470	111	1479	156	0.72 (0.56-0.92)	
Asia	574	41	582	60	0.66 (0.45-0.99)	
Other	764	80	768	117	0.69 (0.52-0.92)	
Age						0.391
<65 years	2371	192	2416	285	0.68 (0.56-0.81)	
≥65 years	437	40	413	48	0.83 (0.54-1.26)	
Progesterone receptor						0.846
Negative	298	42	295	58	0.71 (0.48-1.06)	
Positive	2426	185	2456	270	0.69 (0.57-0.83)	
Tumor stage						0.422
Stage IIA	324	15	353	28	0.57 (0.30-1.07)	
Stage IIB	392	31	387	32	0.99 (0.60-1.62)	
Stage IIIA	1029	73	1026	104	0.70 (0.52-0.95)	
Stage IIIC	950	100	963	156	0.63 (0.49-0.82)	
Baseline ECOG PS						0.207
0	2405	193	2369	280	0.67 (0.56-0.80)	
1	401	39	455	52	0.90 (0.59-1.36)	
Race						0.299
White	1947	166	1978	237	0.71 (0.58-0.86)	
Asian	675	47	669	75	0.60 (0.42-0.86)	
All others	146	17	140	16	1.12 (0.57-2.22)	

Harbeck N et al. *Annals of Oncology* 2021 321571-1581DOI: (10.1016/j.annonc.2021.09.015)

MONARCH-E iDFS by Ki67 (median f/u 27.1 mos)

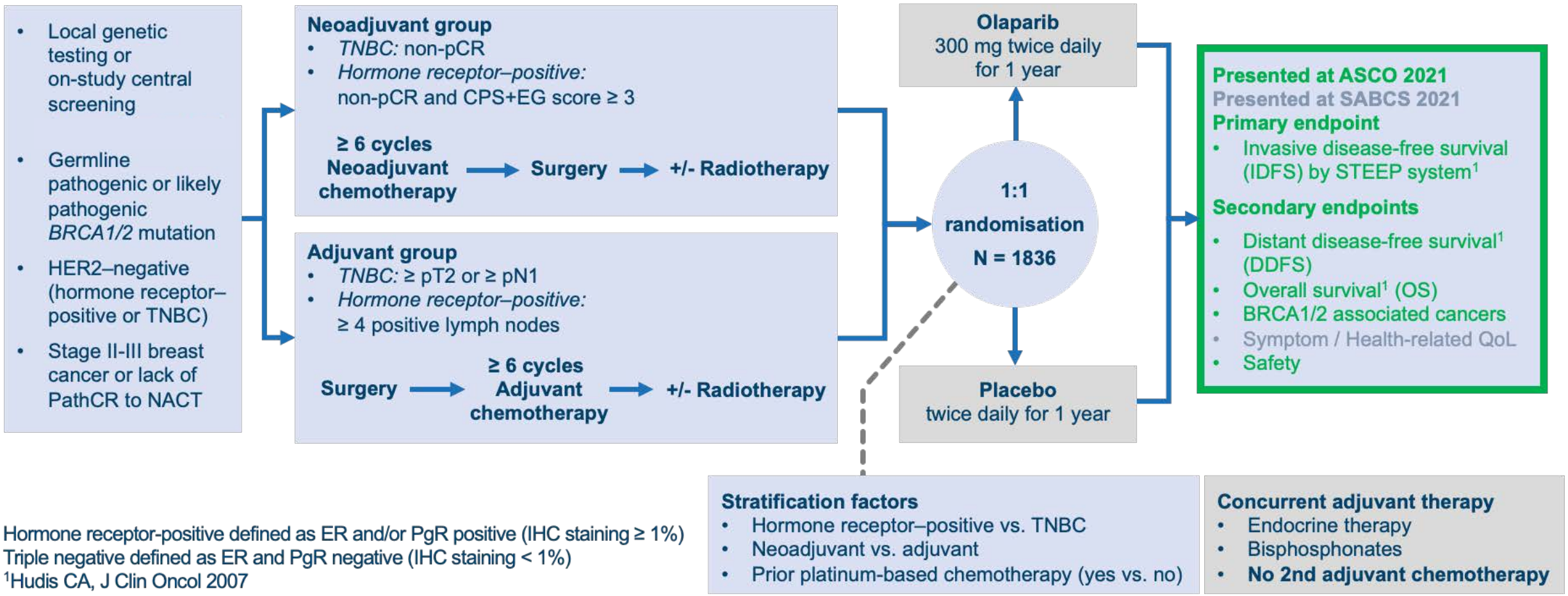


Harbeck N et al. *Annals of Oncology* 2021 321571-1581DOI: (10.1016/j.annonc.2021.09.015)

Adjuvant CDK4/6i Reported Trials

	PALLAS	PENELOPE-B	MONARCH-E
N	5600	1250	5637
Length of CDK4/6i	2 year	1 year	2 year
Prior chemotherapy	82%	100%	95%
Tamoxifen use	32%	50%	30%
Grade 3	29%	47%	38%
Node negative	13%	Unknown	0.2%
N1	49%	Unknown	40%
≥N2	37%	50% (after NAC)	60%
Discontinued IP prematurely	42%	19.5%	28% (at 19 mos f/u)
Still on therapy	26%	0	10%
Median follow up	24 mos	42.8 mos	27.1 mos
2-year iDFS		88.3% vs 84% Δ4.3%	**92.7% vs 90.0%** **Δ2.7%**
3-year iDFS	88.2% vs. 88.5% Δ-0.3%	81.2% vs. 77.7% Δ3.5%	**88.8% vs 83.4%** **Δ5.4%, HR 0.696, P<0.0001**

OLYMPIA: TRIAL SCHEMA



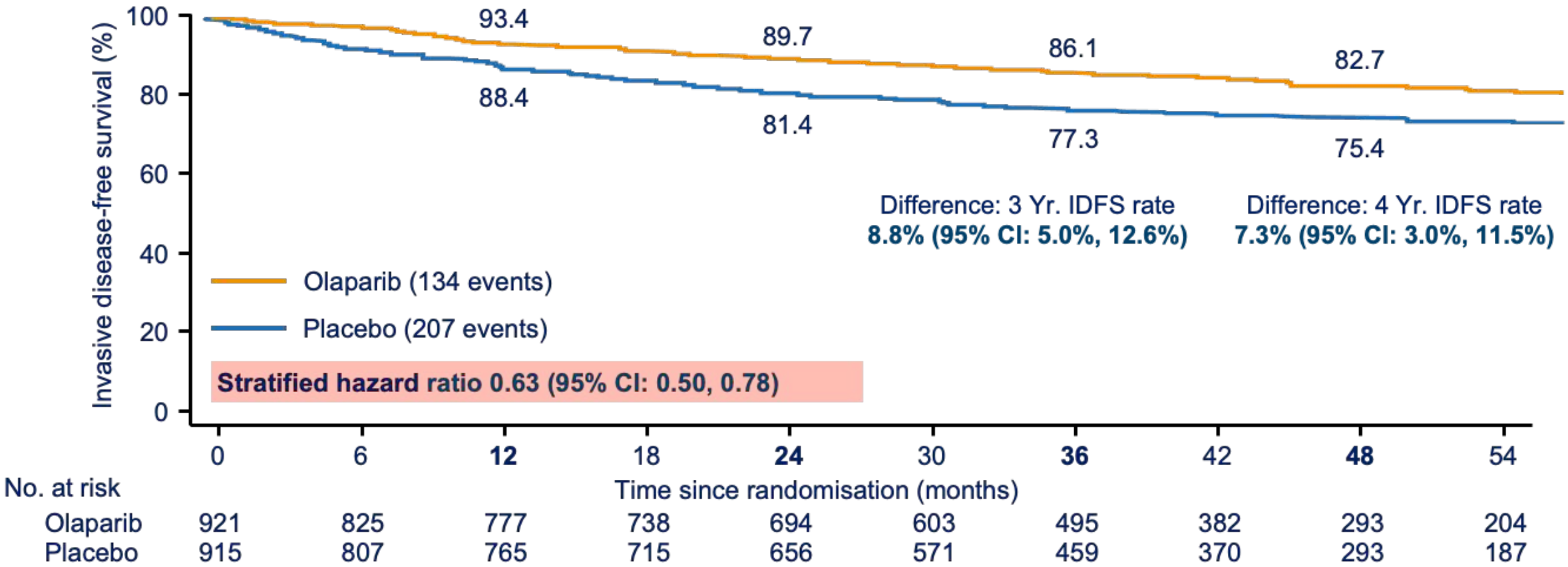
Hormone receptor-positive defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

Comments on study population

- Very young (median 42-43, 25% > 50)
- 72.3% gBRCA1m
- 82.2% TNBC, no HER2+ (by design)
- 74.7% treated with mastectomy (46.5% bilateral)
- RRSO in ~60%

- CPS+EG score unfamiliar to many
  - http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=bcnt
  - Remember to use nuclear grade, not histologic or overall

