Dana-Farber
Cancer Institute

2021 Master Class Course
Breast Cancer: Genetics, and Management of ER+ Tumors

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Faculty Disclosure

- None

Faculty of this CE activity may include discussions of products or devices that are not currently labeled for use by the FDA. The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off label or investigational uses (any uses not approved by the FDA) of products or devices.

Question 1.

A 64 year old woman has been with ER positive, HER2 negative breast. Her family history is notable for an older brother diagnosed with prostate cancer at age 71, and a maternal aunt who had pancreatic cancer at age 73.

Genetic testing suggests a deleterious ATM mutation

Which of the following would you advise?

A. ATM mutation likely accounts for her family history
B. Because of ATM mutation she needs bilateral mastectomy
C. Because of ATM mutation she needs unilateral mastectomy and not radiation
D. If her daughter has an ATM mutation she has a lifetime risk of breast cancer of less than 25%

Question 2.

A 46 yo premenopausal woman has been diagnosed with ER positive, HER2 negative breast cancer. Surgery disclosed a 1.3 cm tumor, grade 2, with metastatic cancer in 1 of 3 sentinel lymph nodes. The OncotypeDX recurrence score is 13.

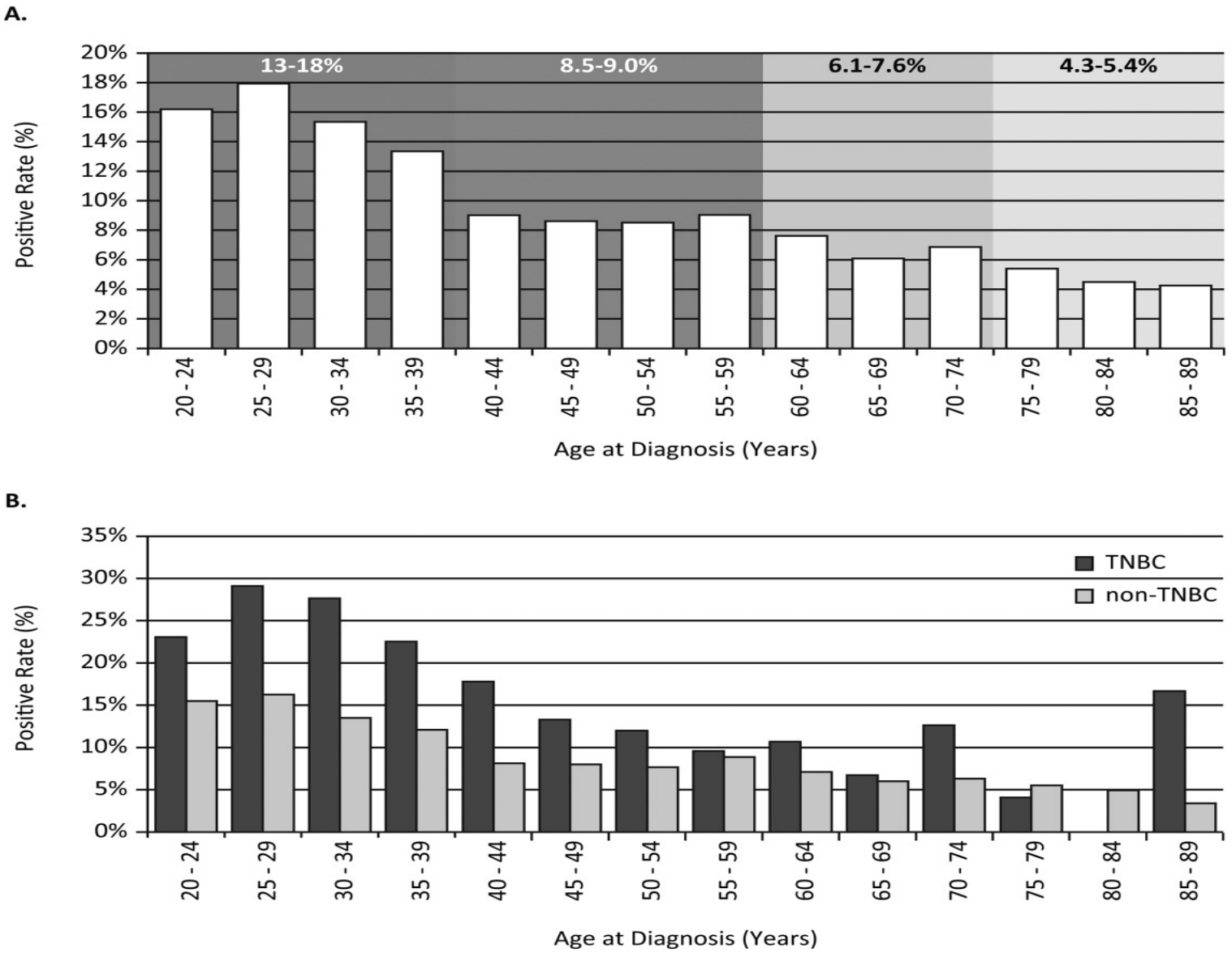
Which of the following would you advise?

A. No studies show benefit to chemotherapy
B. Ovarian suppression and an AI are ‘all’ that she needs as adjuvant treatment
C. Studies show benefit to chemotherapy but only if score is 16 to 25 range in premenopausal women with node-positive breast cancer
D. She should receive adjuvant abemaciclib.

Outline

- Genetic testing and treatment of hereditary cancers
- ER+ breast cancer: metastatic disease management
- ER+ breast cancer: adjuvant/neoadjuvant therapy

A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes

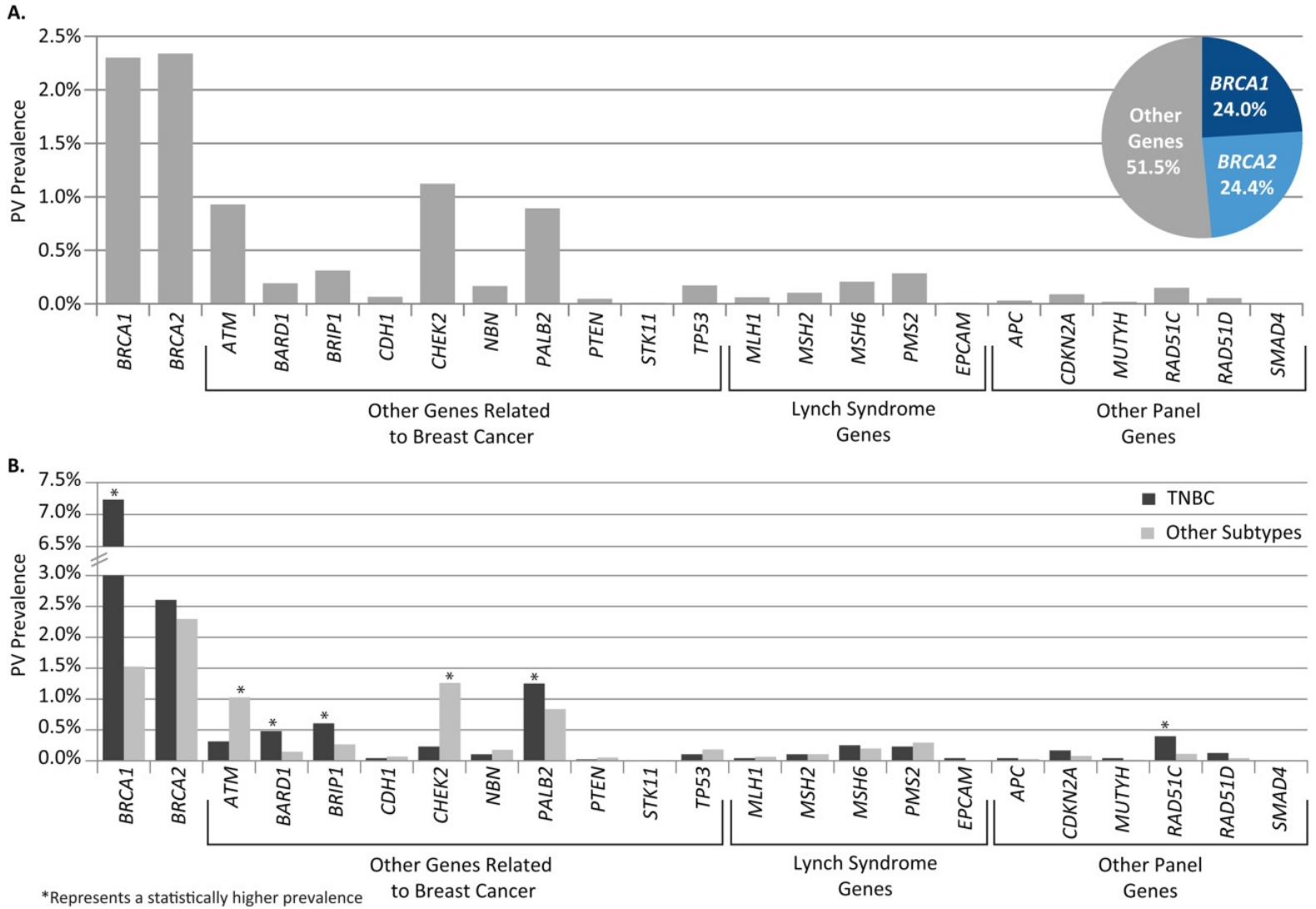


Percent of Breast Cancers Associated With Hereditary Cancer Genes

Age	Percentage
< 40	15%
40 to 60	8-10%
60 to 75	7%
> 75	4%

Buys, et al. Cancer, Volume: 123, Issue: 10, Pages: 1721-1730, First published: 13 January 2017, DOI: (10.1002/cncr.30498)

A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes



Buys, et al. Cancer, Volume: 123, Issue: 10, Pages: 1721-1730, First published: 13 January 2017, DOI: (10.1002/cncr.30498)

NCCN Guidelines Version 2.2017
Breast and/or Ovarian Cancer Genetic Assessment

CRITERIA FOR FURTHER GENETIC RISK EVALUATION[a]

- An individual with an ovarian[e] cancer
- An individual with a breast cancer diagnosis meeting any of the following:
  - A known mutation in a cancer susceptibility gene within the family
  - Early-age-onset breast cancer[b]
  - Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 y
  - Two breast cancer primaries[c] in a single individual
  - Breast cancer at any age, and
    - ◊ ≥1 close blood relative[d] with breast cancer ≤50 y, or
    - ◊ ≥1 close blood relative[d] with invasive ovarian[e] cancer at any age, or
    - ◊ ≥2 close blood relatives[d] with breast cancer and/or pancreatic cancer at any age, or
    - ◊ Pancreatic cancer at any age, or
    - ◊ From a population at increased risk[f]
  - Male breast cancer
- An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age
- An individual with a personal and/or family history of three or more of the following (especially if early onset[b] and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer[i], colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations[g,h] and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract[h]
- An individual with no personal history of cancer but with
  - A close relative with any of the following:[d,f]
    - ◊ A known mutation in a cancer susceptibility gene within the family
    - ◊ ≥2 breast cancer primaries in a single individual
    - ◊ ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 y
    - ◊ Ovarian[e] cancer
    - ◊ Male breast cancer
  - First- or second-degree relative with breast cancer ≤45 y
  - Family history of three or more of the following (especially if early onset[b] and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer[i], colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations[g,h] and/or macrocephaly, hamartomatous polyps of GI tract[h]

Problem

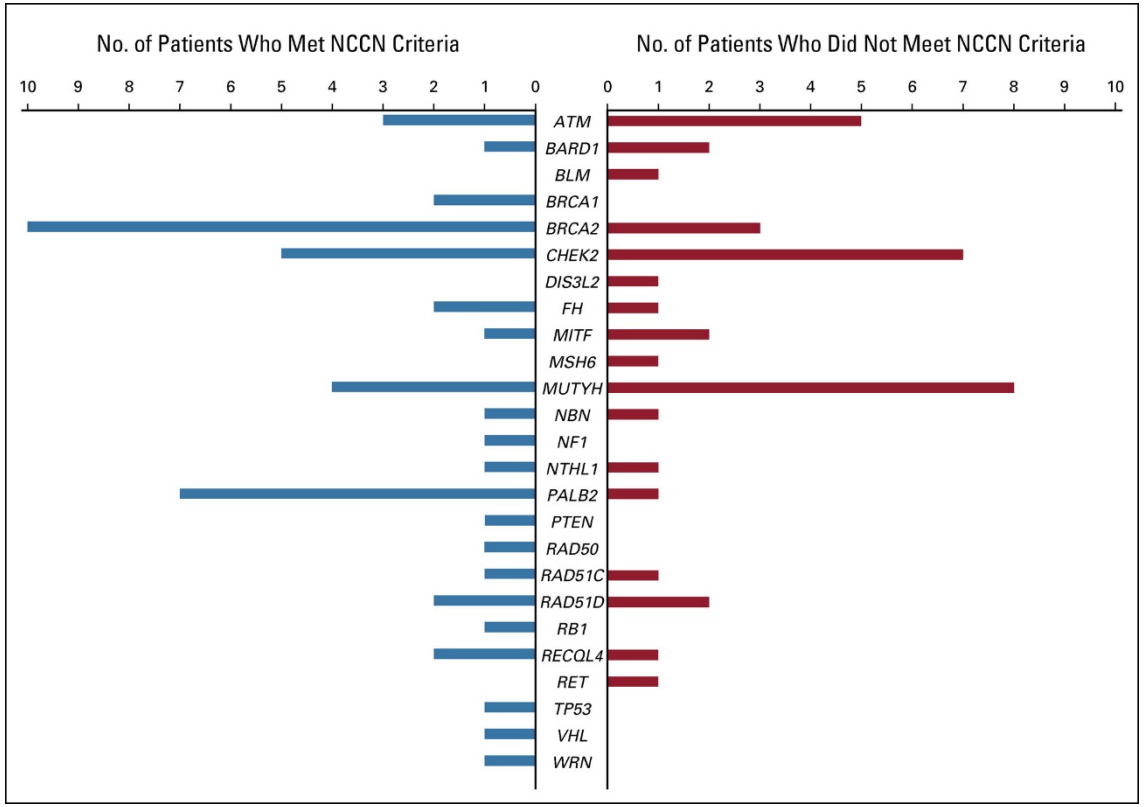
Guideline recommendations are heavily skewed to BRCA1/BRCA2 associated risks and cancers

e.g. TNBC; FH of ovarian cancer, prostate cancer, pancreatic cancer

Studies suggest that guideline recommendations miss about half of hereditary cancers that arise from less common genes with lower penetrance and less predictable clinical patterns

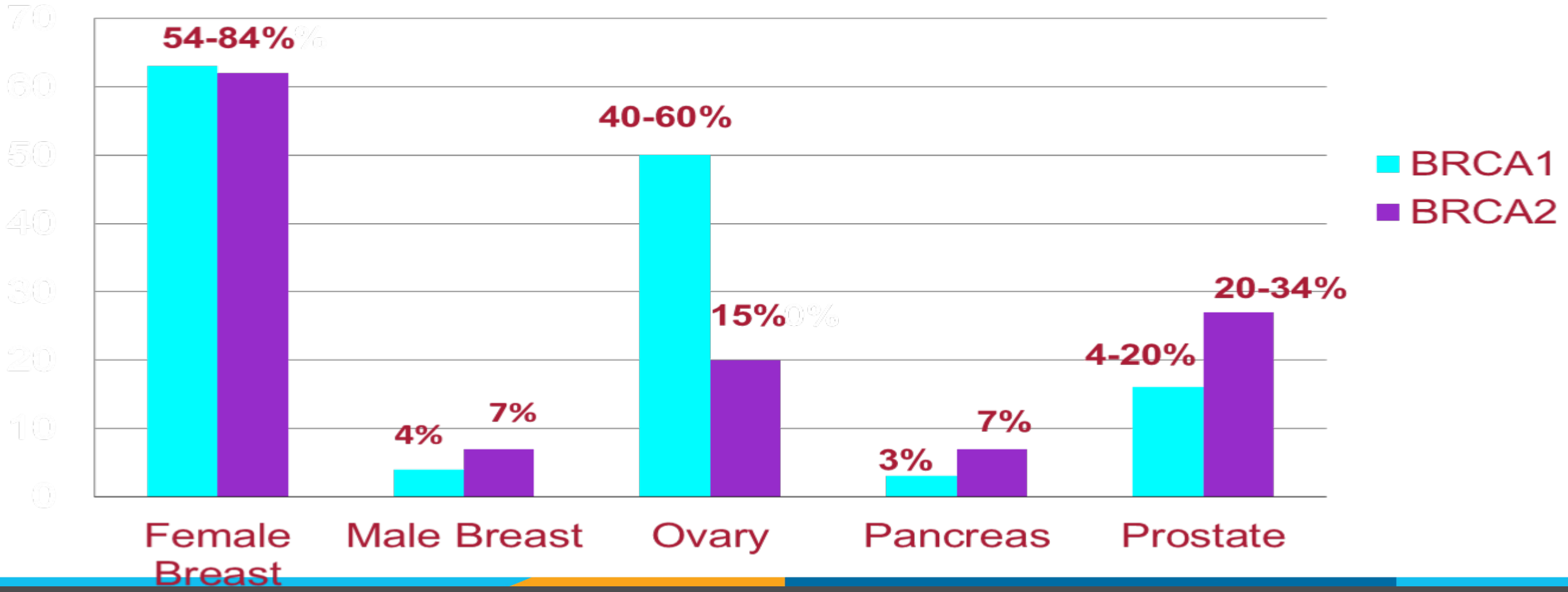
TABLE 2. Patient Genetic Test Positive Result Rate

Group	Positive Result (%)		
	BRCA1/ Alone	HBOC Guidelines Panel (11 genes)	Large Cancer Panel (80 genes)
In guideline	2.51	6.26	9.39
Out of guideline	0.63	3.54	7.92

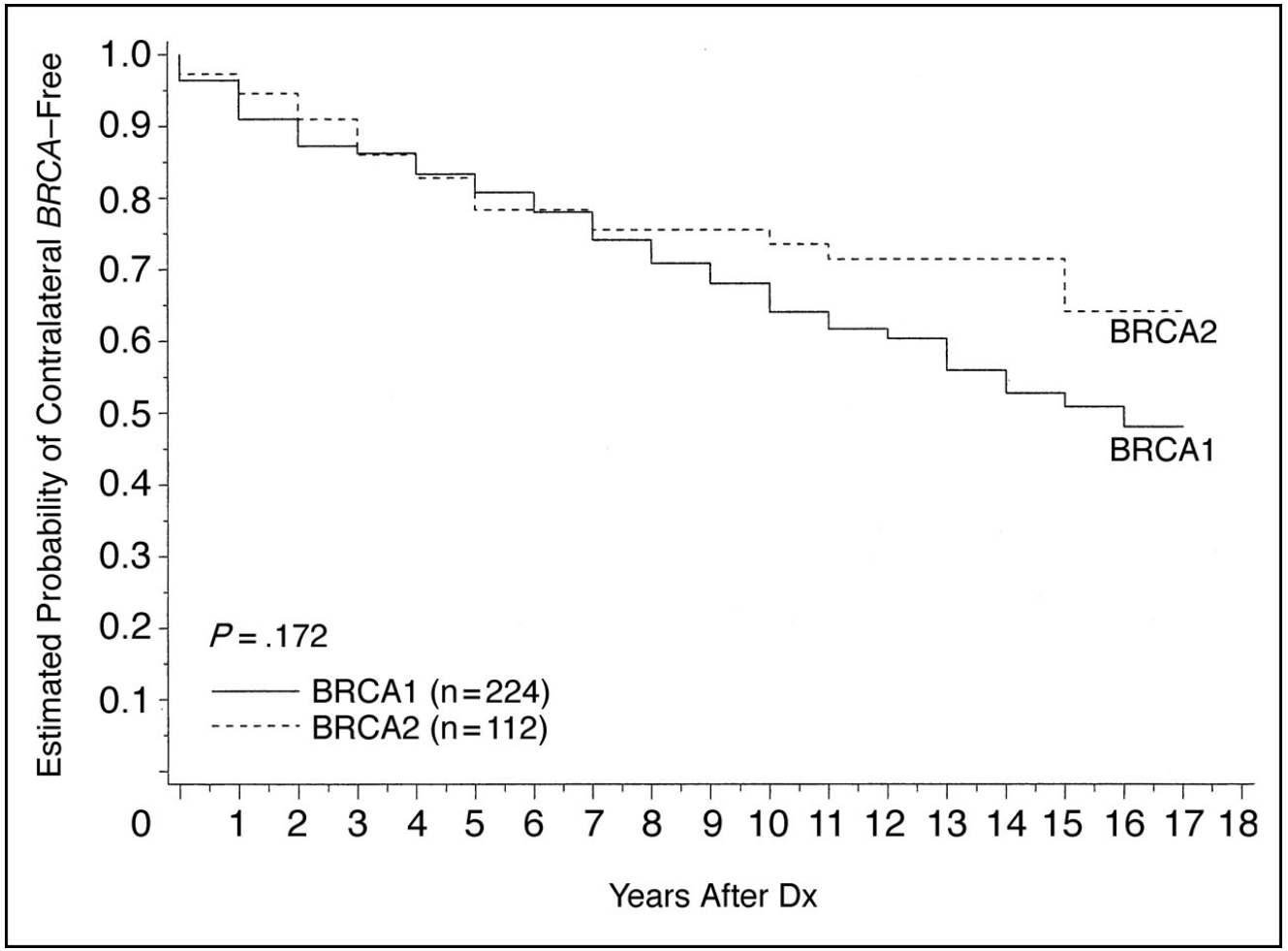


Published in: Peter D. Beitsch; Pat W. Whitworth; Kevin Hughes; Rakesh Patel; Barry Rosen; Gia Compagnoni; Paul Baron; Rache Simmons; Linda Ann Smith; Ian Grady; Michael Kinney; Cynara Coomer; Karen Barbosa; Dennis R. Holmes; Eric Brown; Linsey Gold; Patricia Clark; Lee Riley; Samuel Lyons; Antonio Ruiz; Sadia Kahn; Heather MacDonald; Lisa Curcio; Mary Kay Hardwick; Shan Yang; Ed D. Esplin; Robert L. Nussbaum; *Journal of Clinical Oncology* 2019 37453-460.

Lifetime Cancer Risk in BRCA1/2 Carriers



Risks of contralateral breast cancer in carriers of BRCA1 and BRCA2 mutations.



Metcalfe, et al. *Journal of Clinical Oncology* 2004 222328-2335.

Management Guidelines *BRCA1/2* Carriers

Management Option	Screening Interval/Comments
SCREENING	
• **Clinical Breast Exam** • **Breast MRI** • **Mammogram**	• **Q6-12 mos beginning age 25** • **Yearly age 25-75 (then individualize)** • **Yearly age 30-75 (then individualize)**
• Transvaginal ultrasound* • CA-125*	• Q6 mos beginning age 30 • Q6 mos beginning age 30
PREVENTION	
• Bilateral mastectomy • Bilateral salpingo-oophorectomy	• Discuss option with patient • Recommend by age 35-40 and when childbearing complete
• Consider oral contraceptive • Consider tamoxifen	

Modified from NCCN guidelines – v1.2014

Family History of Breast Cancer and …

Pancreas: BRCA, PALB2, ATM

Ovarian: BRCA, BRIP1, RAD51cd

Colon: CHEK2 100delC

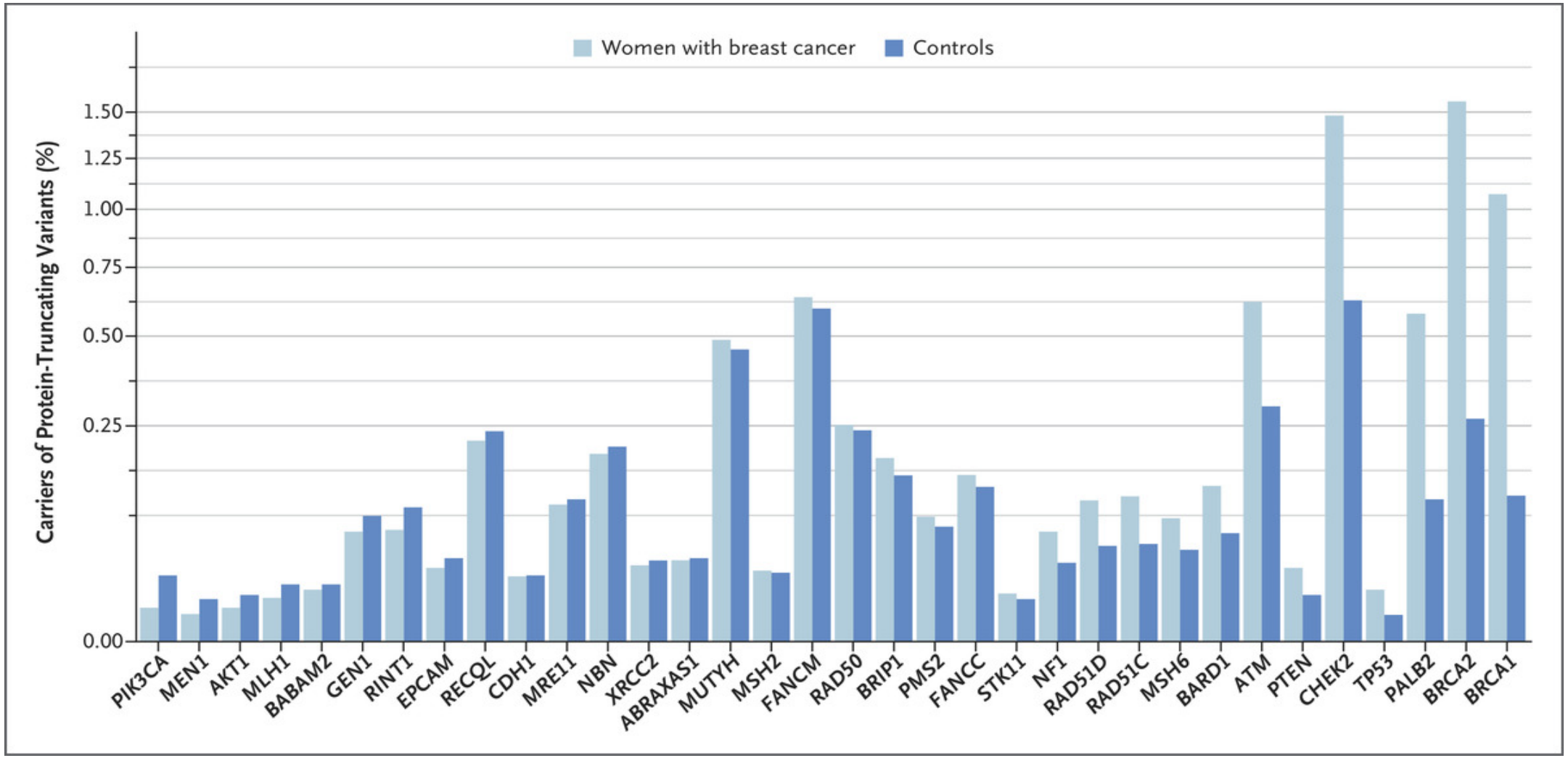
Prostate: BRCA2

Male breast cancer: BRCA2

Gastric cancer: CDH1

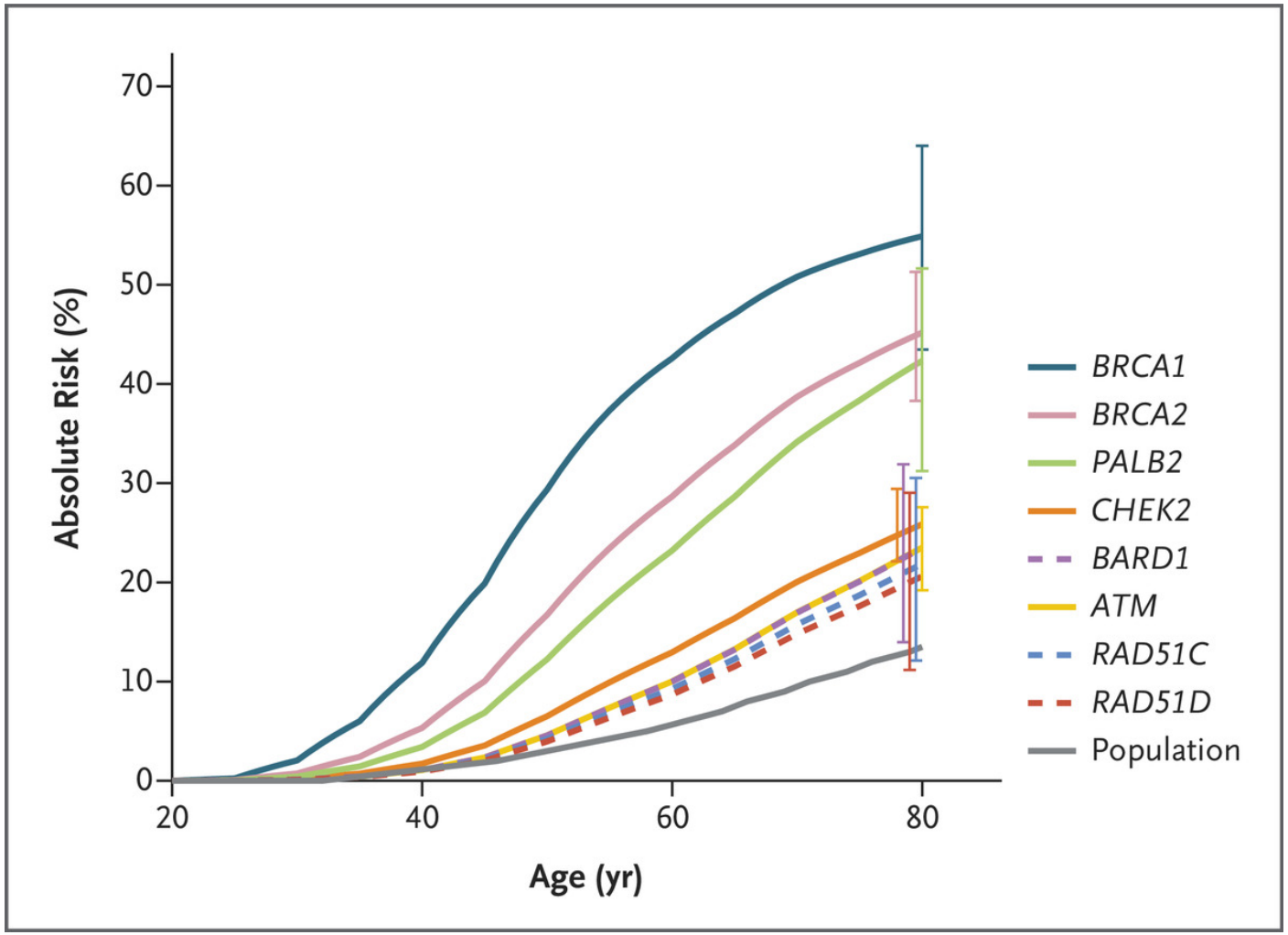
CNS, sarcoma, AML, adrenal cortical, other: TP53

Frequency of Protein-Truncating Variants in 34 Genes in Population-Based Studies. N = 113,000 women



Breast Cancer Association Consortium. N Engl J Med 2021;384:428-439.

Estimated Absolute Risk of Breast Cancer Associated with Protein-Truncating Variants in 8 Genes.



Breast Cancer Association Consortium. N Engl J Med 2021;384:428-439.

