Guidelines In The Use Of Hormonal Therapy In Early Stage Breast Cancer

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Introduction

- Endocrine therapy plays a major role in the treatment of hormone receptor positive breast cancer.
- Adjuvant endocrine therapy has had a significant impact in disease free survival and overall survival for patients with early-stage breast cancer.
- Challenges of endocrine therapy in the adjuvant setting includes optimal treatment for premenopausal woman, duration of therapy, defining recurrence risk, management of side effects, treatment compliance, among others.

Challenges Ahead

- Which is the best hormonal strategy for premenopausal woman?
- What the optimal duration of therapy?
- How can I personalize treatment decisions?
- How to balance risk vs benefits?
- What else can I do for my high risk patients?

Which is the best hormonal strategy for premenopausal women?

Menopause Definition

Because the endocrine options for treatment depends on whether a woman is in menopause, defining menopausal status is important

- ✓ Prior bilateral oophorectomy
- ✓ Age ≥60 years
- ✓ Age <60 with amenorrhea for ≥12 months in the absence of prior chemotherapy, receipt of tamoxifen, toremifene, or ovarian suppression and estradiol and FSH in the post-menopausal range
- ✓ Age <60 years: chemotherapy-induced amenorrhea for ≥12 months with FSH and estradiol in post-menopausal range on serial assessments
- ✓ Age <60 years: on tamoxifen with FSH and estradiol level in post-menopausal range

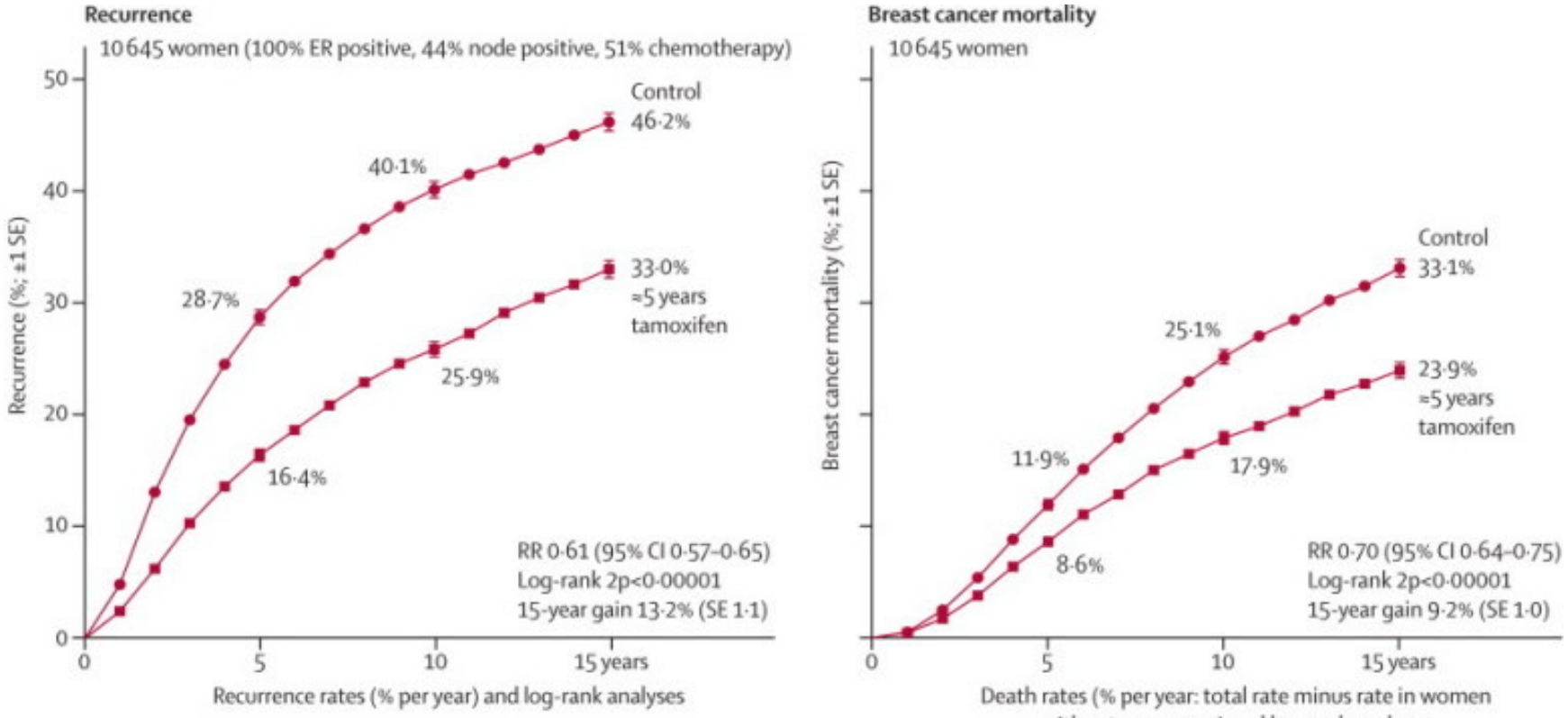
Breast Cancer Frequency and Mortality by Age and Subtype

BC Subtype Frequency	Age≤40 (n=1916)	41-50 9 (n=4854)	51-60 (n=5249)
Luminal A	27%	40%	45%
Luminal B	36%	32%	27%

BC Subtype/Deaths	Age≤40 (n=1916)	41-50 9 (n=4854)	51-60 (n=5249)
Luminal A	7.5%	2.1%	2.4%
Luminal B	12.2	6.7%	7.4%

Patridge et al. JCO 34: 2016

Tamoxifen Efficacy in HR + Breast Cancer in Randomized Trials



	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	3·74 (891/23 819)	2·62 (454/17 315)	2·06 (220/10 657)	1·75 (88/5034)
Control	6·71 (1466/21 862)	3·46 (499/14 420)	2·11 (182/8620)	1·76 (71/4045)
Rate ratio	0·53 (SE 0·03)	0·68 (SE 0·06)	0·97 (SE 0·10)	0·88 (SE 0·16)
(O–E)/V	−343·3/535·1	−82·5/217·5	−3·3/93·3	−4·4/35·5

Years 0–4	Years 5–9	Years 10–14	Year 15+
1·79 (SE 0·08)	2·25 (SE 0·11)	1·54 (SE 0·11)	1·48 (SE 0·16)
2·46 (SE 0·10)	3·23 (SE 0·13)	2·28 (SE 0·14)	1·89 (SE 0·19)
0·71 (SE 0·05)	0·66 (SE 0·05)	0·68 (SE 0·08)	0·88 (SE 0·14)
−84·4/244·8	−95·8/233·2	−38·6/99·4	−5·7/42·6

5 years of adjuvant tamoxifen safely reduces 15-year risks of BC recurrence and death. ER status was the only recorded factor importantly predictive of the proportional reductions.

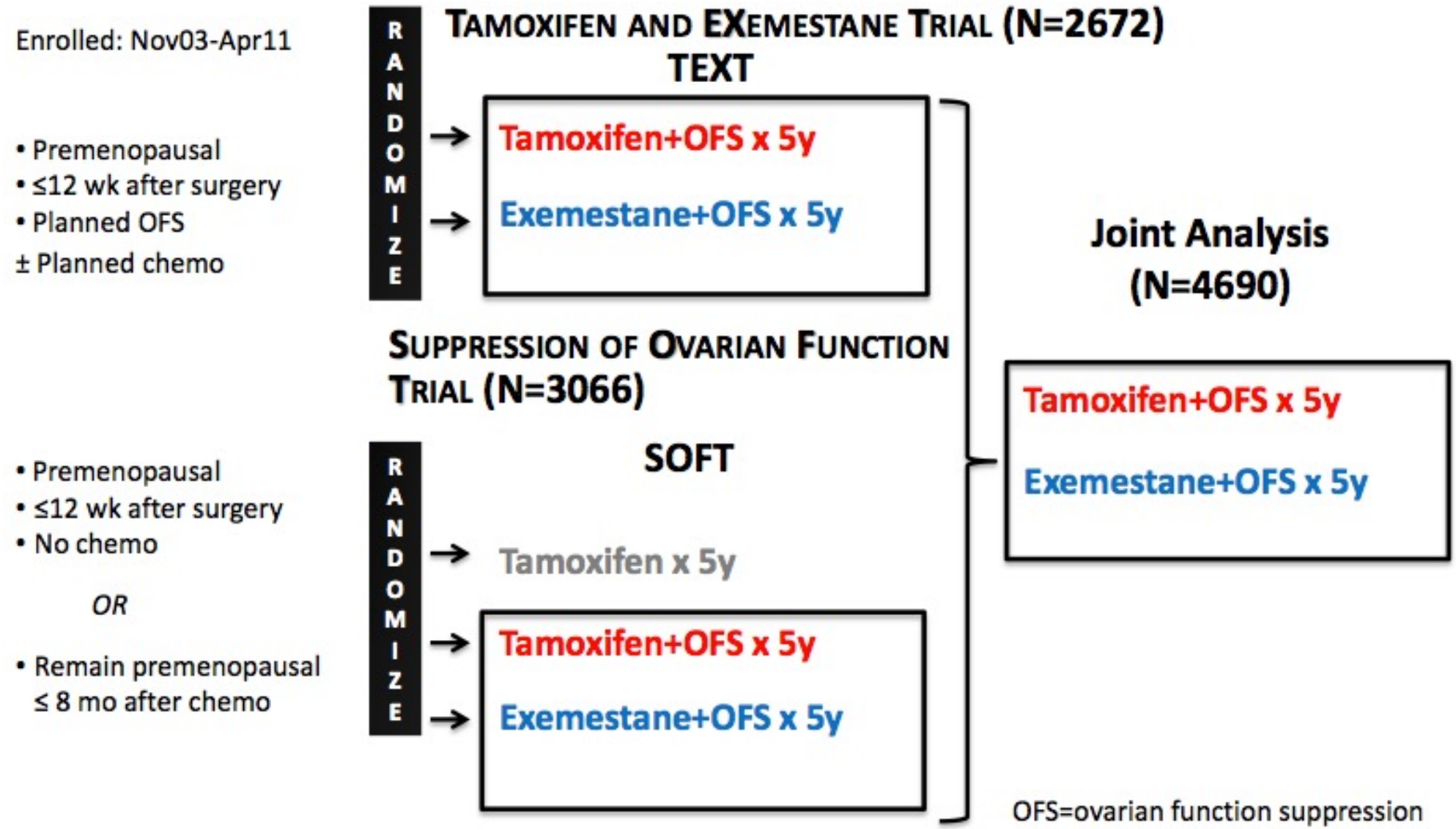
EBCTCG, Lancet 378 (9793) 2011

Ovarian Fuction Supression

- Ovarian function suppression alone improves outcomes in early stage premenopausal breast cancer patients[1]
- Premenopausal women who develop amenorrhea after chemotherapy for estrogen receptor–positive tumors have a lower risk of recurrence[2]
- An analysis according to age subgroups in TAILORx (age <40, 40-45 and 45-50 years) supports the argument that some chemotherapy benefits relate in part to ovarian suppression; benefits of chemotherapy were least noticeable in women least likely to experience chemotherapy-induced menopause (aged <40 years) and more pronounced among those more likely to experience treatment-related amenorrhea (aged >40 years)[3]