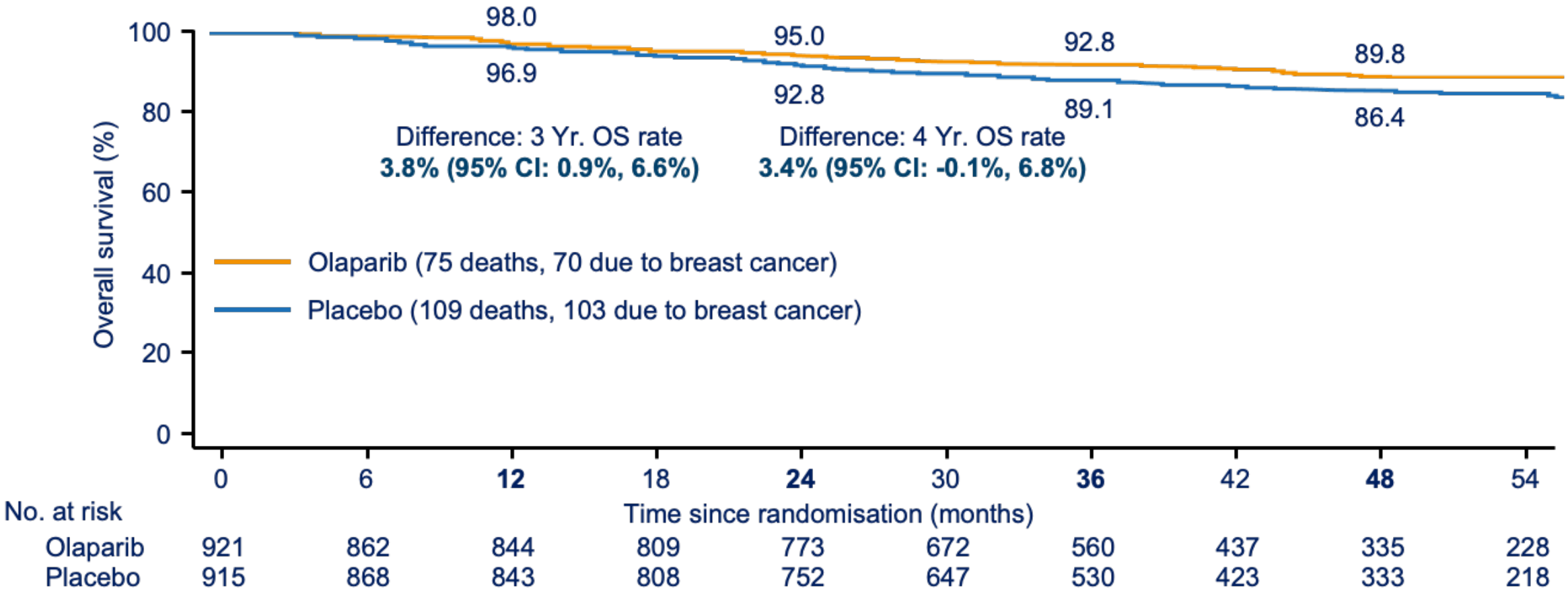
ANALYSIS OF IDFS (ITT) AT OS IA2



No. at risk									
Olaparib	921	825	777	738	694	603	495	382	293	204
Placebo	915	807	765	715	656	571	459	370	293	187

Tutt et al, ESMO Virtual Plenary March 2022

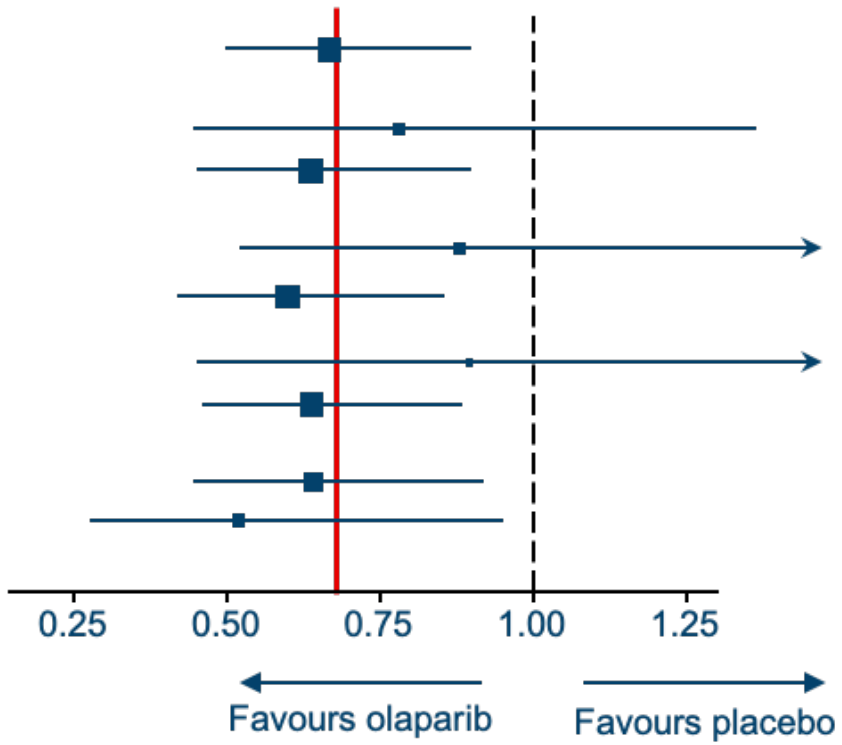
SECOND OVERALL SURVIVAL INTERIM ANALYSIS - OS IA 2 (ITT)



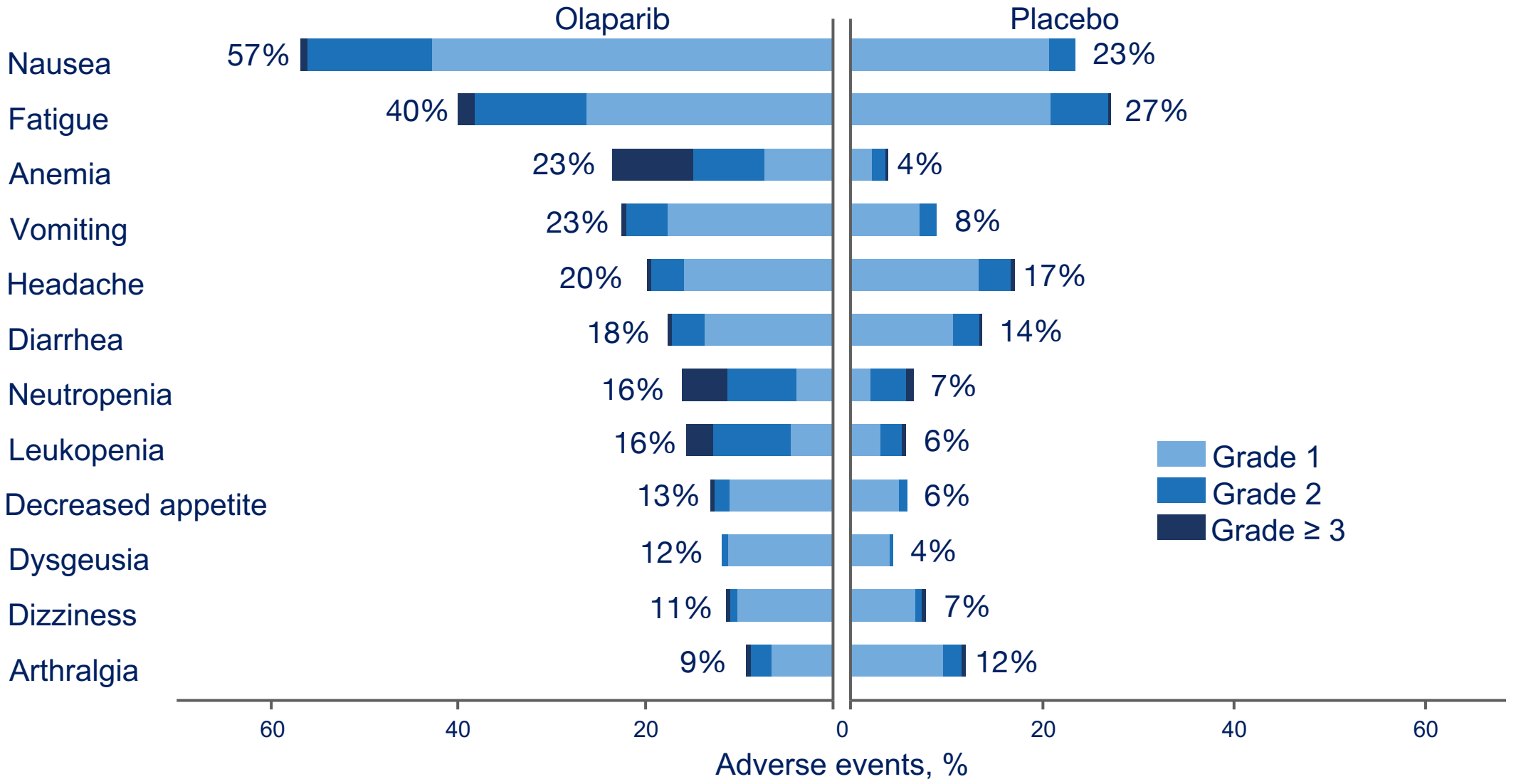
Tutt et al, ESMO Virtual Plenary March 2022

SUBGROUP ANALYSIS OF OS

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


Olaparib
Placebo
Nausea
Fatigue
Anemia
Vomiting
Headache
Diarrhea
Neutropenia
Leukopenia
Decreased appetite
Dysgeusia
Dizziness
Arthralgia
57%
40%
23%
23%
20%
18%
16%
16%
13%
12%
11%
9%
23%
27%
4%
8%
17%
14%
7%
6%
6%
4%
7%
12%
Grade 1
Grade 2
Grade ≥ 3
60
40
20
0
20
40
60
Adverse events, %

Conclusions

- EET benefits few and adds to AEs
- OFS during chemo can preserve ovarian function
- OFS to high risk women. Can it replace chemo?
- CDK4/6i for high risk. Do we trust Ki67?
- PARPi for high risk. Do we perform CPS?