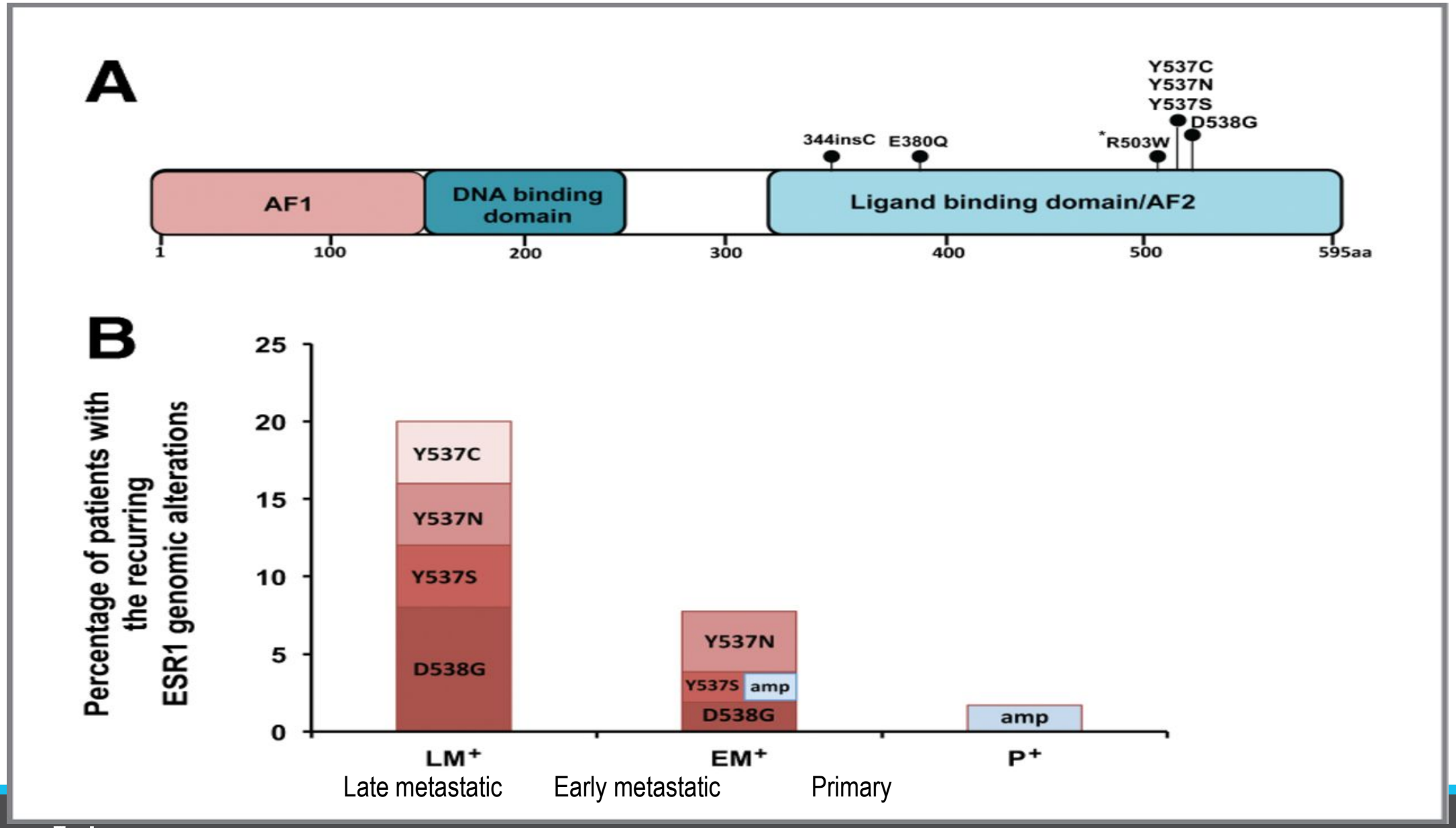
Genetics: Key Take-aways

- Panel testing is the “norm”
- Remember to revisit family history in light of shifting guidelines on which patients should be tested and appreciation for links to other kinds of cancer
- Penetrance / risk is NOT uniform for all ‘mutant’ genes
- Personally, I think we should test nearly all patients

Genomic era reaches breast cancer

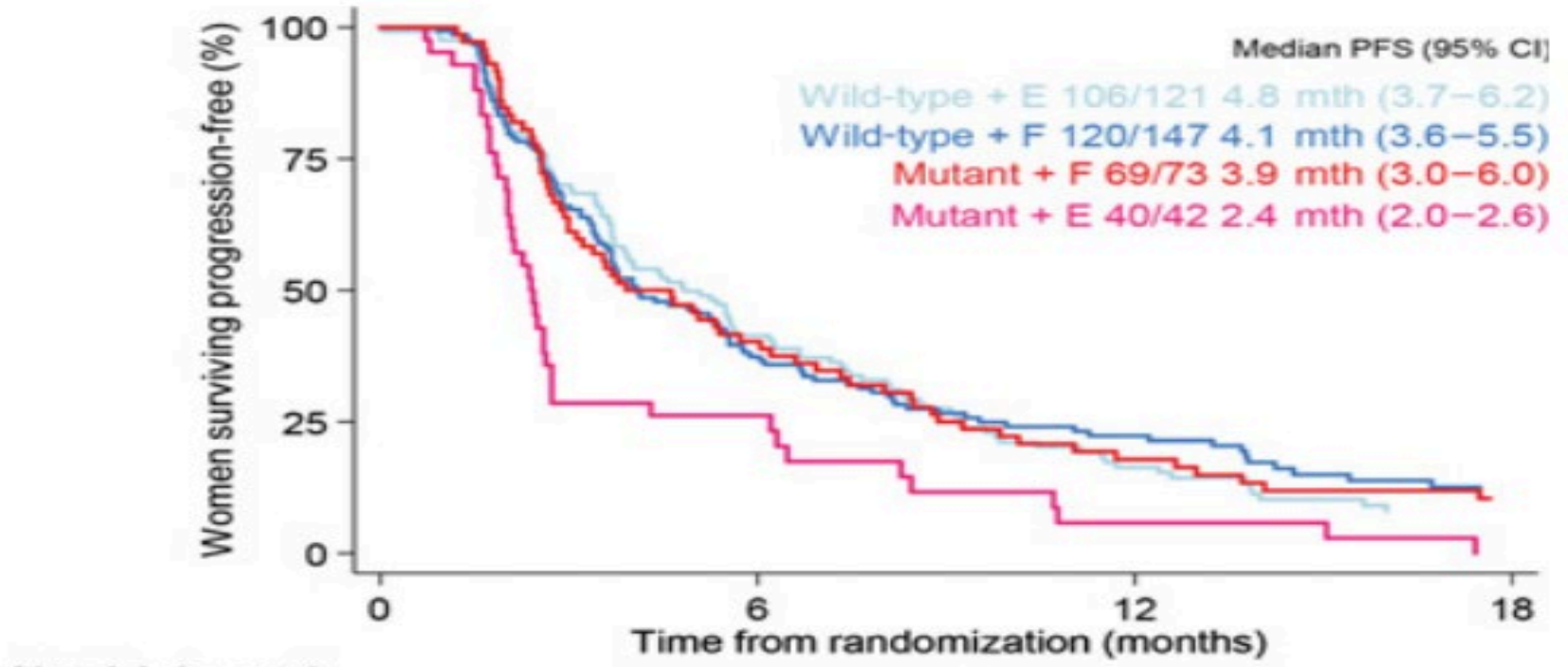
INNOVATIONS IN ADVANCED ER+ BREAST CANCER

Emergence of constitutively active ER-α mutations in breast cancers



Jeselsohn R et al. Clin Cancer Res 2014;20:1757-1767

Effect of ESR1 mutations on outcomes in SoFEA and EFECT trials of Exemestane vs Fulvestrant after Prior AI Therapy

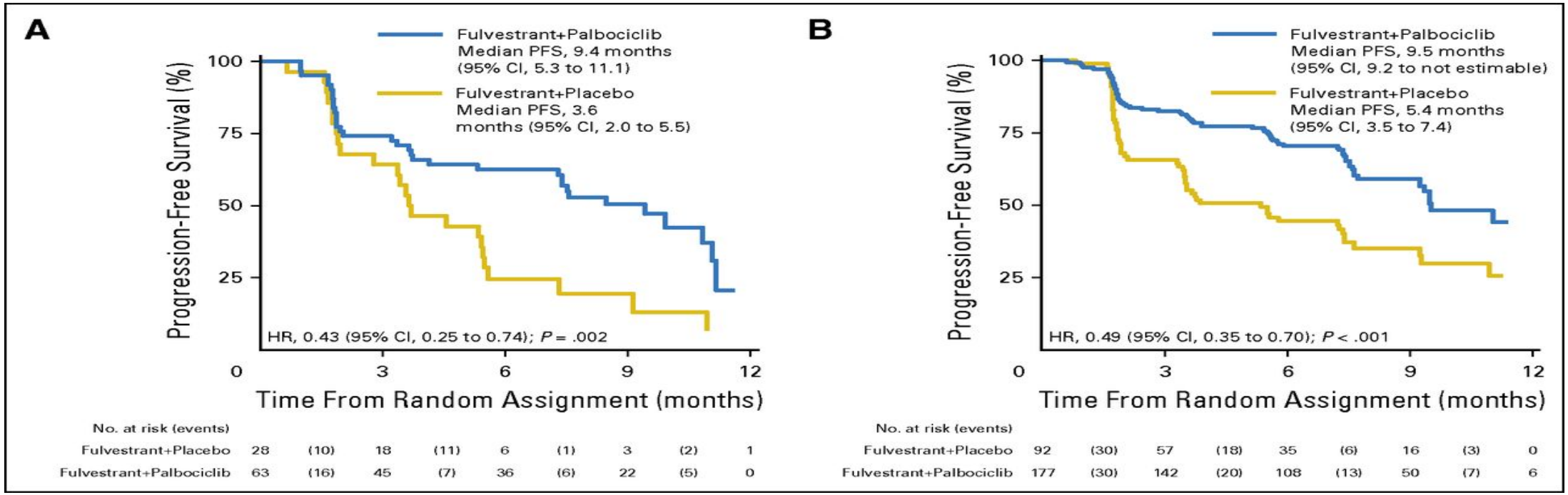


Turner NC, et al. Clin Cancer Res 2020

Progression-free survival (PFS) in PALOMA3 by ESR1 mutation status.

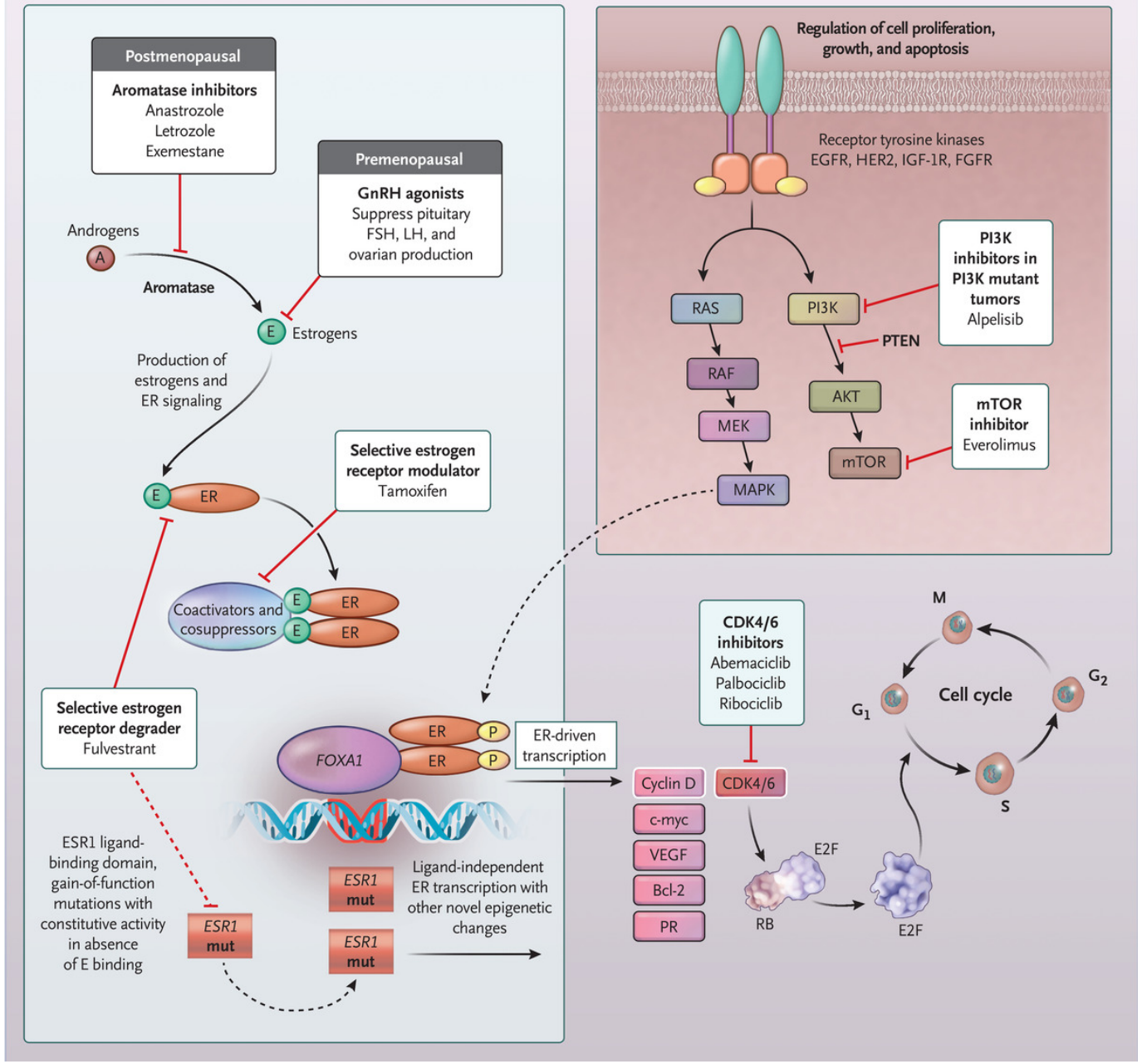
ESR1 mutation

ESR1 wildtype



ESR1 mutation associated with diminished PFS, but still with benefit from CDk4/6i

Charlotte Fribbens et al. JCO 2016;34:2961-2968



HJ Burstein. N Engl J Med 2020;383:2557-2570.

Line	Study Name	Endocrine Agent	CDK4/6i	PFS	HR
1st	PALOMA1 Lancet 2015	Letrozole	Palbociclib	10.2m → 20.2m	0.49
	PALOMA2 NEJM 2016	Letrozole	Palbociclib	14.5m → 24.8 m	0.58
	MONALEESA2 NEJM 2016	Letrozole	Ribociclib	14.5 → ~26m	0.56
	MONALEESA7* SABCS 2017	Letrozole + OFS	Ribociclib	13.0m → 23.8m	0.55
	MONARCH3 JCO 2017	NSAI	Abemaciclib	14.7m → NR	0.54
2nd	PALOMA3 NEJM 2015	Fulvestrant	Palbociclib	3.8m → 9.2m	0.42
	MONALEESA3 ASCO 2018	Fulvestrant	Ribociclib	12.8 m → 20.5m	0.59
	MONARCH2 JCO 2017	Fulvestrant	Abemaciclib	9.3m → 16.4m	0.55
	MONARCH2* ASCO 2018	Fulvestrant + OFS	Abemaciclib	10.5 m → NR	0.45

premenopausal women

Side effects of CDK4/6 inhibitors

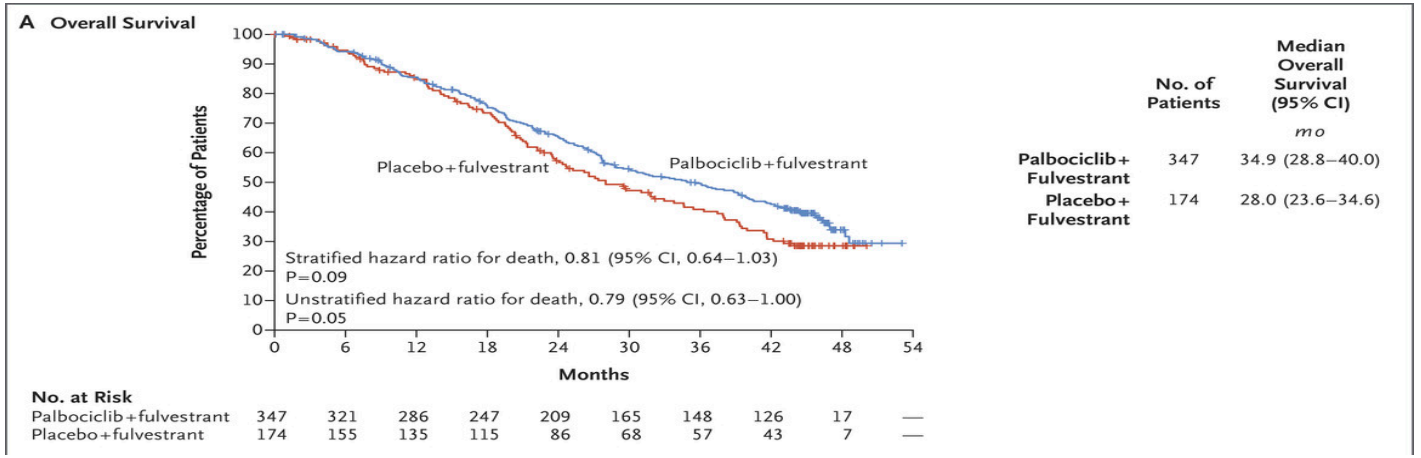
Table 2. Dosing and Toxicity for Cyclin-Dependent Kinase 4/6 Inhibitors

	Palbociclib (125 mg per day [3 weeks on, 1 week off])		Ribociclib (600 mg per day [3 weeks on, 1 week off])		Abemaciclib (200 mg twice per day [continuous])	
Common Adverse Event*	All Grades	Grade 3 and 4	All Grades	Grade 3 and 4	All Grades	Grade 3 and 4
Neutropenia	74-81	54-67	74	59	46	27
Thrombocytopenia	16-22	2-3	NR	NR	16	3
Fatigue	37-46	2-4	37	2	40	3
Diarrhea	21-26	1-4	35	1	86	13
Nausea	25-35	0-2	52	2	45	3
QTc prolongation	NR	NR	3	NR	NR	NR

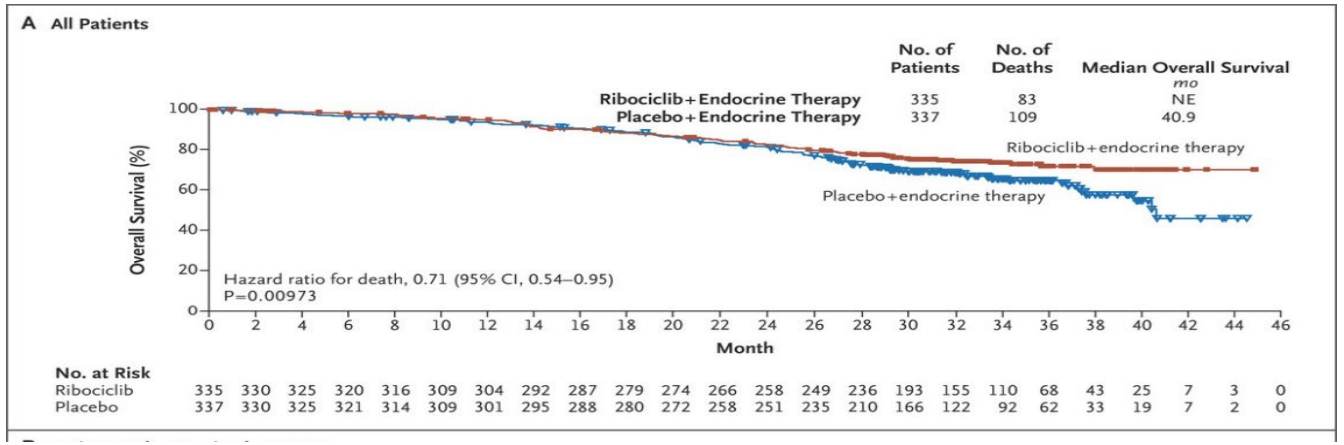
NOTE. Data are given as percent.
Abbreviation: NR, not reported; QTc, corrected QT interval.
*Common adverse events in phase III trials in the metastatic setting.

Wander S, Mayer EL, Burstein HJ. J Clin Oncol 2017

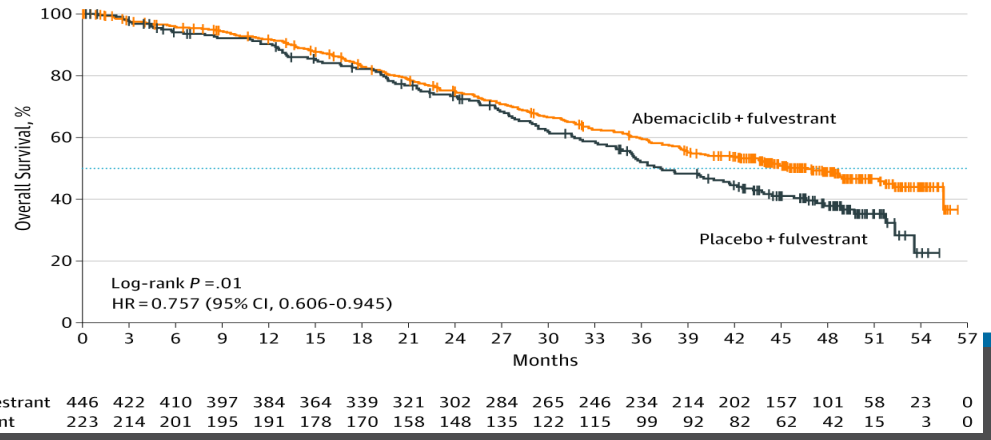
PALOMA 3: Overall Survival



MONALEESA 7: Overall Survival

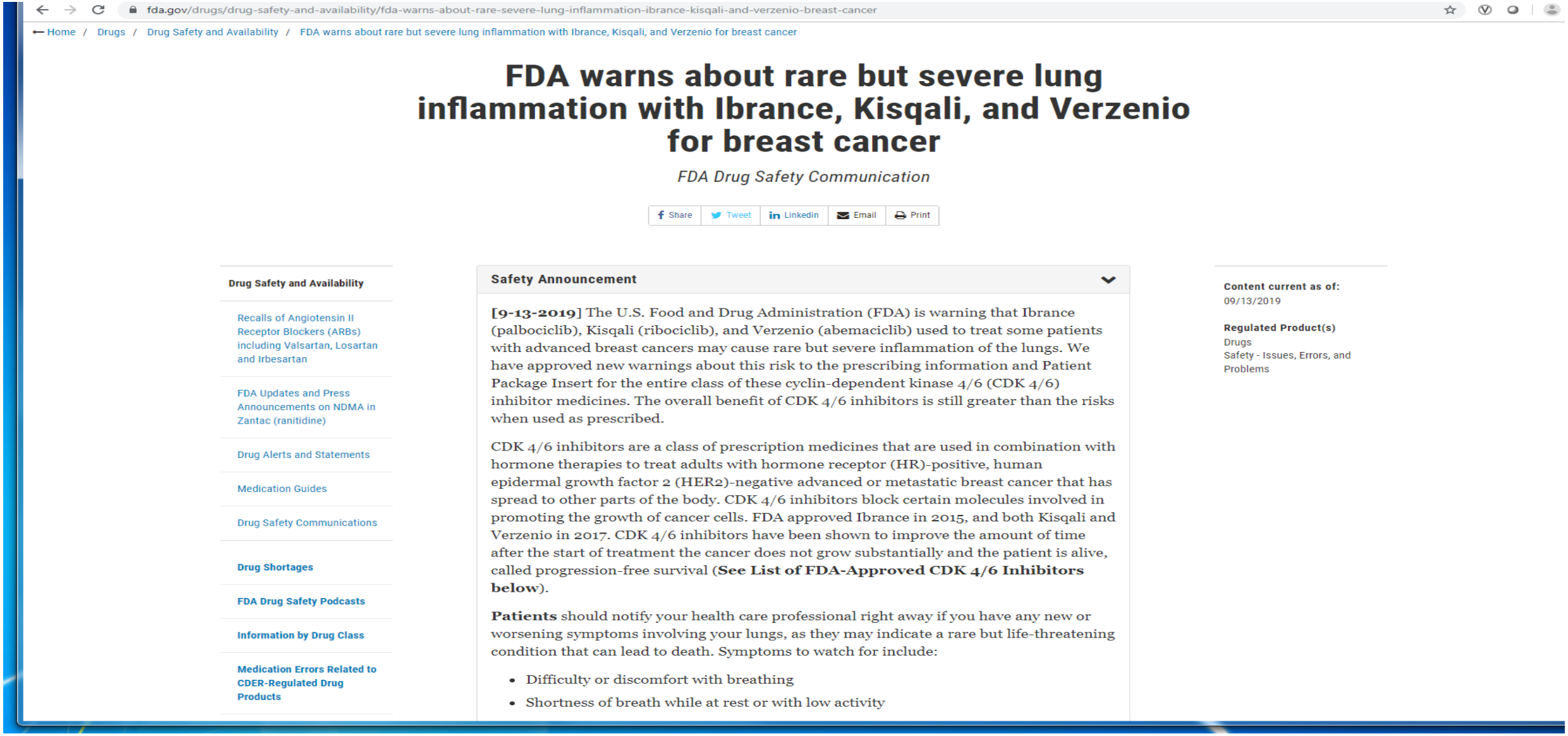


MONARCH 2: Overall Survival



NC Turner et al. N Engl J Med 2018;379:1926-1936.
Sledge G, JAMA Oncol 2019

S Im et al. N Engl J Med 2019;381:307-316.


fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-severe-lung-inflammation-ibrance-kisqali-and-verzenio-breast-cancer
Home / Drugs / Drug Safety and Availability / FDA warns about rare but severe lung inflammation with Ibrance, Kisqali, and Verzenio for breast cancer
FDA warns about rare but severe lung inflammation with Ibrance, Kisqali, and Verzenio for breast cancer
FDA Drug Safety Communication
Share
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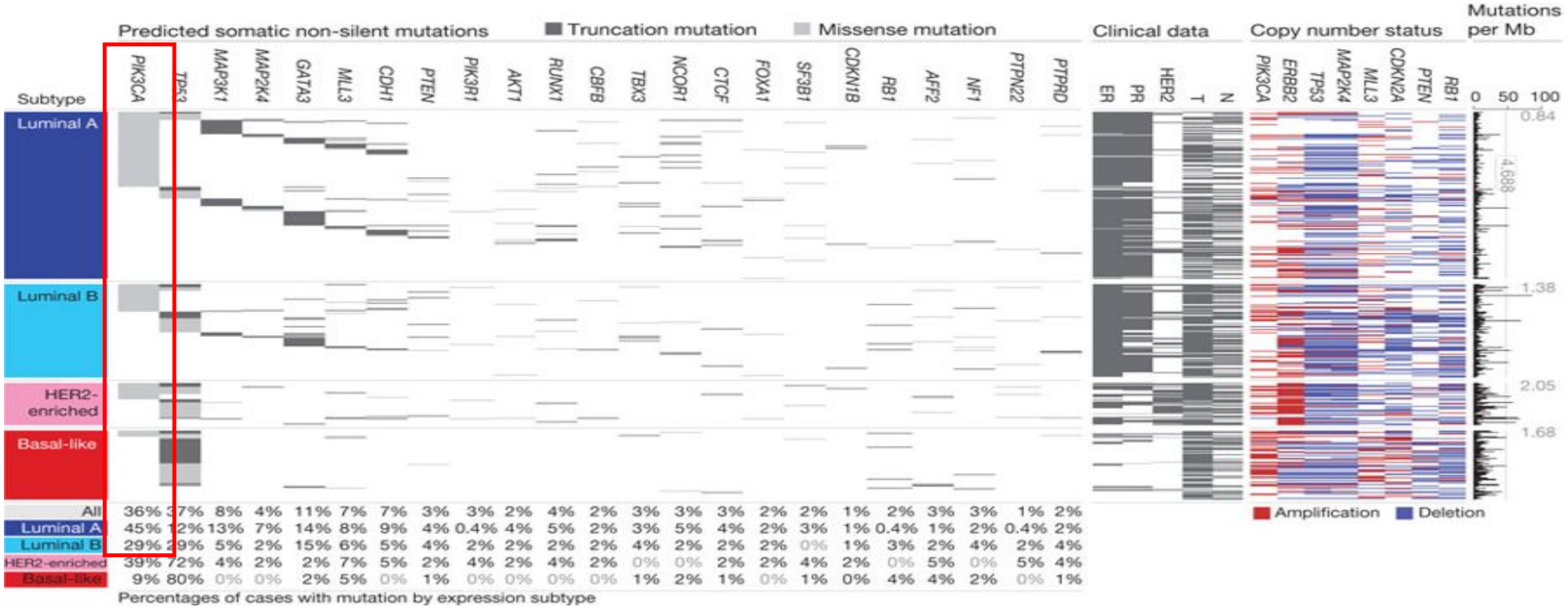
Recalls of Angiotensin II Receptor Blockers (ARBs) including Valsartan, Losartan and Irbesartan
FDA Updates and Press Announcements on NDMA in Zantac (ranitidine)
Drug Alerts and Statements
Medication Guides
Drug Safety Communications
Drug Shortages
FDA Drug Safety Podcasts
Information by Drug Class
Medication Errors Related to CDER-Regulated Drug Products
Safety Announcement
[9-13-2019] The U.S. Food and Drug Administration (FDA) is warning that Ibrance (palbociclib), Kisqali (ribociclib), and Verzenio (abemaciclib) used to treat some patients with advanced breast cancers may cause rare but severe inflammation of the lungs. We have approved new warnings about this risk to the prescribing information and Patient Package Insert for the entire class of these cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor medicines. The overall benefit of CDK 4/6 inhibitors is still greater than the risks when used as prescribed.
CDK 4/6 inhibitors are a class of prescription medicines that are used in combination with hormone therapies to treat adults with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative advanced or metastatic breast cancer that has spread to other parts of the body. CDK 4/6 inhibitors block certain molecules involved in promoting the growth of cancer cells. FDA approved Ibrance in 2015, and both Kisqali and Verzenio in 2017. CDK 4/6 inhibitors have been shown to improve the amount of time after the start of treatment the cancer does not grow substantially and the patient is alive, called progression-free survival (See List of FDA-Approved CDK 4/6 Inhibitors below).
Patients should notify your health care professional right away if you have any new or worsening symptoms involving your lungs, as they may indicate a rare but life-threatening condition that can lead to death. Symptoms to watch for include:
Difficulty or discomfort with breathing
Shortness of breath while at rest or with low activity
Content current as of:
09/13/2019
Regulated Product(s)
Drugs
Safety - Issues, Errors, and Problems

Molecular Portraits of Human Breast Tumors



Cancer Genome Atlas Network. Nature 2012;490:61-70.

SOLAR-1

Men or postmenopausal women with HR+, HER2– ABC

- Recurrence/progression on/after prior AI
- Identified *PIK3CA* status (in archival or fresh tumor tissue[a])
- Measurable disease or ≥ 1 predominantly lytic bone lesion
- ECOG performance status ≤ 1

(N = 572)

PIK3CA-mutant cohort (n = 341) → R
- **ALP** 300 mg PO QD + **FUL** 500 mg IM[b] **n = 169**
- **PBO** + **FUL** 500 mg IM[b] **n = 172**

1:1, stratified by presence of liver/lung metastases and prior CDK4/6 inhibitor treatment

PIK3CA-non-mutant cohort (n = 231) → R
- **ALP** 300 mg PO QD + **FUL** 500 mg IM[b] **n = 115**
- **PBO** + **FUL** 500 mg IM[b] **n = 116**

Primary endpoint

- PFS in *PIK3CA*-mutant cohort (locally assessed)

Secondary endpoints include

- OS (*PIK3CA*-mutant cohort)
- PFS (*PIK3CA*-non-mutant cohort)
- PFS (*PIK3CA* mutation in ctDNA)
- PFS (*PIK3CA*-non-mutant in ctDNA)
- ORR/CBR (both cohorts)
- Safety

- The primary endpoint included all randomized patients in the *PIK3CA*-mutant cohort; PFS was analyzed in the *PIK3CA*-non-mutant cohort as a proof of concept
- Safety was analyzed for all patients who received ≥ 1 dose of study treatment, in both cohorts

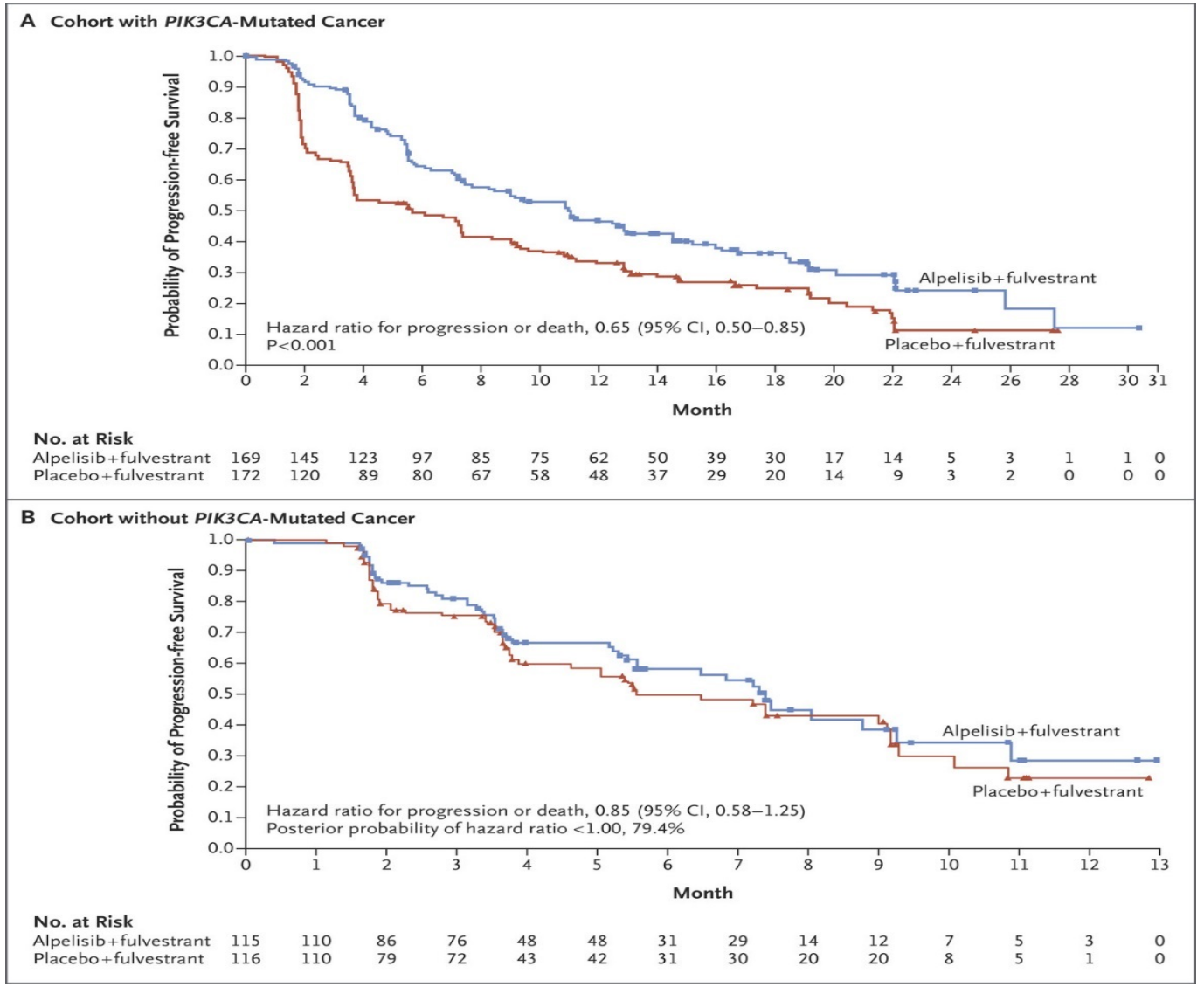
ABC, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; HER2–, human epidermal growth factor receptor-2–negative; IM, intramuscular; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, oral; QD, once daily; R, randomization.