1. EBCTCG Lancet 1996 2. Pagani et al. Eur J Cancer 1998 3. Sparano et al. NEJM 2019

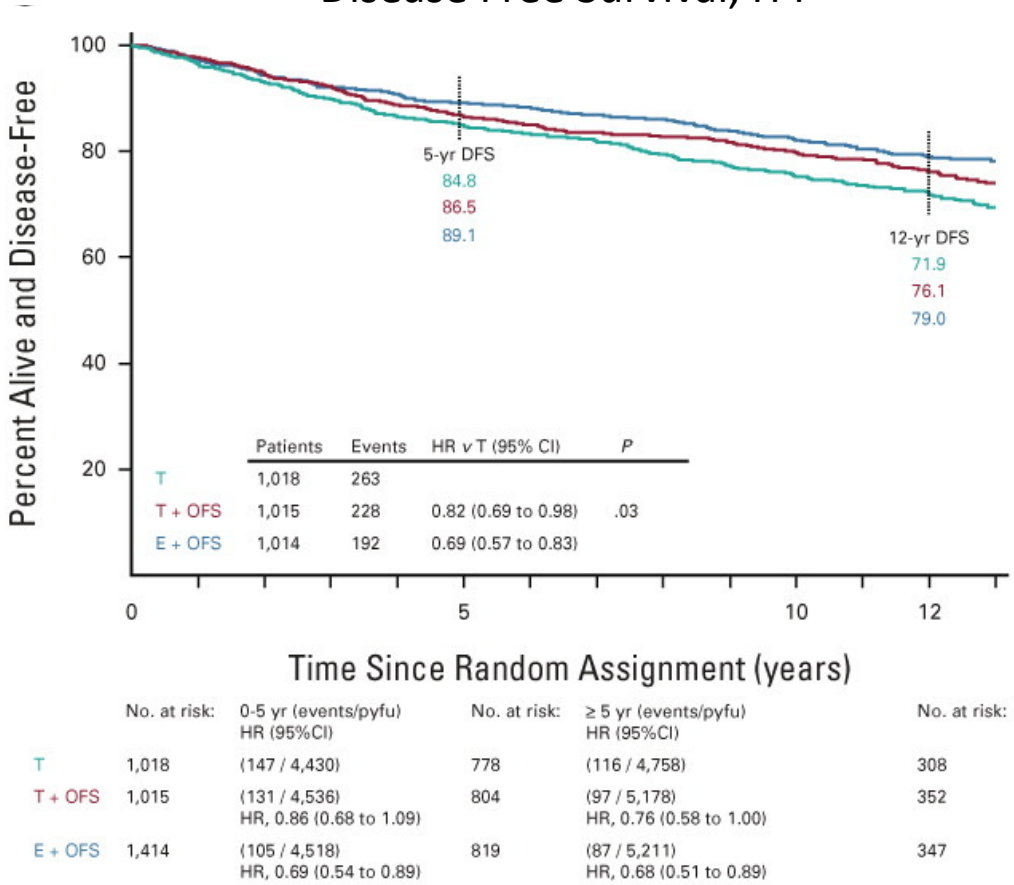
TEXT and SOFT Joint Analysis



Pagani O, et al. ASCO 2014. Abstract LBA1.

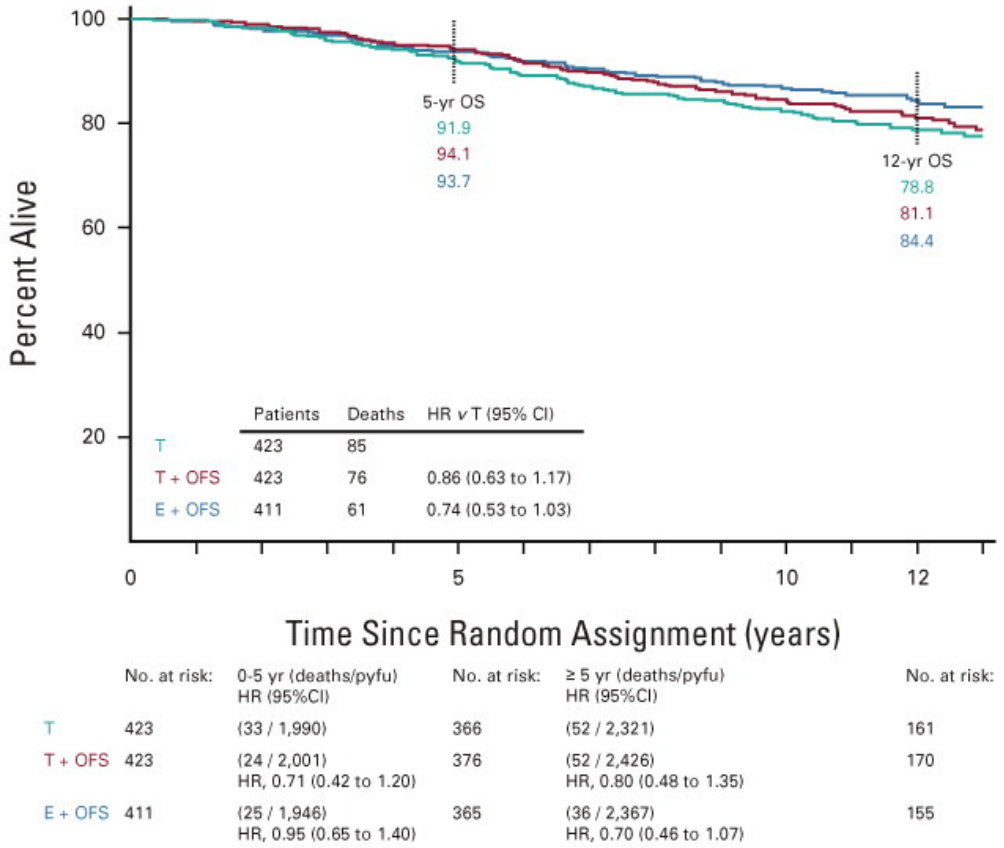
Outcomes after median F/U 12 years, SOFT Trial

Disease Free Survival, ITT



	No. at risk:	0-5 yr (events/pyfu) HR (95%CI)	No. at risk:	≥ 5 yr (events/pyfu) HR (95%CI)	No. at risk:
T	1,018	(147 / 4,430)	778	(116 / 4,758)	308
T + OFS	1,015	(131 / 4,536) HR, 0.86 (0.68 to 1.09)	804	(97 / 5,178) HR, 0.76 (0.58 to 1.00)	352
E + OFS	1,414	(105 / 4,518) HR, 0.69 (0.54 to 0.89)	819	(87 / 5,211) HR, 0.68 (0.51 to 0.89)	347

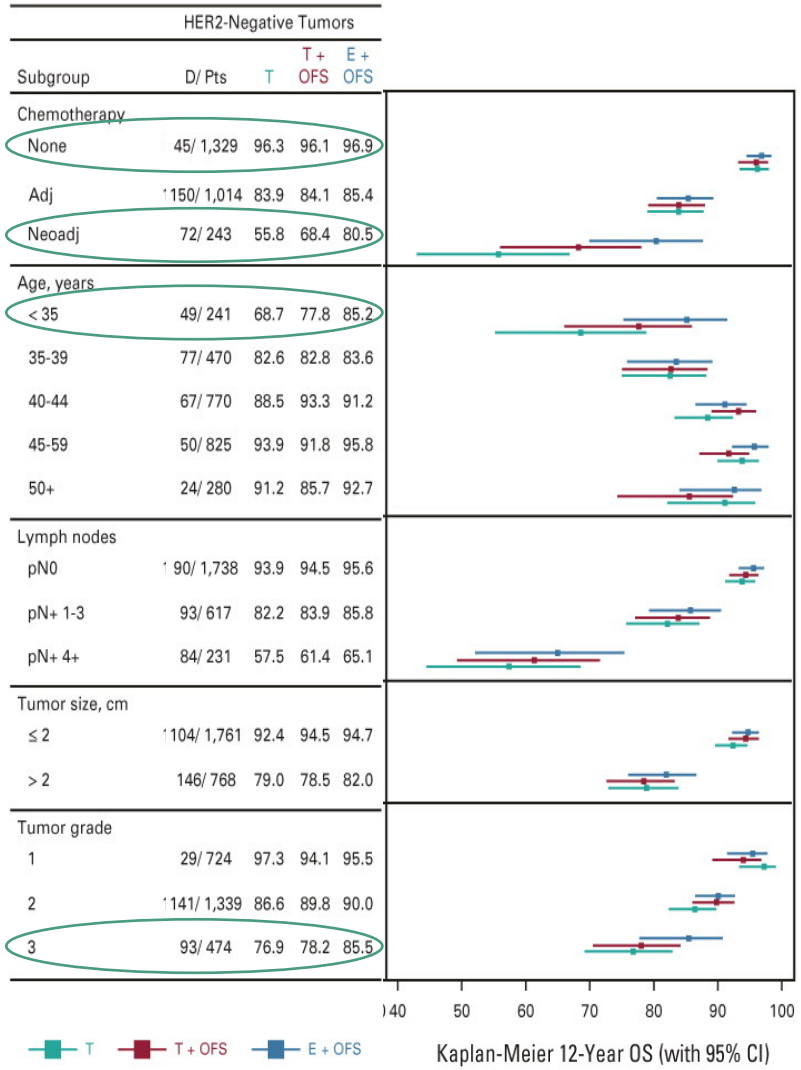
Overall Survival in Her 2 neg who received chemo



	No. at risk:	0-5 yr (deaths/pyfu) HR (95%CI)	No. at risk:	≥ 5 yr (deaths/pyfu) HR (95%CI)	No. at risk:
T	423	(33 / 1,990)	366	(52 / 2,321)	161
T + OFS	423	(24 / 2,001) HR, 0.71 (0.42 to 1.20)	376	(52 / 2,426) HR, 0.80 (0.48 to 1.35)	170
E + OFS	411	(25 / 1,946) HR, 0.95 (0.65 to 1.40)	365	(36 / 2,367) HR, 0.70 (0.46 to 1.07)	155