Thank you !

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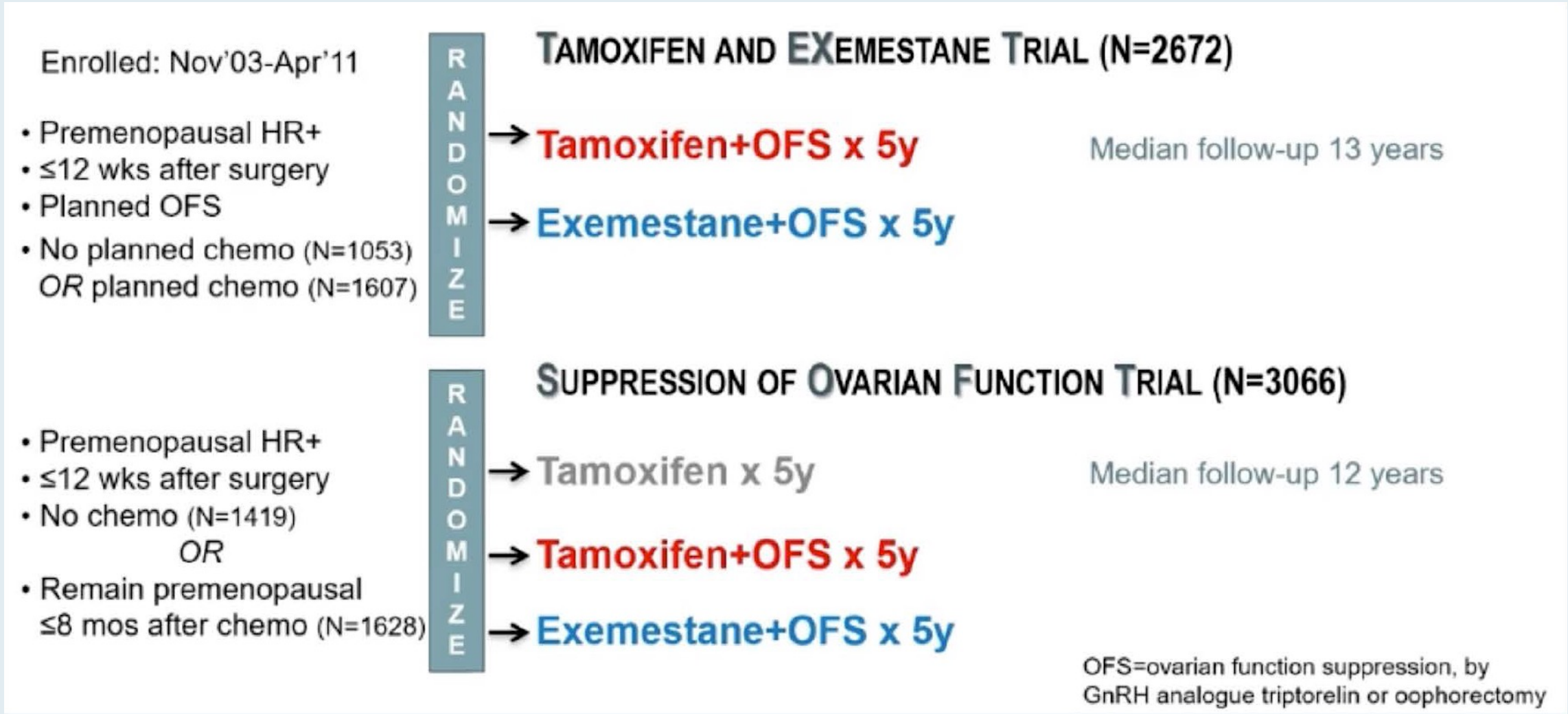
APPENDIX

Randomized Comparisons of Adjuvant Exemestane + Ovarian Function Suppression (OFS) vs Tamoxifen + OFS vs Tamoxifen in Premenopausal Women in HR+ Early Breast Cancer: Update of the TEXT and SOFT Trials

Regan MM et al.

SABCS 2021;Abstract GS2-05.

TEXT and SOFT Trial Designs

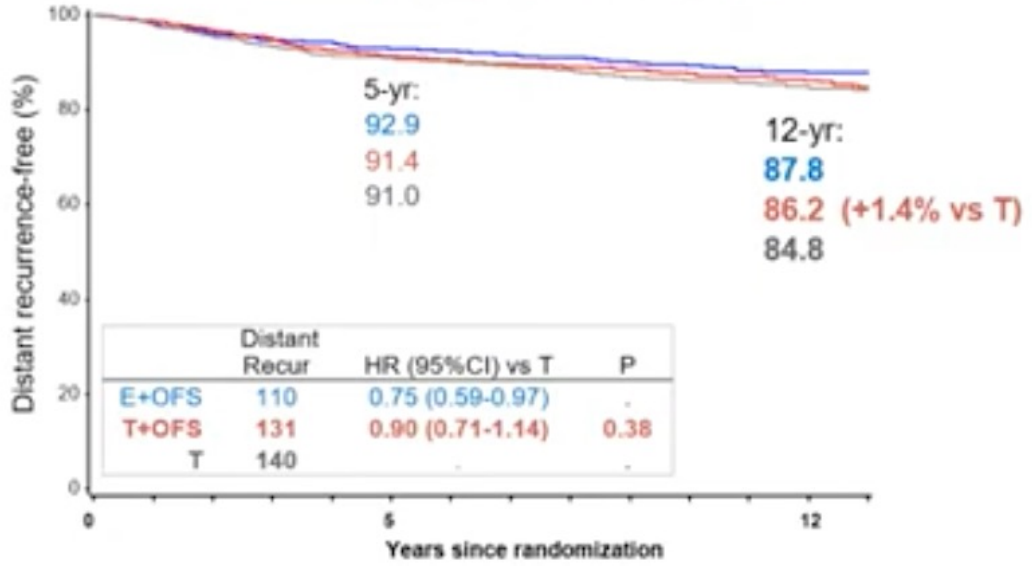


Regan MM et al. SABCS 2021;Abstract GS2-05.

OFS Question: SOFT Overall Population

35% LN+; 12 years median follow-up

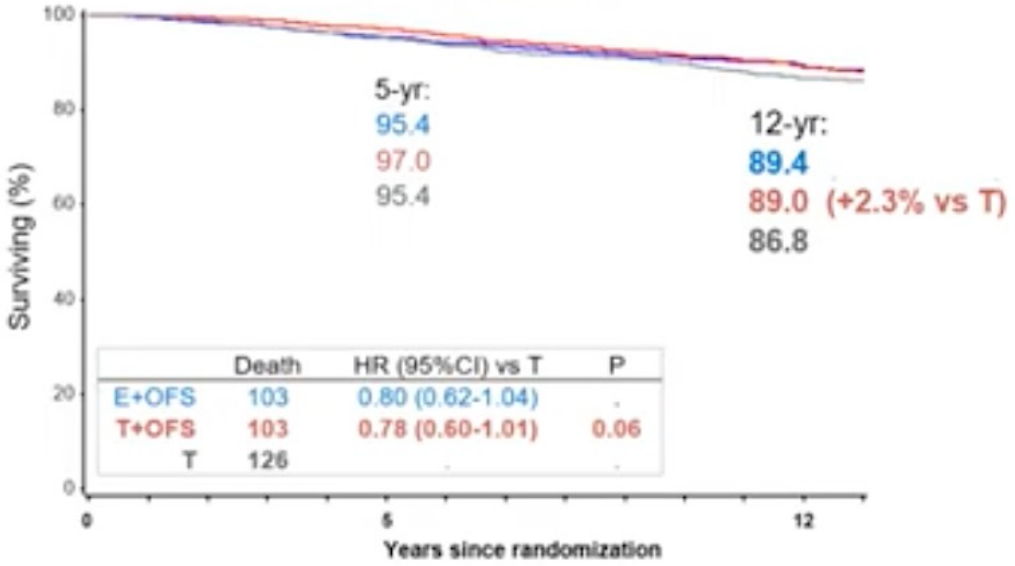
Distant Recurrence-free Interval



	Distant Recur	HR (95%CI) vs T	P
E+OFS	110	0.75 (0.59-0.97)	.
T+OFS	131	0.90 (0.71-1.14)	0.38
T	140	.	.