[a] More than 90% of patients had mutational status identified from archival tissue.

[b] Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.

1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

SOLAR Trial -1



F André et al. N Engl J Med 2019;380:1929-1940.

Alpelisib: Toxicity Management

Table 3. Most Frequent Adverse Events, According to Single Preferred Term and Regardless of Relationship to Intervention, in the Overall Patient Population.*

Adverse Event	Alpelisib–Fulvestrant Group (N=284)			Placebo–Fulvestrant Group (N=287)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia†	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea‡	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea‡	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash§	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting‡	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Weight loss	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0
Alopecia	56 (19.7)	0	0	7 (2.4)	0	0
Mucosal inflammation	52 (18.3)	6 (2.1)	0	3 (1.0)	0	0
Pruritus	51 (18.0)	2 (0.7)	0	16 (5.6)	0	0
Headache	50 (17.6)	2 (0.7)	0	38 (13.2)	0	0
Dysgeusia	47 (16.5)	0	0	10 (3.5)	0	0
Arthralgia	32 (11.3)	1 (0.4)	0	47 (16.4)	3 (1.0)	0

* Safety analyses included all the patients who received at least one dose of any trial agent; one patient who was randomly assigned to the placebo–fulvestrant group did not receive either placebo or fulvestrant. The events that are listed were reported as a single term in at least 15% of the patients for any grade in either group. Three adverse events of special interest (pancreatitis, severe cutaneous reactions, and pneumonitis) fell below the reporting threshold listed here. Hypersensitivity, which occurred in 16.5% of the patients in the alpelisib–fulvestrant group (grade ≥3 in 1.8%) and in 4.2% of those in the placebo–fulvestrant group (grade ≥3 in none), was not reported as any single preferred term that reached the reporting threshold listed here.

† Adverse events of any grade related to hyperglycemia (including diabetes mellitus, hyperglycemia, insulin resistance, and metabolic syndrome [preferred terms] and others [see the Methods section in the Supplementary Appendix for a complete list]) were reported in 65.8% of the patients in the alpelisib–fulvestrant group (grade ≥3 in 38.0%) and in 10.5% of those in the placebo–fulvestrant group (grade ≥3 in 0.7%).

‡ Gastrointestinal toxic effects of any grade (including nausea, vomiting, and diarrhea [preferred terms] and others [see the Methods section in the Supplementary Appendix for a complete list]) were reported in 75.4% of the patients in the alpelisib–fulvestrant group (grade ≥3 in 8.8%) and in 34.8% of those in the placebo–fulvestrant group (grade ≥3 in 1.0%). Diarrhea was assessed at a maximum grade 2 severity in 18.3% of the patients.

§ Adverse events of any grade related to rash (including rash, rash follicular, rash generalized, and rash maculopapular [preferred terms] and others [see the Methods section in the Supplementary Appendix for a complete list]) were reported in 53.9% of the patients in the alpelisib–fulvestrant group (grade ≥3 in 20.1%) and in 8.4% of those in the placebo–fulvestrant group (grade ≥3 in 0.3%).

Table S7. Protocol Guidance for Treatment of Hyperglycemia in SOLAR-1

Hyperglycemia	

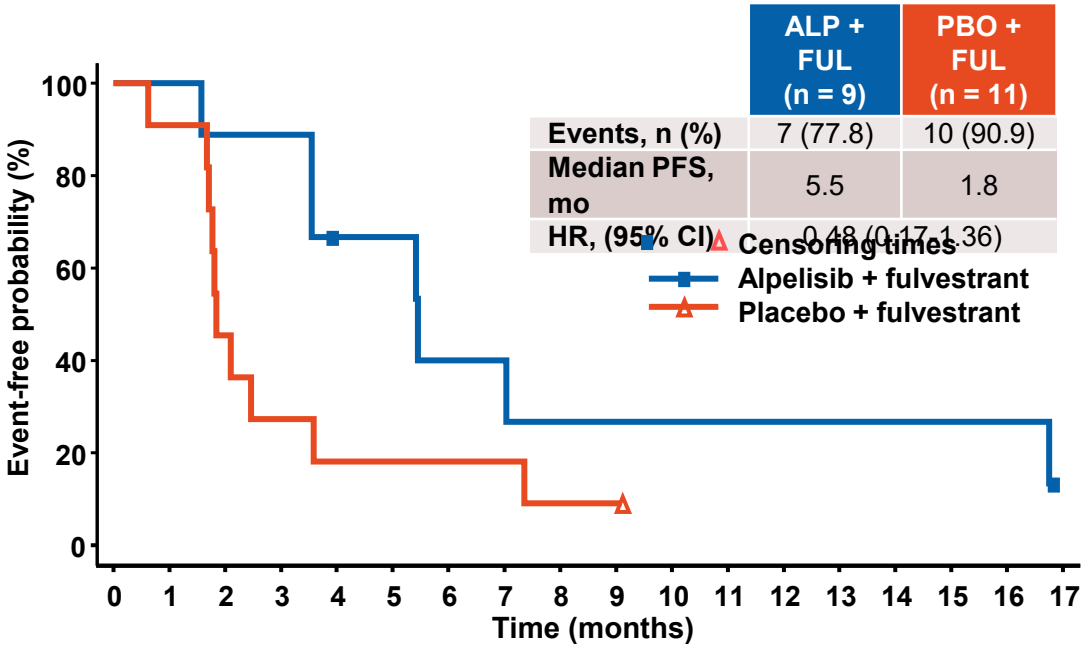
Grade 1	• **Maintain dose level** and remind patient of lifestyle changes.
	  ○ If FPG <140 mg/dL, consider adding metformin*
	  ○ If FPG 140–60 mg/dL, start or intensify metformin*
	• Initiate metformin 500 mg once daily with dinner.
	  ○ If no GI intolerance after several days, increase to 500 mg twice daily with breakfast and dinner
	  ○ If tolerated, 1 g twice daily with breakfast and dinner
	  ○ If not tolerated, reduce to prior tolerated dose
	• Monitor FPG as clinically indicated and at least weekly for 8 weeks, then every 2 weeks until FPG is within baseline values.

Grade 2	• **Maintain dose level** and remind patient of lifestyle changes.
	  ○ Metformin 500 mg twice daily with breakfast and dinner
	  ○ If no GI intolerance, increase to 500 mg with breakfast, 1000 mg with dinner
	  ○ If tolerated, 1000 mg bid with breakfast and dinner
	  ○ If not tolerated, reduce to prior tolerated dose
	  ○ Titrate to the maximum tolerated dose over a period of 3 weeks
	• Exclude confounding factors such as UTI and consider consultation with a diabetologist.
	• If FPG continues to rise, or is persistently >160 mg/dL (>8.9 mmol/L), on MTD of metformin, add an insulin-sensitizer, e.g. pioglitazone 30 mg.
	• Monitor FPG as clinically indicated, and at least weekly, until FPG resolves to ≤Grade 1.
	  ○ If FPG does not resolve to ≤Grade 1 within 21 days after initiation of appropriate antidiabetic treatment, reduce alpelisib/placebo by one dose level.
	  ○ Continue with antidiabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks.
	  ○ Alert treating physician if FPG >250 mg/dL.

Grade 3	• **Interrupt treatment with alpelisib/placebo** and confirm fasting status of the assessment. If non-fasting, re-check within 24 hours.
	• Exclude confounding factors such as UTI and consider consultation with a diabetologist.
	• Administer IV hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate.
	• Start metformin and titrate as outlined for Grade 2, add pioglitazone as outlined for Grade 2.
	• Insulin may be used for 1–2 days until hyperglycemia resolves; however this may not be necessary in the majority of cases of alpelisib-induced hyperglycemia, given the short half-life of alpelisib.
	• Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤Grade 1.
	  ○ If FPG resolves to ≤Grade 1 within 3–5 days, while off study treatment and on metformin, re-start alpelisib/placebo and reduce one dose level, continue with antidiabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG >250 mg/dL.
	  ○ If FPG does not resolve to Grade 1 within 3–5 days while off study treatment and on metformin, consultation with a diabetologist for management of diabetes is strongly recommended.
	  ○ If FPG does not resolve to ≤Grade 1 within 21 days after initiation of appropriate antidiabetic treatment in cooperation with a diabetologist, and exclusion of confounding factors e.g. urinary tract infection, permanently discontinue patient from alpelisib/placebo treatment.

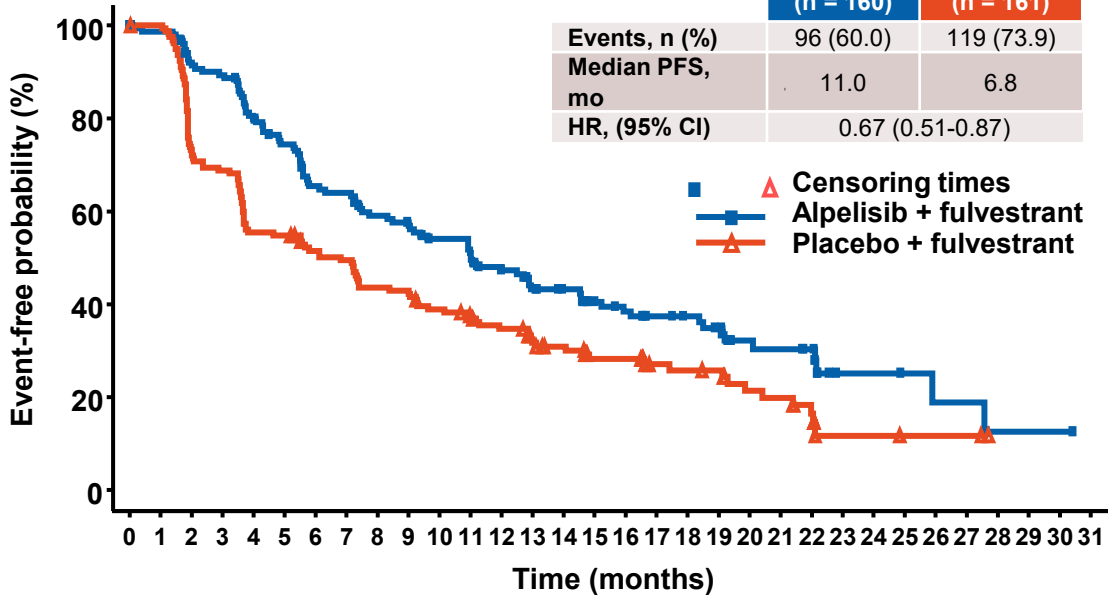
PFS by Prior CDK4/6 Inhibitor Treatment in the *PIK3CA*-mutant Cohort[a]

With Prior CDK4/6 inhibitor therapy



	ALP + FUL (n = 9)	PBO + FUL (n = 11)
Events, n (%)	7 (77.8)	10 (90.9)
Median PFS, mo	5.5	1.8
HR, (95% CI)	0.48 (0.17-1.36)	

Without Prior CDK4/6 inhibitor therapy

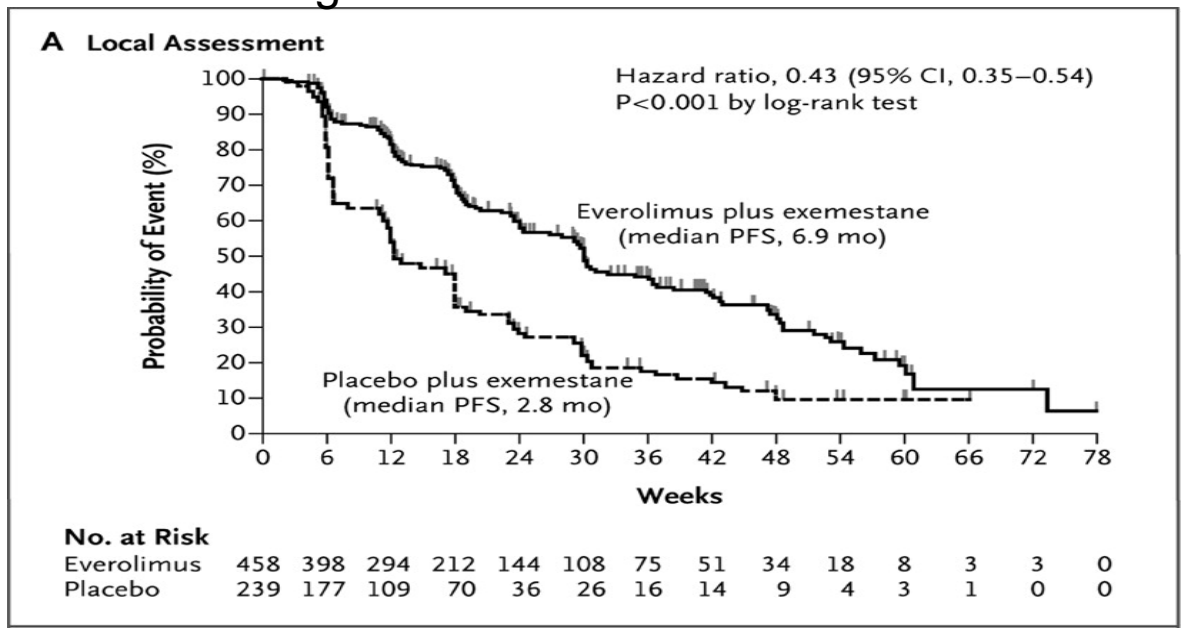


	ALP + FUL (n = 160)	PBO + FUL (n = 161)
Events, n (%)	96 (60.0)	119 (73.9)
Median PFS, mo	11.0	6.8
HR, (95% CI)	0.67 (0.51-0.87)	

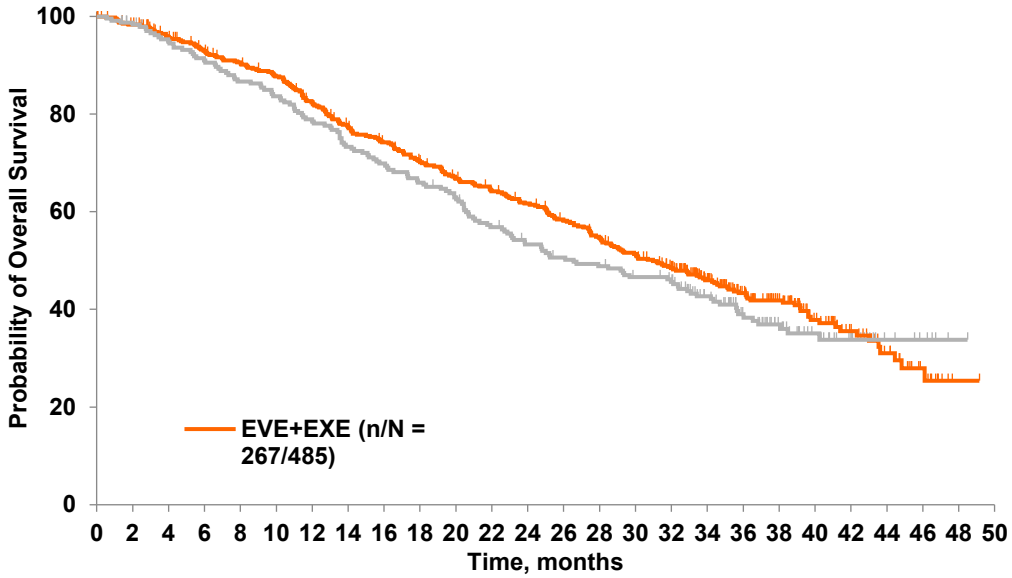
- Previous treatment with any CDK4/6 inhibitor was a stratification factor, however the number of patients enrolled who had received prior CDK4/6 inhibitor therapy was small
- Treatment benefit with alpelisib was observed regardless of prior use with a CDK4/6 inhibitor

BOLERO-2. PFS
EXE +/- everolimus after prior AI

Progression-free Survival



Overall Survival

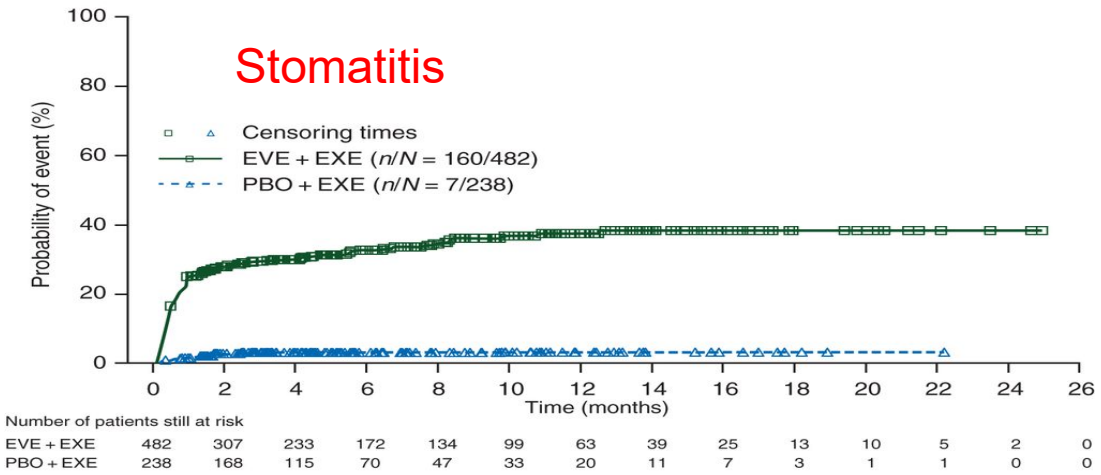


RR:
EXE 1%
EXE + EVO 13%

Baselga J et al. N Engl J Med 2011. DOI: 10.1056/NEJMoa1109653

BOLERO-2. Cumulative risks for grade ≥ 2 adverse events

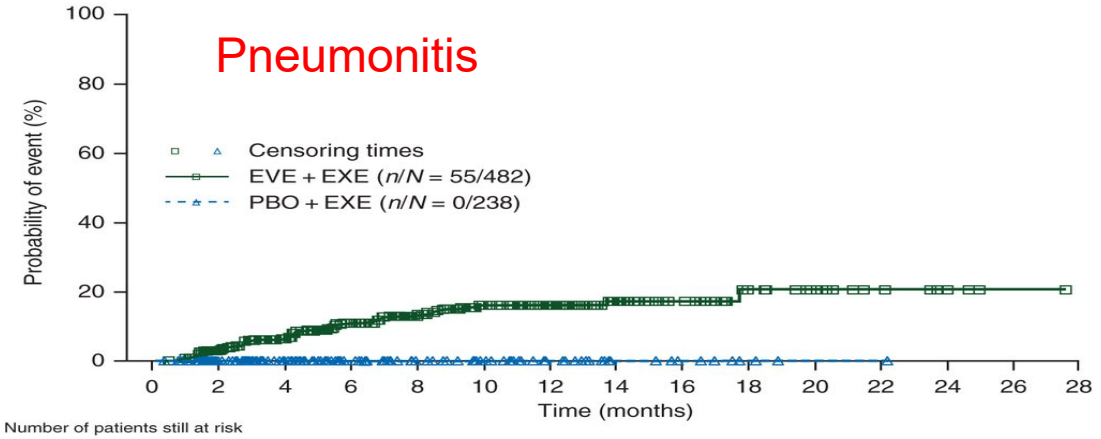
A



Number of patients still at risk

EVE + EXE	482	307	233	172	134	99	63	39	25	13	10	5	2	0
PBO + EXE	238	168	115	70	47	33	20	11	7	3	1	1	0	0

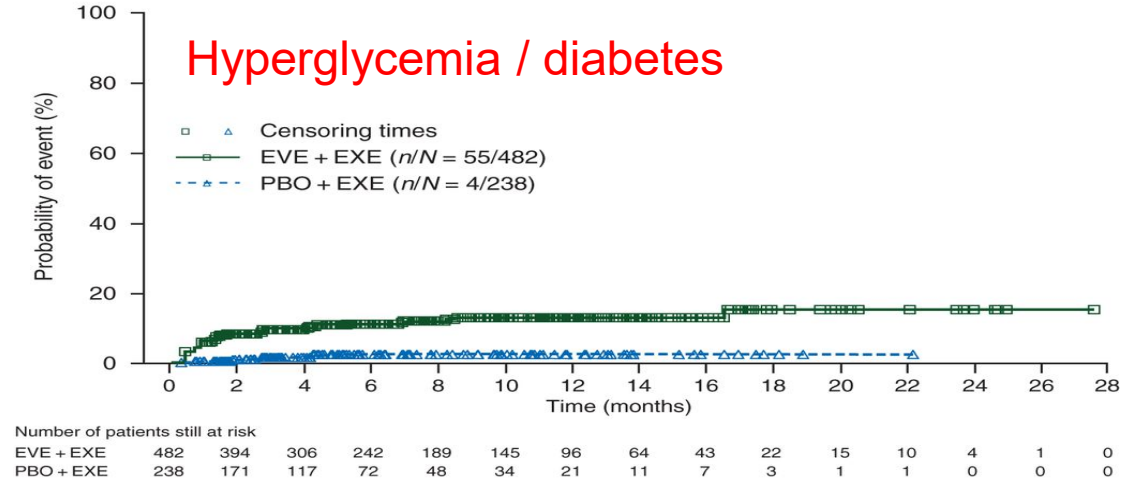
B



Number of patients still at risk

EVE + EXE	482	417	317	242	184	136	94	59	38	21	15	9	3	1	0
PBO + EXE	238	173	119	72	48	34	21	11	7	3	1	1	0	0	0

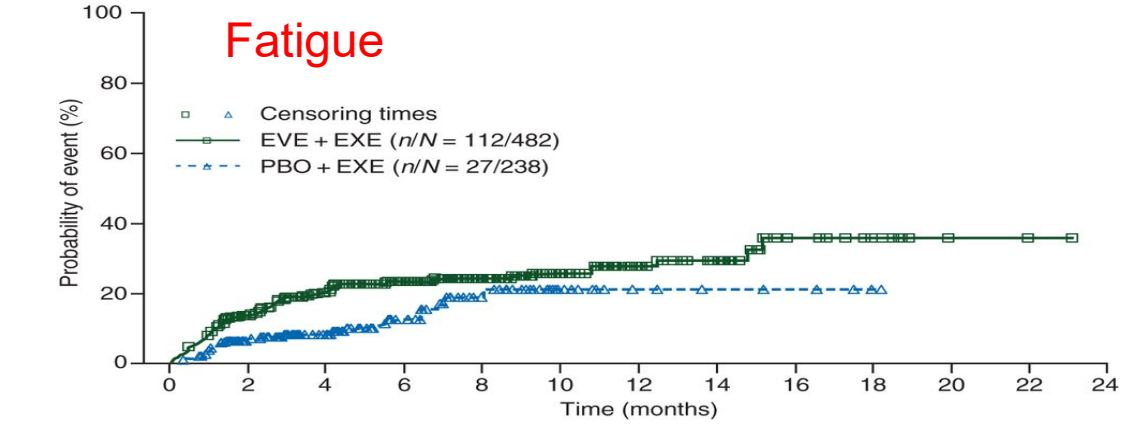
C



Number of patients still at risk

EVE + EXE	482	394	306	242	189	145	96	64	43	22	15	10	4	1	0
PBO + EXE	238	171	117	72	48	34	21	11	7	3	1	1	0	0	0

D



Number of patients still at risk

EVE + EXE	482	378	284	216	141	87	49	33	13	8	2	1	0
PBO + EXE	238	164	110	64	34	18	7	5	4	1	0	0	0

Rugo HS, et al. Ann Oncol 2014;annonc.mdu009

CROSSOVER THERAPEUTICS

Response rates to PARPi in ER+ breast cancers with hereditary mutations contributing to homologous recombination deficiency

	Olaparib vs chemo Robson, NEJM		Talazoparib vs chemo Litton, NEJM		Olaparib Tung, JCO
Mutation	***BRCA1/2***		***BRCA1/2***		***PALB2***
Treatment	**PARPi**	**STD**	**PARPi**	**STD**	**PARPi**
Response rates	**65%**	**36%**	**63%**	**38%**	**81%**

Takeaway: all patients with metastatic breast cancer need genetic testing

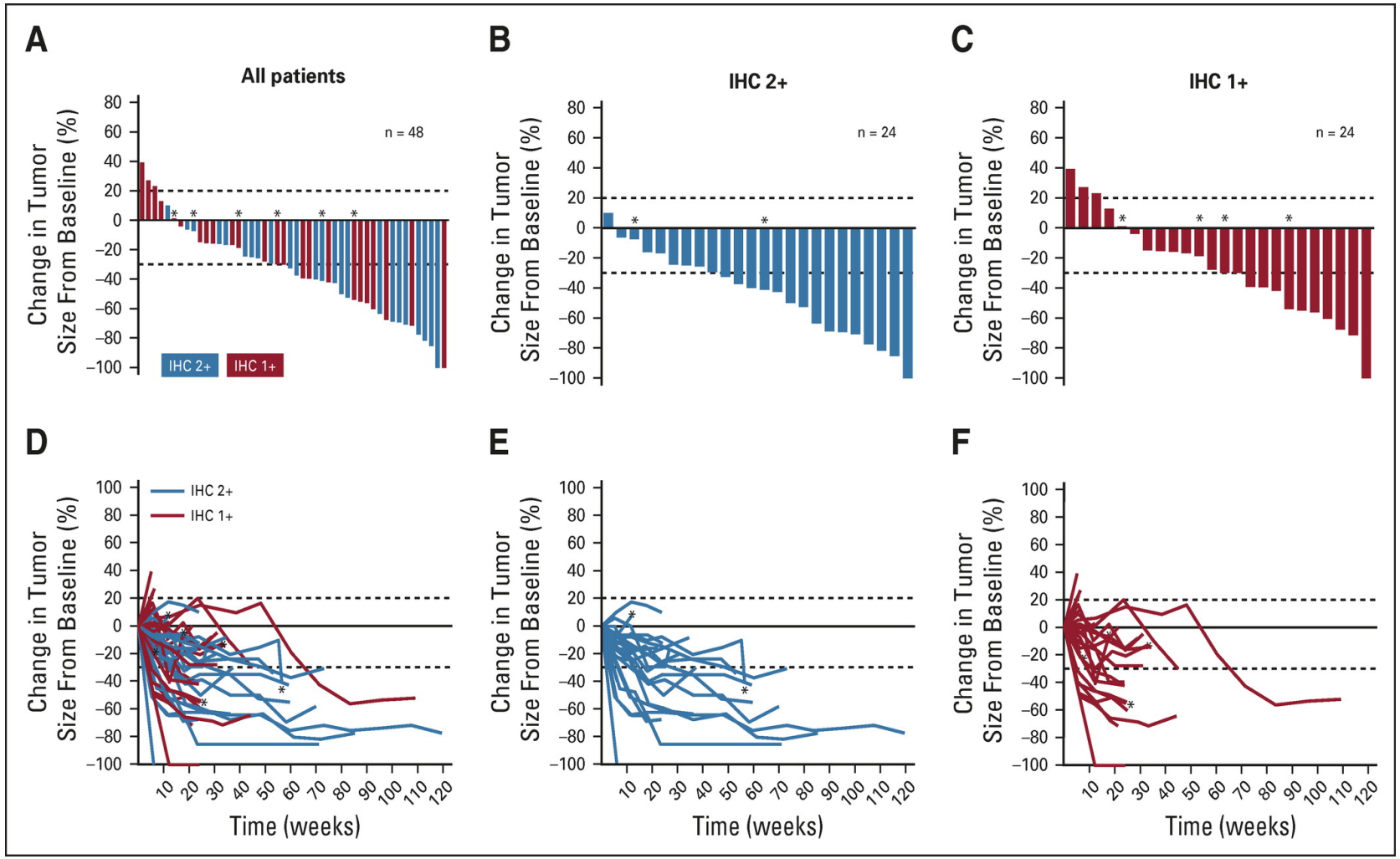
Trastuzumab deruxtecan in HER2 “low” 1+ or 2+ breast cancers

Median Prior Rx
7 agents

87% ER+

RR 37%

PFS 11.1 m

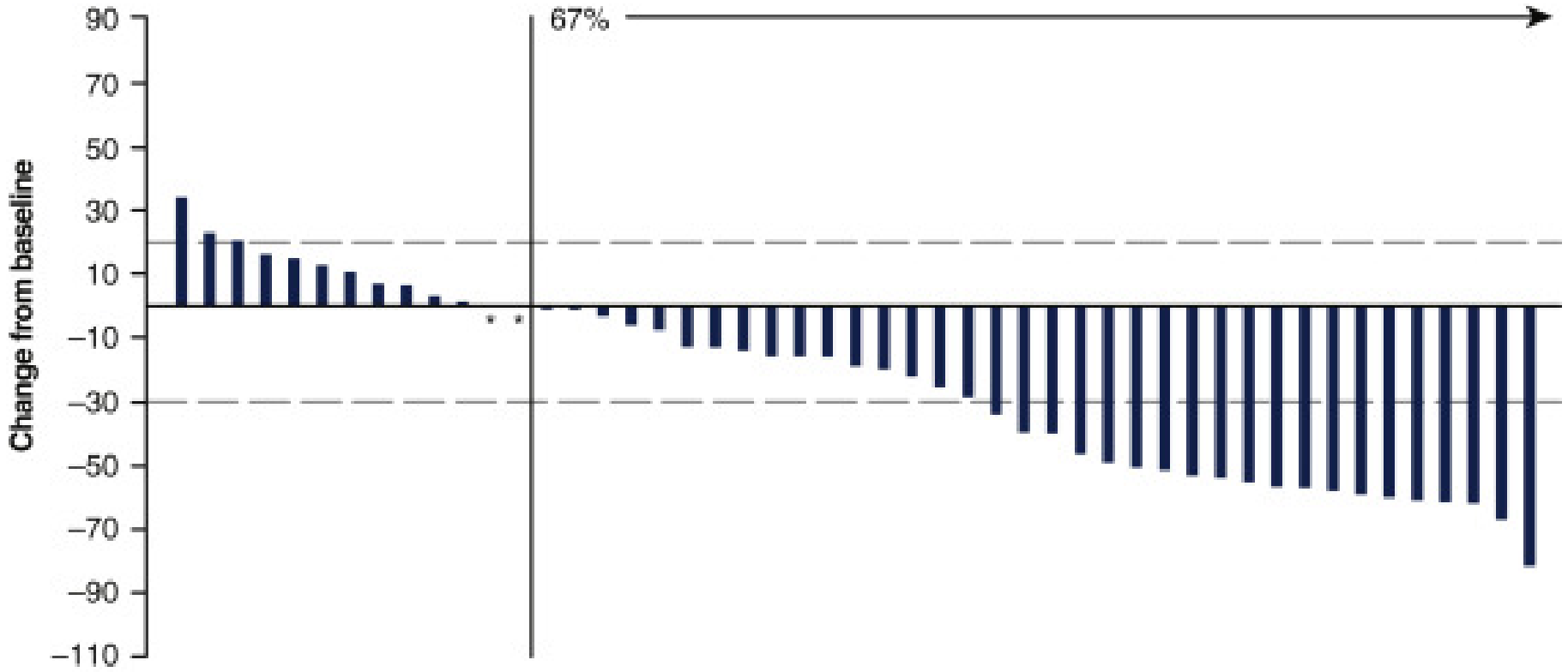


Published in: Shanu Modi; Haeseong Park; Rashmi K. Murthy; Hiroji Iwata; Kenji Tamura; Junji Tsurutani; Alvaro Moreno-Aspitia; Toshihiko Doi; Yasuaki Sagara; Charles Redfern; Ian E. Krop; Caleb Lee; Yoshihiko Fujisaki; Masahiro Sugihara; Lin Zhang; Javad Shahidi; Shunji Takahashi; *Journal of Clinical Oncology* 2020 381887-1896.
DOI: 10.1200/JCO.19.02318

Sacituzimab govitecan in refractory, ER+ breast cancer

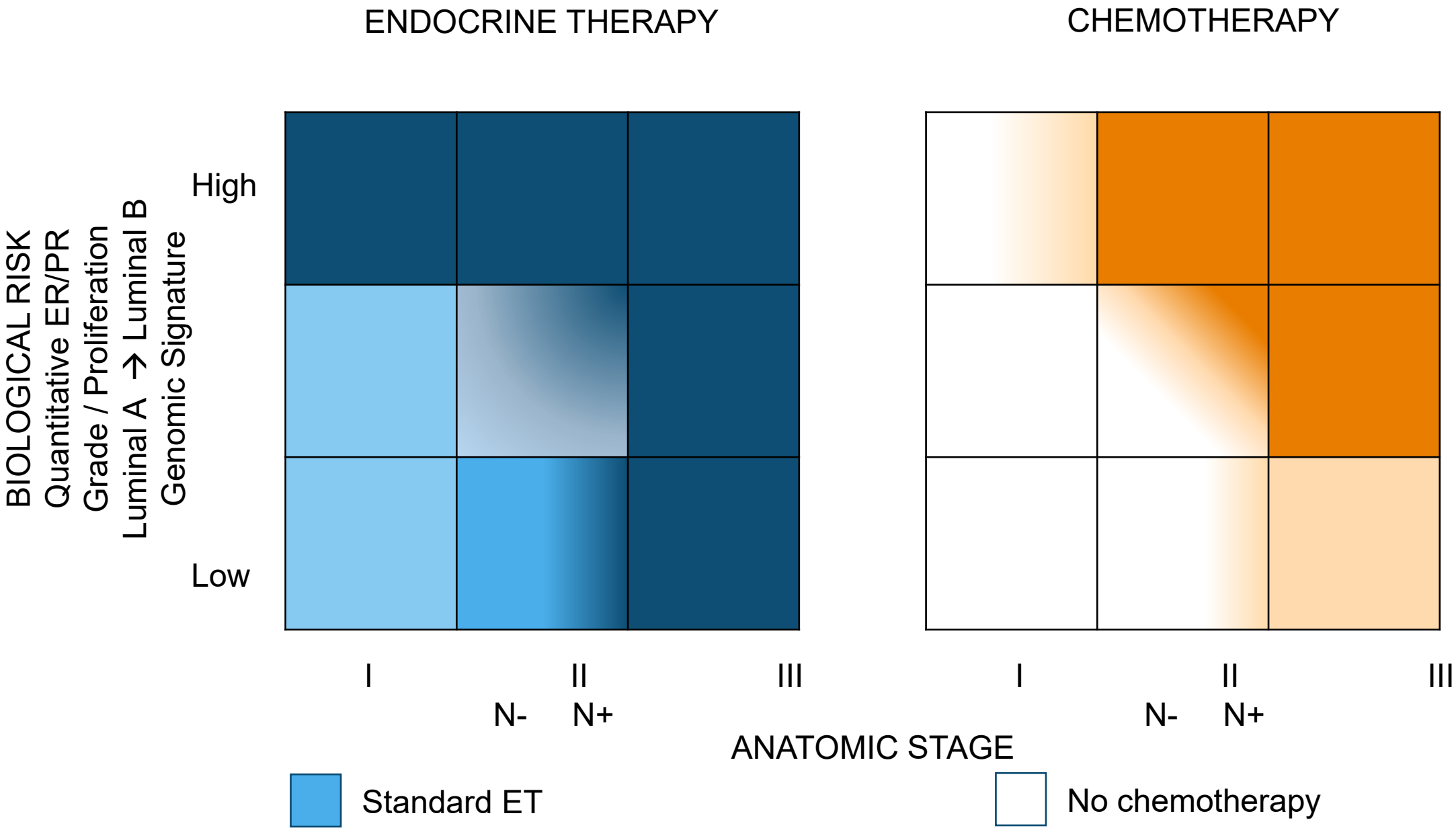
RR: 32%

PFS: 5.5m



Kalinsky K, et al. Ann Oncol 2020:31:1709-18

EARLY STAGE ER+ BREAST CANCER


ENDOCRINE THERAPY
CHEMOTHERAPY
BIOLOGICAL RISK
Quantitative ER/PR
Grade / Proliferation
Luminal A → Luminal B
Genomic Signature
High
Low
I
II
III
N-
N+
I
II
III
N-
N+
ANATOMIC STAGE
Standard ET
Escalated ET (+ OFS, ↑duration)
No chemotherapy
Adjuvant chemotherapy

SOFT & TEXT

Premeno.