Francis PA et al JCO Dec 2022

12-year OS (95% CIs) in subgroups in SOFT Trial

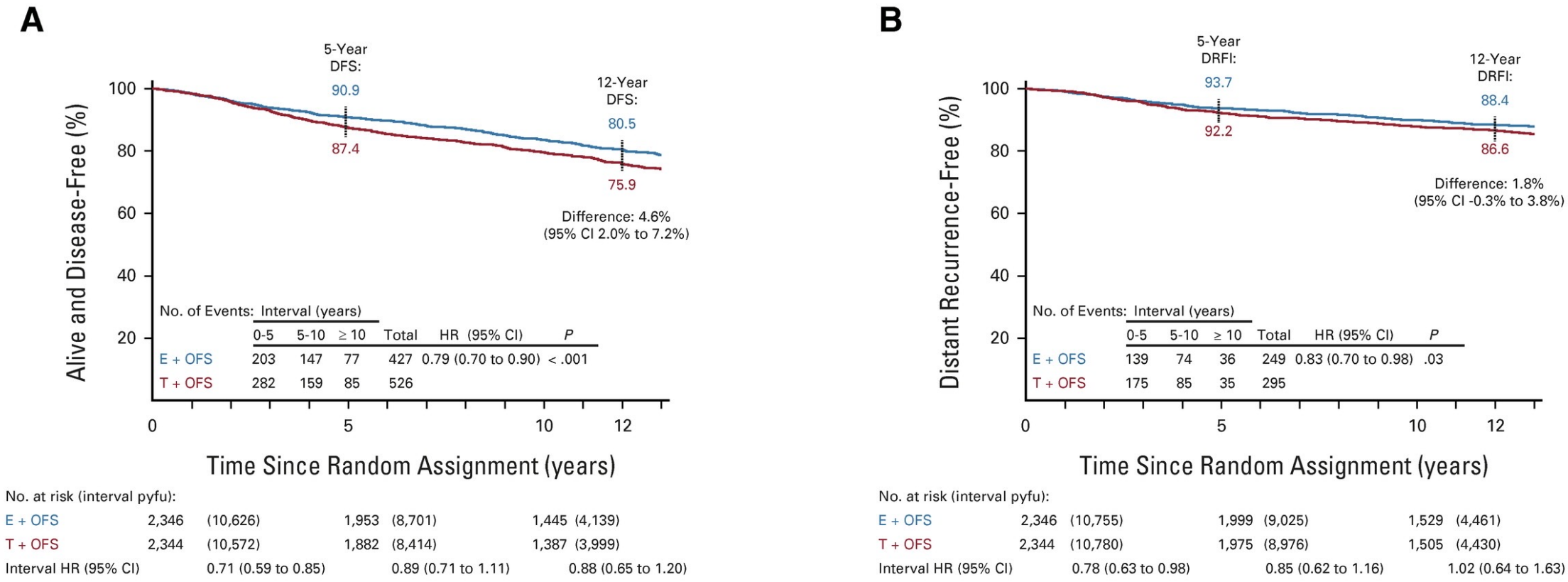


In the no-chemotherapy cohort, 12-year OS exceeded 95% in all three treatment groups

Meaningful absolute improvements in 12-year OS in subgroups associated with higher-risk clinical-pathologic features, including prior neoadjuvant chemotherapy, age <35 years, and grade 3 tumors

Francis PA et al JCO Dec 2022

Outcomes after median F/U 13 years, SOFT/TEXT trials



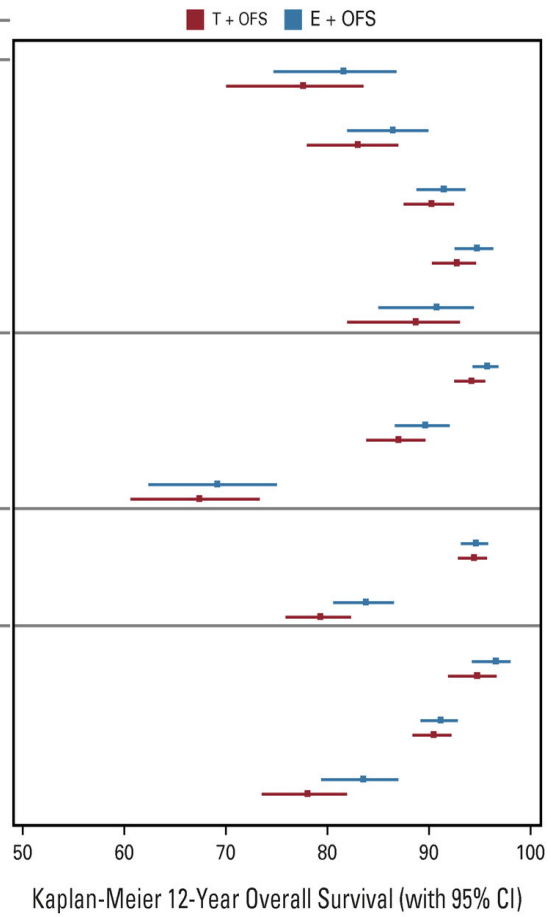
No overall survival (90.1% *v* 89.1%, HR, 0.93; 95% CI, 0.78 to 1.11) in ITT

Pagani et al JCO Dec 2022

OS in HR +/HER2-neg Breast Cancer Subgroups, SOFT/TEXT

Subgroup		No. of Deaths/ No. of Patients	12-Year Overall Survival (%) T + OFS	E + OFS	Difference
Age at random assignment (years)	< 35	67/350	77.6	81.6	4.0 (-5.0 to 12.9)
	35 – 39	98/653	83.0	86.5	3.5 (-2.5 to 9.4)
	40 – 44	114/1,303	90.3	91.5	1.2 (-2.2 to 4.6)
	45 – 49	87/1,352	92.8	94.8	2.0 (-0.8 to 4.8)
	50 +	32/377	88.7	90.8	2.1 (-5.0 to 9.1)
Positive LNs	pN0	117/2,365	94.2	95.8	1.5 (-0.4 to 3.5)
	pN+ 1-3	136/1,193	87.0	89.7	2.6 (-1.3 to 6.6)
	pN+ 4+	145/477	67.4	69.2	1.8 (-7.2 to 10.7)
Tumor size	≤ 2 cm	140/2,567	94.5	94.6	0.2 (-1.8 to 2.1)
	> 2 cm	245/1,409	79.3	83.8	4.5 (0.1 to 8.9)
Tumor grade	1	40/903	94.8	96.6	1.8 (-1.1 to 4.8)
	2	203/2,259	90.5	91.2	0.7 (-1.9 to 3.3)
	3	151/828	78.1	83.6	5.5 (-0.1 to 11.1)

Omitted are 59 unknown T sizes and 45 unknown T grades



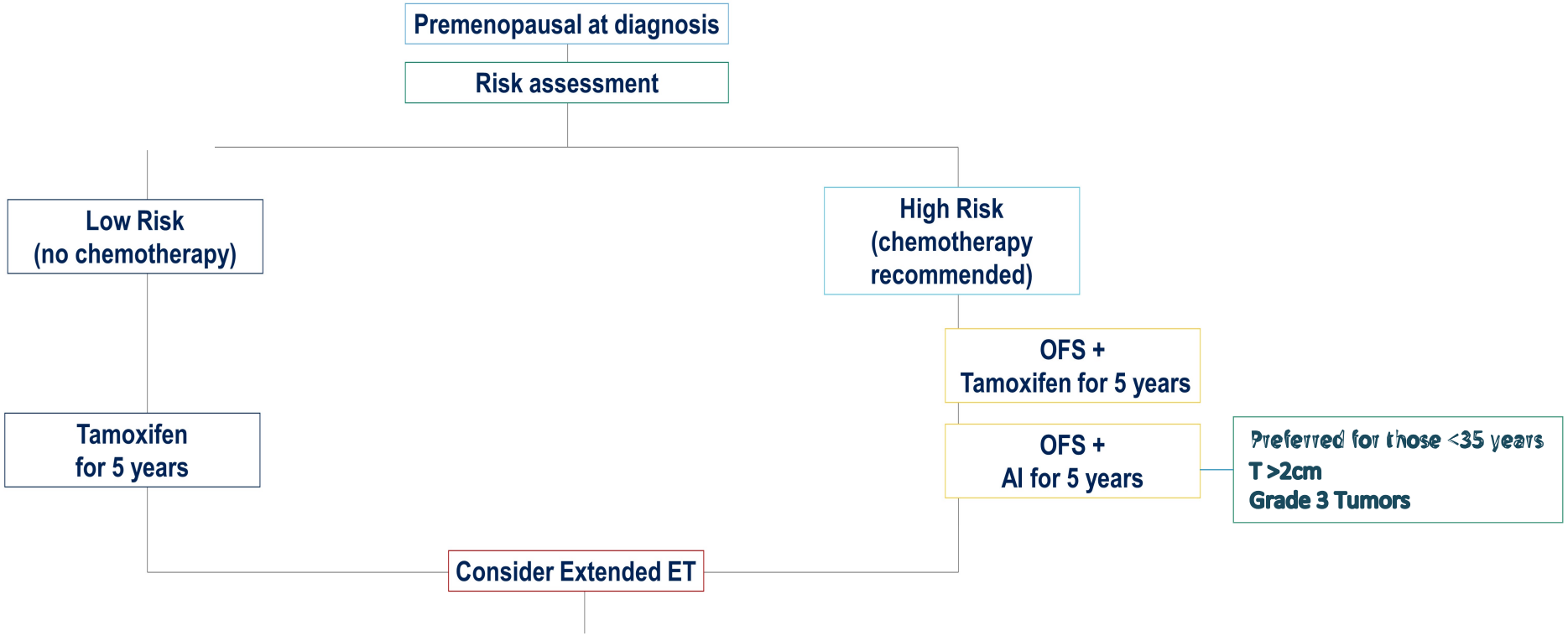
OS benefit was clinically significant in high-risk patients

- women age < 35 years (4.0%)
- T> 2 cm (4.5%)
- Grade 3 tumors (5.5%)

These sustained reductions of the risk of recurrence with adjuvant E+ OFS, compared with T+ OFS, provide guidance for selecting patients for whom exemestane should be preferred over tamoxifen in the setting of OFS

Pagani et al JCO Dec 2022

Adjuvant ET Approach for Premenopausal HR+ BC Patients



Vaz-Luis I, Francis PA,
Di Meglio A, Stearns V;
ASCO 2021 Educational Book

*No evidence that continuing ovarian function suppression alone beyond 5 years provides additional benefit

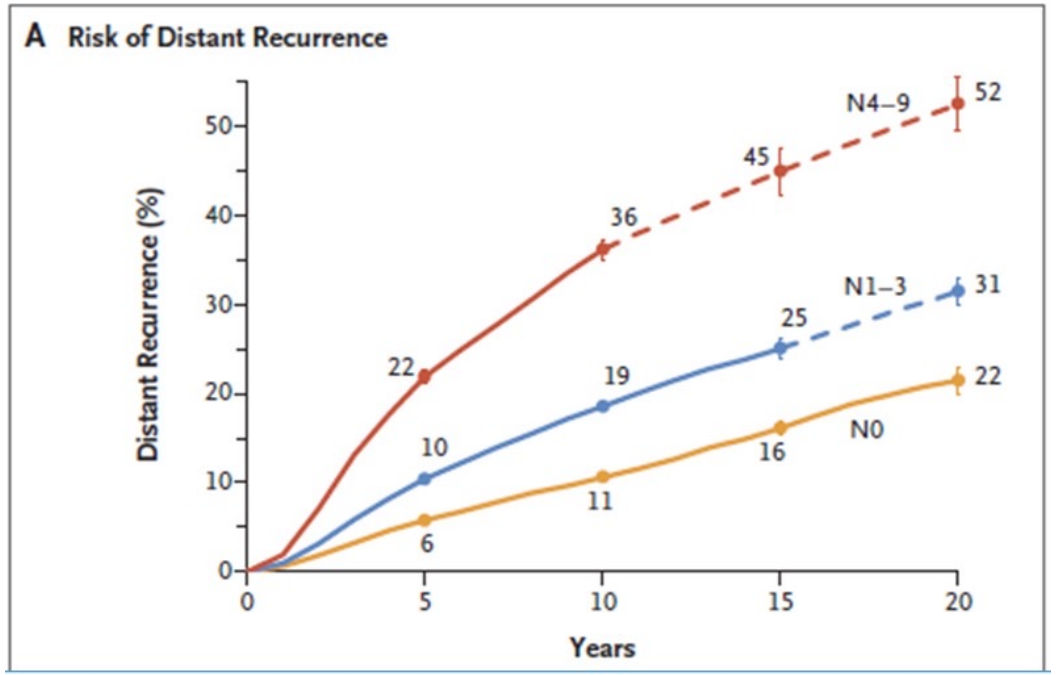
What is the optimal duration of adjuvant endocrine therapy?