	0-5 years		>5 years	
	Recur	HR (95% CI) vs T	Recur	HR (95% CI) vs T
E+OFS:	68	0.76 (0.55-1.04)	42	0.74 (0.50-1.12)
T+OFS:	83	0.93 (0.69-1.25)	48	0.85 (0.58-1.26)
T:	87		53	
At risk:	**3047** pts	13787 pyfu	2521 pts	16343 pyfu

Overall Survival



	Death	HR (95%CI) vs T	P
E+OFS	103	0.80 (0.62-1.04)	.
T+OFS	103	0.78 (0.60-1.01)	0.06
T	126	.	.

	0-5 years		>5 years	
	Deaths	HR (95% CI) vs T	Deaths	HR (95% CI) vs T
E+OFS:	45	1.00 (0.66-1.51)	58	0.70 (0.50-0.98)
T+OFS:	29	0.63 (0.40-1.01)	74	0.86 (0.63-1.18)
T:	45		81	
At risk:	**3047** pts	14524 pyfu	2745 pts	18383 pyfu

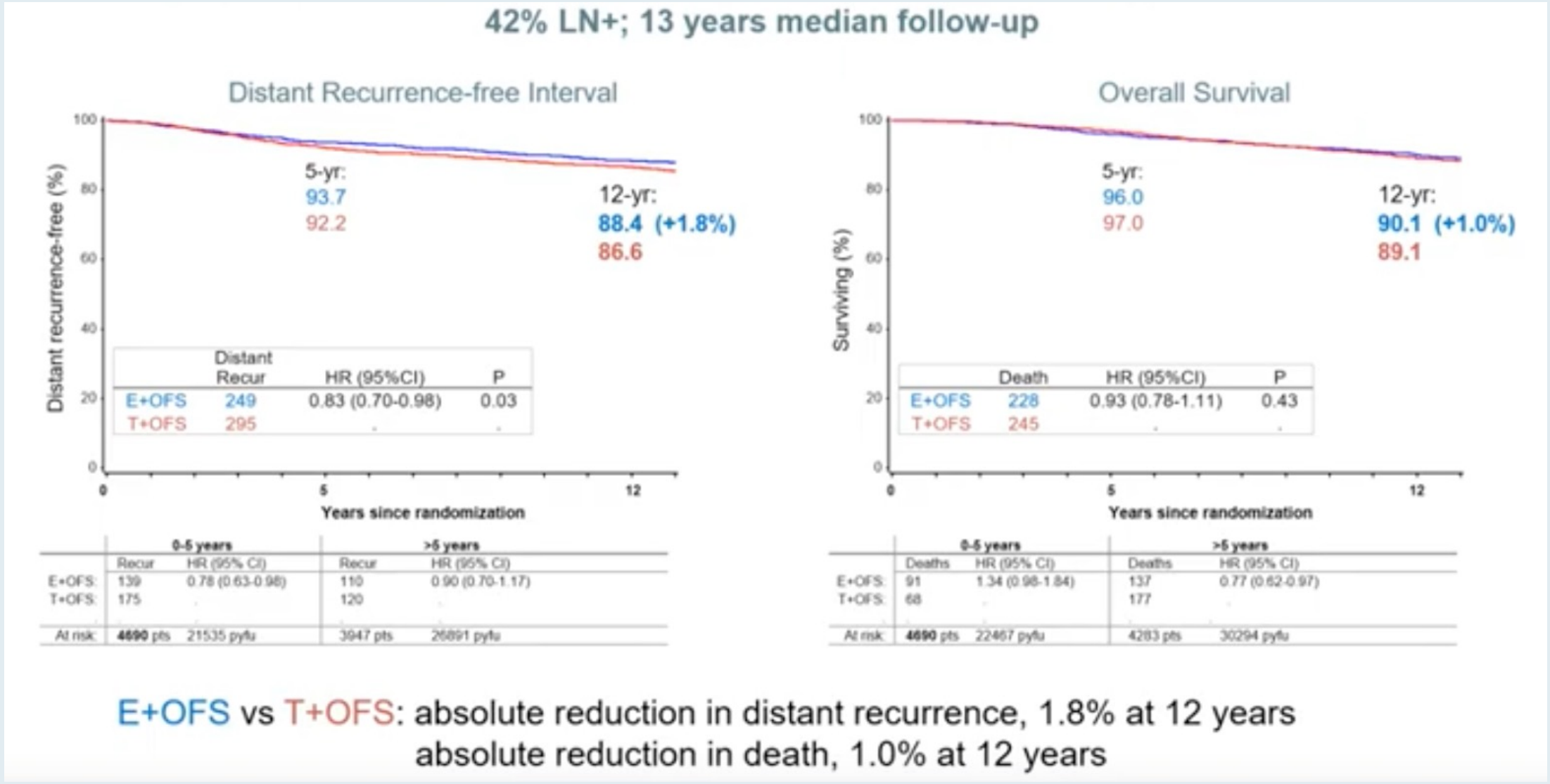
T+OFS vs T: absolute reductions in distant recurrence and death 1.4% and 2.3% at 12 years

E+OFS vs T: absolute reductions in distant recurrence and death 3.0% and 2.6% at 12 years

Regan MM et al. SABCS 2021;Abstract GS2-05.

RTP RESEARCH TO PRACTICE

AI Question: SOFT and TEXT Overall Populations



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

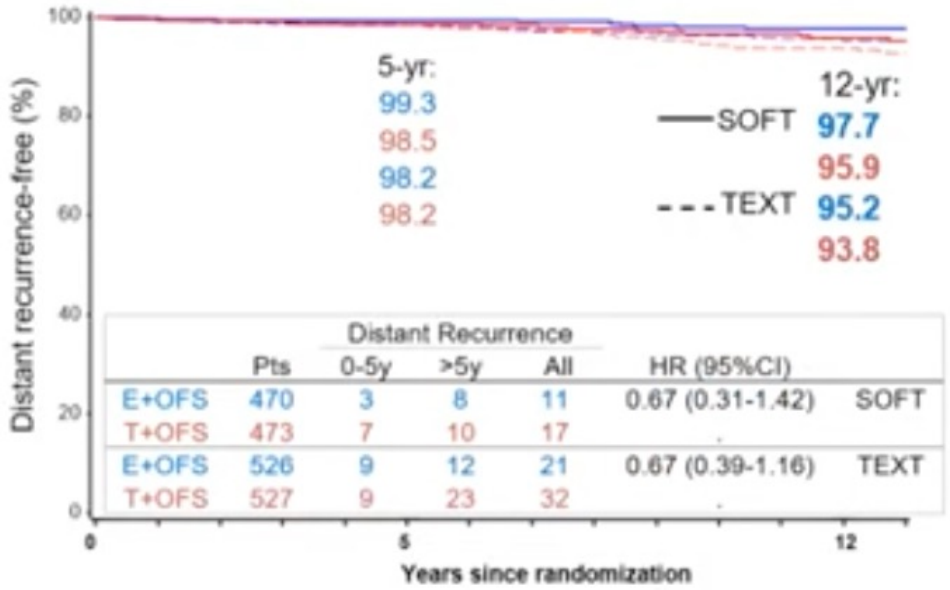
Regan MM et al. SABCS 2021;Abstract GS2-05.