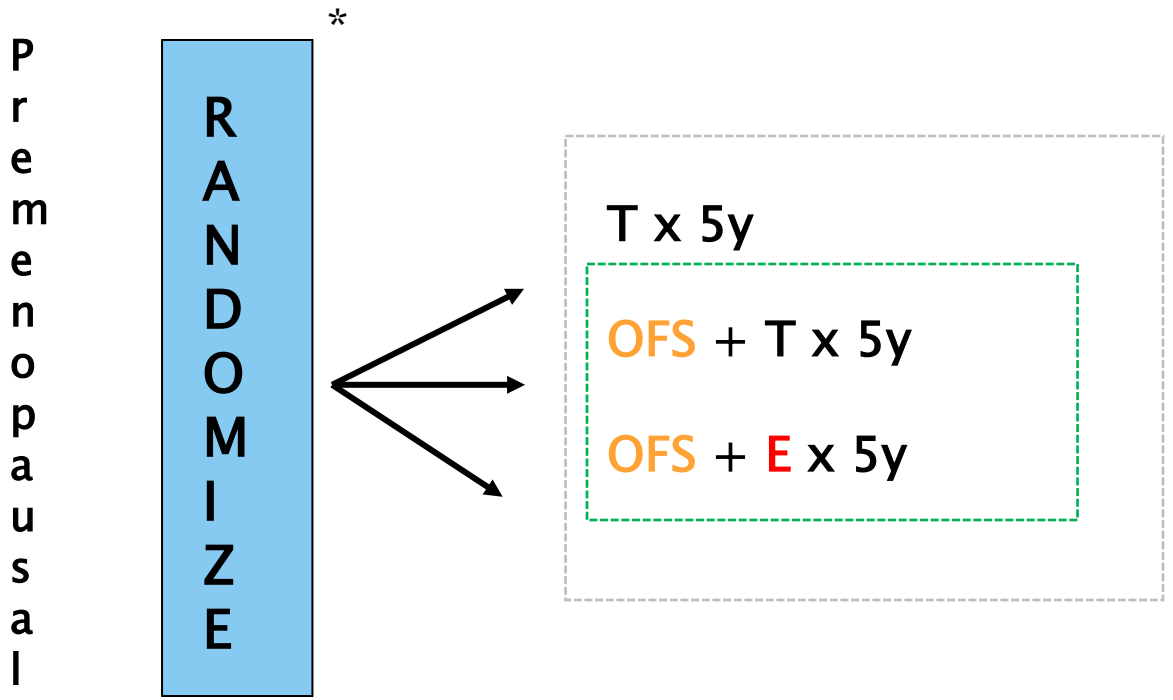
ER ≥ 10% and/or
PgR ≥ 10%

Patients with estradiol (E_2) in the premenopausal range either after CT or without CT

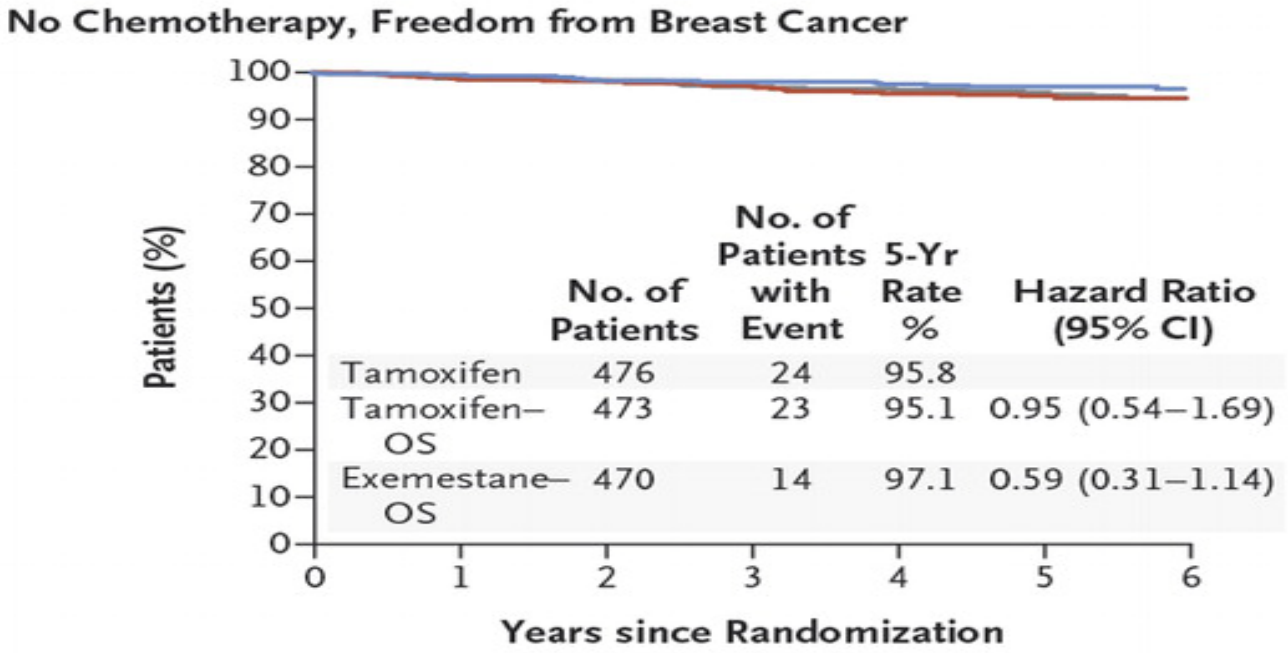
Strata

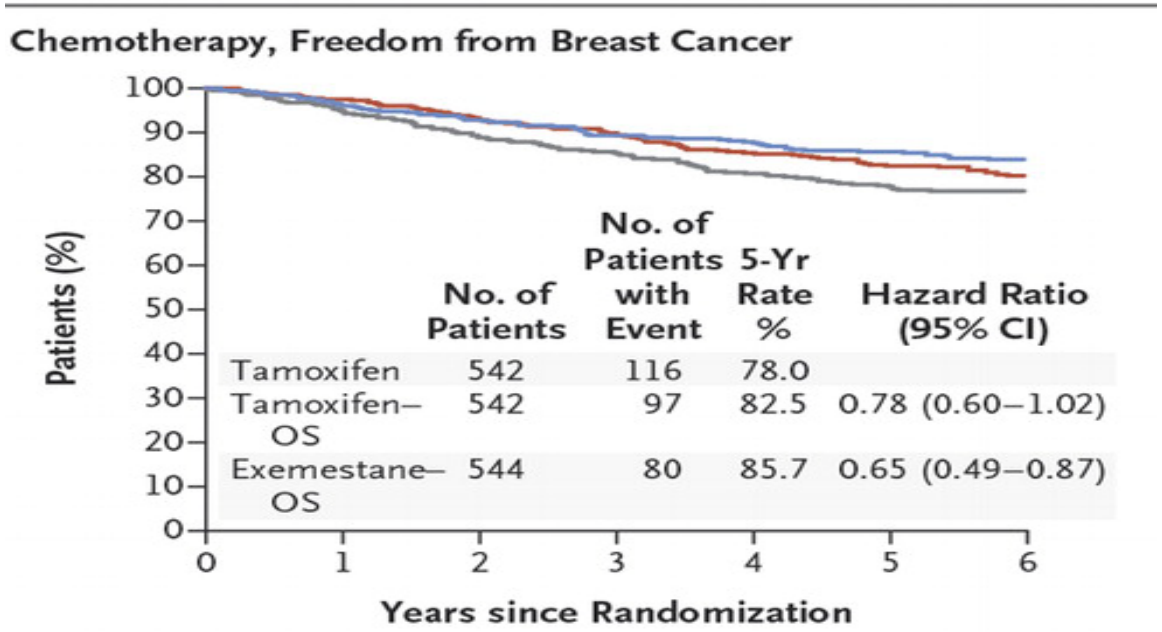
Any CT

No CT



Resolving the Paradox:
SOFT / TEXT – a Tale of Two Populations
The role of ovarian suppression in premenopausal ER+ breast cancer



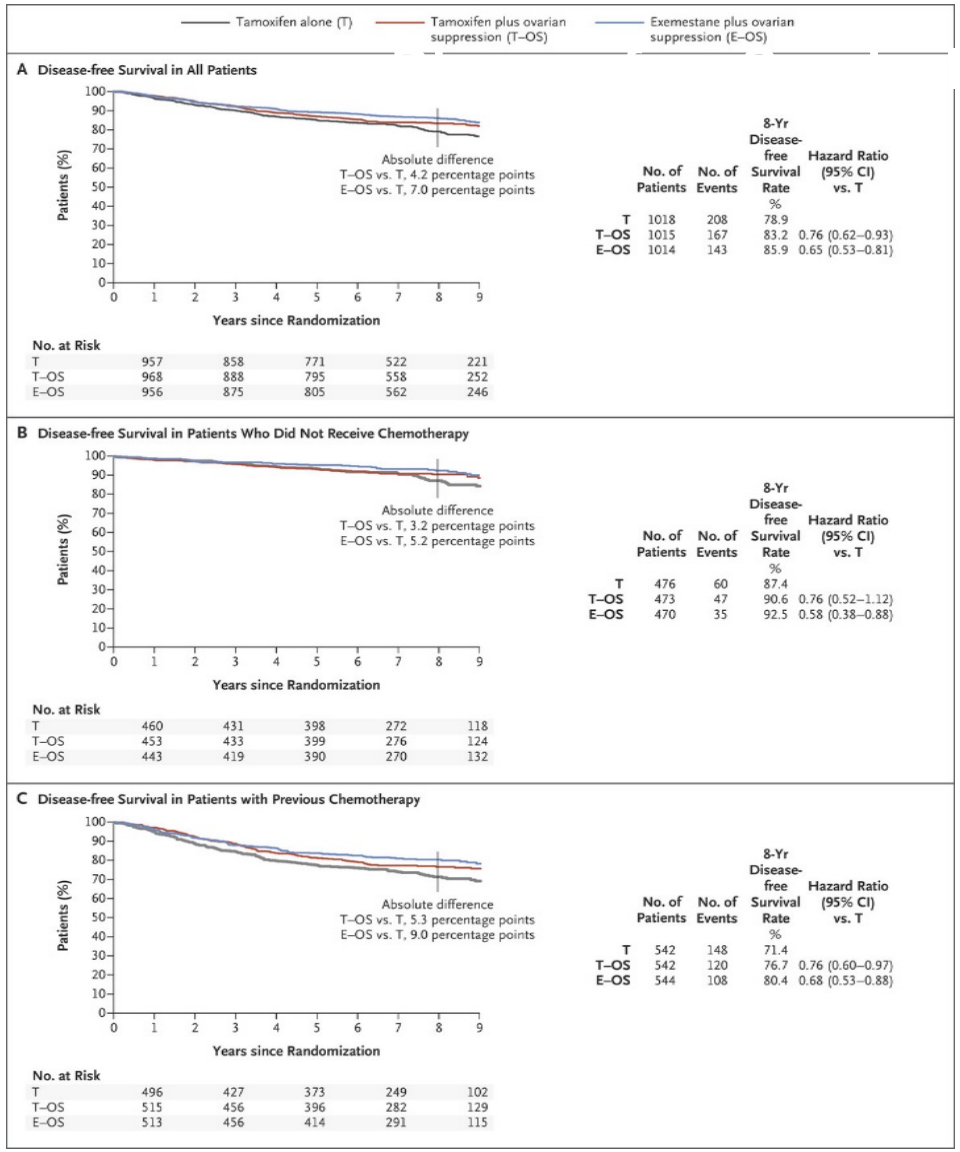


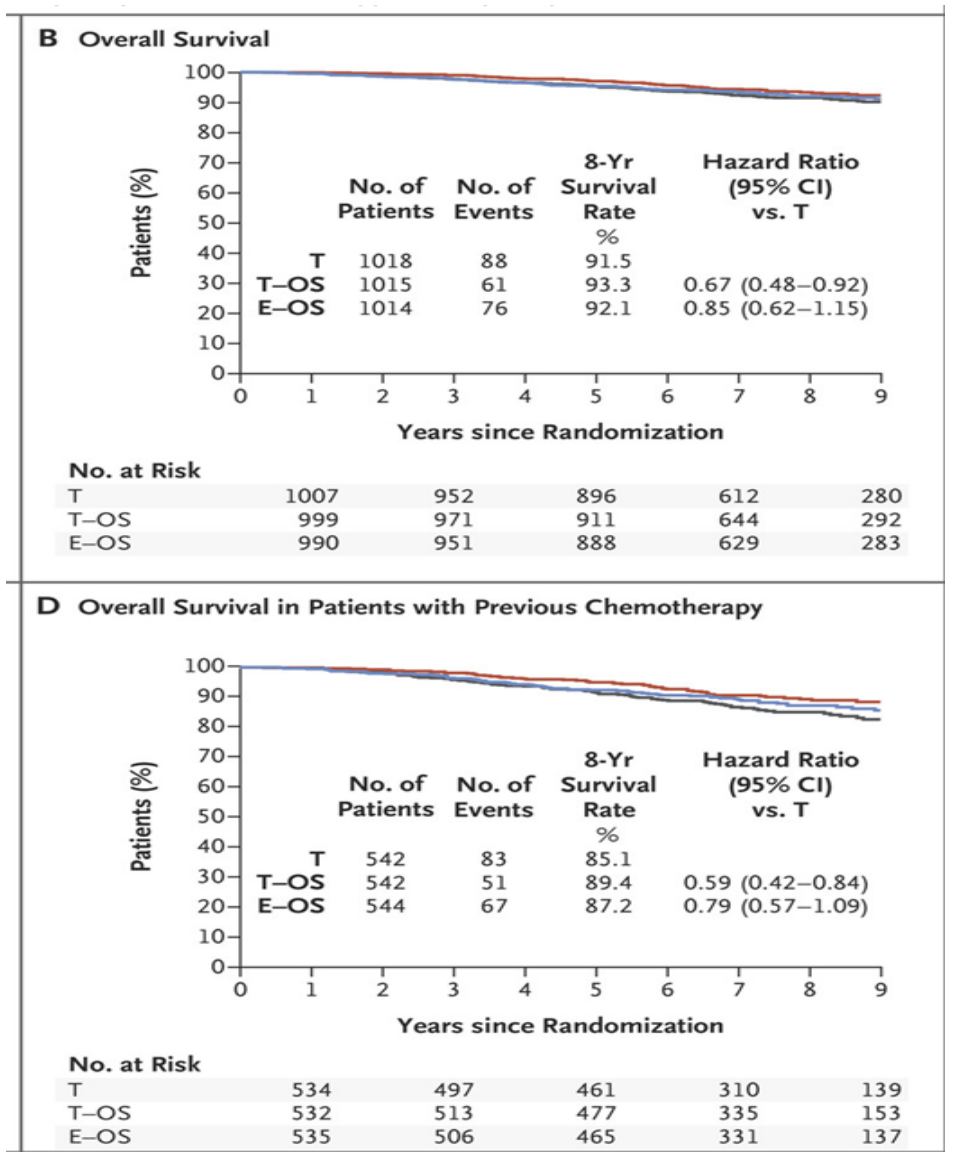
Clinical Assessment	Low Risk	Higher Risk
Chemotherapy	No	Yes
Benefit from OFS	No	Yes

DFS: women < 35 years old

Tam	68%
Tam + OFS	79%
Exe + OFS	83%

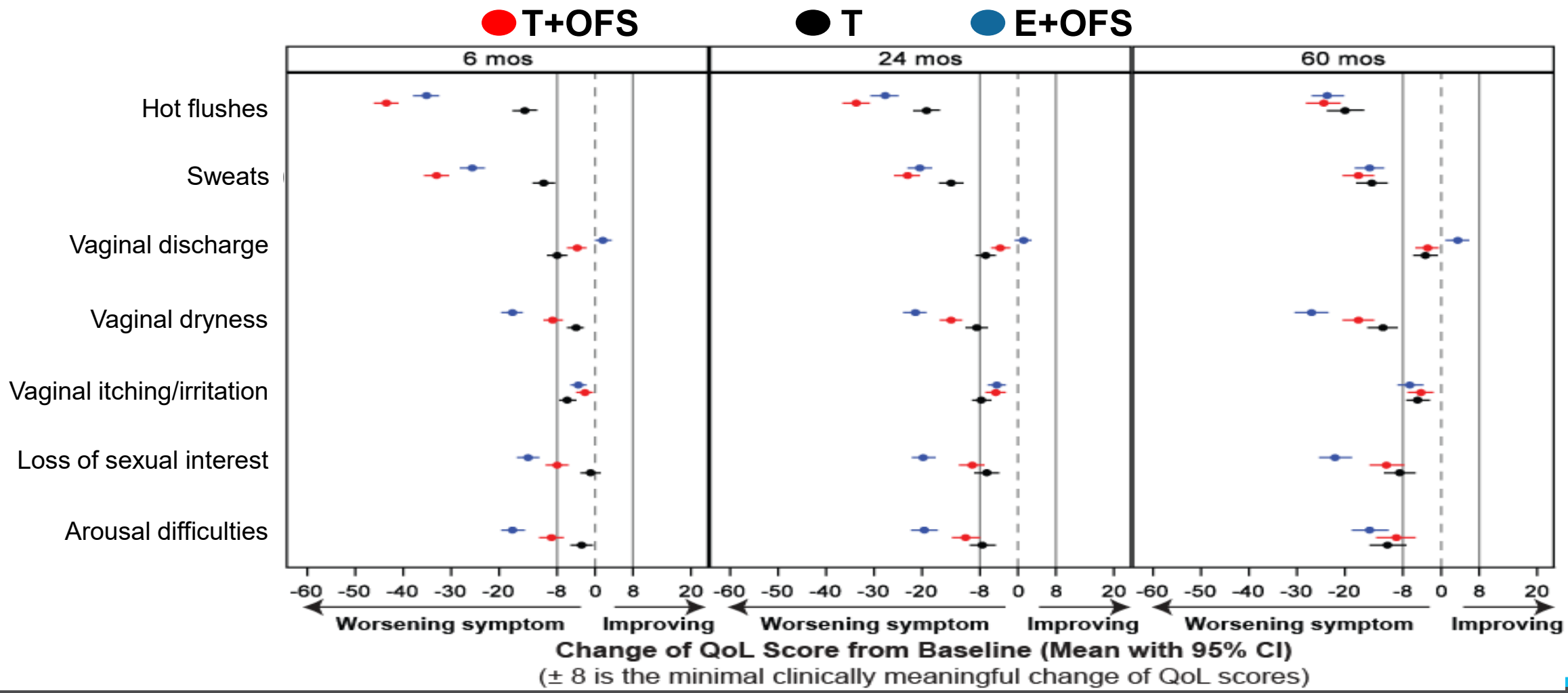
Francis PA et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1412379





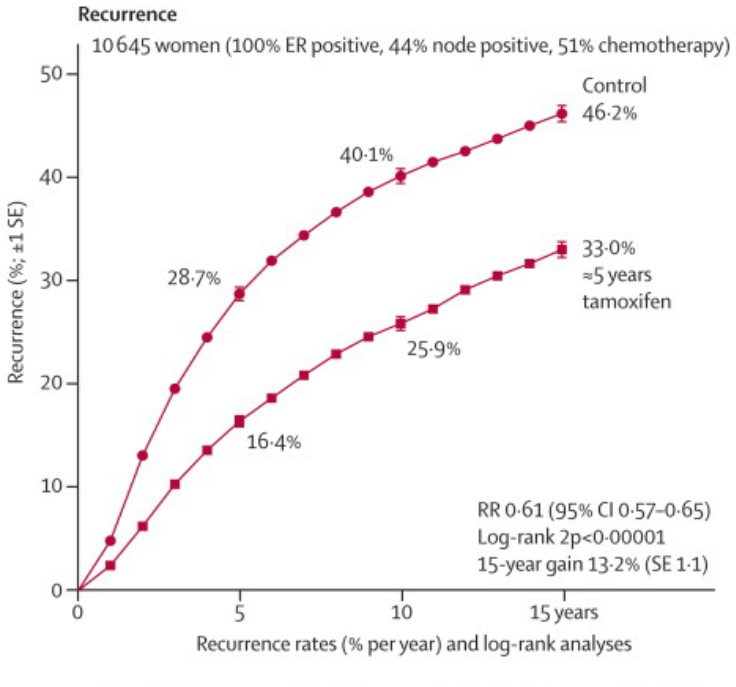
PA Francis et al. N Engl J Med 2018;379:122-137.

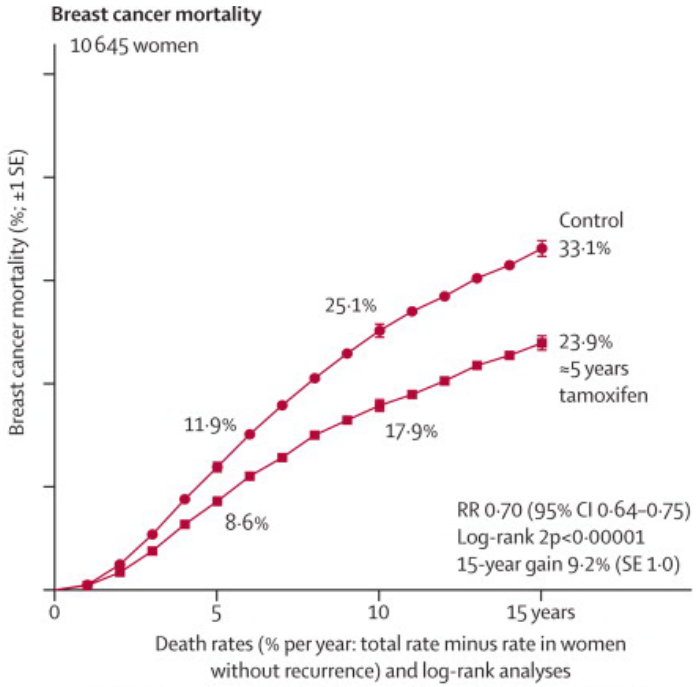
Treatment Effect: Symptoms

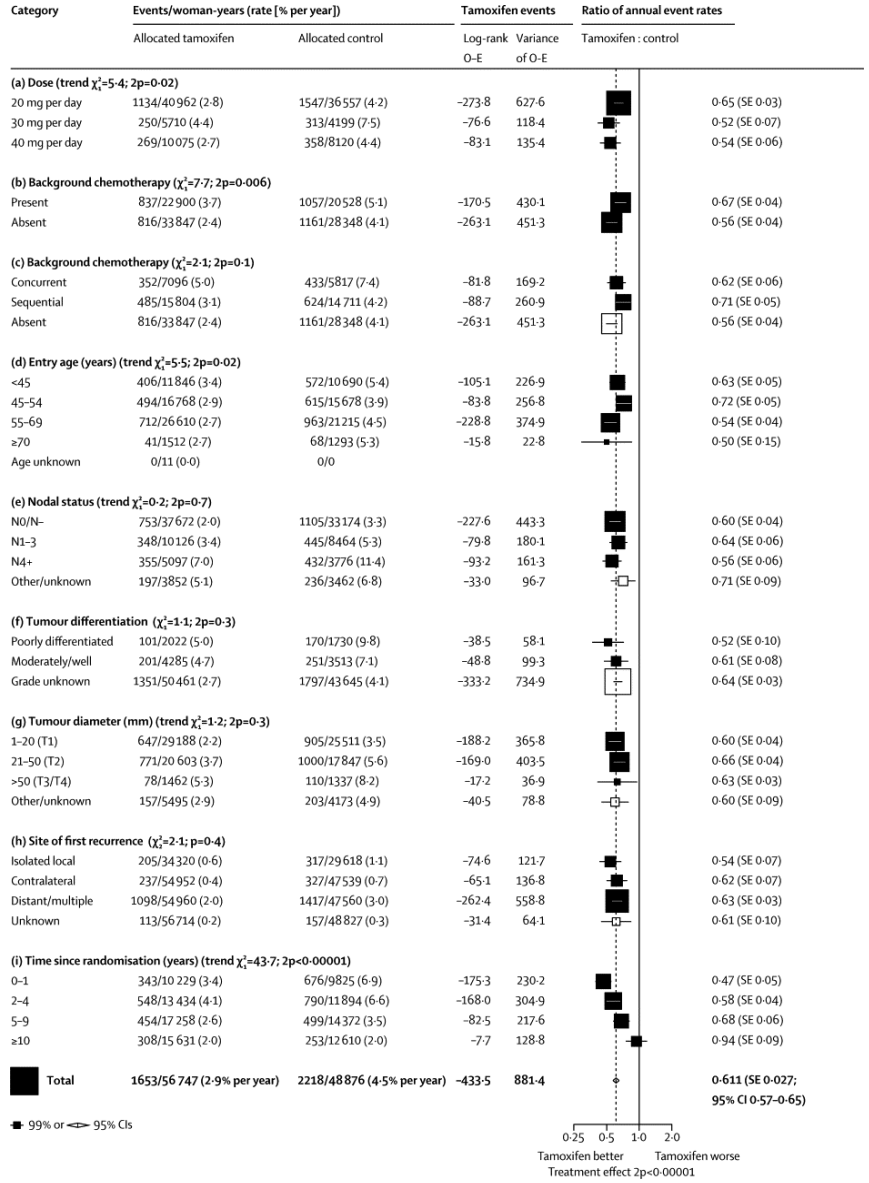


Luo BJ, et al. Lancet Oncol. 2015 Jul;16(7):848-58.

Benefits of Adjuvant Endocrine Therapy





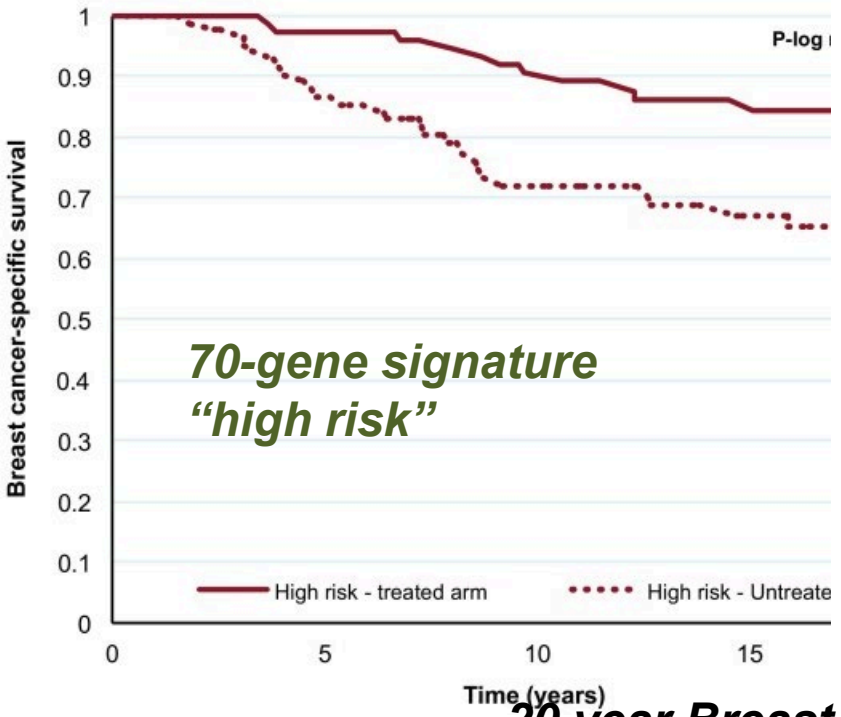


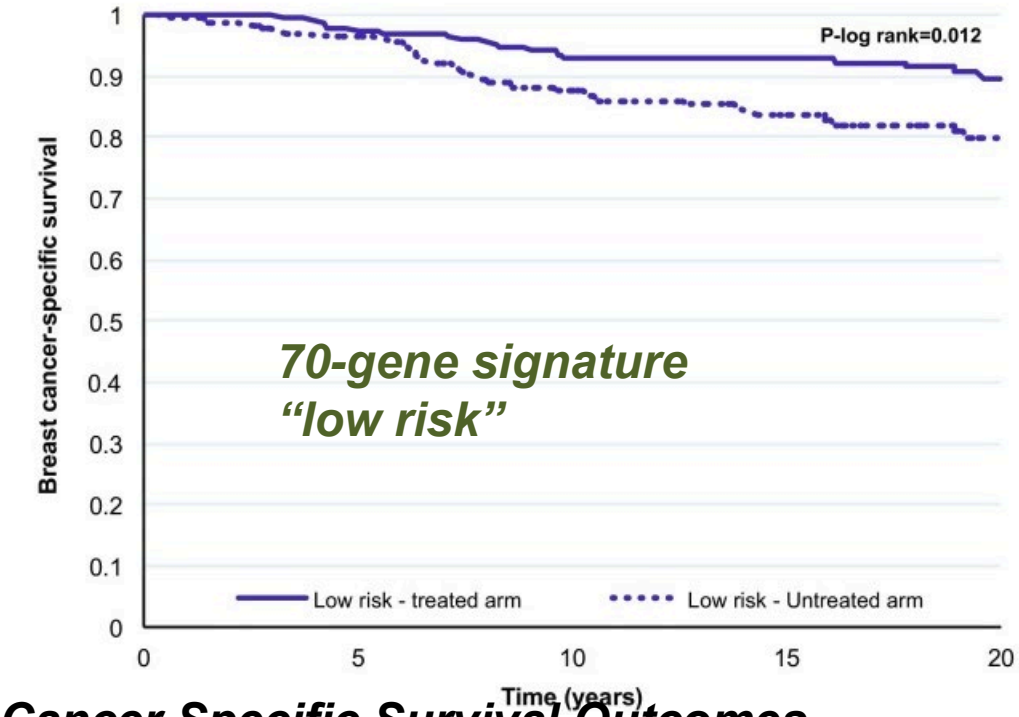
Category	Events/woman-years (rate [% per year])		Tamoxifen events		Ratio of annual event rates
	Allocated tamoxifen	Allocated control	Log-rank O–E	Variance of O–E	Tamoxifen : control
(a) Dose (trend χ^2_1=5·4; 2p=0·02)					
20 mg per day	1134/40 962 (2·8)	1547/36 557 (4·2)	−273·8	627·6	0·65 (SE 0·03)
30 mg per day	250/5710 (4·4)	313/4199 (7·5)	−76·6	118·4	0·52 (SE 0·07)
40 mg per day	269/10 075 (2·7)	358/8120 (4·4)	−83·1	135·4	0·54 (SE 0·06)
(b) Background chemotherapy (χ^2_1=7·7; 2p=0·006)					
Present	837/22 900 (3·7)	1057/20 528 (5·1)	−170·5	430·1	0·67 (SE 0·04)
Absent	816/33 847 (2·4)	1161/28 348 (4·1)	−263·1	451·3	0·56 (SE 0·04)
(c) Background chemotherapy (χ^2_1=2·1; 2p=0·1)					
Concurrent	352/7096 (5·0)	433/5817 (7·4)	−81·8	169·2	0·62 (SE 0·06)
Sequential	485/15 804 (3·1)	624/14 711 (4·2)	−88·7	260·9	0·71 (SE 0·05)
Absent	816/33 847 (2·4)	1161/28 348 (4·1)	−263·1	451·3	0·56 (SE 0·04)
(d) Entry age (years) (trend χ^2_1=5·5; 2p=0·02)					
<45	406/11 846 (3·4)	572/10 690 (5·4)	−105·1	226·9	0·63 (SE 0·05)
45–54	494/16 768 (2·9)	615/15 678 (3·9)	−83·8	256·8	0·72 (SE 0·05)
55–69	712/26 610 (2·7)	963/21 215 (4·5)	−228·8	374·9	0·54 (SE 0·04)
≥70	41/1512 (2·7)	68/1293 (5·3)	−15·8	22·8	0·50 (SE 0·15)
Age unknown	0/11 (0·0)	0/0			
(e) Nodal status (trend χ^2_1=0·2; 2p=0·7)					
N0/N–	753/37 672 (2·0)	1105/33 174 (3·3)	−227·6	443·3	0·60 (SE 0·04)
N1–3	348/10 126 (3·4)	445/8464 (5·3)	−79·8	180·1	0·64 (SE 0·06)
N4+	355/5097 (7·0)	432/3776 (11·4)	−93·2	161·3	0·56 (SE 0·06)
Other/unknown	197/3852 (5·1)	236/3462 (6·8)	−33·0	96·7	0·71 (SE 0·09)
(f) Tumour differentiation (χ^2_1=1·1; 2p=0·3)					
Poorly differentiated	101/2022 (5·0)	170/1730 (9·8)	−38·5	58·1	0·52 (SE 0·10)
Moderately/well	201/4285 (4·7)	251/3513 (7·1)	−48·8	99·3	0·61 (SE 0·08)
Grade unknown	1351/50 461 (2·7)	1797/43 645 (4·1)	−333·2	734·9	0·64 (SE 0·03)
(g) Tumour diameter (mm) (trend χ^2_1=1·2; 2p=0·3)					
1–20 (T1)	647/29 188 (2·2)	905/25 511 (3·5)	−188·2	365·8	0·60 (SE 0·04)
21–50 (T2)	771/20 603 (3·7)	1000/17 847 (5·6)	−169·0	403·5	0·66 (SE 0·04)
>50 (T3/T4)	78/1462 (5·3)	110/1337 (8·2)	−17·2	36·9	0·63 (SE 0·03)
Other/unknown	157/5495 (2·9)	203/4173 (4·9)	−40·5	78·8	0·60 (SE 0·09)
(h) Site of first recurrence (χ^2_1=2·1; p=0·4)					
Isolated local	205/34 320 (0·6)	317/29 618 (1·1)	−74·6	121·7	0·54 (SE 0·07)
Contralateral	237/54 952 (0·4)	327/47 539 (0·7)	−65·1	136·8	0·62 (SE 0·07)
Distant/multiple	1098/54 960 (2·0)	1417/47 560 (3·0)	−262·4	558·8	0·63 (SE 0·03)
Unknown	113/5674 (0·2)	157/4827 (0·3)	−31·4	64·1	0·61 (SE 0·10)
(i) Time since randomisation (years) (trend χ^2_1=43·7; 2p<0·00001)					
0–1	343/10 229 (3·4)	676/9825 (6·9)	−175·3	230·2	0·47 (SE 0·05)
2–4	548/13 434 (4·1)	790/11 894 (6·6)	−168·0	304·9	0·58 (SE 0·04)
5–9	454/17 258 (2·6)	499/14 372 (3·5)	−82·5	217·6	0·68 (SE 0·06)
≥10	308/15 631 (2·0)	253/12 610 (2·0)	−7·7	128·8	0·94 (SE 0·09)
Total	**1653/56 747 (2·9% per year)**	**2218/48 876 (4·5% per year)**	**−433·5**	**881·4**	**0·611 (SE 0·027; 95% CI 0·57–0·65)**

EBCTCG Investigators. Lancet 2011;378:771-84.