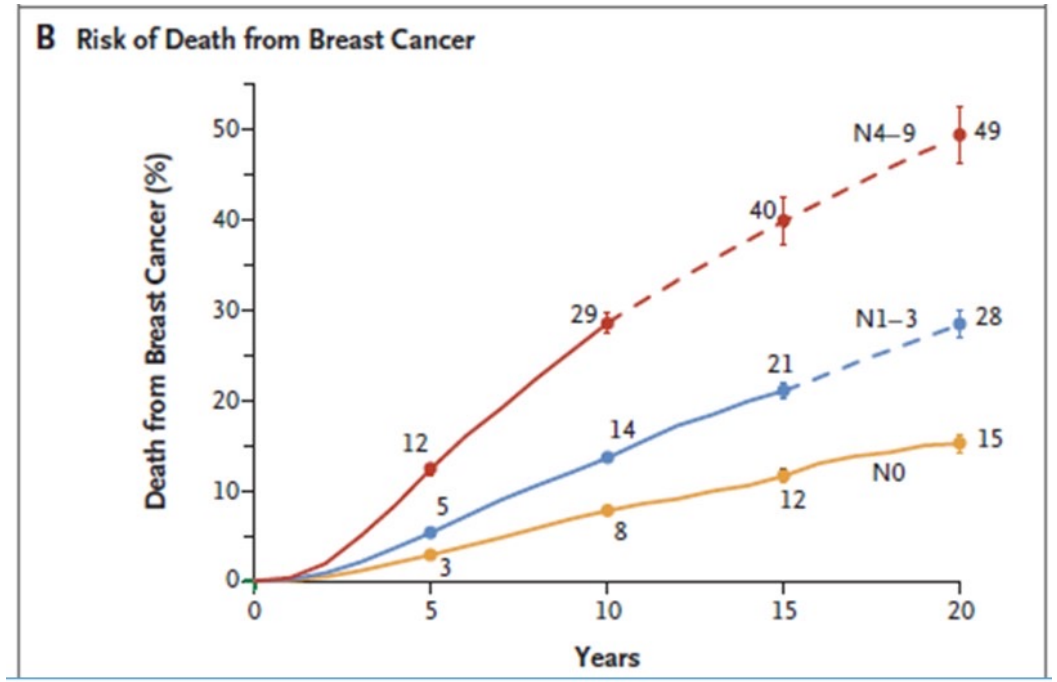
Extending Endocrine Therapy

The Rational:

- ✓ Several studies have shown that after discontinuation of endocrine therapy at 5 years, there is a steady increased risk for distant recurrence at least for the subsequent 20 years

Risk Of Distant Recurrence And Death 10 - 20 Years After Dx And Discontinuation Of ET At 5 Years: EBCTCG Meta-analysis

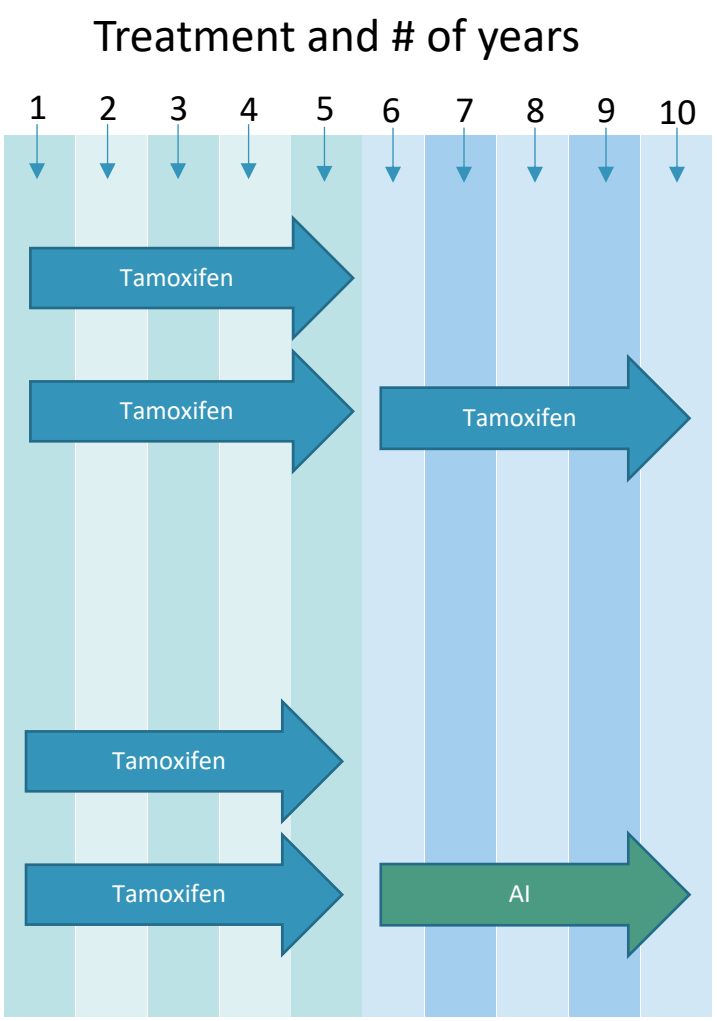




Pan el al. NEJM 2017

Prolonging adjuvant endocrine therapy beyond 5 years will improve the long term outcome of for HR+ breast cancer patients?

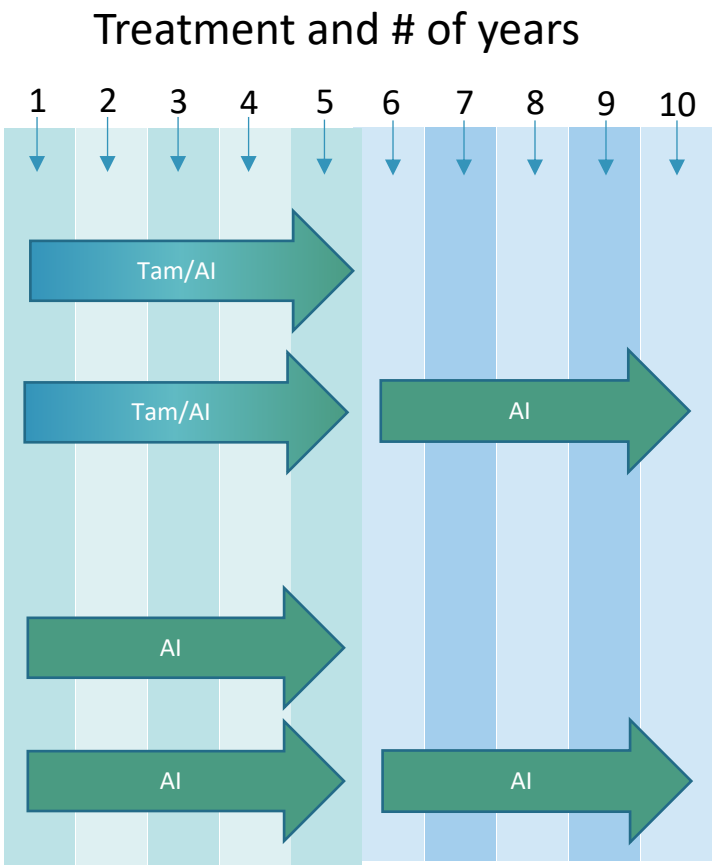
Extended Endocrine Therapy



Study	Number of subjects	Median F/U (months)	iDFS (95% CI)	OS (95% CI)	Comments
ATLAS	6953	108	>10 years RR 0.75 (0.66-0.86)	>10 year RR 0.86 (0.75-0.97)	Proportional risk reduction was similar across subgroups
aTTom	6846	120	>10 year RR 0.75 (0.62-0.90) Absolute reduction 3.7%	BCSS 0.71 (0.58-0.88) Absolute reduction 2.6%	
MA-17	5187	80	0.58 (0.45-0.76) Absolute reduction 4.6%	0.82 (0.57-1.19) No difference	OS improved for N+

Gray et al. JCO 2013, Davies et al. Lancet 2013, Goss et al. JNCI 2005

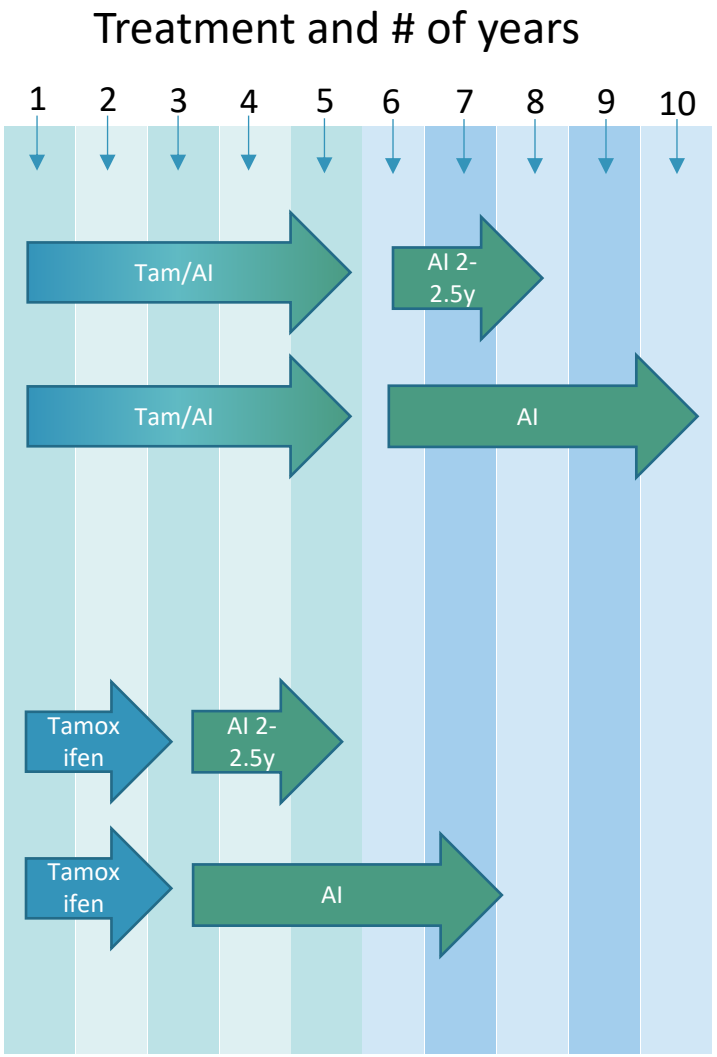
Extended Endocrine Therapy



Study	Number of subjects	Median F/U (months)	iDFS (95% CI)	OS (95% CI)	Comments
NSABP B 42	3923	83	0.84 (0.74-0.96) Absolute reduction 3.8%	0.97 (0.82-1.16) No difference	Contralateral BC reduction 1.5%
MA-17R	1918	76	0.66 (0.48-0.91) Absolute reduction 4%	0.97 (0.73-1.28) No difference	Contralateral BC reduction 1.8%