RTP RESEARCH TO PRACTICE

SOFT and TEXT: No-Chemotherapy Cohorts

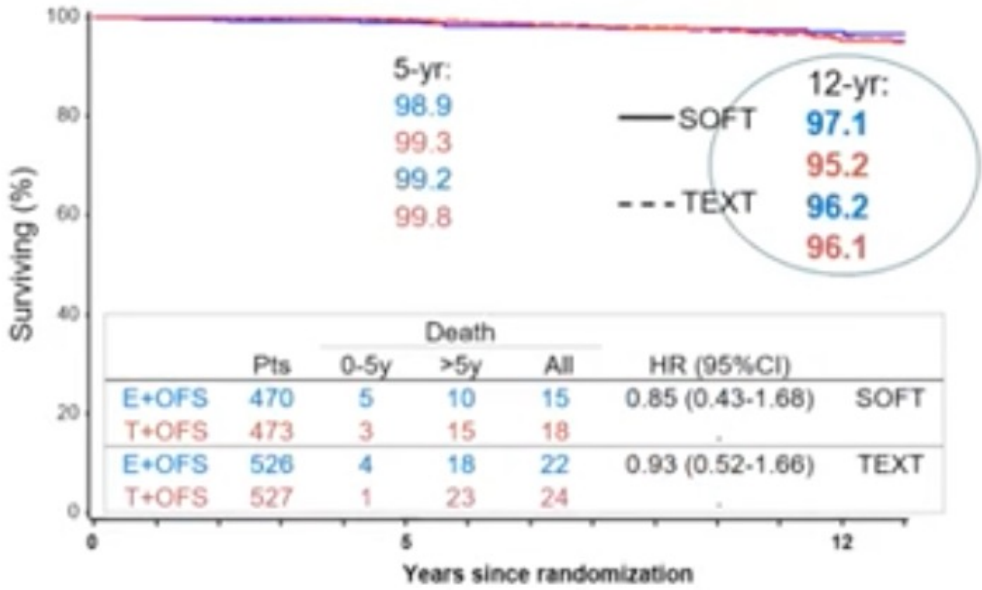
9% & 21% LN+; 13 years median follow-up

Distant Recurrence-free Interval



	Pts	Distant Recurrence 0-5y	>5y	All	HR (95%CI)	
E+OFS	470	3	8	11	0.67 (0.31-1.42)	SOFT
T+OFS	473	7	10	17		
E+OFS	526	9	12	21	0.67 (0.39-1.16)	TEXT
T+OFS	527	9	23	32		

Overall Survival



	Pts	Death 0-5y	>5y	All	HR (95%CI)	
E+OFS	470	5	10	15	0.85 (0.43-1.68)	SOFT
T+OFS	473	3	15	18		
E+OFS	526	4	18	22	0.93 (0.52-1.66)	TEXT
T+OFS	527	1	23	24		

Numbers of deaths, relative to a BC event or 2nd (non-breast) cancer

SOFT	All Deaths	After BC Event	2nd Cancer	No Cancer	Unkn. Cancer
E+OFS	15	7	4	2	2
T+OFS	18	10	4	1	3
TEXT					
E+OFS	22	19	2	0	1
T+OFS	24	19	2	3	0

Unkn (unknown)=death with no information about breast or 2nd (non-breast) cancer event

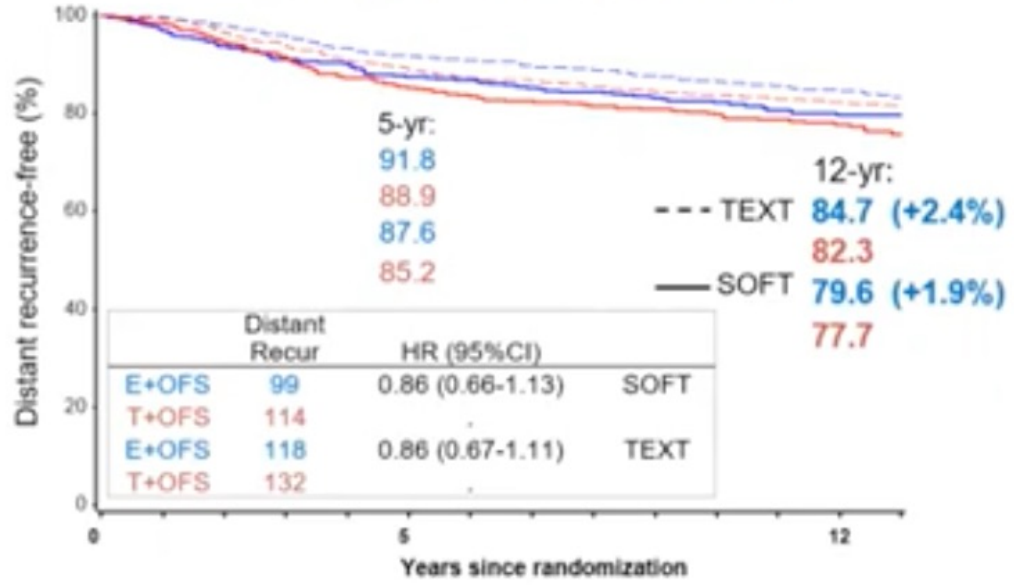
>95% of women surviving at 12 years
70% deaths after a BC event

Regan MM et al. SABCS 2021;Abstract GS2-05.

SOFT and TEXT: Chemotherapy Cohorts

57% & 66% LN+; 13 years median follow-up

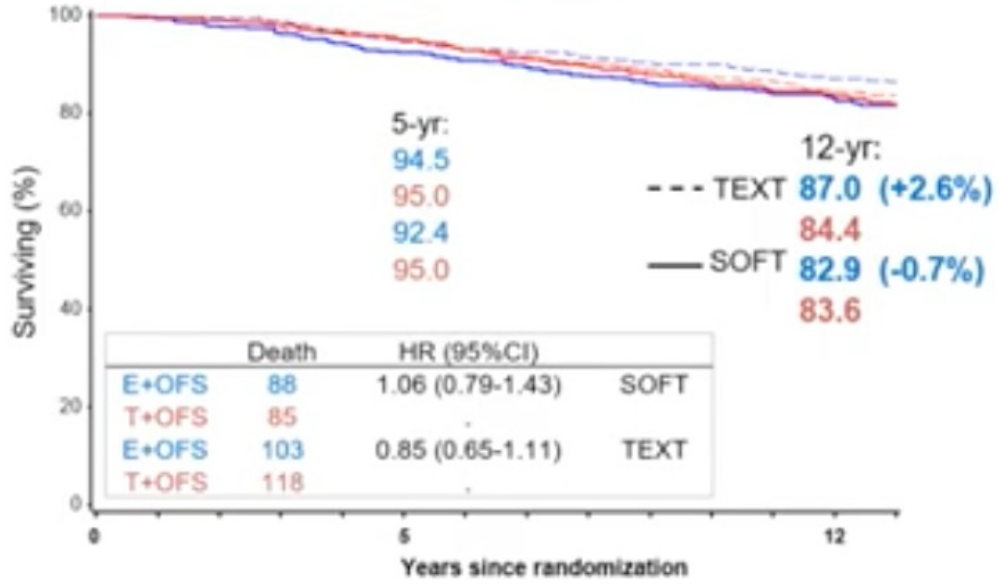
Distant Recurrence-free Interval



	Distant Recur	HR (95%CI)	
E+OFS	99	0.86 (0.66-1.13)	SOFT
T+OFS	114		
E+OFS	118	0.86 (0.67-1.11)	TEXT
T+OFS	132		

		0-5 years		>5 years	
		Recur	HR (95% CI)	Recur	HR (95% CI)
SOFT	E+OFS:	65	0.85 (0.61-1.19)	34	0.88 (0.56-1.41)
	T+OFS:	76		38	
TEXT	E+OFS:	62	0.73 (0.52-1.01)	56	1.10 (0.75-1.61)
	T+OFS:	83		49	
	At risk:	2694 pts	12086 pyfu	2166 pts	14702 pyfu

Overall Survival



	Death	HR (95%CI)	
E+OFS	88	1.06 (0.79-1.43)	SOFT
T+OFS	85		
E+OFS	103	0.85 (0.65-1.11)	TEXT
T+OFS	118		

		0-5 years		>5 years	
		Deaths	HR (95% CI)	Deaths	HR (95% CI)
SOFT	E+OFS:	40	1.57 (0.96-2.57)	48	0.84 (0.57-1.22)
	T+OFS:	26		59	
TEXT	E+OFS:	42	1.10 (0.71-1.70)	61	0.74 (0.53-1.03)
	T+OFS:	38		80	
	At risk:	2694 pts	12774 pyfu	2395 pts	16928 pyfu

E+OFS vs T+OFS: reductions in distant recurrence 1.9% SOFT and 2.4% TEXT at 12 years
overall survival, -0.7% SOFT and +2.6% TEXT at 12 years

Regan MM et al. SABCS 2021;Abstract GS2-05.