Adjuvant Tamoxifen: Effect by Genomic Subtype

STO-3 Trial 1976-1990, T<3 cm, N0, postmenopausal
Tamoxifen (2-5 years) vs nil



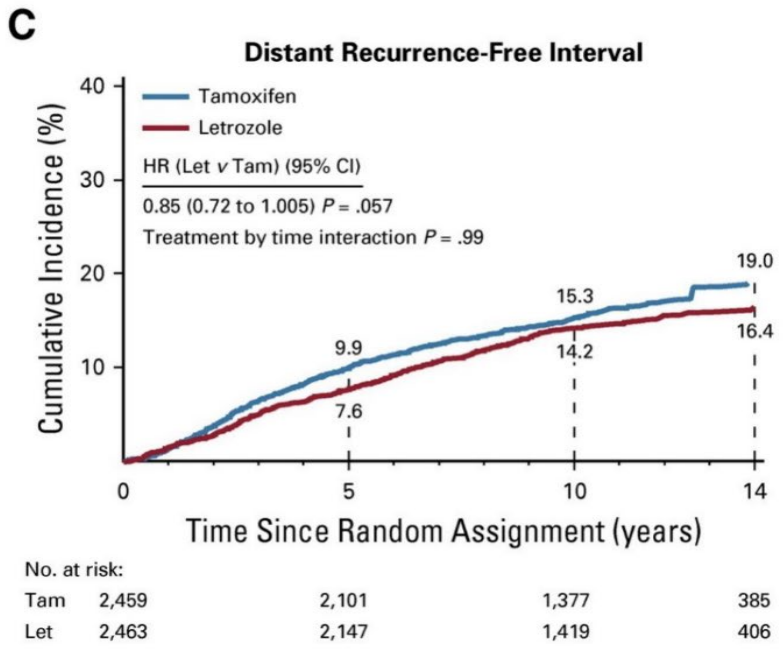


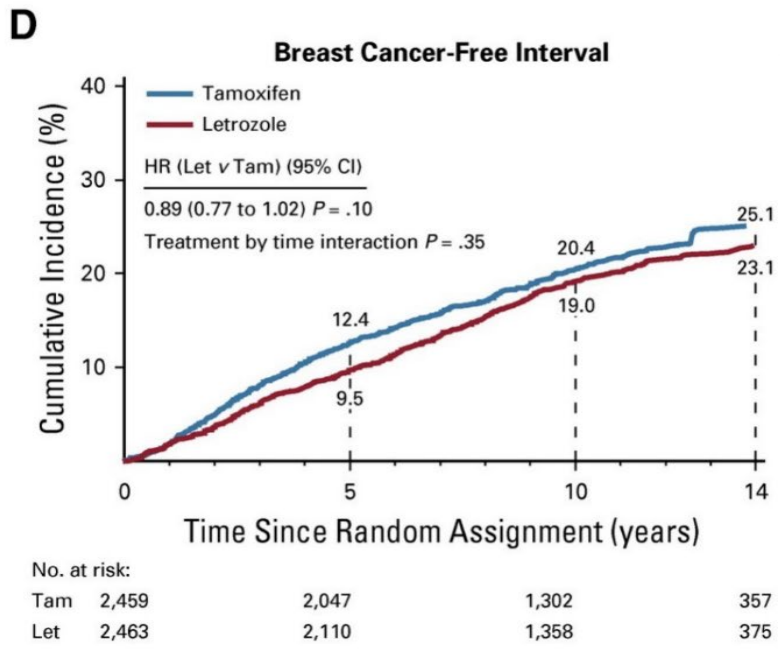
20 year Breast Cancer Specific Survival Outcomes

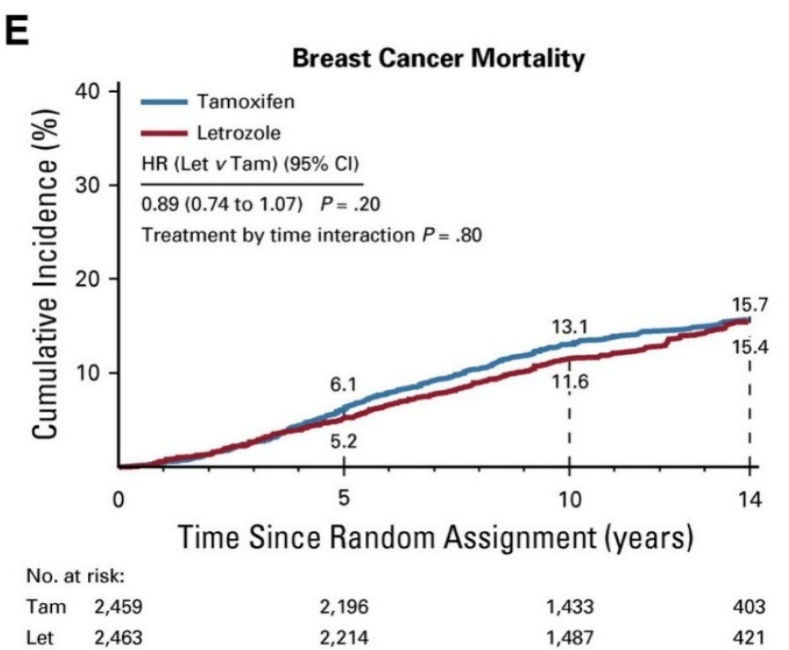
70-gene	No Therapy	Tamoxifen	HR	Benefit
"High"	65%	83%	0.42	18%
"Low"	80%	90%	0.46	10%

Van't Veer LJ, et al. Breast Cancer Res Treatment 2017;166:593-601

BIG 1-98. Long Term Outcomes AI vs Tamoxifen

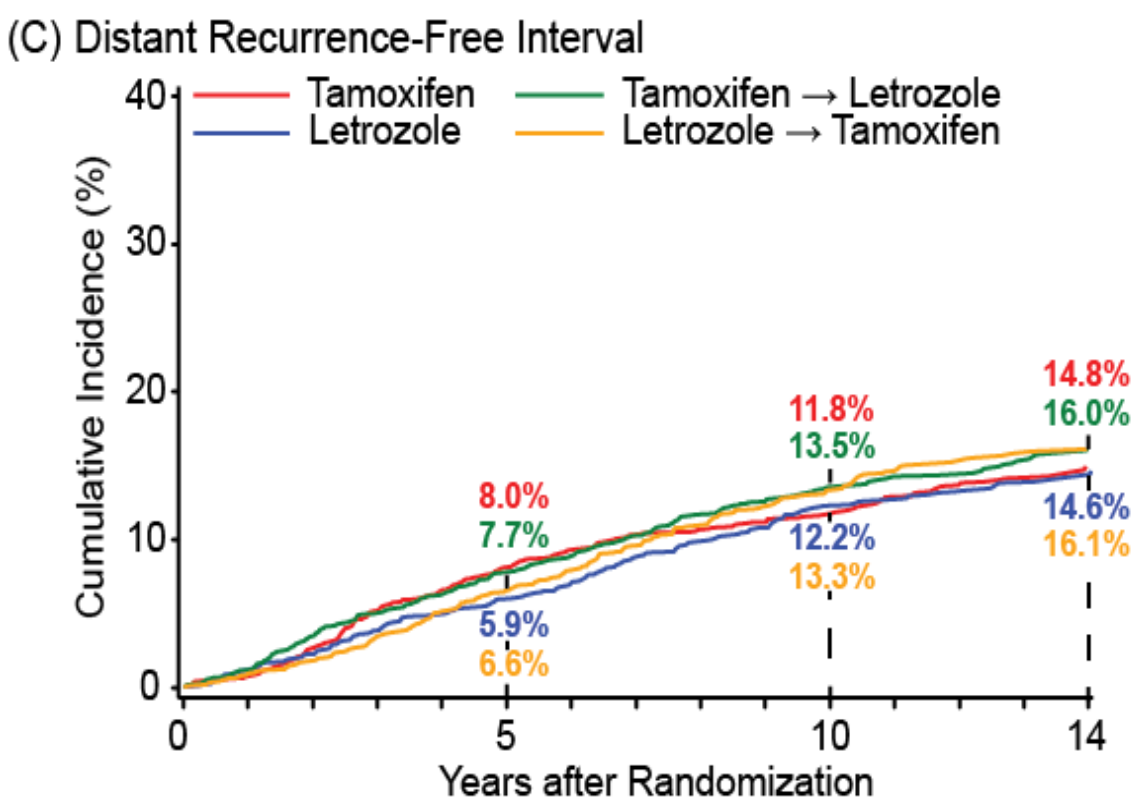


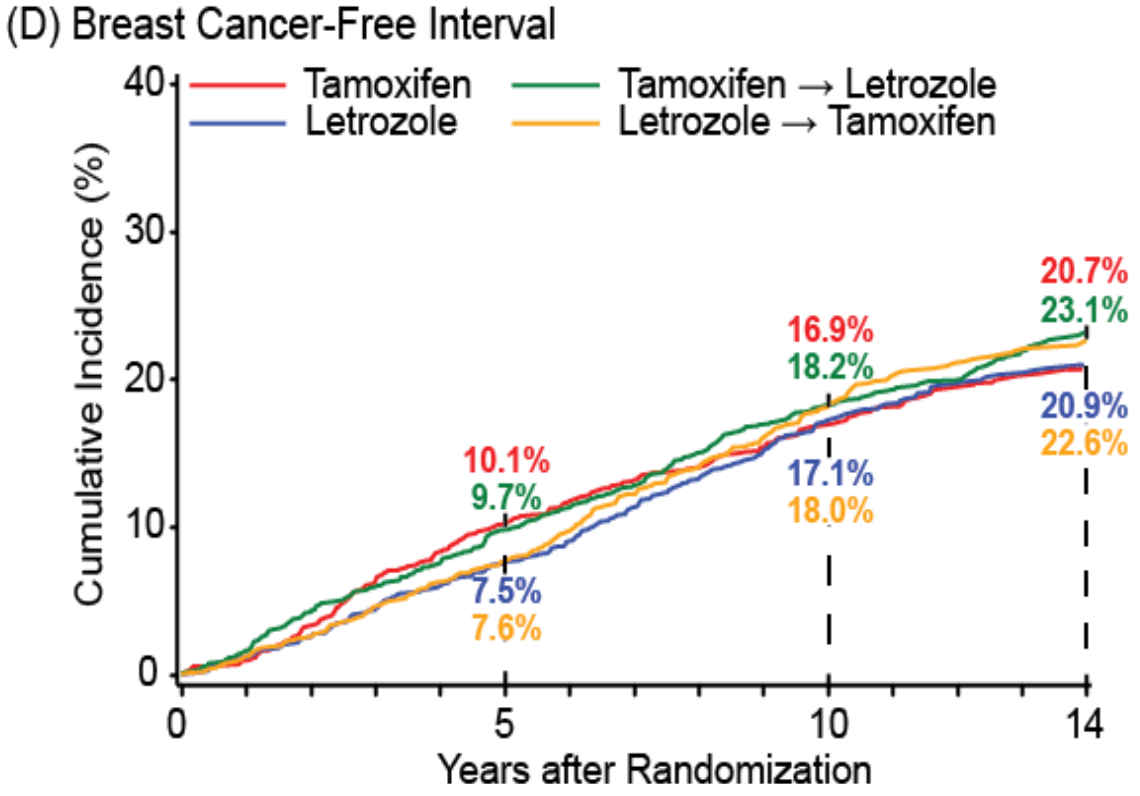




Ruhstaller T, et al. *Journal of Clinical Oncology* 2019 37105-114.

BIG 1-98. Long Term Outcomes
AI vs Tamoxifen vs Sequential

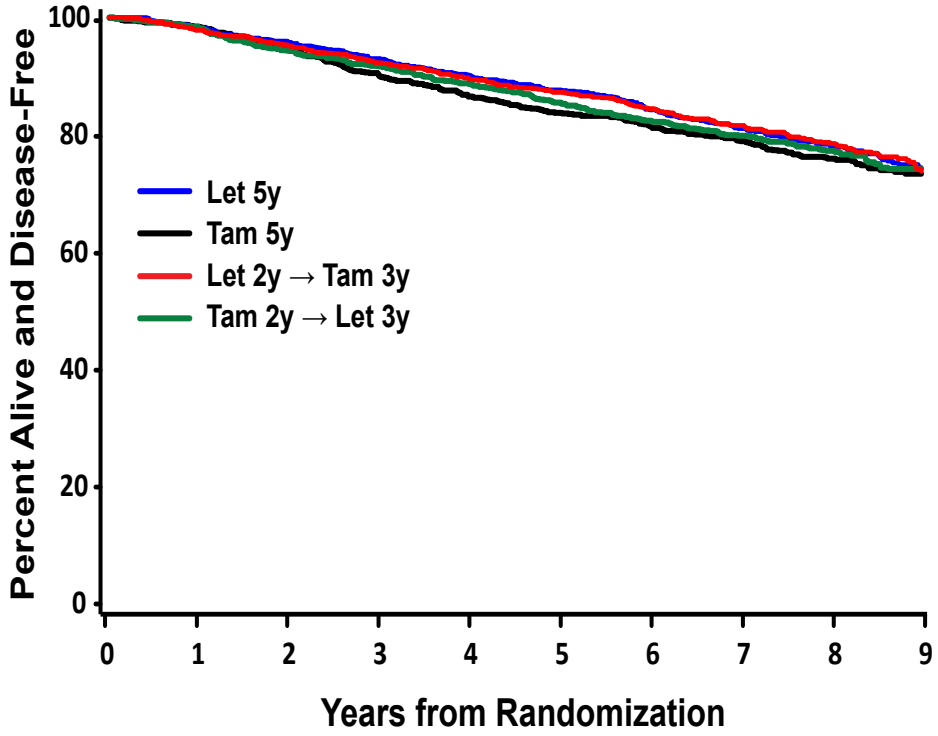




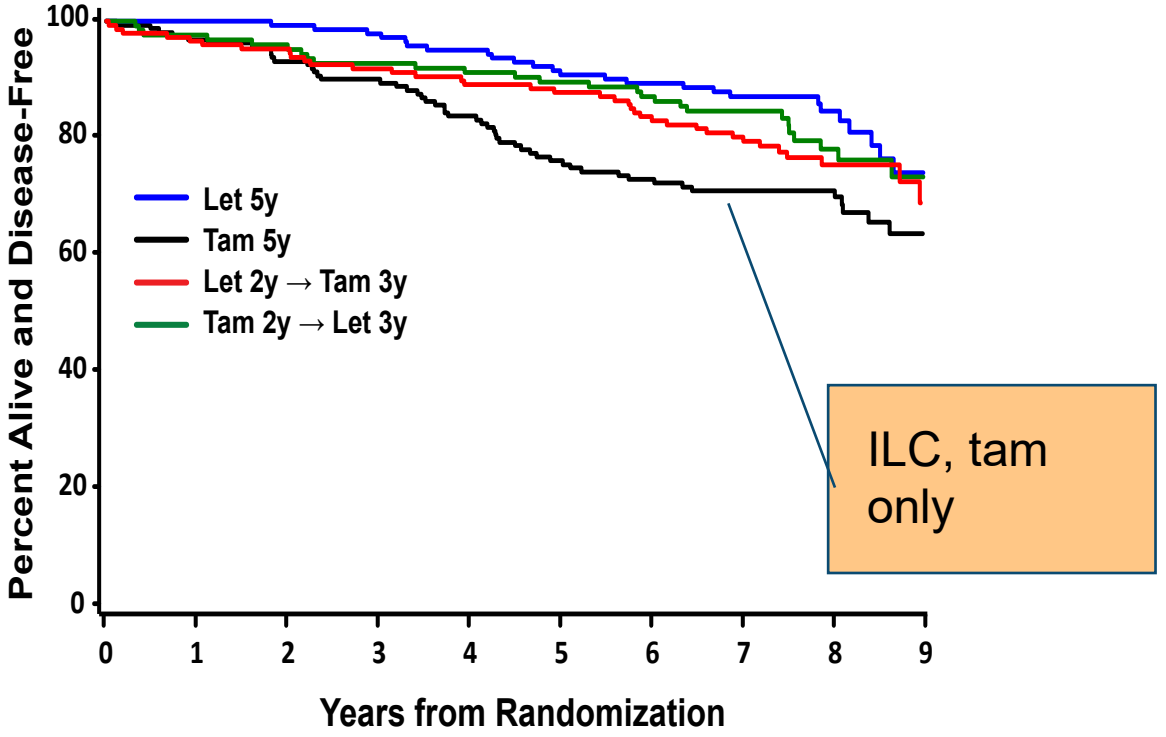
Ruhstaller T, et al. *Journal of Clinical Oncology* 2019 37105-114.

BIG 1-98. Outcomes by Histological Subtype

Ductal



Lobular

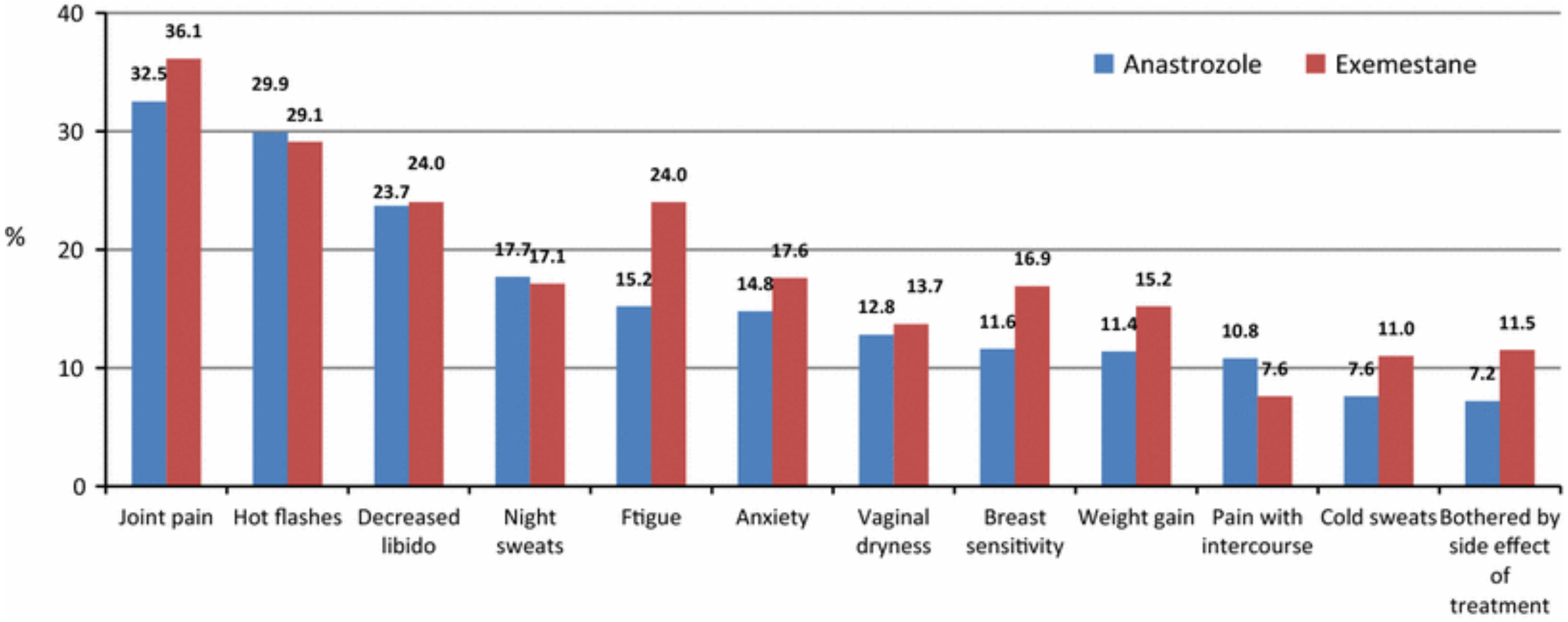


	Ductal HR (95% CI)	Lobular HR (95% CI)
Let vs. Tam-Let	0.989 (0.82 to 1.20)	0.709 (0.40 to 1.25)
Let vs. Let-Tam	0.970 (0.80 to 1.18)	0.655 (0.38 to 1.12)
Let vs. Tam	0.903 (0.75 to 1.09)	0.492 (0.30 to 0.82)
Let-Tam vs. Tam	0.931 (0.77 to 1.13)	0.751 (0.48 to 1.18)
Tam-Let vs. Tam	0.913 (0.76 to 1.10)	0.693 (0.43 to 1.12)

Log-rank p= 0.06 Interaction p-value (Histology by treatment) = 0.18

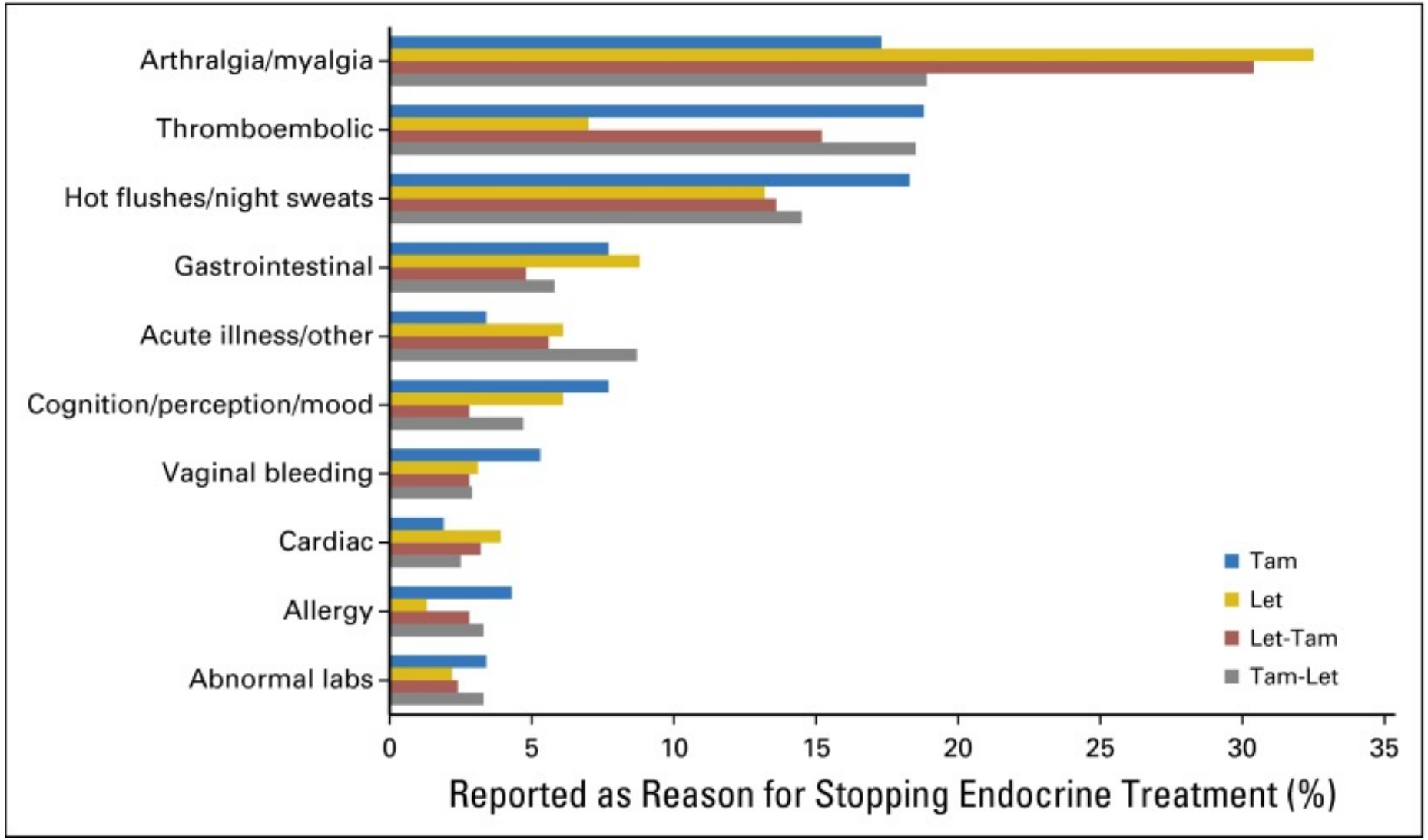
Metzger O, et al.

New onset of symptoms with adjuvant AI therapy: MA27 study



Wagner LI, et al. Breast Cancer Res Treatment 2018;169:537-548

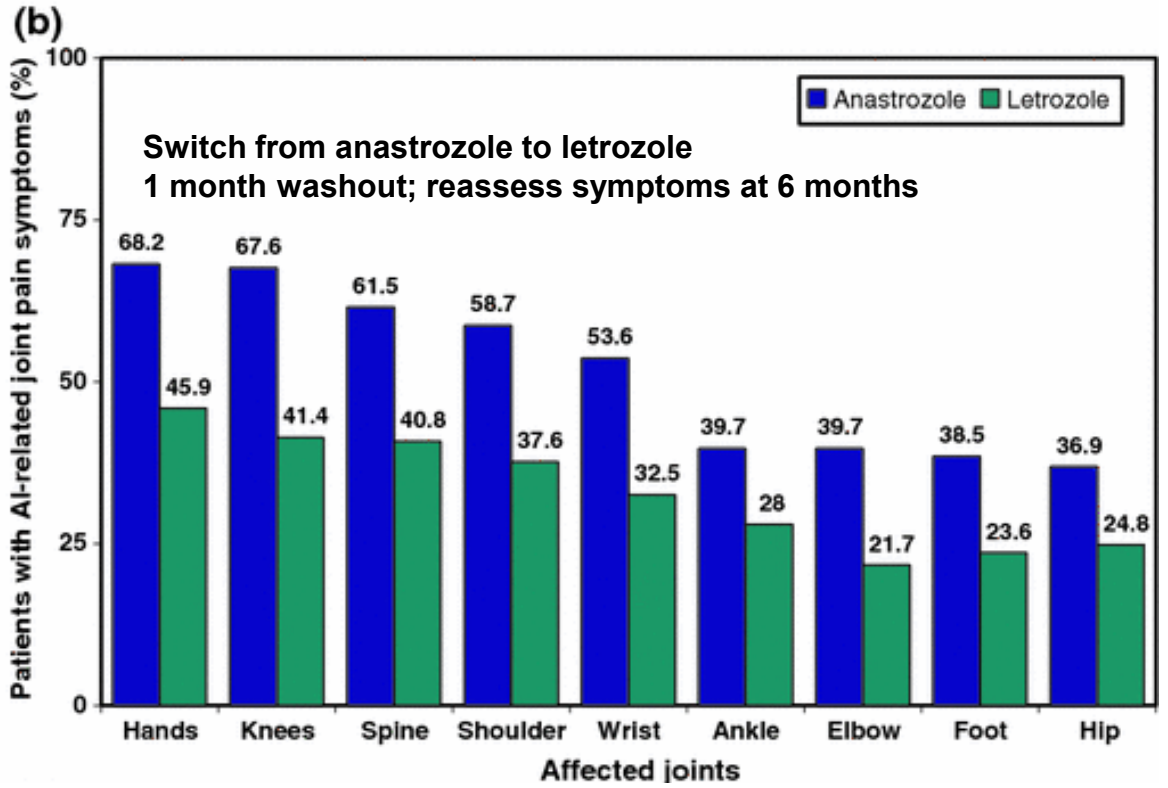
Reasons for Stopping Endocrine Therapy in BIG 1-98



Chirgwin JH et al. J Clin Oncol 2016:34:2452-2459

Switching ET may address symptoms affecting persistence/compliance

	Number of switches	% successful switches
Total	82	65.9%
Tamoxifen → AI	36	58.3%
AI → tamoxifen	17	76.5%
AI → AI	29	69.0%

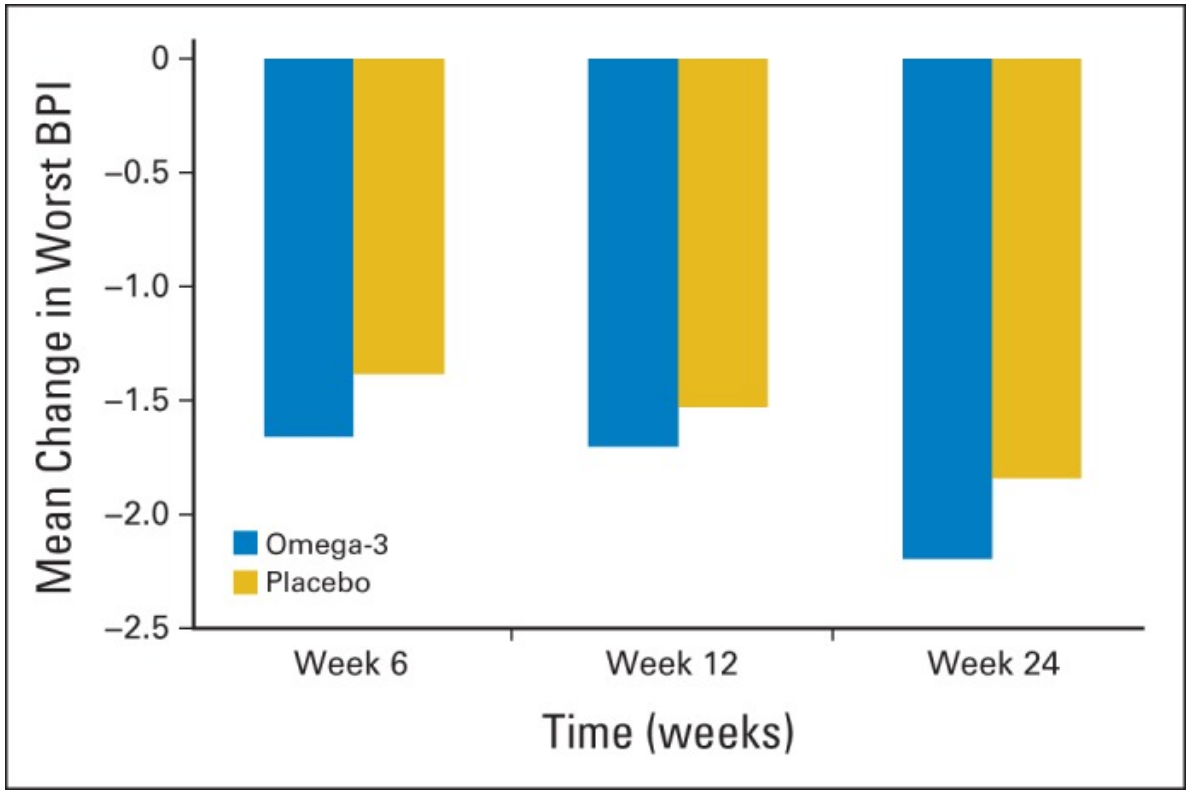


Guth U, et al.
Breast Cancer Res Treatment 2011;129:799

Briot K, et al.
Breast Cancer Res Treatment 2010;120:127-134.