Mamounas et al, Lancet 2019, Goss et al. NEJM 2016

Extended Endocrine Therapy



Study	Number of subjects	Median F/U (months)	iDFS (95% CI)	OS (95% CI)	Comments
IDEAL	1824	79	0.92 (0.74-1.16) No difference	1.04 (0.78-1.38) No difference	Contralateral BC 0.39 (0.12-0.81)
ABCSG 16	3484	118	0.99 (0.85-1.15) No difference	1.02 (0.83-1.25) No difference	
DATA	1860	49	0.79 (0.62-1.02) No difference	0.91 (0.65-1.29) No difference	Contralateral BC 0.59 (0.23—1.07) Benefit in DFS for N+ pts
GIM-4	2056	140	0.78 (0.65-0.93) Absolute reduction 5%	0.77 (0.60-0.98) Absolute reduction 4%	Benefit seen in all sub groups, but higher in N+

Gray et al. JCO 2013, Davies et al. Lancet 2013, Goss et al. JNCI 2005

Who benefits from Extended Adjuvant ET?

Prior Treatment		Tumor/Patient Characteristic	Extended Adjuvant therapy
Tamoxifen 5 y		**T1a/b N0** **T1c grade 1** Premenopausal and post menopausal patients	No significant benefit
Tamoxifen 2-3 y	AI 2-3 years		
AI 5 y			
Tamoxifen 5 y		**Any N** Premenopausal who remains premenopausal after T x 5 y	AI x 5 years
		Any N Premenopausal who remains premenopausal after T x 5 y Postmenopausal patient who do not tolerate AIs	Tamoxifen 5 years
Tamoxifen 2-3 y	AI 2-3 years	**N0-N1** Postmenopausal patients Premenopausal patients who have become postmenopausal after tamoxifen	AI 2-3 years
AI 5 y		**N2-N3** Postmenopausal patients Premenopausal patients who have become postmenopausal after tamoxifen	AI 5 years

Pistilli B. ASCO 2022

ASCO Guidelines Recommendations Extended ET

- Many women with N0 BC are potential candidates for and may be offered extended AI therapy for up to a total of 10 years of adjuvant ET based on considerations of recurrence risk using established prognostic factors. Women with **low-risk N0** tumors should **not** routinely be offered extended therapy.

- Women with **N+** BC should be offered **extended AI** therapy for up to a total of 10 years of adjuvant endocrine treatment.

- As prevention of secondary or contralateral breast cancers is a major benefit of extended AI therapy, the risk of second breast cancers (or not) based on prior therapy should inform the decision to pursue extended treatment.

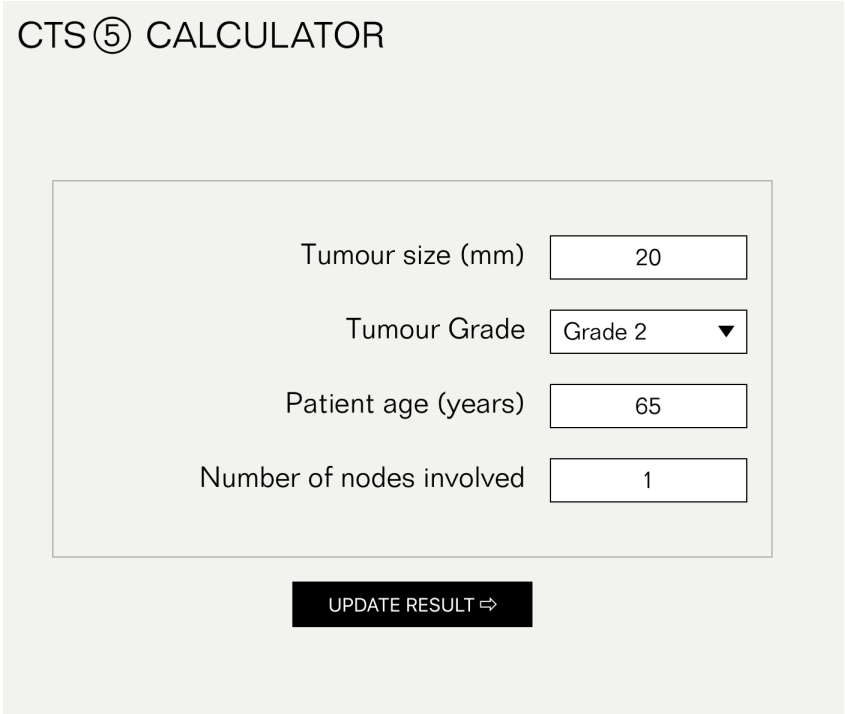
- Extended therapy carries ongoing risks and side effects, which should be weighed against the potential absolute benefits of longer treatment in a shared decision-making process between the clinical team and the patient.

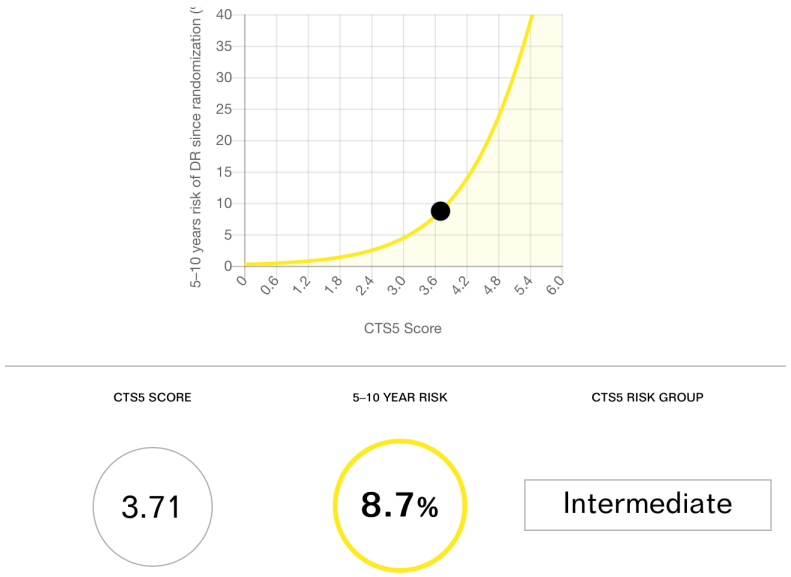
Burstein H, JCO 2019

How can I personalize treatment decisions?

CTS⑤ Calculator

- Online prognostic tool to evaluate late distant recurrence (DR) risk for breast cancer after 5-year adjuvant endocrine therapy
- Easy to use and only requires information that is readily available to clinicians
- not quite as discriminatory in the premenopausal
- Calibration of the CTS5 was good in patients who did not receive extended endocrine therapy.





If a patient is postmenopausal and had IBC and is recurrence-free after 5 y of adjuvant ET, the CTS5 may be used to calculate the estimated risk of late recurrence (between years 5-10), which could assist in decisions about extended ET. (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate

Richman J et al. Breast Cancer Res Treat 2021, Andre et al JCO 2022

Breast Cancer Index Genomic Assay

BCI was developed through the algorithmic combination of 2 biomarkers, *HOXB13:IL17BR* ratio (H/I) and the Molecular Grade Index (MGI

STUDY	N	BCI (H/I) AND OUTCOME
MA-17	249 Postmenopausal or premenopausal who became postmenopausal	High H/I ratio benefit from letrozole (DR OR = 0.33; 95% CI, 0.15 to 0.73; p=0.006); **abs risk reduction 16.5%**
Trans-aTTom	583 Postmenopausal and premenopausal	High H/I ratio benefit from tamoxifen (RFI HR = 0.35; 95%CI, 0.15-0.86; p=0.027); **abs risk reduction 10.2%**
IDEAL	908 73% N+	High H/I ratio benefit from letrozole (RFI HR 0.42; 95% CI 0.21-0.84; p = 0.011); **abs risk reduction 10.8%**
NSABP-B42	2179 40% N+	High H/I ratio benefit from letrozole (DR HR 0.29; 95% CI 0.12-0.69; p = 0.003); **abs risk reduction 3.8%**

ASCO

If a patient has N0 or N+ BC with 1-3 positive nodes and has been treated with 5 years of primary ET without recurrence, the clinician may use BCI test to guide decisions about extended ET (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

NCCN GUIDELINES

- T1-T2 HR-pos, HER2-neg, a BCI (H/I) low, regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0, M0 and have lower risk distant recurrence and no benefit in DFS or OS compared to the control arm in terms of extending ET duration
- Patients with T1-T2 N0 BCI (H/I) high demonstrated significant rates of late distant recurrence and have significant improvement in DFS with extended ET