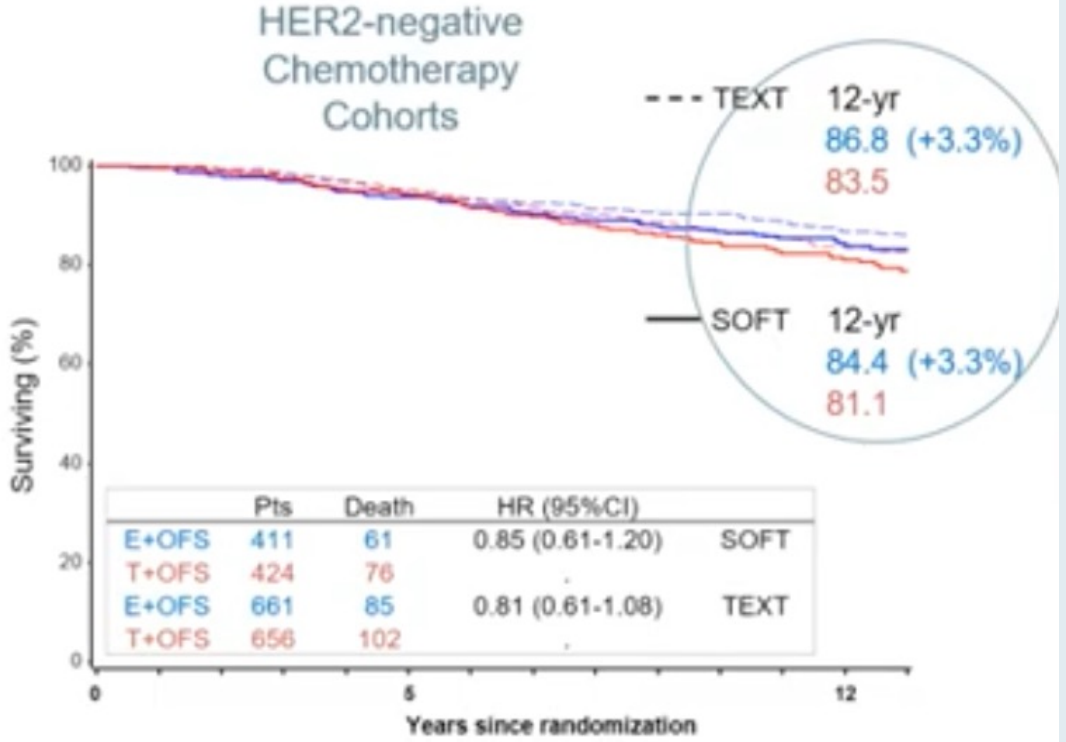
RTP RESEARCH TO PRACTICE

SOFT and TEXT Overall Survival by HER2 Status and Cohort

13 years median follow-up

12-yr OS (95% CI) by HER2 Status and Cohort

HER2	Cohort	Pts	Death E+OFS	Death T+OFS
Overall		4690	228	245
Negative	SOFT no chemo	892	15	14
	SOFT prior chemo	835	61	76
	TEXT no chemo	991	21	24
	TEXT chemo	1317	85	102
Positive	SOFT	249	23	9
	TEXT	329	19	15
Unknown		77	4	5



HER2-negative cancers predominate in each trial:
E+OFS vs T+OFS, absolute improvement in overall survival 3.3% at 12 years

Regan MM et al. SABCS 2021;Abstract GS2-05.

RTP RESEARCH TO PRACTICE

SOFT and TEXT After 12 and 13 Years Median Follow-Up

- Distant recurrences and deaths from BC continue to occur among this premenopausal HR+ population
  - Follow-up continues for a further 5 years
- Meaningful relative reductions in distant recurrence and death persist for use of OFS (with either oral ET) vs tamoxifen alone, requires appropriate selection of patients to receive OFS
  - Absolute reductions at 12 years more clinically substantial (~10%) for those at higher clinical risk
  - With low clinical risk, >95% were surviving at 12 years with all 3 treatments (and no chemotherapy)
- Reduction in distant recurrence with E+OFS vs T+OFS is consistent with postmenopausal women, of substantial magnitude for those at higher risk
  - Emergent later survival improvement with E+OFS, 3.3% at 12 years for those with HER2-negative BC who had received chemotherapy

Regan MM et al. SABCS 2021;Abstract GS2-05.

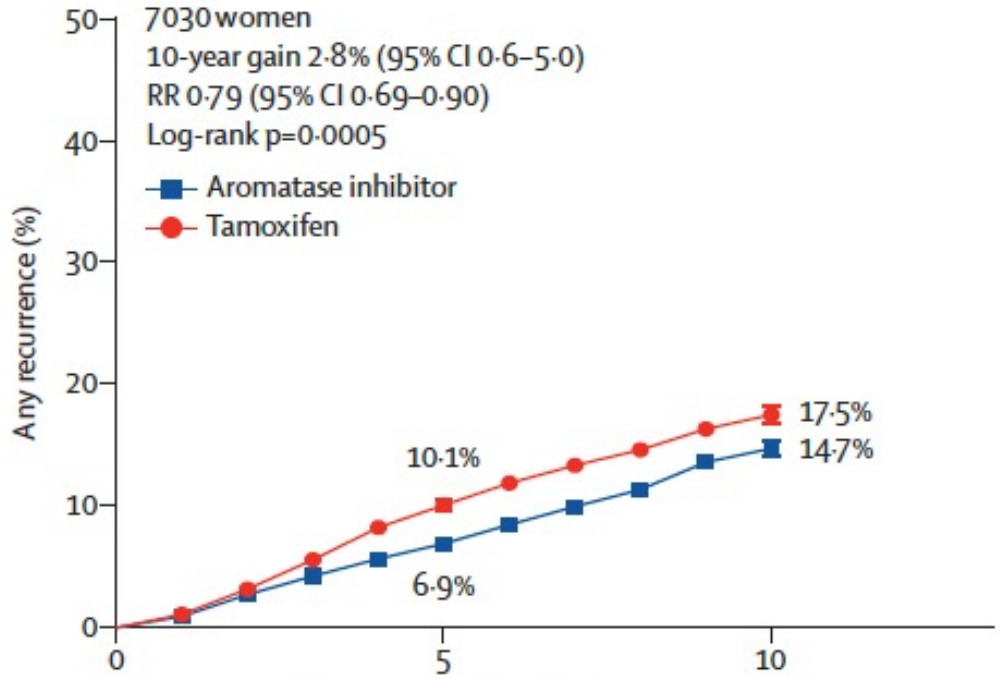
Lancet Oncol 2022;23:382-92.

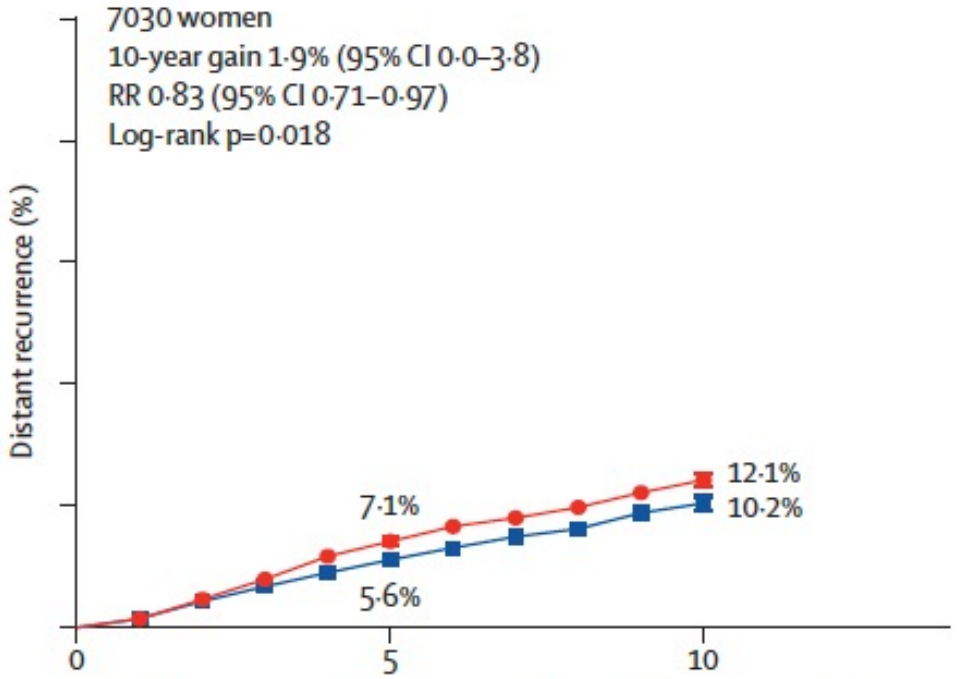
Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

EBCTCG. *Lancet Oncol* 2022;23:382-92.