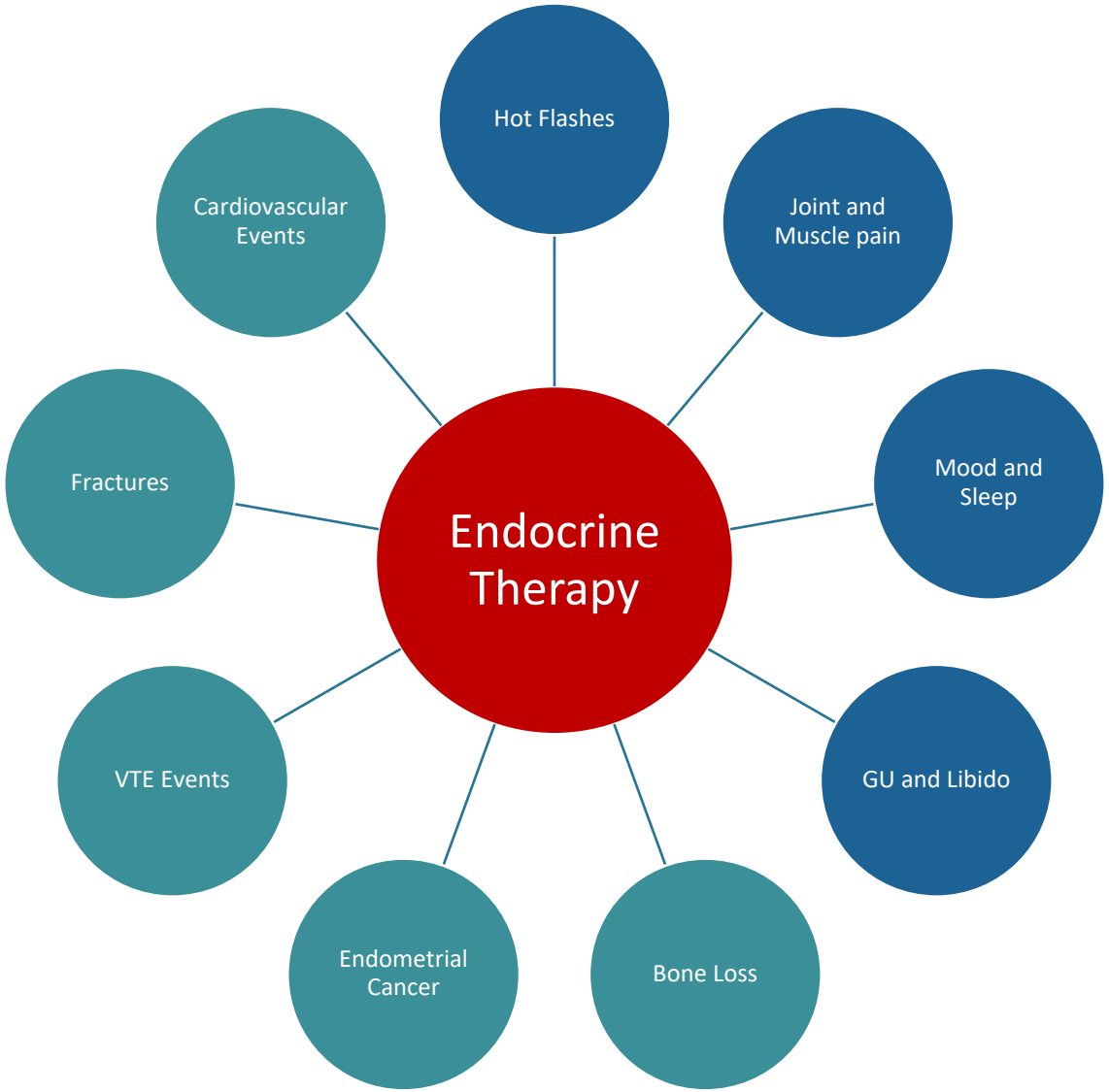
Sgroi D et al, JNCI 2013, Pistilli B. ASCO 2022, Andre et al JCO 2022, NCCN guidelines version 2.2023

How to balance risk vs benefits of adjuvant and extended adjuvant therapy?

Adverse Events of Endocrine Therapy

Serious AE's:

Extended adjuvant ET also increases the risk of this rare but serious adverse events



Non Serious AE's:

- Frequent and have an impact in QOL
- Might increase risk of non adherence

Risk of Serious Adverse Events with Extended ET

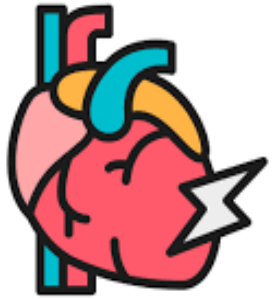
Extended Tamoxifen

- Risk of endometrial cancer: 1.5% for 5 years vs 3.2 % for 10 years

Extended AIs

- Bone Fractures: OR 1.34 (1.16-1.55) abs diff 1.4%

- Cardiovascular events: OR 1.18 (1.00-1.40) abs diff 0.8%



Davies et al. Lancet 2012, Godvaser et al J Nat Can Inst 2018

Prevalence of AE and SAE with Endocrine Therapy

Side effect	Prevalence	Class of ET
Musculoskeletal symptoms	>50%	Tamoxifen and AI (+)
Vasomotor symptoms	≈40%	Tamoxifen and AI
Sexual dysfunction	26-45%	Tamoxifen and AI (+)
Vulvovaginal symptoms	8-26%	Tamoxifen and AI (+)
Fatigue	30%	Tamoxifen and AI
Insomnia	20-70%	Tamoxifen and AI
Cognitive impairment	35%	Tamoxifen and AI
Venous thromboembolic events	<2%	Tamoxifen (+)
Endometrial cancer	<1%	Tamoxifen (+)
Fracture	5-10%	AI

Vaz-Luis, ASCO Educational Book 2021

Barriers to Compliance

- Most common reason is toxicity
- Might be due to a combination of factors: extremes of age, race, increased number of comorbidities, prescriptions written by nonmedical oncologists, being single, number of total prescriptions, history of nonadherence to other chronic medications, insurance status, and higher out-of-pocket costs
- Most common reason is toxicity
- What is most important for patients: cancer recurrence or QOL? What about patient's expectations?

Dawn L. Hershman JCO 2016 34:21, 2440-2442

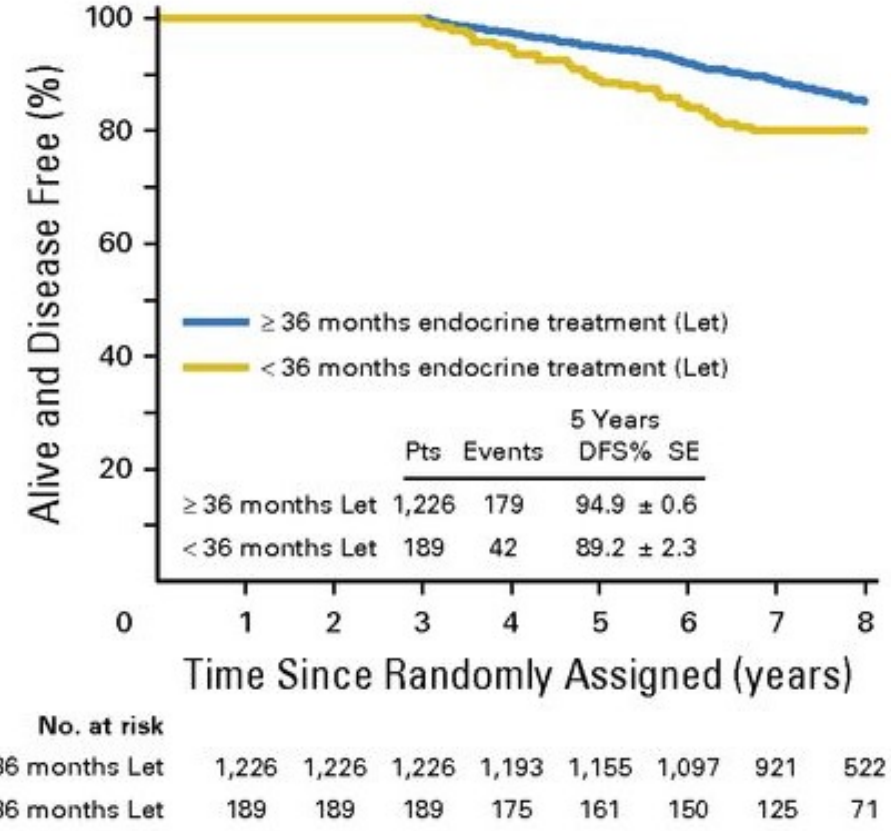
Is it best to expect the worst? Influence of patients' side-effect expectations on endocrine treatment outcome in a 2-year prospective clinical cohort study

- 111 enrolled patients, assessed before, at at 3 and 24 after starting adjuvant ET
- After 2 years of ET, patients reported high rates of side-effects (arthralgia: 71.3%, weight gain: 53.4%, hot flashes: 46.5%), including symptoms not directly attributable to the medication (breathing problems: 28.1%, dizziness: 25.6%).
- Pre-treatment expectations significantly predicted patient-reported long-term side-effects and QOL in multivariate models controlling for relevant medical and psychological variables.
- Baseline expectations were associated with adherence at 24 months ($r = -0.25$, $P = 0.006$).
- Negative expectations increase the risk of treatment-specific side-effects, nocebo side-effects, and non-adherence

Optimizing individual expectations might be a promising strategy to improve side-effect burden, quality of life, and adherence during longer-term drug intake.

Nestoric et al. Ann Oncol. 2016 Oct;27(10):1909-15

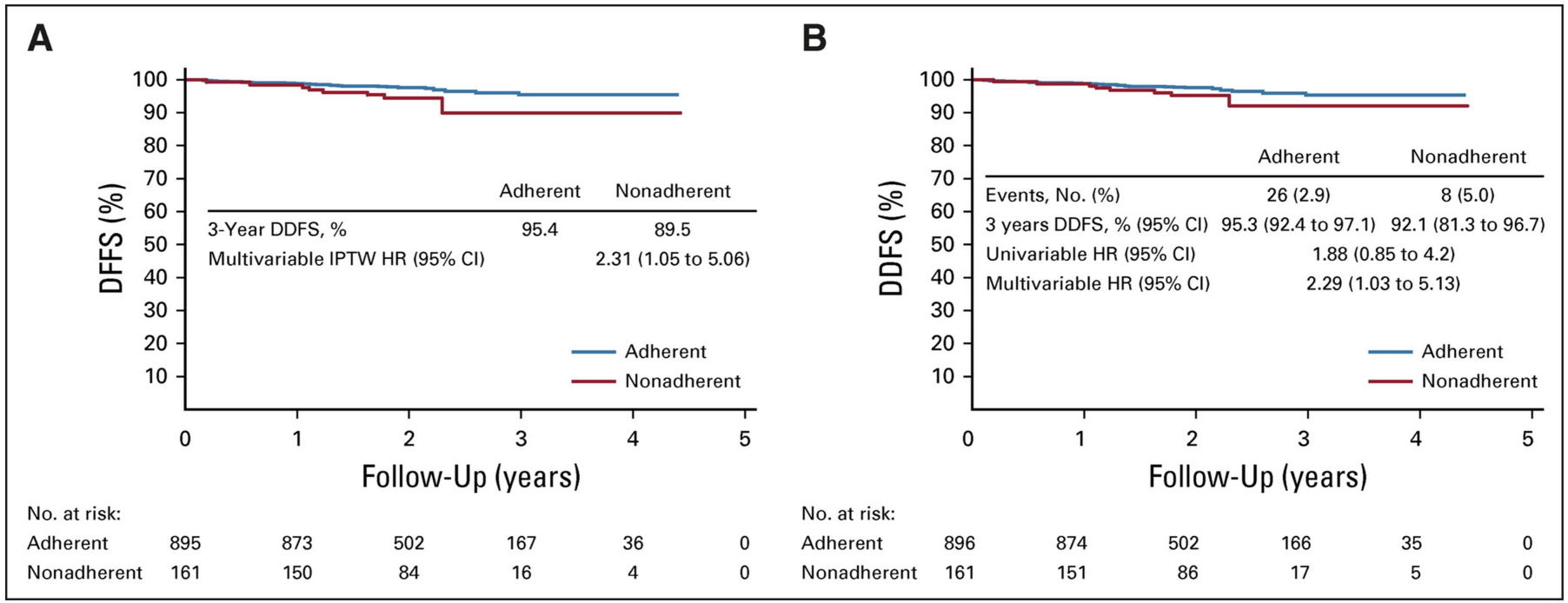
Poorer Adherence to Endocrine Treatment Associated With Poorer Outcome in Postmenopausal Hormone Receptor–Positive Breast Cancer



Both aspects of low adherence (early cessation of letrozole and a compliance score of < 90%) were associated with reduced DFS (HR, 1.45 (95% CI, 1.09 to 1.93) *P* = .01; and 1.61 (95% CI, 1.08 to 2.38)*P* = .02 respectively).

Chirgwin J, et al JCO 34, 2016

Adherence to ET and Survival Outcomes



N=1,177 patients,
CANTO cohort(NCT01993498)

DDFS=Distant disease-free survival
IPTW=inverse probability treatment weighting
HR= hazard ratio

A. IPTW cohort
B. non-IPTW cohort.
Time 0= post-tamoxifen prescription visit and date of serum assessment

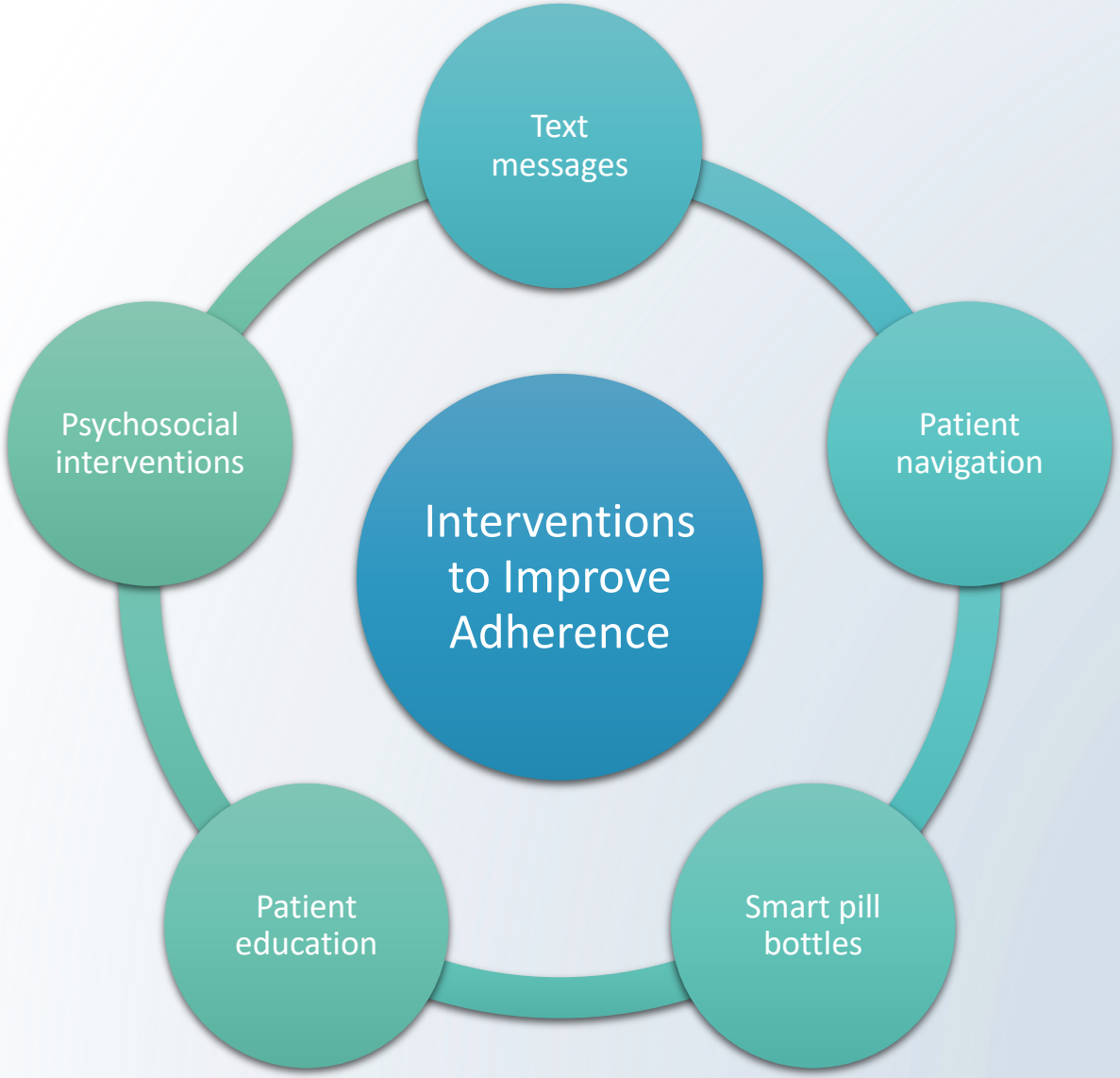
Worst distant DFS among non-adherent patients by serum tamoxifen assessment

Pistilli JCO, 2020.

Pharmacologic and Nonpharmacologic Strategies Manage Side Effects of Endocrine Therapy

	Management Strategy	
Side Effect	**Pharmacologic**	**Nonpharmacologic**
Musculoskeletal symptoms	Switching strategy duloxetine	Physical activity
		Acupuncture
Vasomotor symptoms (hot flashes)	Antidepressants	Cognitive behavioral therapy
	SSRIs (citalopram, escitalopram, sertraline)	Hypnosis
	SNRIs (venlafaxine)	
	Anticonvulsants (gabapentin and pregabalin)	
	Oxybutynin	
Sexual dysfunction (other than vulvovaginal symptoms)	Switch from AI + OFS to tamoxifen ± OFS	Cognitive behavioral therapy
	Switch from tamoxifen + OFS to tamoxifen alone	
	If patient is on antidepressants that can affect sexual function (e.g., SSRI and SNRI), switch to antidepressants that may be less likely to cause sexual side effects (e.g., mirtazapine)	
Vulvovaginal symptoms (vaginal dryness/ dyspareunia)	Moisturizers	Laser therapy**
	Lubricants	
	Lidocaine	
	Switch from AI + OFS to tamoxifen + OFS or tamoxifen alone	
	Vaginal low-dose estrogen (estradiol)*	
Fatigue	—	Physical activity
		Cognitive behavioral therapy
Weight gain	—	Physical activity
		Diet
		Cognitive behavioral therapy

Interventions Under Investigation to Improve ET Adherence

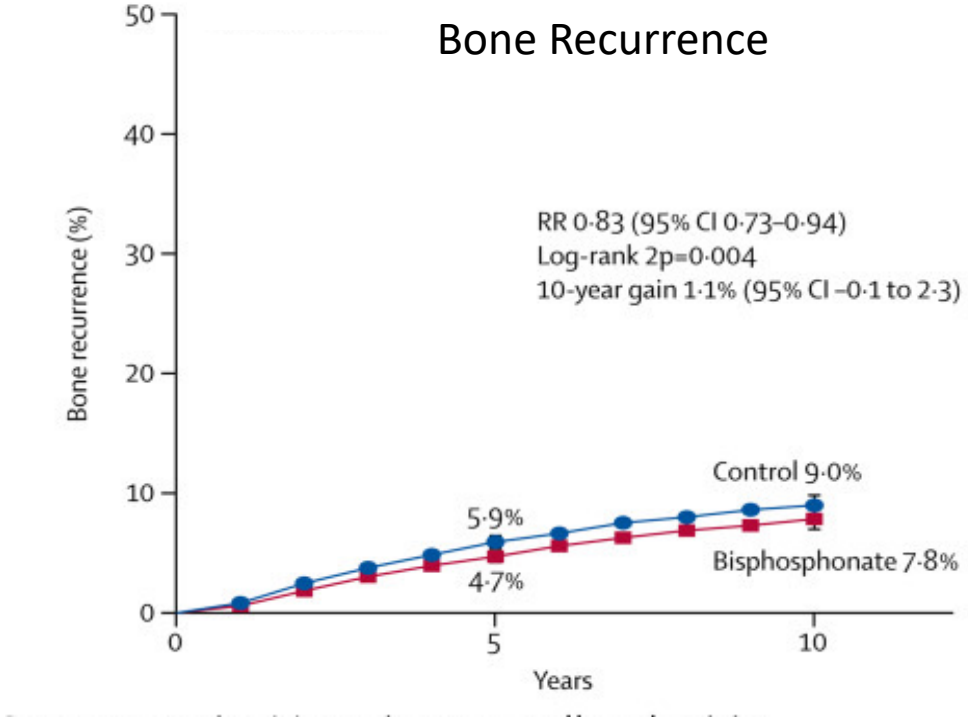


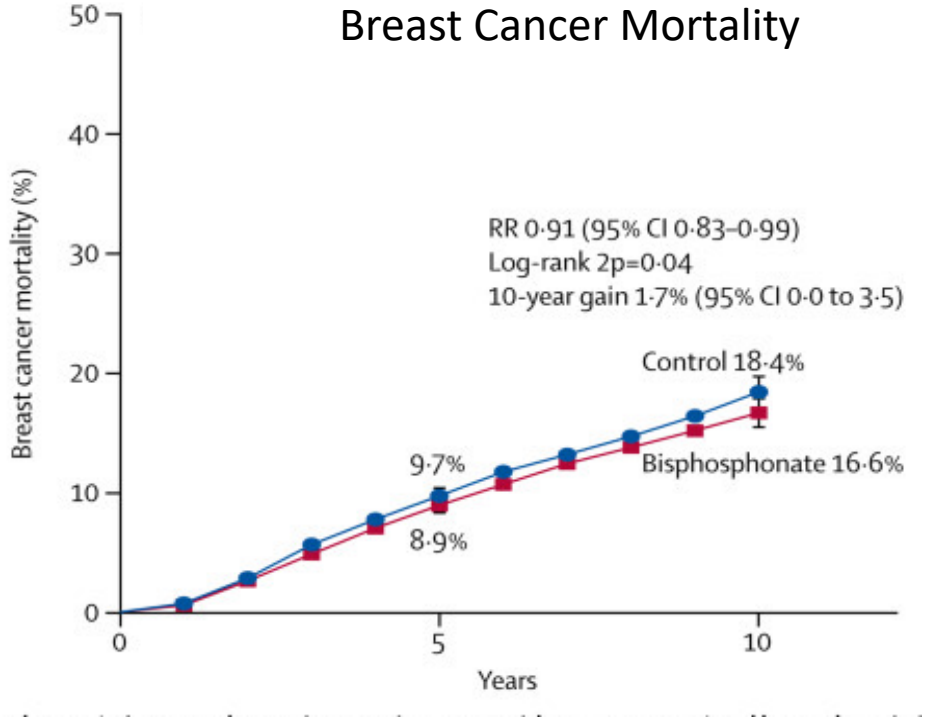
What else can I do for my high risk patients?

Adding Other Agents To Improve Outcomes

- ✓Biphosphonates
- ✓CDK4/6 inhibitors
- ✓PARP inhibitors for BRCA mutant patients

Adjuvant bisphosphonate treatment in early breast cancer: EBCTCG meta-analysis





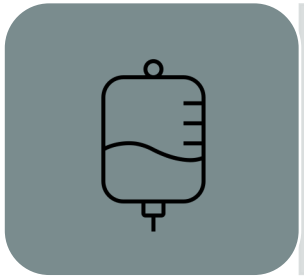
Adjuvant bisphosphonates reduce the rate of breast cancer recurrence in the bone and improve breast cancer survival, but there is definite benefit only in women who were postmenopausal when treatment began

EBCTCG Lancet 2015

Adjuvant Biphosphonates: ASCO Recommendations

- Discuss with all postmenopausal patients (natural or therapy-induced) with primary breast cancer, irrespective of hormone receptor status and human epidermal growth factor receptor 2 status, who are candidates to receive adjuvant systemic therapy.