EBCTCG Meta-Analysis: Aromatase Inhibitors versus Tamoxifen for Premenopausal Women: Recurrence and Distant Recurrence Rates





Recurrence rates per year (% [events/women-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Aromatase inhibitor	1·46 (237/16 276)	1·76 (158/8999)	1·89 (9/476)
Tamoxifen	2·08 (332/15 958)	1·74 (150/8639)	0·44 (2/459)
RR (95% CI)	0·68 (0·58–0·80)	0·98 (0·78–1·23)	3·31 (0·99–11·06)
from (o–e)/v	–52·9/137·2	–1·2/74·5	3·2/2·6

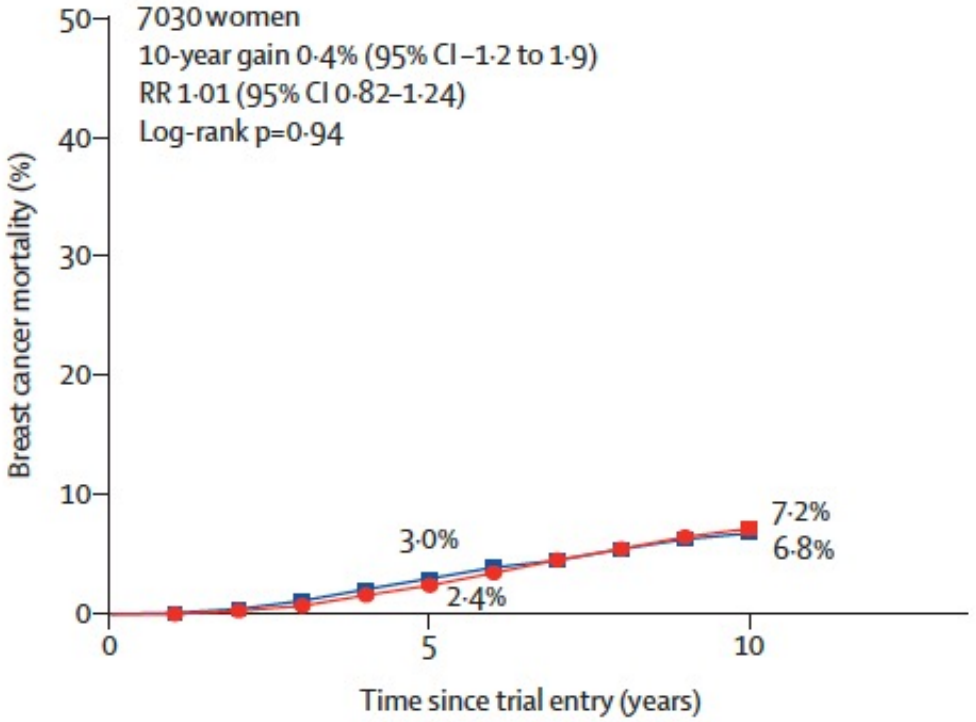
Distant recurrence rates per year (% [events/women-years]) and log-rank analyses

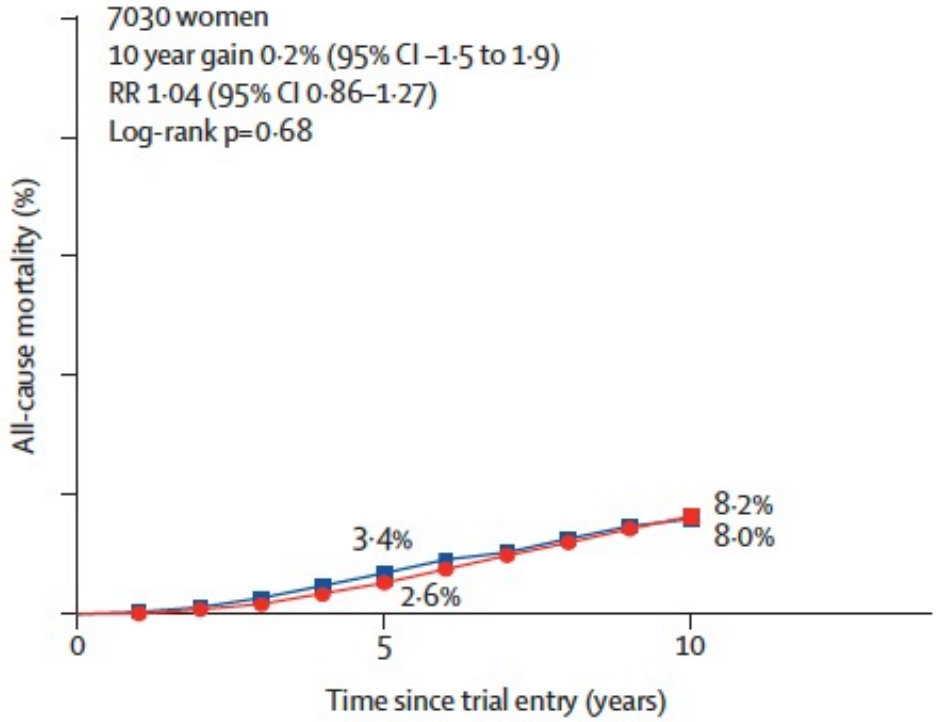
Years 0–4	Years 5–9	Years ≥10
1·16 (190/16 386)	1·01 (93/9222)	0·60 (3/502)
1·44 (233/16 169)	1·08 (97/9016)	0·00 (0/490)
0·78 (0·65–0·95)	0·91 (0·68–1·22)	7·86 (0·72–85·91)
–24·8/101·8	–4·3/45·8	1·4/0·7

EBCTCG. *Lancet Oncol* 2022;23:382-92.

RTP RESEARCH TO PRACTICE

EBCTCG Meta-Analysis: Aromatase Inhibitors versus Tamoxifen for Premenopausal Women: Breast Cancer and All-Cause Mortality





Death rates from breast cancer per year (% [95% CI]) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Aromatase inhibitor	0·60 (0·48–0·72)	0·85 (0·66–1·03)	0·76 (0·02–1·51)
Tamoxifen	0·47 (0·37–0·57)	1·03 (0·82–1·23)	0·57 (0·08–1·22)
RR (95% CI)	1·25 (0·93–1·68)	0·80 (0·60–1·08)	1·45 (0·33–6·44)
from (o–e)/v	9·7/43·4	−9·6/43·5	0·6/1·7

Death rates per year (% [events/women-years]) and log-rank analyses

Years 0–4	Years 5–9	Years ≥10
0·69 (115/16 663)	1·01 (96/9515)	0·76 (4/525)
0·51 (85/16 573)	1·17 (111/9481)	1·33 (7/525)
1·33 (1·00–1·76)	0·84 (0·64–1·11)	0·64 (0·18–2·24)
13·8/48·9	−8·6/50·2	−1·1/2·5

EBCTCG. *Lancet Oncol* 2022;23:382-92.

RTP RESEARCH TO PRACTICE

Menopause: The Journal of The North American Menopause Society
Vol. 29, No. 9, pp. 1093-1100
DOI: 10.1097/GME.0000000000002019

OPEN

REVIEW - SYSTEMATIC

Gonadotropin-releasing hormone agonists for ovarian protection during breast cancer chemotherapy: a systematic review and meta-analysis

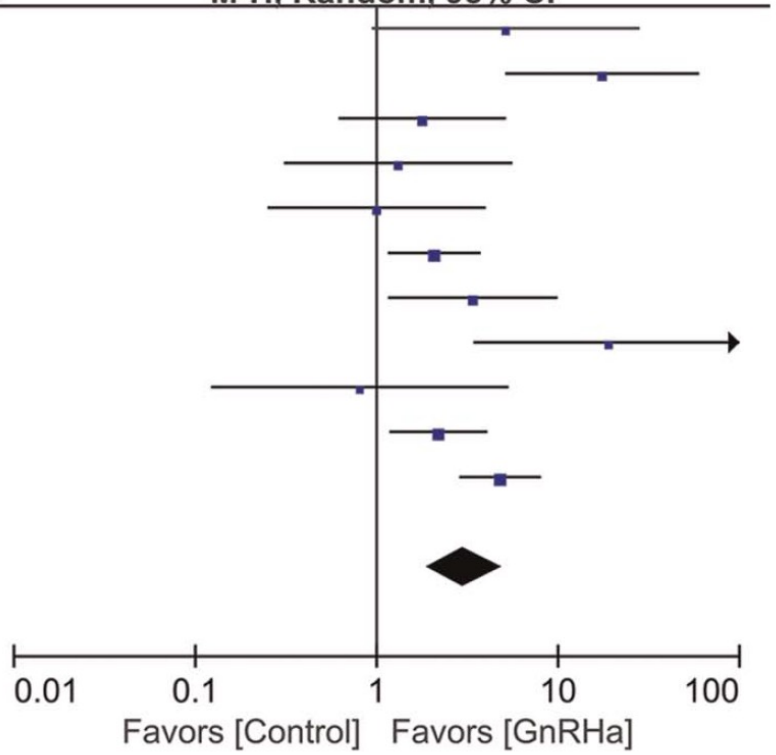
Zhen-Yu Li, MD,[1] Ying-Li Dong, M. Med,[2] Xiao-Zhong Cao, M. Med,[1] Sha-Sha Ren, M. Med,[1] and Zhen Zhang, M. Med[1]

Forest Plot of the Rate of Resumed Ovarian Function with GnRHa and Chemotherapy versus Chemotherapy Alone: All Patients

Study or Subgroup	GnRHa Events	GnRHa Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
A. Sverrisdottir et al.	8	22	2	20	5.6%	5.14 [0.94, 28.14]
Ahmed Badawy et al.	35	39	13	39	8.3%	17.50 [5.11, 59.88]
Bernd Gerber et al.	21	30	17	30	9.6%	1.78 [0.62, 5.17]
Eman A. Elgindy et al.(A)	21	25	20	25	6.9%	1.31 [0.31, 5.60]
Eman A. Elgindy et al.(B)	20	25	20	25	7.3%	1.00 [0.25, 4.00]
Guiping Song et al.	53	89	39	94	14.1%	2.08 [1.15, 3.74]
Halle C. F. Moore et al.	61	66	54	69	9.5%	3.39 [1.16, 9.94]
M. Karimi-Zarchi et al.	19	21	7	21	5.5%	19.00 [3.41, 105.73]
Pamela N. Munster et al.	23	26	19	21	4.8%	0.81 [0.12, 5.34]
R. C. F. Leonard et al.	74	95	66	107	13.8%	2.19 [1.18, 4.08]
Xiangyun Zong et al.	139	165	87	165	14.8%	4.79 [2.85, 8.05]
Total (95% CI)		**603**		**616**	**100.0%**	**3.04 [1.87, 4.94]**
Total events	474		344			

Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 24.88$, df = 10 (P = 0.006); $I^2 = 60\%$

Test for overall effect: Z = 4.50 (P < 0.00001)



Li ZY et al. *Menopause: J N American Menopaus Soc* 2022;29(9):1093-100.