- Recommended therapies include oral ibandronate (50 mg daily for 3 years)



- Zoledronic acid; dosing regimens as per the protocols of the clinical
- 4 mg once every 6 months for 3 years or
- 4 mg once every 3 months for 2 years

- The Panel does not recommend the use of adjuvant denosumab

Eisen et al. JCO 2022

Trials on Adjuvant CDK 4/6 inhibitors

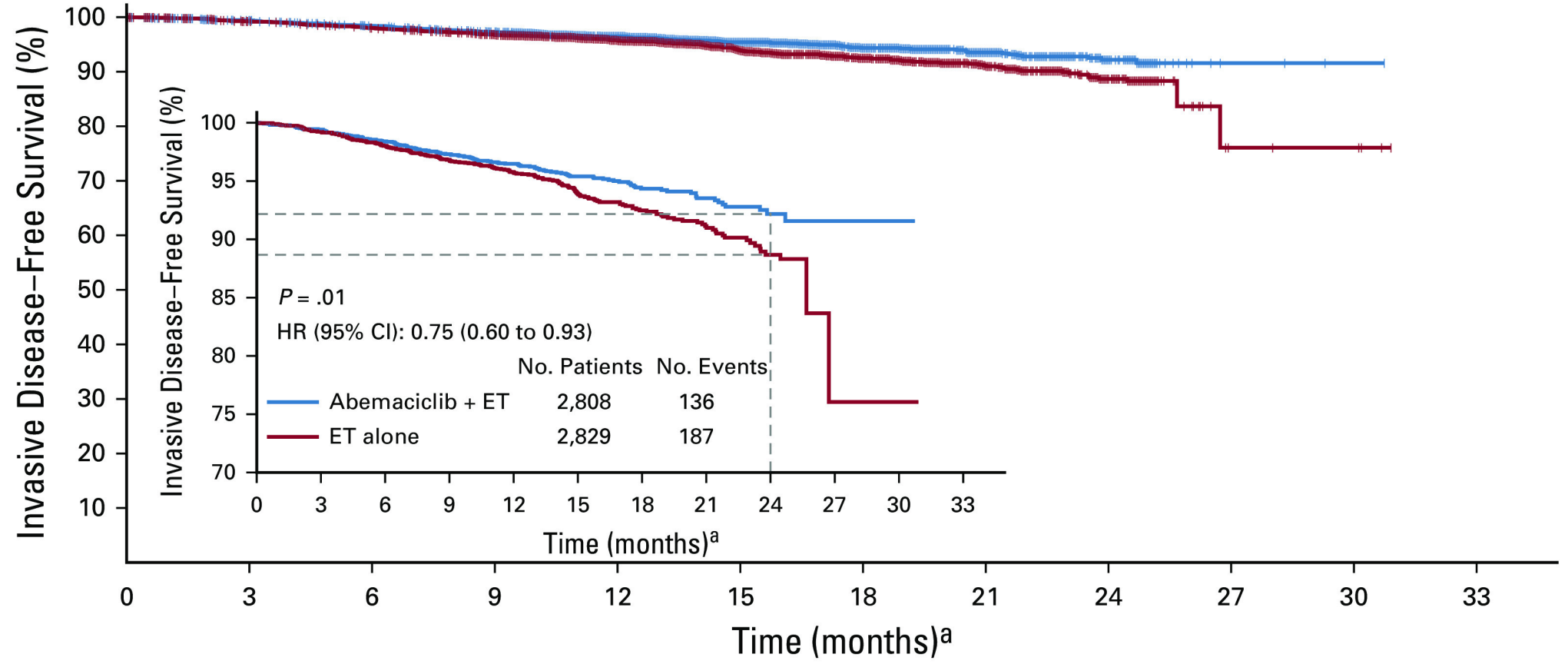
Trial	Design	Duration of CDKi	Status
PALLAS (palbociclib)	No placebo Standard ET	2 years	Reported, no benefit in iDFS or DRFS
Monarch-E (abemaciclib)	No placebo Standard ET	2 years	Reported, iDFS impovement (0.75 HR)*
NATALEE (ribociclib)	No placebo AI (no Tam) OS if premenopausal	3 years	Enrollement completed, awating results
PENELOPE-B (palbociclib)	Placebo controlled Standard ET	1 year	Reported/no benefit in iDFS at 42 mo median f/u

***High-risk breast cancer**

- ≥4 positive lymph nodes (confirmed preoperatively and/or at surgery)
- 1–3 positive lymph nodes with one or more of the following:
  - grade 3 disease,
  - tumor size ≥5 cm (on pre-operative imaging and/or at surgery)
  - Ki-67 score of ≥20%

Mayer Lancet 2021, Johnston JCO 2020, Loibl JCO 2021

Adjuvant Abemaciclib + ET in High-Risk, Node-Positive, HR+/HER2- EBC: MonarchE Primary endpoint, iDFS



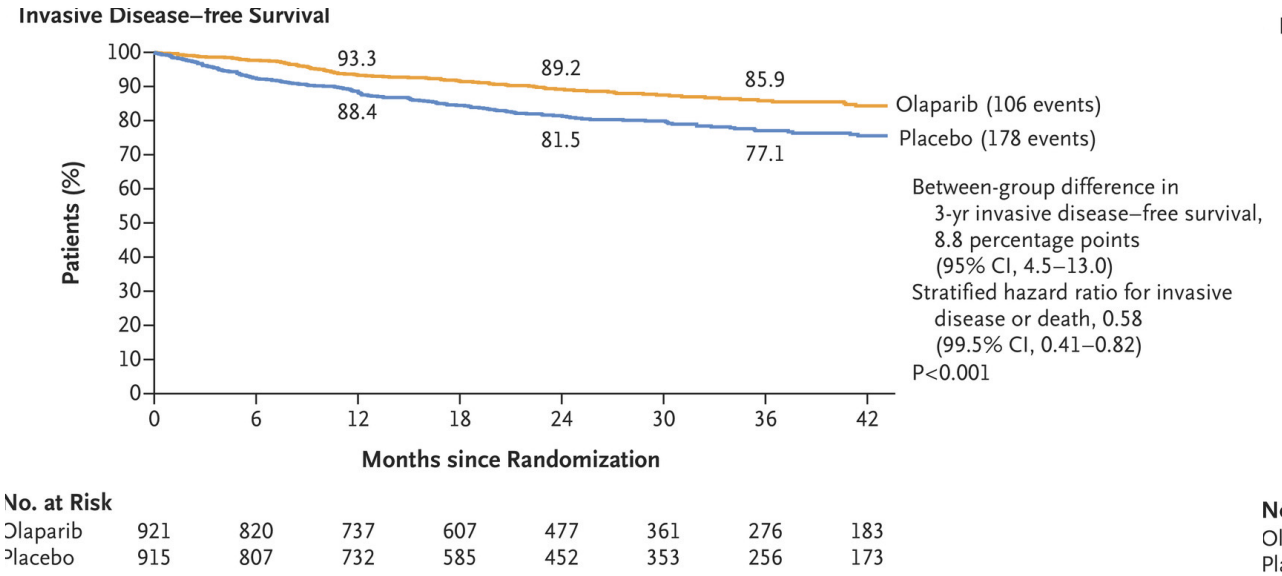
No. at risk:

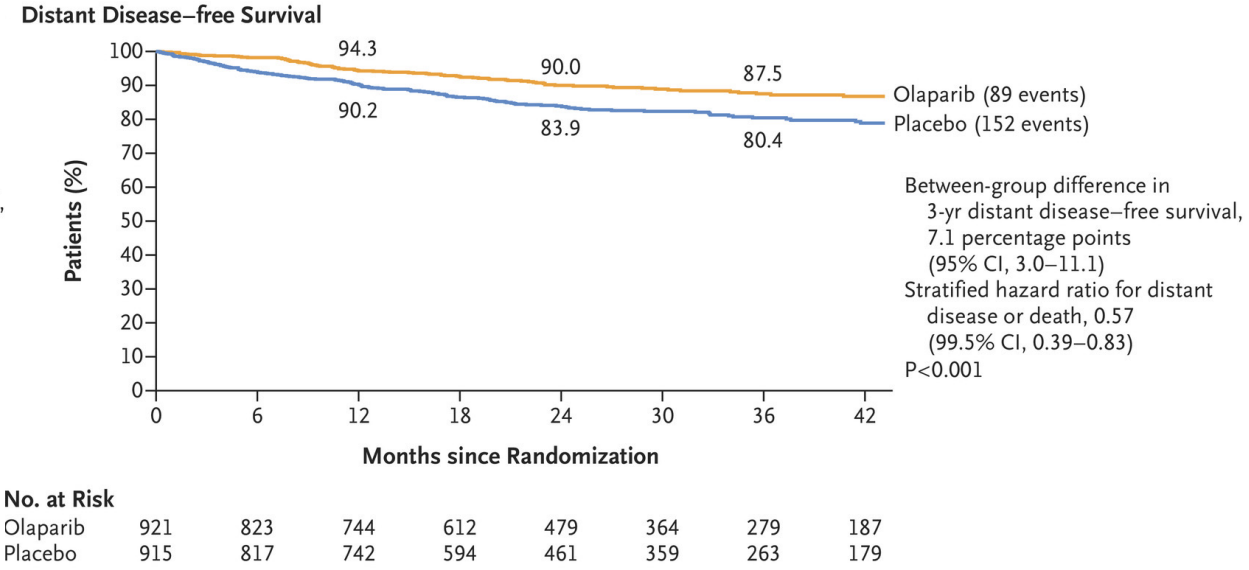
Abemaciclib + ET	2,808	2,676	2,613	2,543	1,996	1,371	918	566	245	3	1	0
ET alone	2,829	2,699	2,649	2,562	2,013	1,405	932	586	262	7	6	0

Johnston. JCO. 2020;38:3987.

Adjuvant Olaparib for Patients with g*BRCA1*- or g*BRCA2*-Mutated Breast Cancer: OlympiA

Included patients with HER 2 neg early breast cancer with *BRCA1* or *BRCA2* germline pathogenic or likely pathogenic variants and high-risk clinicopathological factors who had received local treatment and neoadjuvant or adjuvant chemotherapy. Patients received 1 year of oral olaparib or placebo





Tutt AN et al. NEJM 2021

Conclusion

- There is no “one-size-fits-all” approach regarding adjuvant endocrine therapy
- Decisions must be individualized based on patient’s menopausal status, and risk of recurrence
- Clinicopathological factors, as well as risk calculators, and genomic tools might help in guiding the recommendations
- Balancing risk vs benefits when choosing the type and duration of endocrine therapy is important to ensure compliance and outcomes
- Role of CDK 4/6 inhibitors and other target agents in the adjuvant setting is evolving, longer follow up is warranted