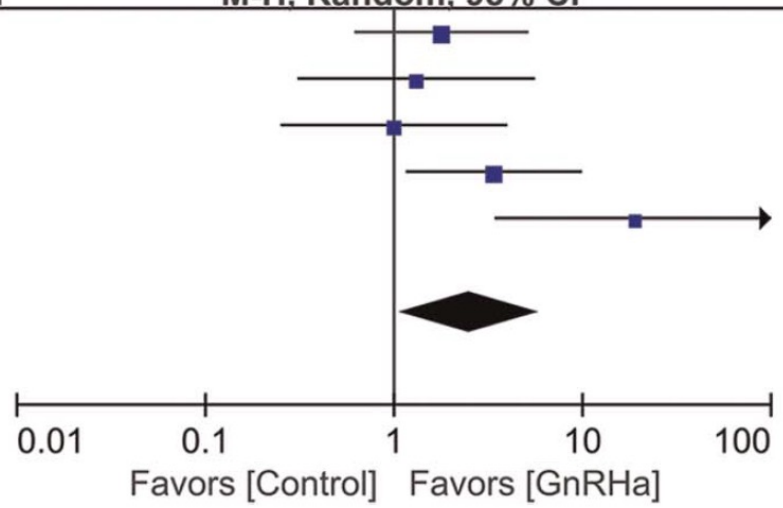
RTP RESEARCH TO PRACTICE

Forest Plot of the Rate of Resumed Ovarian Function with GnRHa and Chemotherapy versus Chemotherapy Alone: HR-Negative Disease

Study or Subgroup	GnRHa Events	GnRHa Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Bernd Gerber et al.	21	30	17	30	24.0%	1.78 [0.62, 5.17]
Eman A. Elgindy et al.(A)	21	25	20	25	18.2%	1.31 [0.31, 5.60]
Eman A. Elgindy et al.(B)	20	25	20	25	19.0%	1.00 [0.25, 4.00]
Halle C. F. Moore et al.	61	66	54	69	23.8%	3.39 [1.16, 9.94]
M. Karimi-Zarchi et al.	19	21	7	21	15.0%	19.00 [3.41, 105.73]
Total (95% CI)		**167**		**170**	**100.0%**	**2.51 [1.07, 5.89]**
Total events	142		118			

Heterogeneity: Tau² = 0.49; Chi² = 8.53, df = 4 (P = 0.07); I² = 53%

Test for overall effect: Z = 2.12 (P = 0.03)



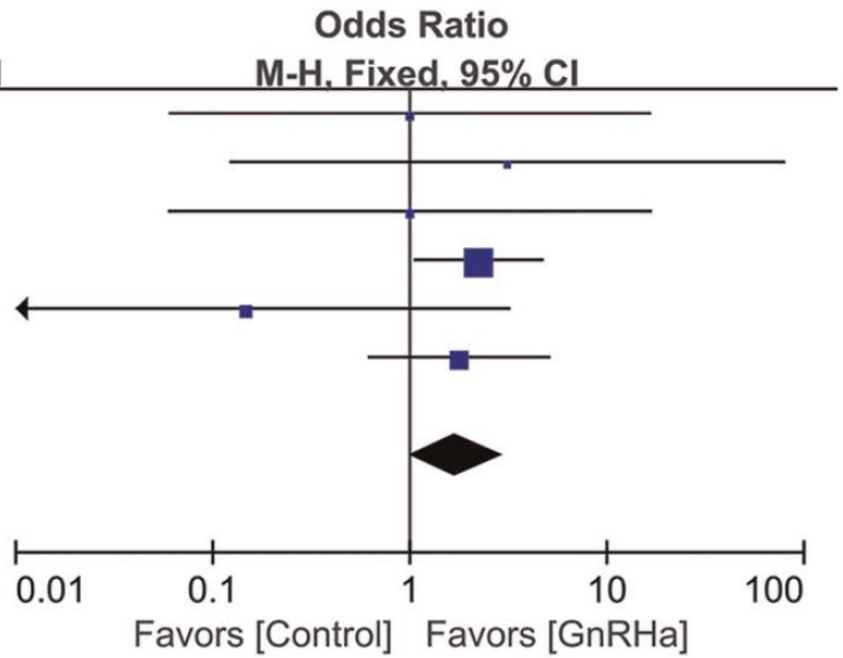
Li ZY et al. *Menopause: J N American Menopaus Soc* 2022;29(9):1093-100.

Forest Plot of the Rate of Spontaneous Pregnancy Achieved with GnRHa and Chemotherapy versus Chemotherapy Alone: All Patients

Study or Subgroup	GnRHa Events	GnRHa Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bernd Gerber et al.	1	30	1	30	5.0%	1.00 [0.06, 16.76]
Eman A. Elgindy et al.(A)	1	25	0	25	2.4%	3.12 [0.12, 80.39]
Eman A. Elgindy et al.(B)	1	25	1	25	5.0%	1.00 [0.06, 16.93]
Halle C. F. Moore et al.	22	105	12	113	47.2%	2.23 [1.04, 4.77]
Pamela N. Munster et al.	0	26	2	21	14.0%	0.15 [0.01, 3.24]
R. C. F. Leonard et al.	9	106	6	121	26.5%	1.78 [0.61, 5.17]
Total (95% CI)		**317**		**335**	**100.0%**	**1.72 [0.99, 2.99]**
Total events	34		22			

Heterogeneity: $Chi^2 = 3.29$, $df = 5$ ($P = 0.65$); $I^2 = 0\%$

Test for overall effect: $Z = 1.92$ ($P = 0.06$)



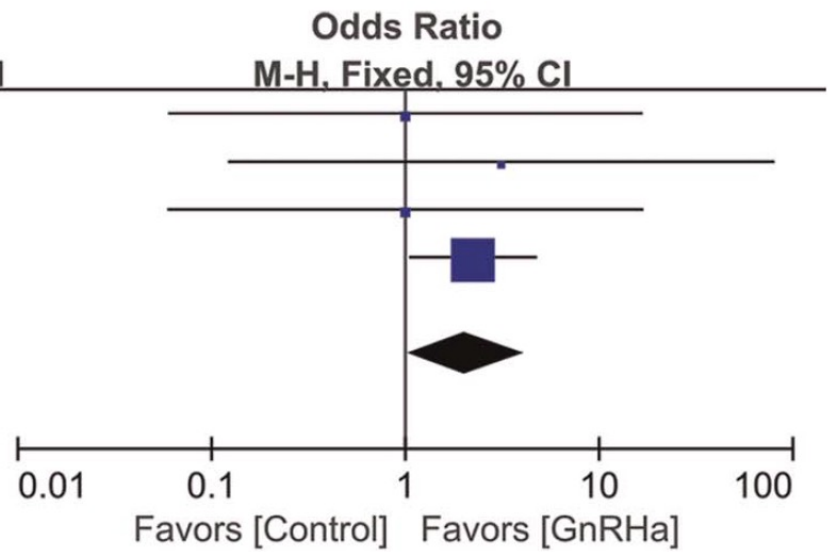
Li ZY et al. *Menopause: J N American Menopaus Soc* 2022;29(9):1093-100.

Forest Plot of the Rate of Spontaneous Pregnancy Achieved with GnRHa and Chemotherapy versus Chemotherapy Alone: HR-Negative Patients

	GnRHa		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Bernd Gerber et al.	1	30	1	30	8.4%	1.00 [0.06, 16.76]
Eman A. Elgindy et al.(A)	1	25	0	25	4.1%	3.12 [0.12, 80.39]
Eman A. Elgindy et al.(B)	1	25	1	25	8.3%	1.00 [0.06, 16.93]
Halle C. F. Moore et al.	22	105	12	113	79.2%	2.23 [1.04, 4.77]
Total (95% CI)		**185**		**193**	**100.0%**	**2.06 [1.03, 4.11]**
Total events	25		14			

Heterogeneity: $Chi^2 = 0.61$, $df = 3$ ($P = 0.89$); $I^2 = 0\%$

Test for overall effect: $Z = 2.06$ ($P = 0.04$)



Li ZY et al. *Menopause: J N American Menopaus Soc* 2022;29(9):1093-100.