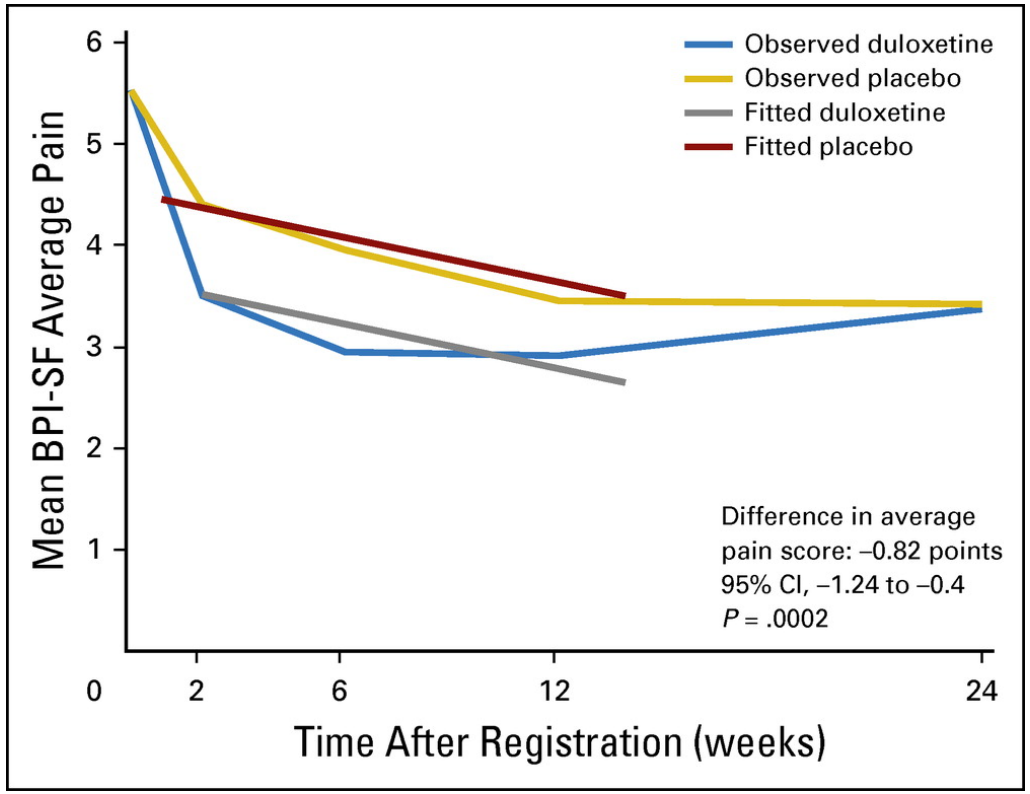
Interventions for AI-associated Arthralgias

Omega-3 Fatty Acid Supplements: SWOG S0927



Hershman DL, et al. J Clin Oncol 2015;33:1910-1917.

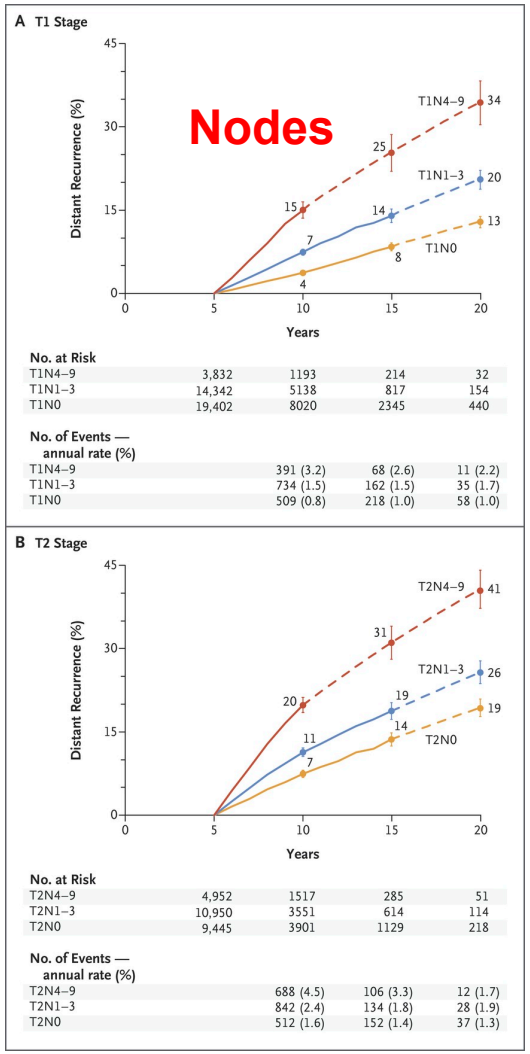
Duloxetine: SWOG S1201

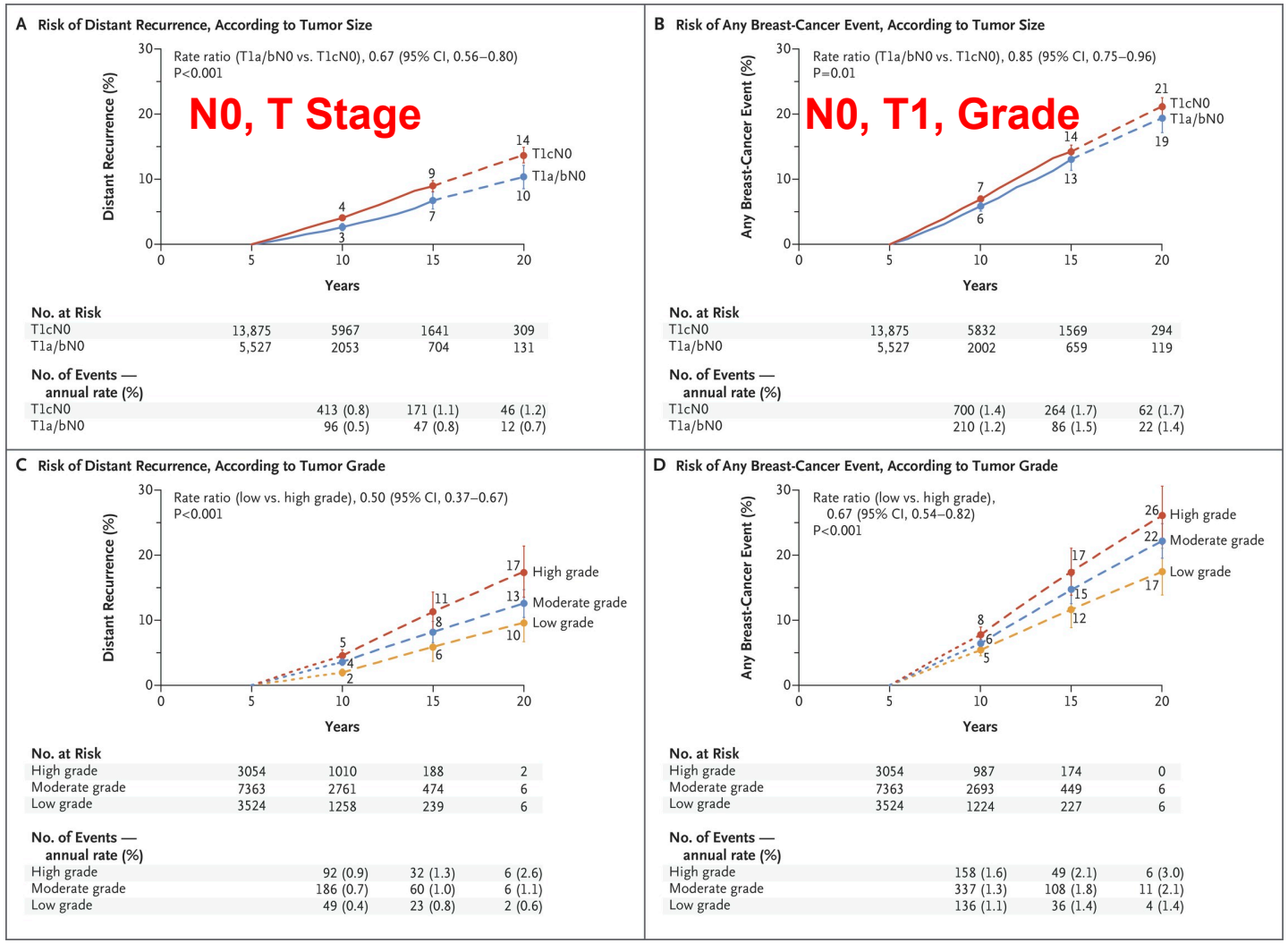


Henry NL, et al. J Clin Oncol 2018; 36: 326-332.

Duration of endocrine therapy

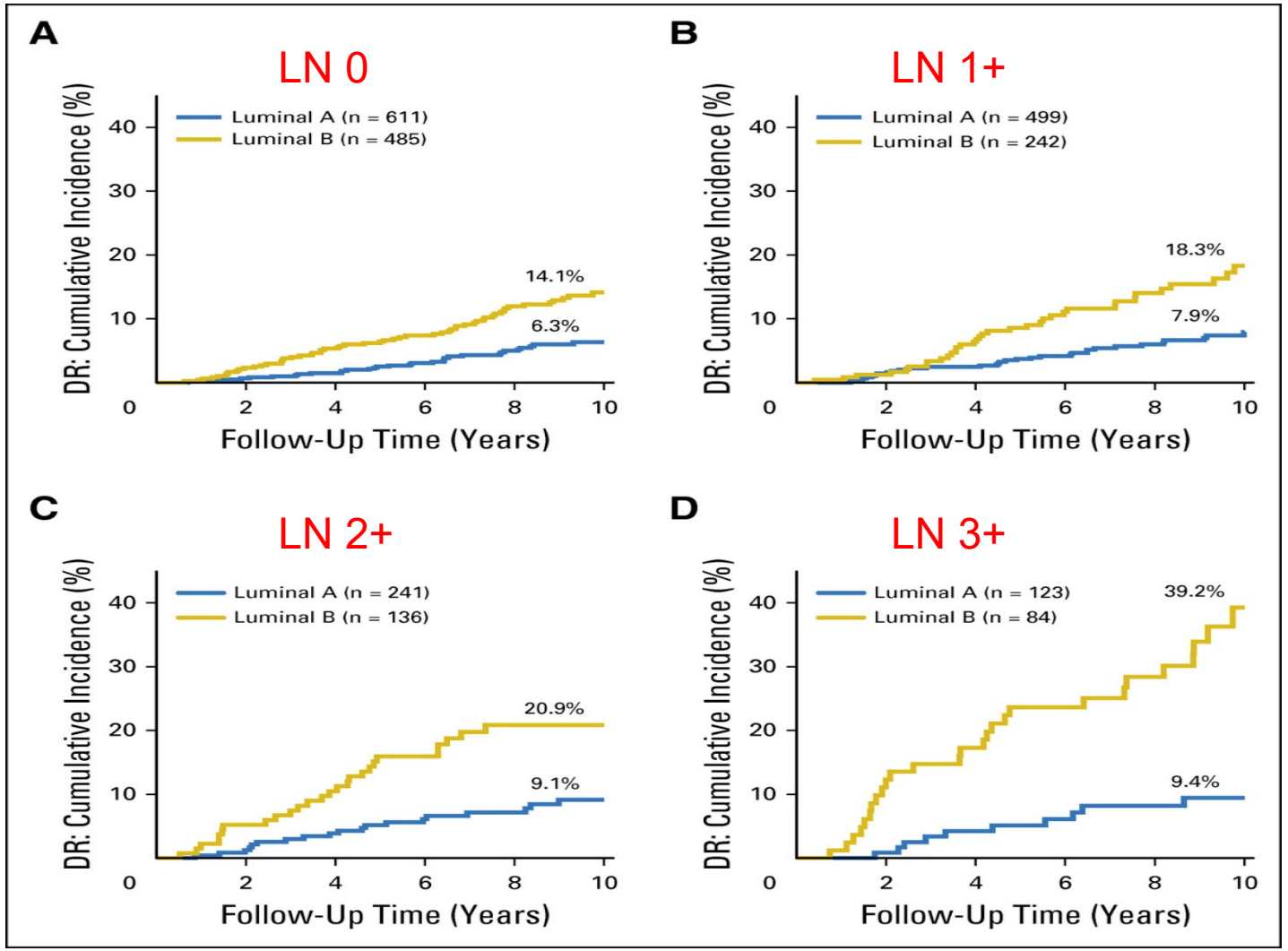
Association of Nodal Status Tumor Diameter and Tumor Grade with the Risk of Distant Recurrence or Any Breast-Cancer Event during Years 5 to 20 of the Study.



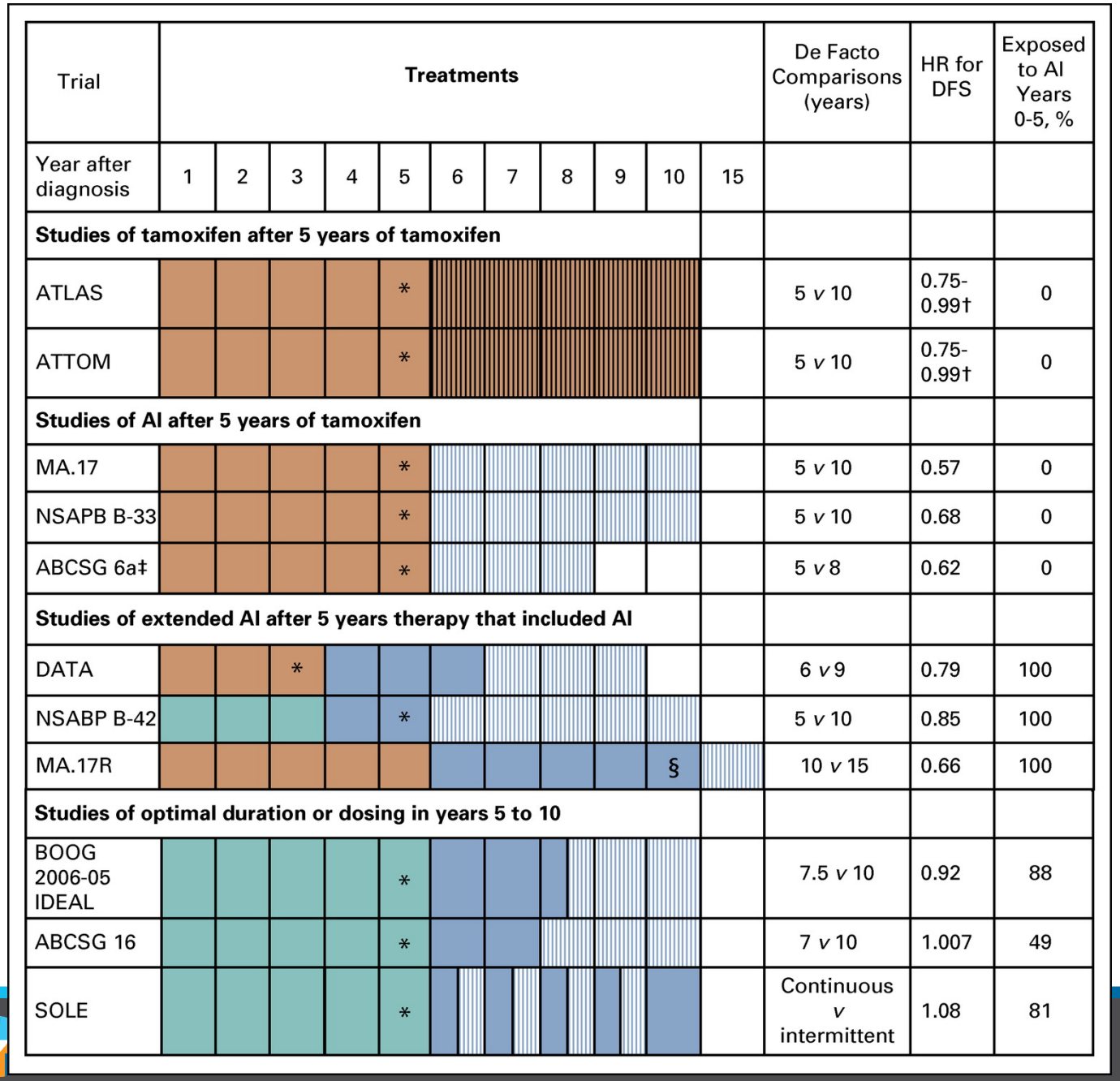


Ren H et al. N Engl J Med 2017;377:1836-1846

LN Status, Genomic Subtype and Recurrence Risk after 5 years of ET: Danish Cohort Study



Lænkholm; et al
J Clin Oncol 2018;36:735-740.



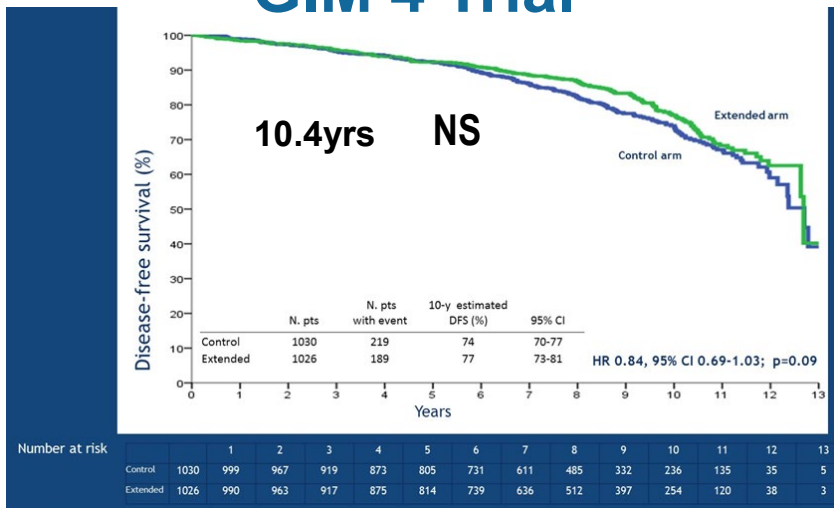
TRIALS of EXTENDED ADJUVANT ENDOCRINE THERAPY

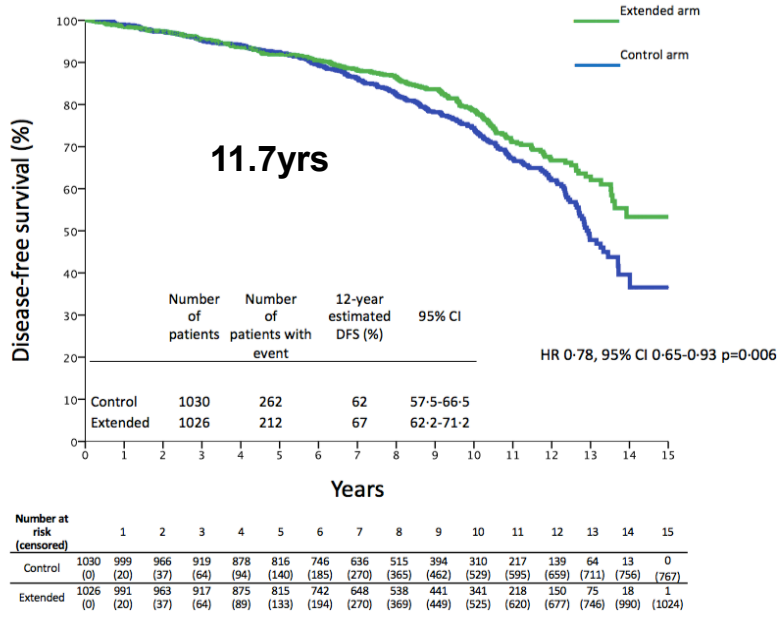
Strategy	DFS HR Ranges	EBCTCG DFS HR
Tam → Tam	0.75	
Tam → AI	0.57- 0.68	0.67
AI ± Tam → AI	0.55 – 0.85	0.82
AI → AI		0.76
7+ years → 10	0.92 – 1.08	

Burstein HJ, Griggs JJ, et al.
J Clin Oncol 2019;37:423-438

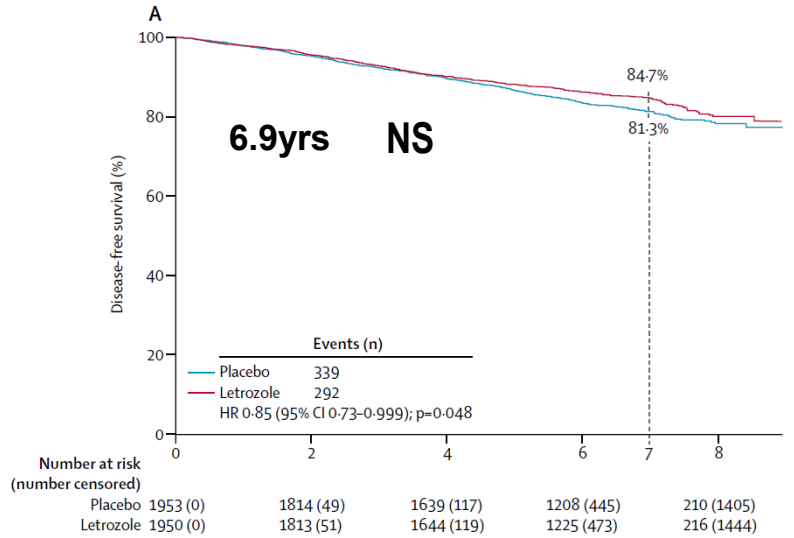
Late benefit of extended AI

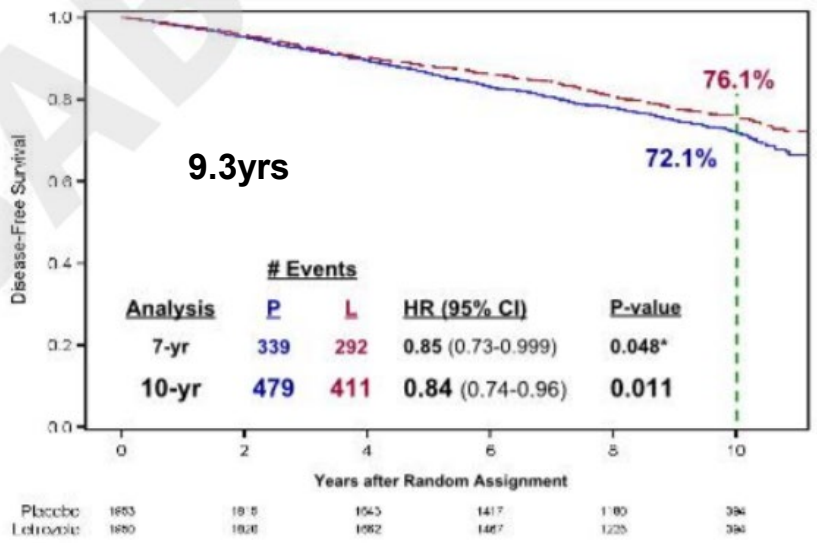
GIM 4 Trial





NSABP B42



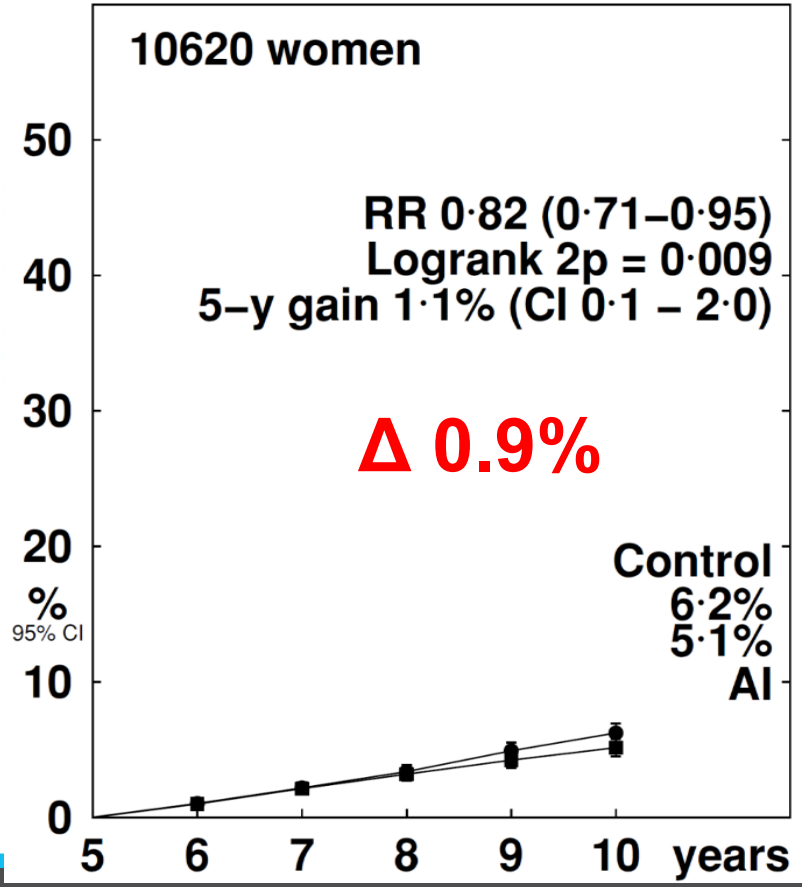


Content of this

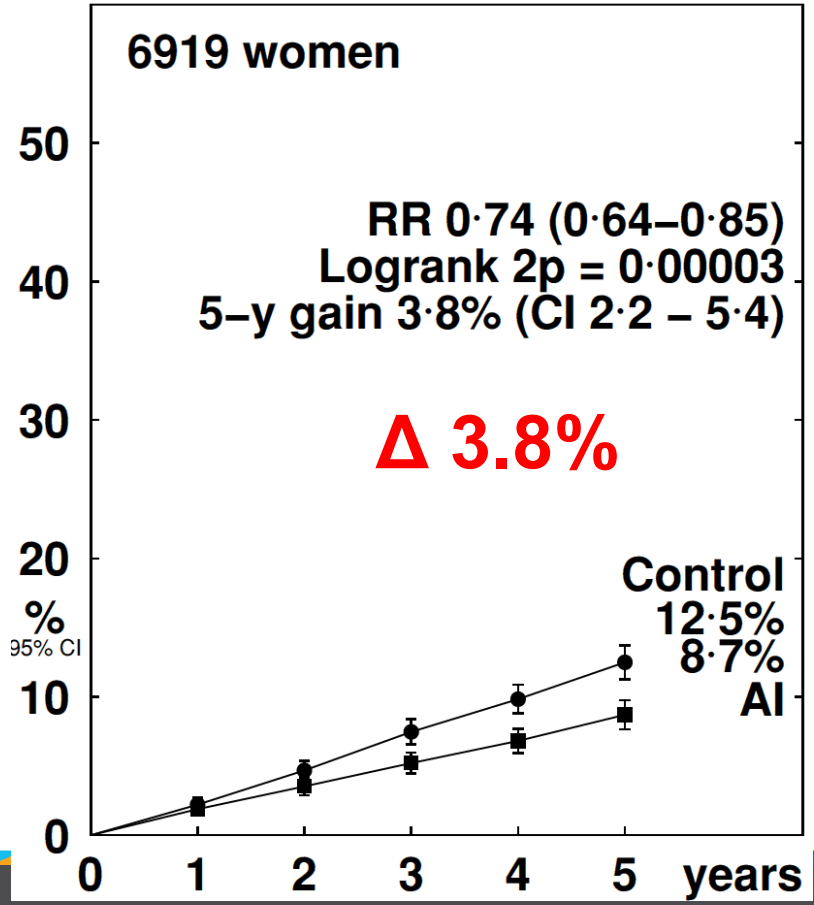
Del Mastro ASCO 2019; Del Mastro ESMO 2021; Mamounas Lancet Oncol 2019; Mamounas SABCS 2019

EBCTCG: Extended therapy benefit by N status

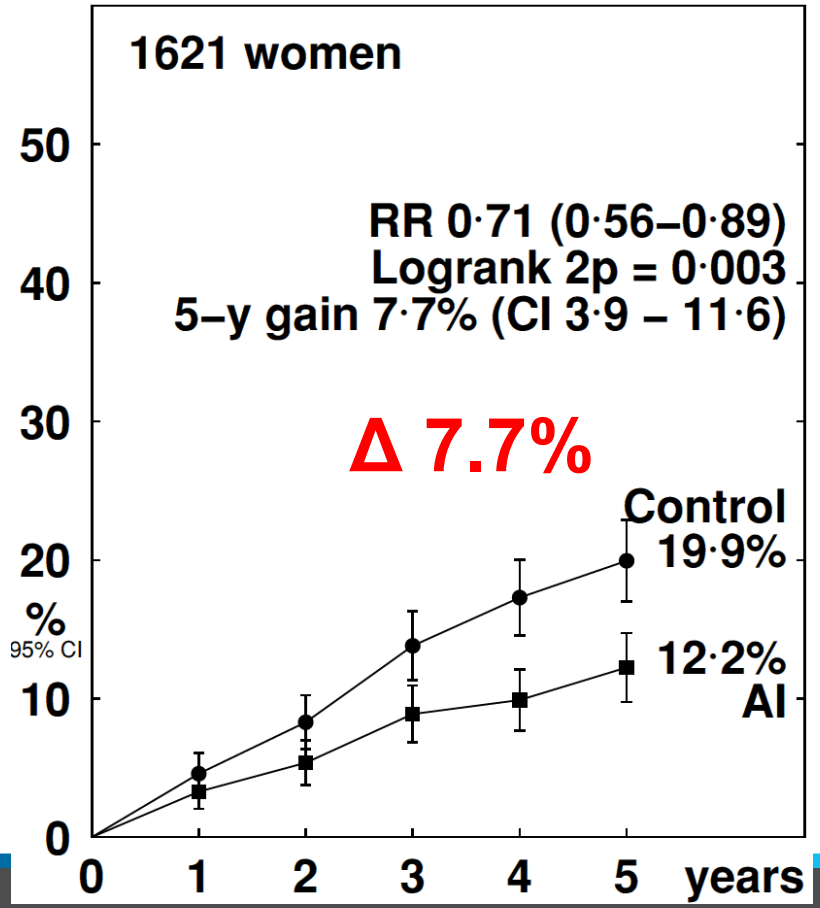
Node-negative



N 1 to 3+

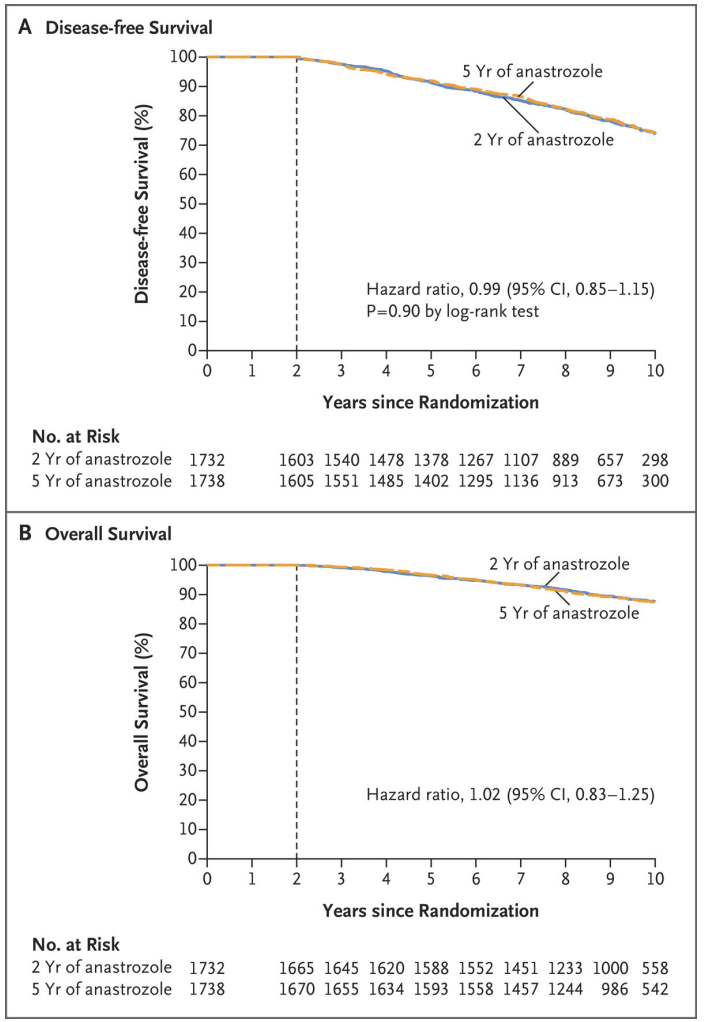


N ≥ 4+



Gray, et al. SABCS 2018

ABCSG-16 “SALSA” Study of 7 vs 10 years AI therapy

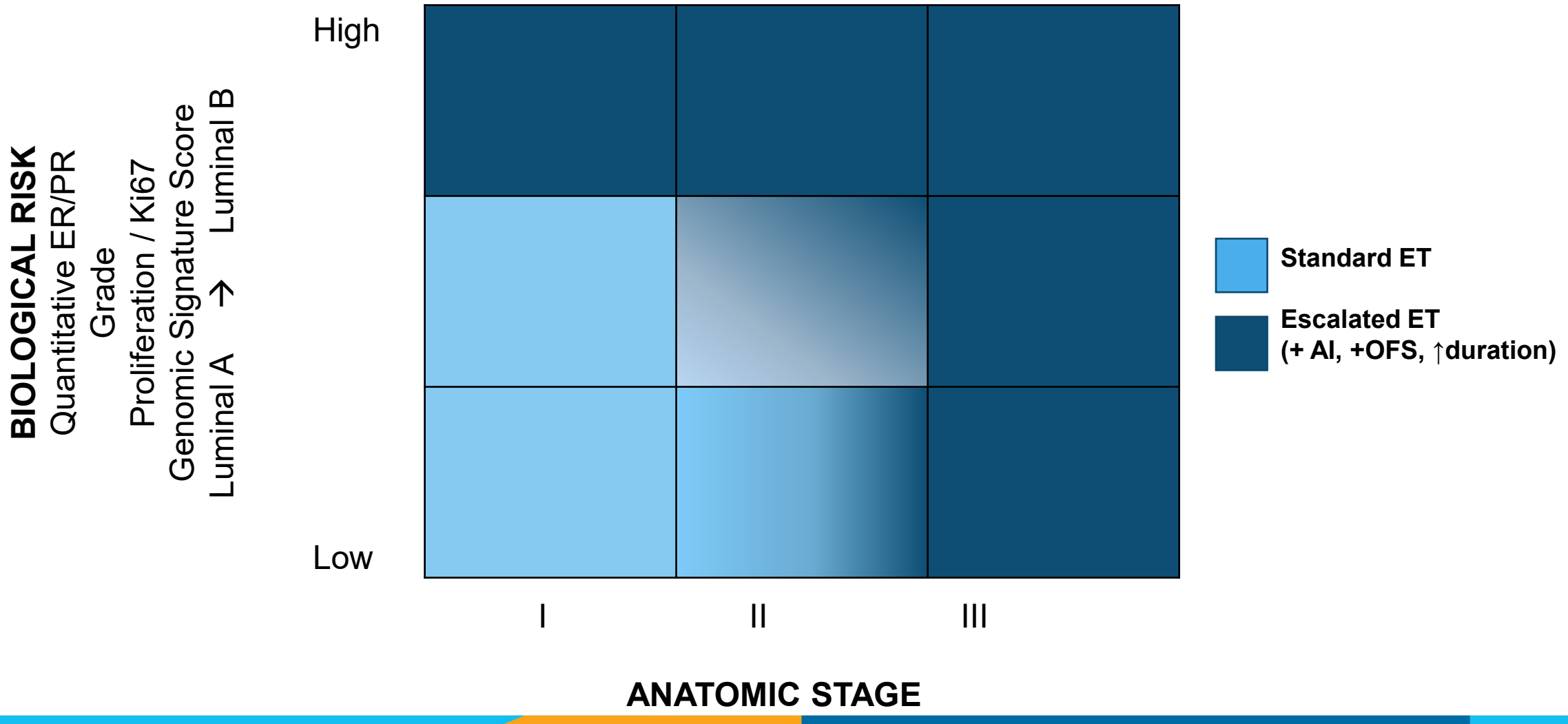


NB:

Node-negative: 2/3^{rds}

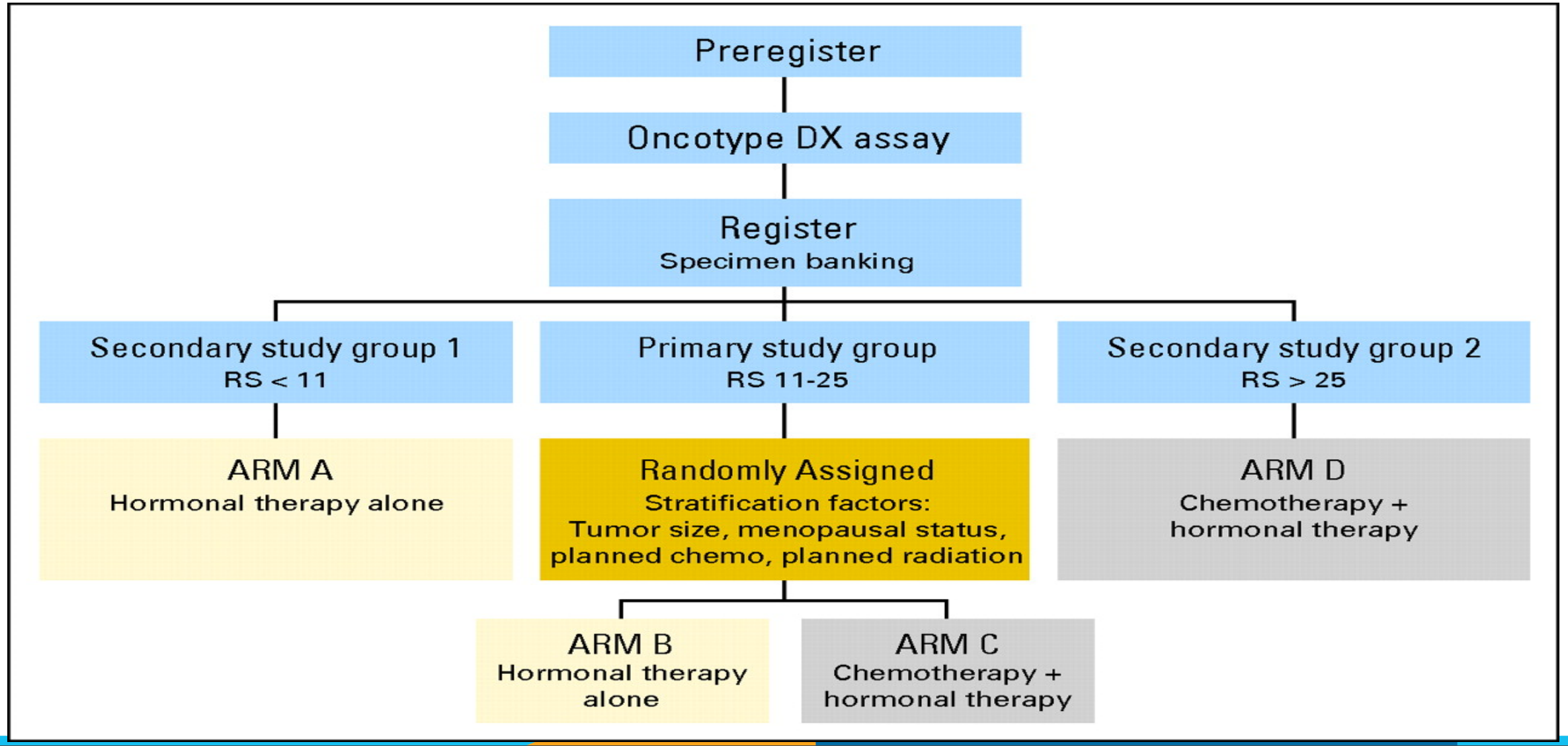
M Gnant et al. N Engl J Med 2021;385:395-405.

ENDOCRINE THERAPY RECOMMENDATIONS: TAILORED by BIOLOGY and STAGE



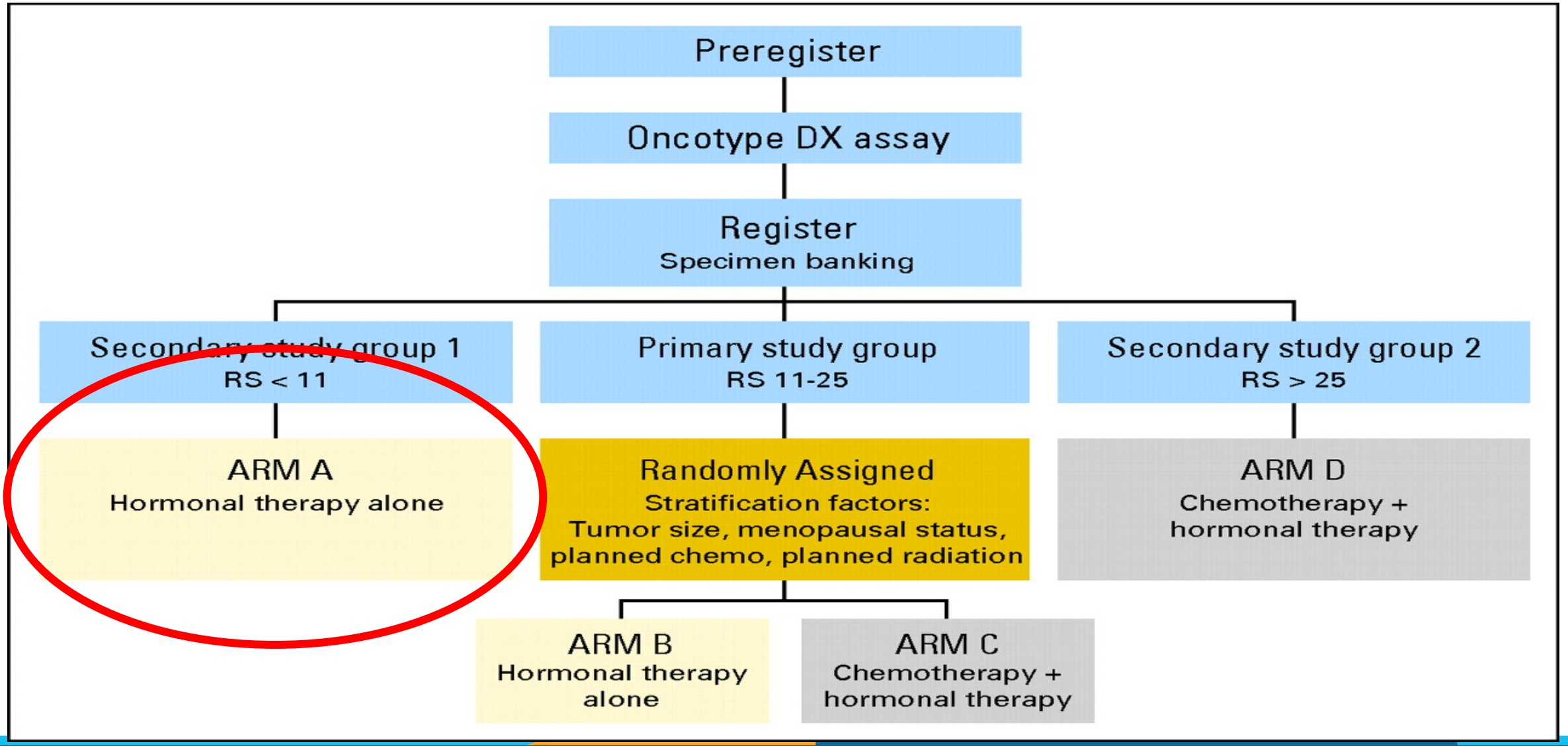
DECISION MAKING: ADJUVANT CHEMOTHERAPY FOR ER+ BREAST CANCER

TAILORx



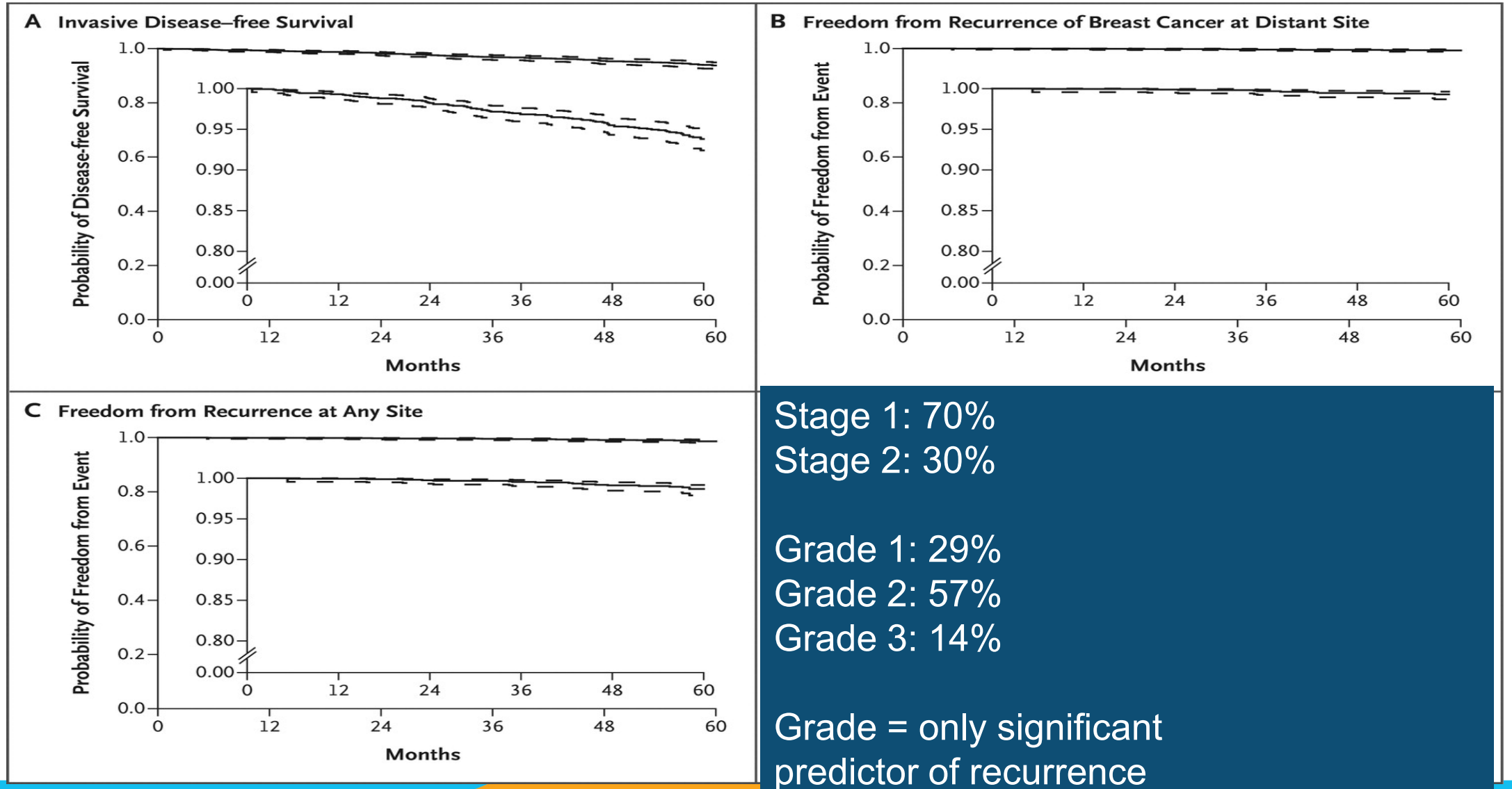
Sparano, J. A. et al. J Clin Oncol; 26:721-728 2008

TAILORx



Sparano, J. A. et al. J Clin Oncol; 26:721-728 2008

TAILORx: Outcomes for node-negative, ER positive, HER2 negative cancers with low recurrence score (≤ 10)



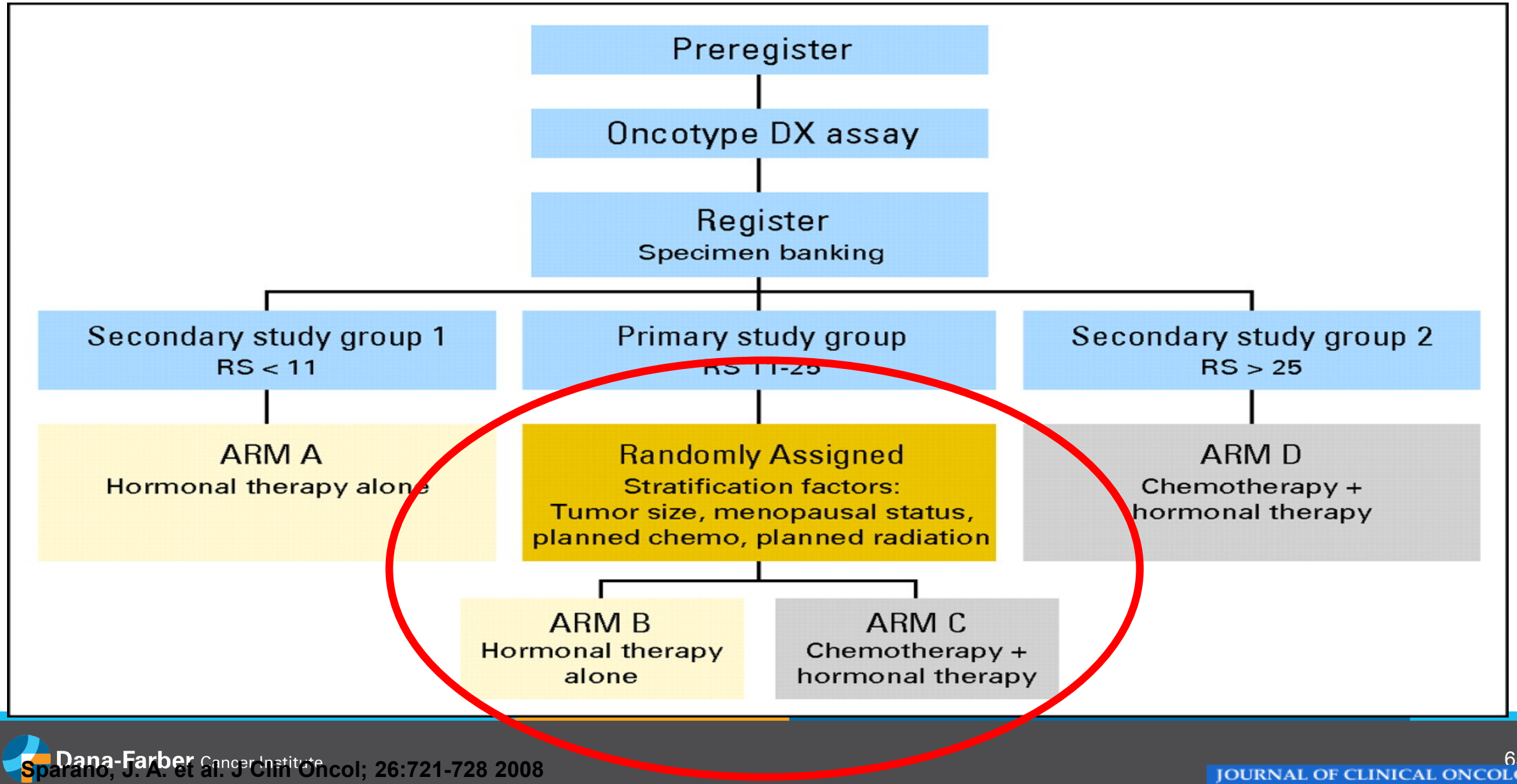
Stage 1: 70%
Stage 2: 30%

Grade 1: 29%
Grade 2: 57%
Grade 3: 14%

Grade = only significant predictor of recurrence

Sparano JA et al. N Engl J Med 2015; 373:2005-14

TAILORx



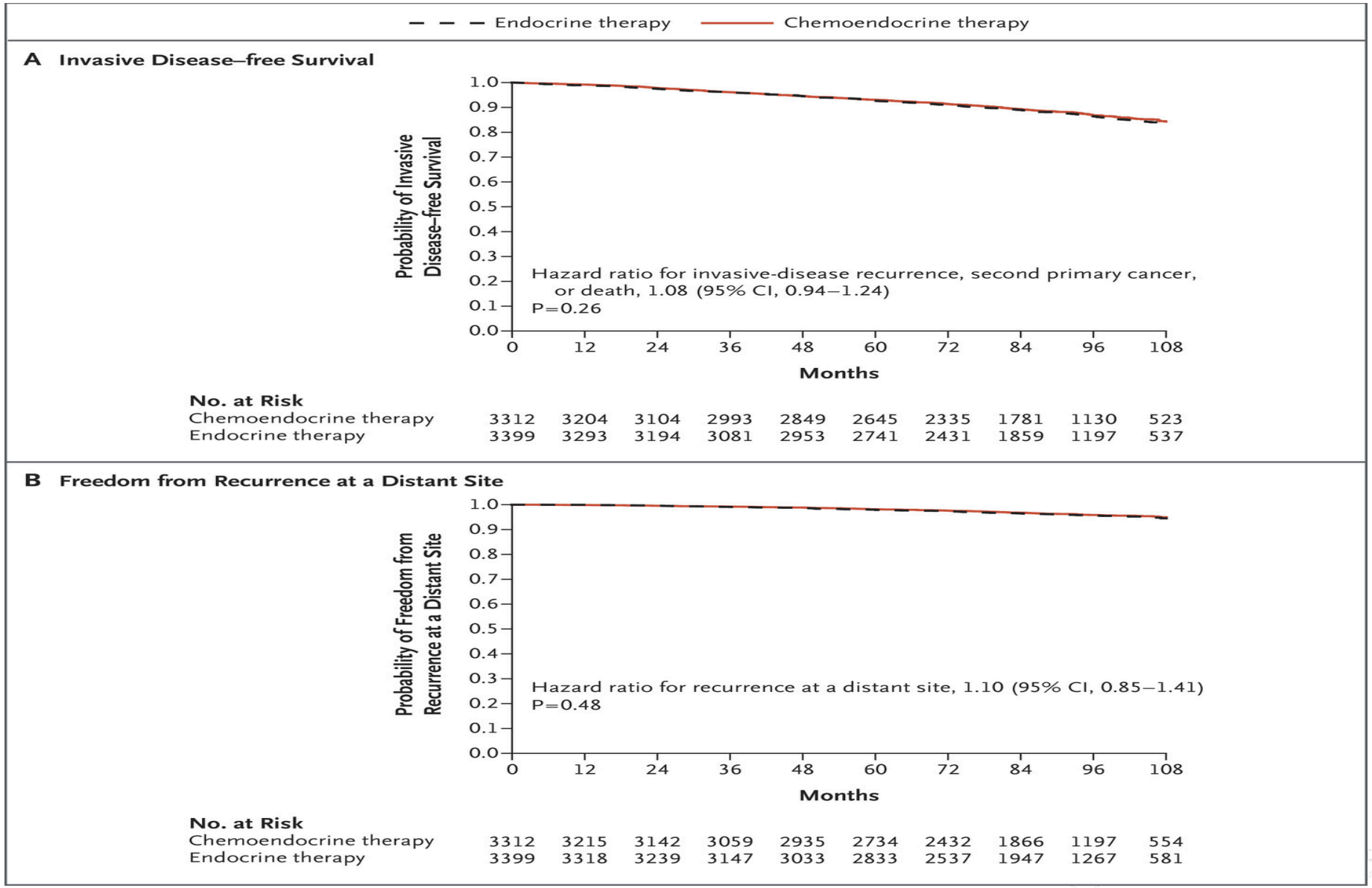
Sparano, J. A. et al. J Clin Oncol; 26:721-728 2008

TAILORx –

RS 11-25

Overall

Result



JA Sparano et al.
N Engl J Med 2018.
DOI: 10.1056/NEJMoa1804710

RxPONDER Schema

Key Entry Criteria

- Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- breast cancer with 1*-3 LN+ without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy**
- Axillary staging by SLNB or ALND

REGISTRATION

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by
Endocrine Therapy Recommended

RANDOMIZATION

N = 5,000 pts

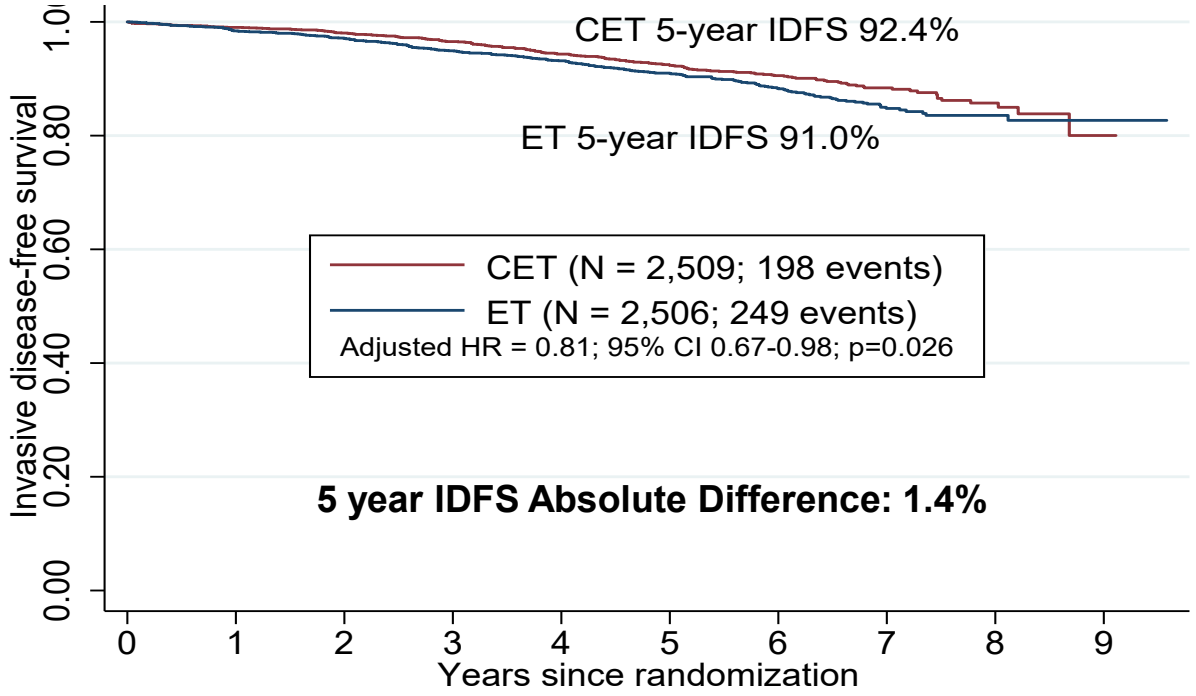
Arm 1:
Chemotherapy Followed by
Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

Stratification Factors
Recurrence Score: 0-13 vs.14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.
** Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.
ALND = Axillary Lymph Node Dissection, SLNB = Sentinel Lymph Node Biopsy

IDFS in Overall Population by Treatment Arm

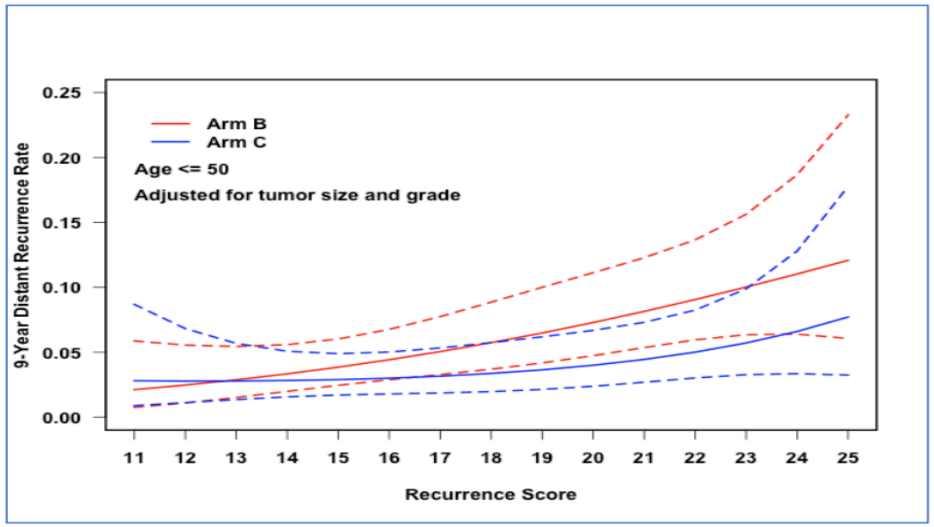


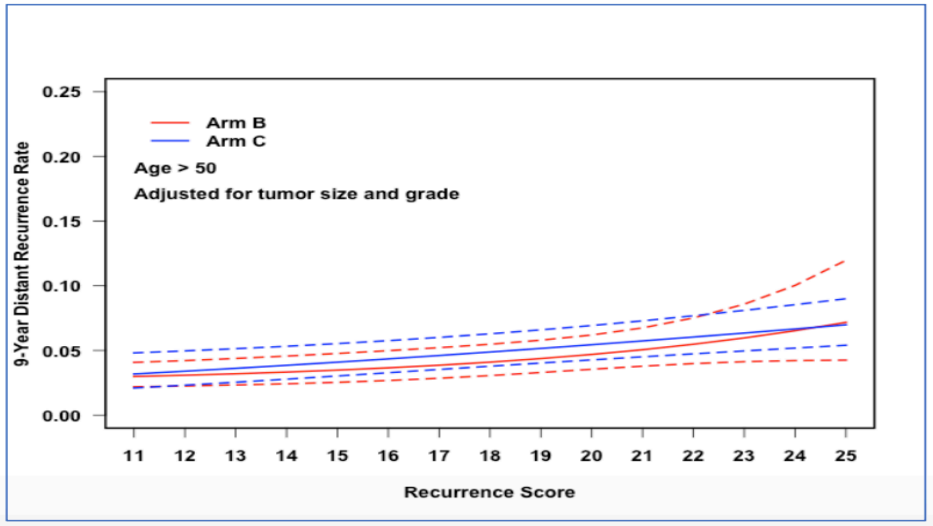
Number at risk

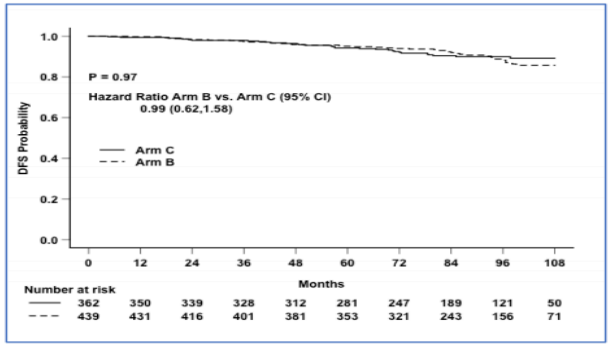
CET	2509	2277	2104	1893	1648	1397	857	403	122	4
ET	2506	2327	2161	1910	1696	1404	846	397	135	11

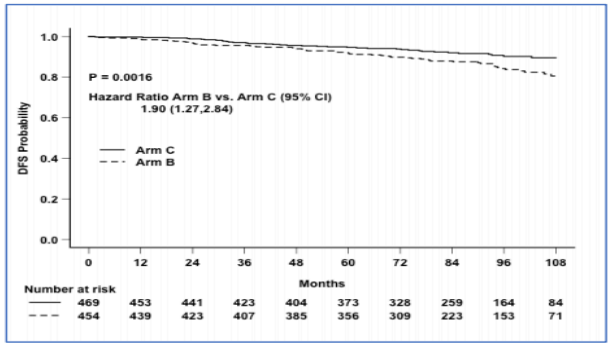
CET = Chemotherapy + Endocrine Therapy; ET = Endocrine Therapy Alone

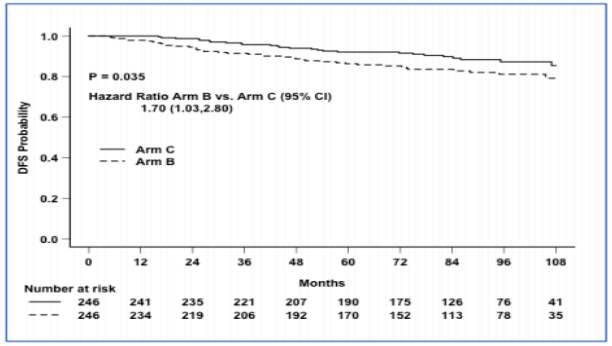
447 observed IDFS events (54% of expected at final analysis) at a median follow-up of 5.1 years











Recurrence Score

11-15

16-20

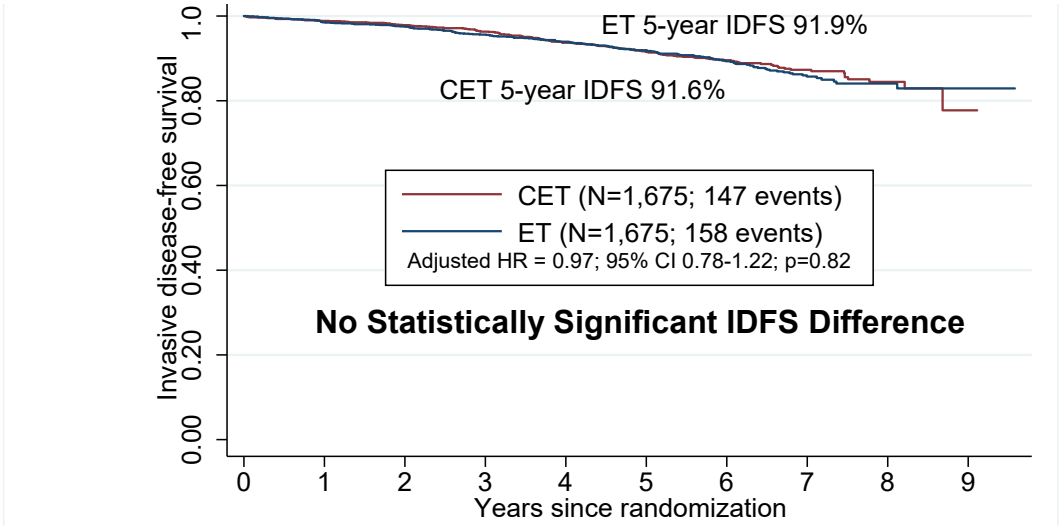
21-25

JA Sparano et al.
N Engl J Med 2018. DOI:

The NEW ENGLAND JOURNAL of MEDICINE

IDFS Stratified by Menopausal Status

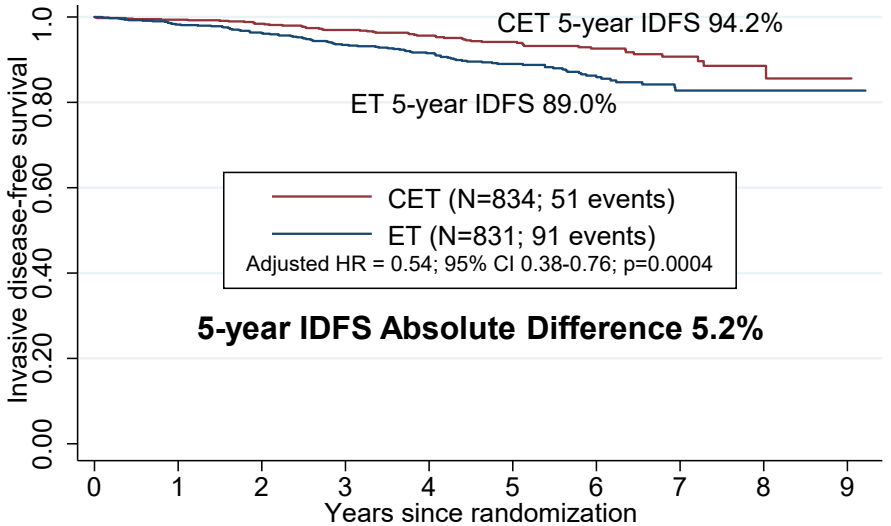
Postmenopausal



IDFS Event	CET	ET	Total (%)
Distant	39	44	83 (27%)
Local-Regional	10	14	24 (8%)
Contralateral	10	9	19 (6%)
Non-Breast Primary	44	47	91 (30%)
Recurrence Not Classified	9	7	16 (5%)
Death not due to Recurrence or Second Primary	35	37	72 (24%)

Absolute Difference in Distant Recurrence as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

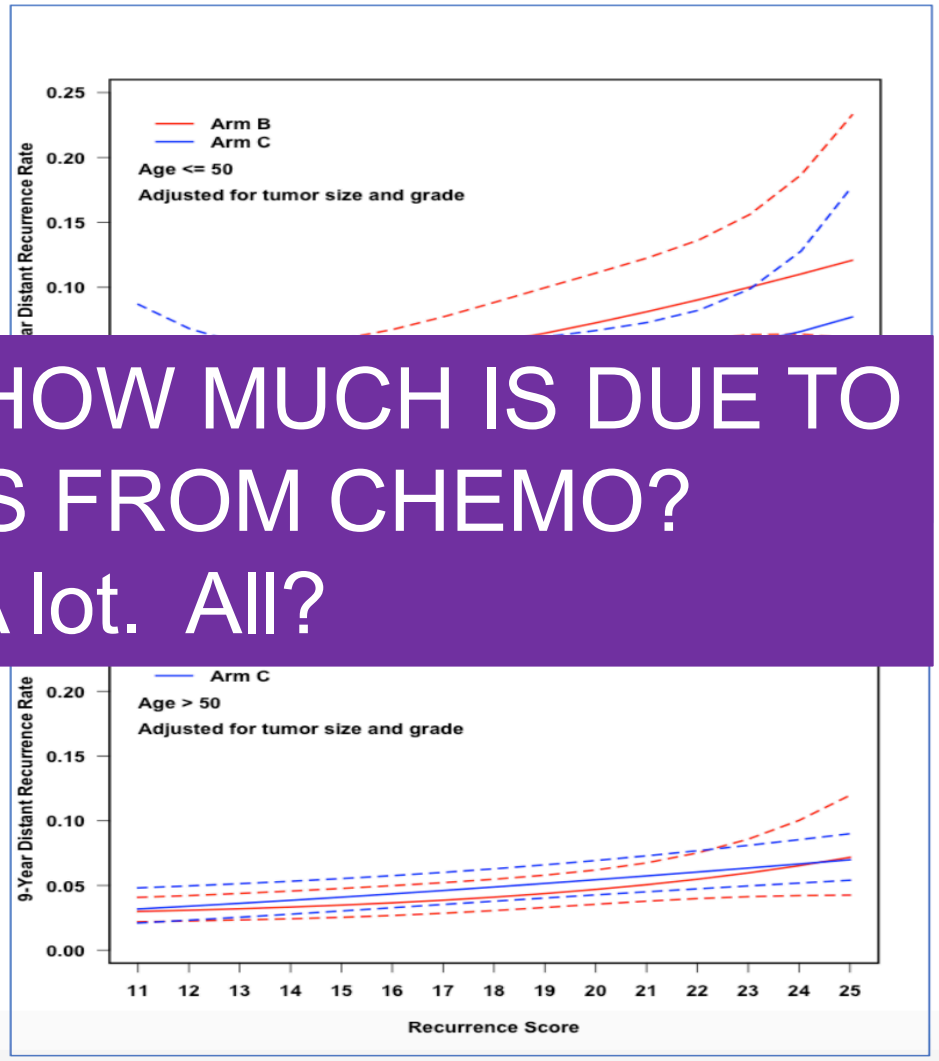
Premenopausal



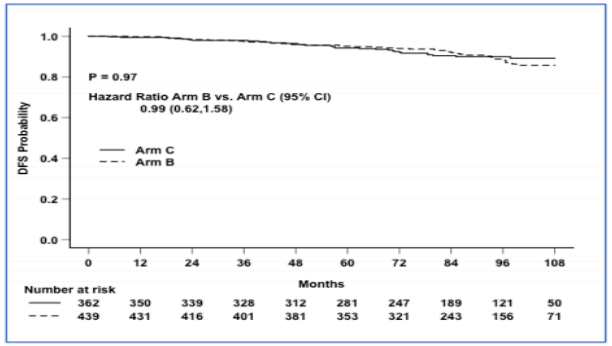
IDFS Event	CET	ET	Total (%)
Distant	26	50	76 (54%)
Local-Regional	8	17	25 (18%)
Contralateral	4	8	12 (8%)
Non-Breast Primary	10	10	20 (14%)
Recurrence Not Classified	1	1	2 (1%)
Death not due to Recurrence or Second Primary	2	5	7 (5%)

Absolute Difference in Distant Recurrence as 1st site: 2.9% (3.1% CET vs. 6.0% ET)

Q: HOW MUCH IS DUE TO OFS FROM CHEMO?
A: A lot. All?

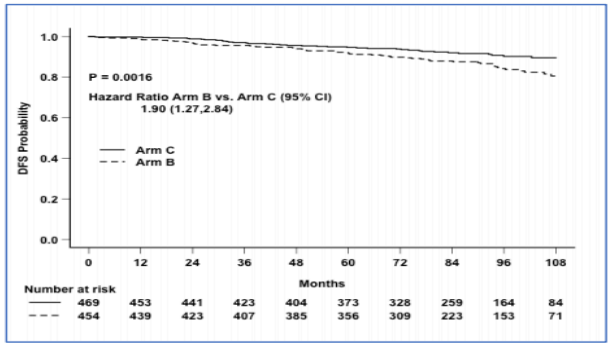


JA Sparano et al.
N Engl J Med 2018. DOI:

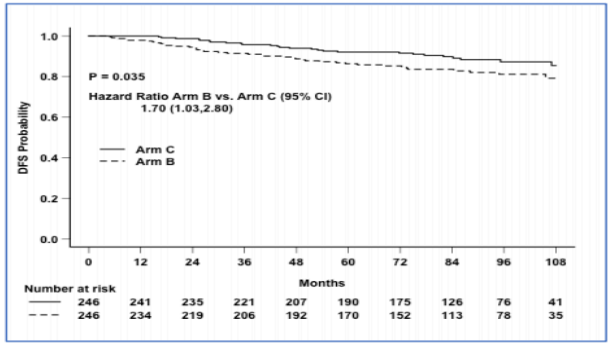


Recurrence Score

11-15



16-20



21-25

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Hypothesis: benefits of chemotherapy in women ≤ age 50 with recurrence scores 16 to 25 ***are due to endocrine consequences of chemotherapy***

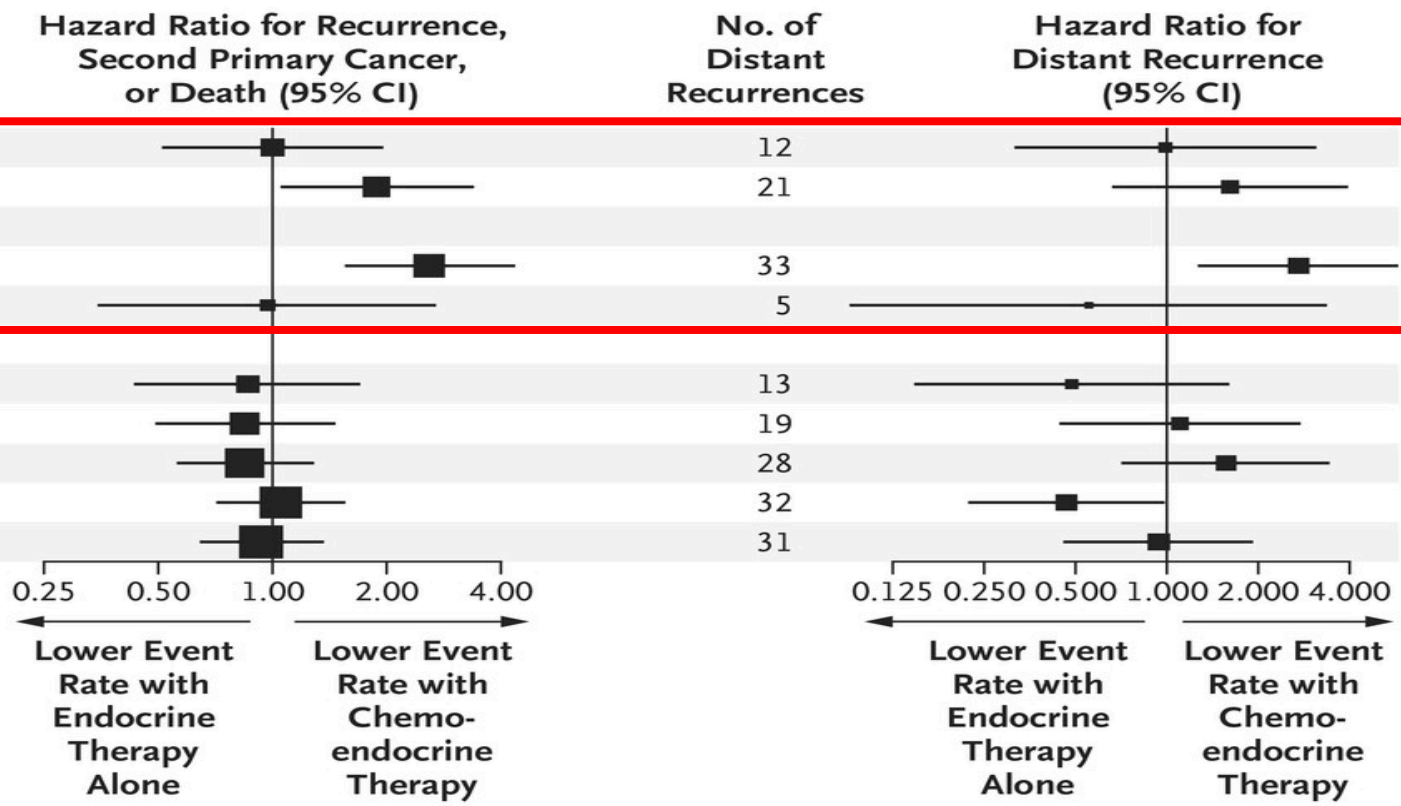
Population	Likelihood of chemotherapy – induced amenorrhea	Predicted benefit from chemotherapy if hypothesis is correct
Premenopausal ≤ Age 40	**Low**	**None**
Premenopausal Age 41 – 45	**Moderate**	**Yes; moderate**
Premenopausal Age 46 – 50	**High**	**Yes; high**
Postmenopausal Age < 50	**N/A**	**None**

Hypothesis: benefits of chemotherapy in women ≤ age 50 with recurrence scores 16 to 25 ***are due to endocrine consequences of chemotherapy***

Population	Likelihood of chemotherapy – induced amenorrhea	Predicted benefit from chemotherapy if hypothesis is correct	Hazard Ratio for chemotherapy iDFS / DRFI
Premenopausal ≤ Age 40	Low	None	1.0 / 1.0
Premenopausal Age 41 – 45	Moderate	Yes; moderate	2.0 / 1.7
Premenopausal Age 46 – 50	High	Yes; high	3.0 / 3.0
Postmenopausal Age < 50	N/A	None	0.9 / 0.7

Effect of Age and Menopausal Status on Chemotherapy Benefit.

Subgroup	No. of Patients	No. of Events	No. of Distant Recurrences
≤40 Yr of age	203	35	12
41–45 Yr of age	441	51	21
46–50 Yr of age			
Before menopause	630	69	33
After menopause	141	15	5
51–55 Yr of age			
Before menopause	287	34	13
After menopause	472	54	19
56–60 Yr of age	826	94	28
61–65 Yr of age	710	109	32
>65 Yr of age	628	117	31



JA Sparano et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1904819

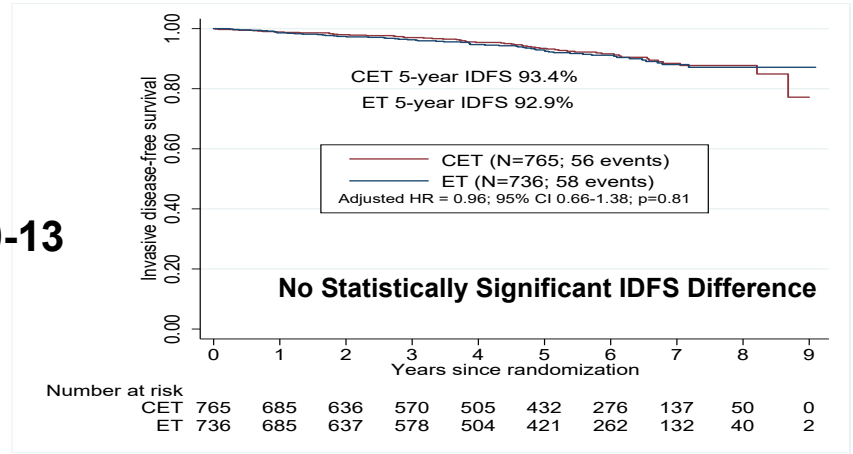
Hypothesis: benefits of chemotherapy in women ≤ age 50 with recurrence scores 16 to 25 ***are due to endocrine consequences of chemotherapy***

Population	Likelihood of chemotherapy – induced amenorrhea	Predicted benefit from chemotherapy if hypothesis is correct	Hazard Ratio for chemotherapy iDFS / DRFI	
Premenopausal ≤ Age 40	Low	None	1.0 / 1.0	*No benefit when endocrine effects are neutral*
Premenopausal Age 41 – 45	Moderate	Yes; moderate	2.0 / 1.7	*Substantial benefit when endocrine effects are likely*
Premenopausal Age 40 – 45	High	Yes; high	3.0 / 3.0	
Postmenopausal Age < 50	N/A	None	0.9 / 0.7	*No benefit when endocrine effects are neutral*

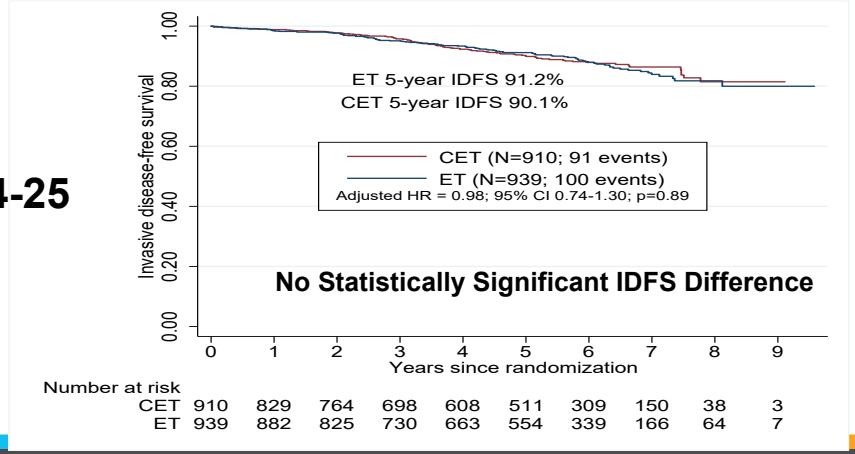
IDFS Stratified by Recurrence Score and Menopausal Status

Postmenopausal

RS 0-13

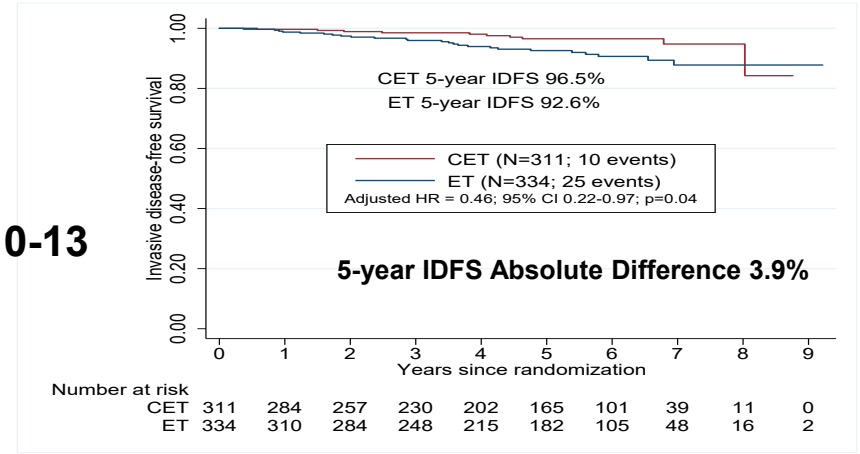


RS 14-25



Premenopausal

RS 0-13



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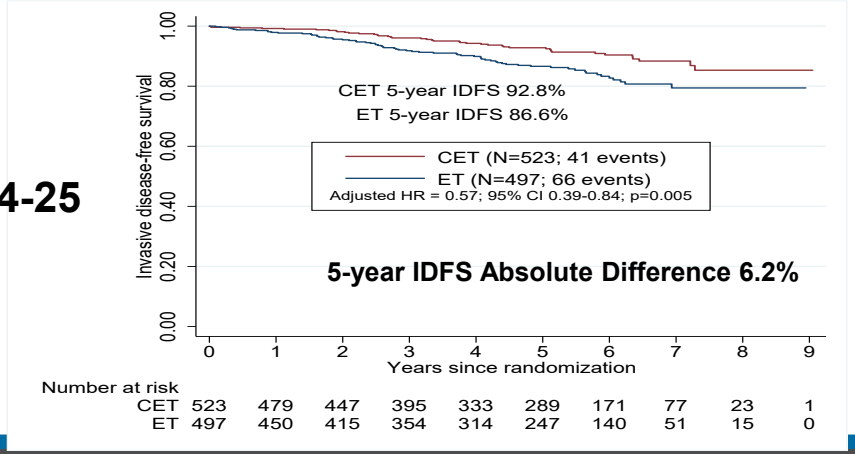
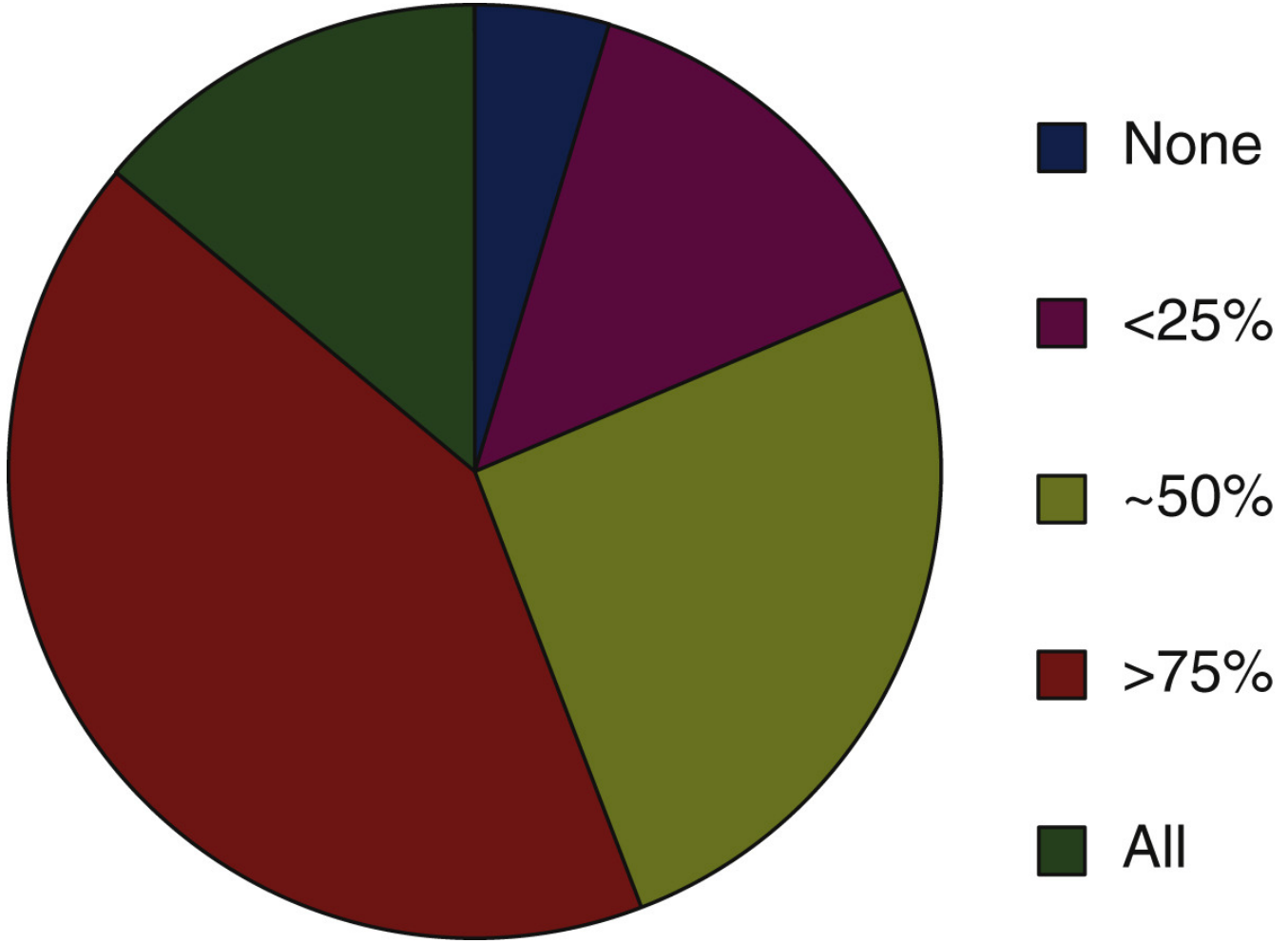


Survey: Percentage of benefit due to chemotherapy-induced menopause in premenopausal women with recurrence score < 25



Annals of Oncology 2021 321216-1235DOI: (10.1016/j.annonc.2021.06.023)

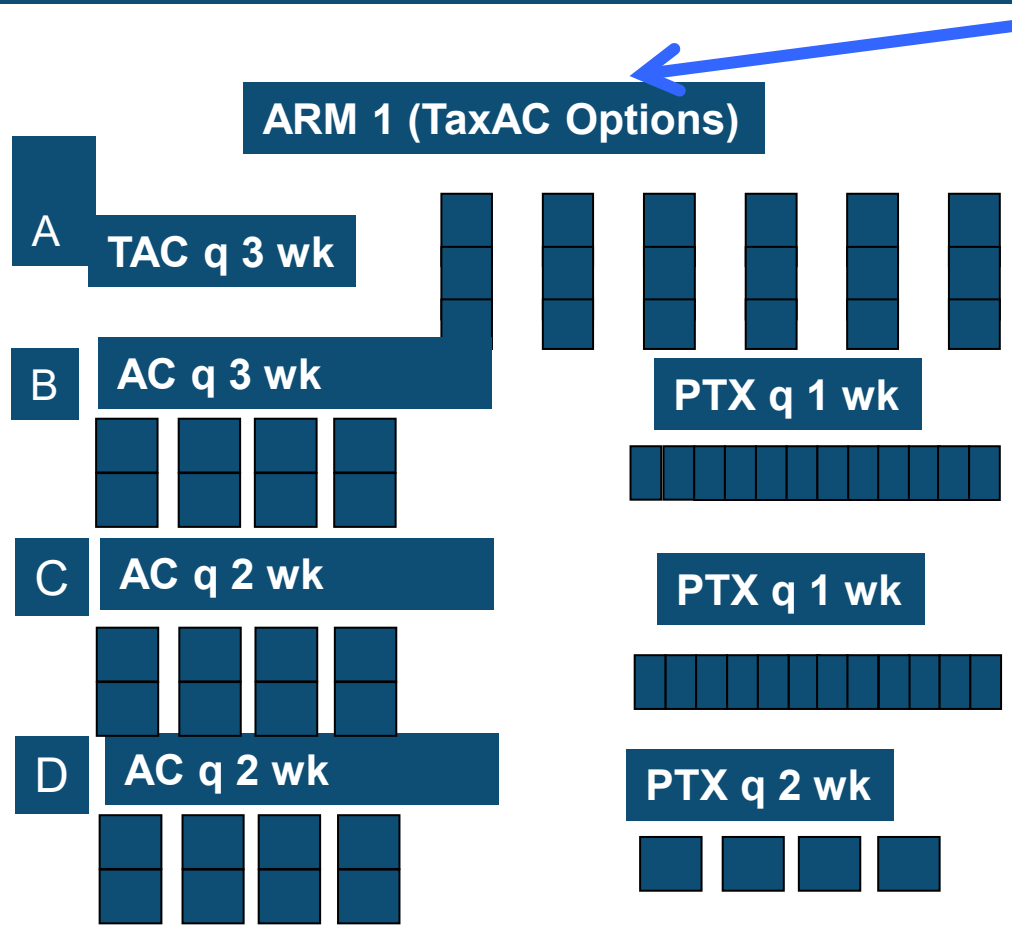
ABC Trials Schema (nee TC/TAC, B-46I, B-49)

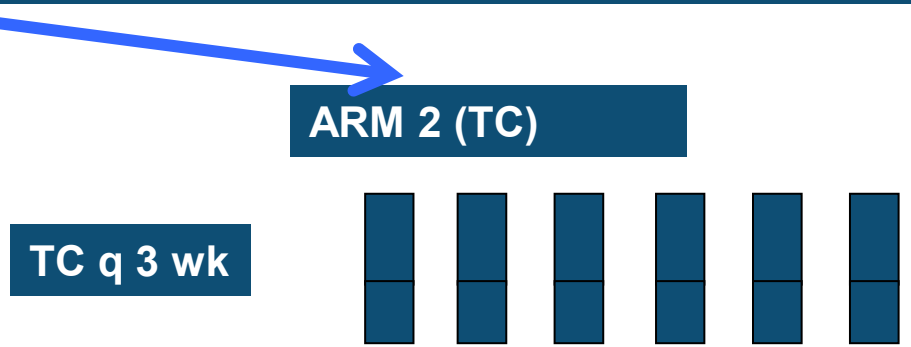
Node+ or High Risk Node-Negative

Stratification Variables

(0, 1-3, 4-9, 10+); Hormone Receptor (ER or PgR+, Both Negative)

Number of + Nodes





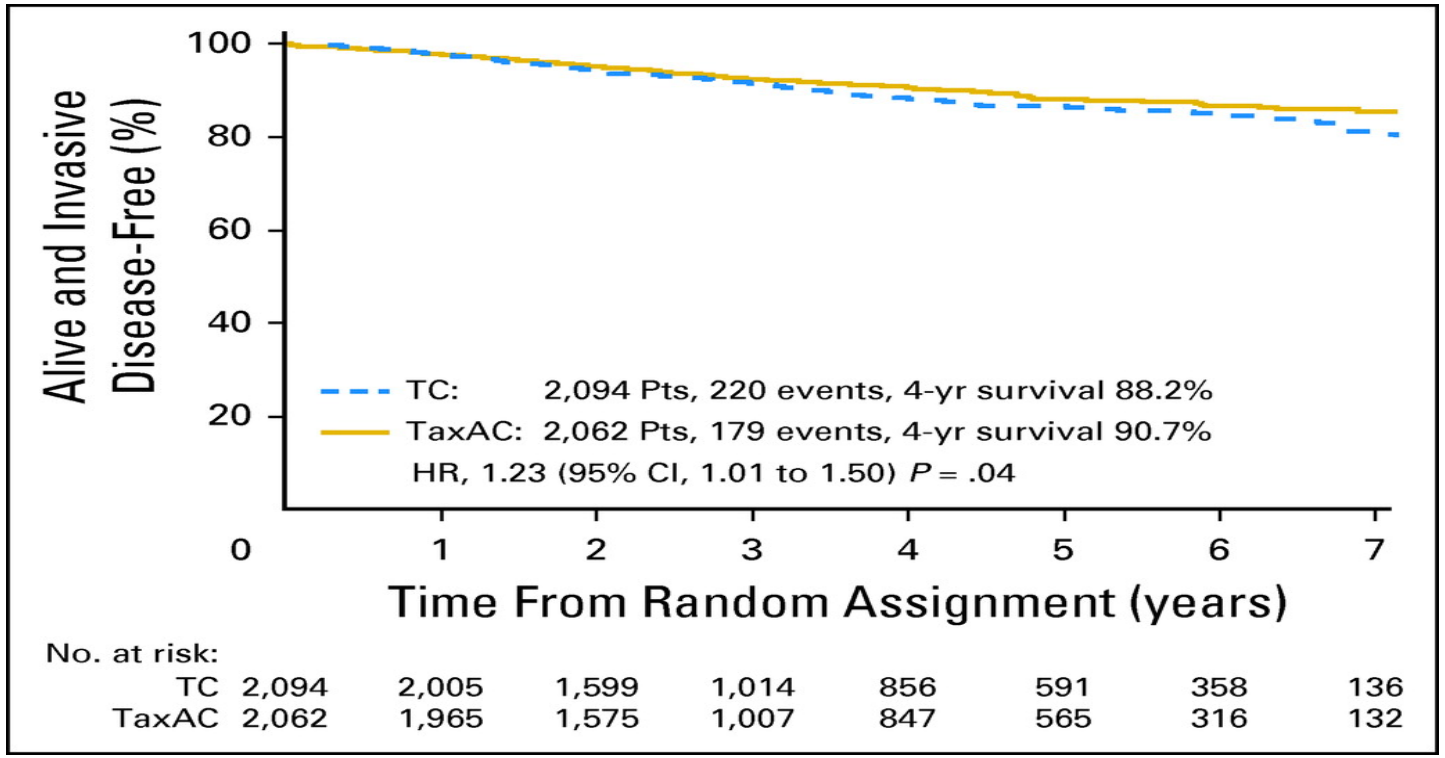
Arm 1 Options Per Study

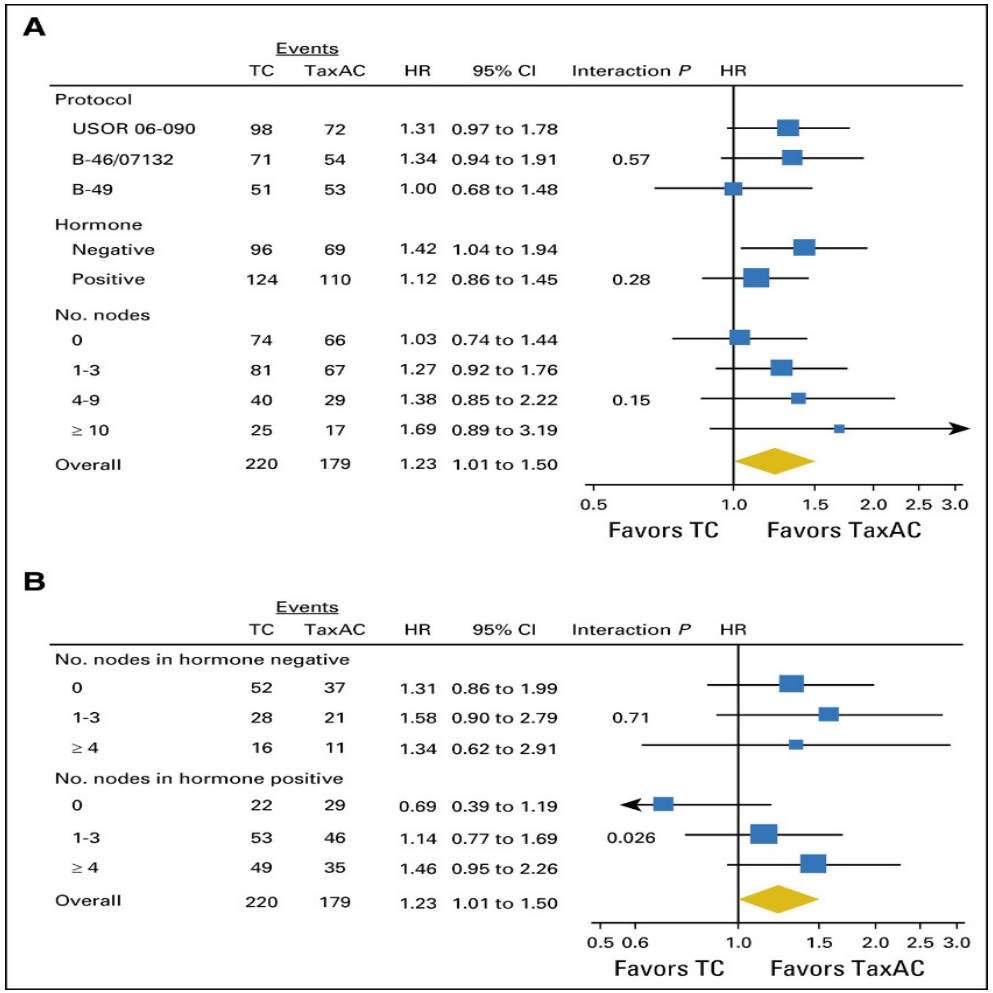
- **USOR 06-090 - 1A only**
- **NSABP B-46I/USOR 07132 - 1A only**
- **NSABP B-49 - investigator choice 1A-1D**

Endocrine therapy for ER+ or PgR+ patients for minimum of 5 years

Designed to prove noninferiority of nonanthracycline arm

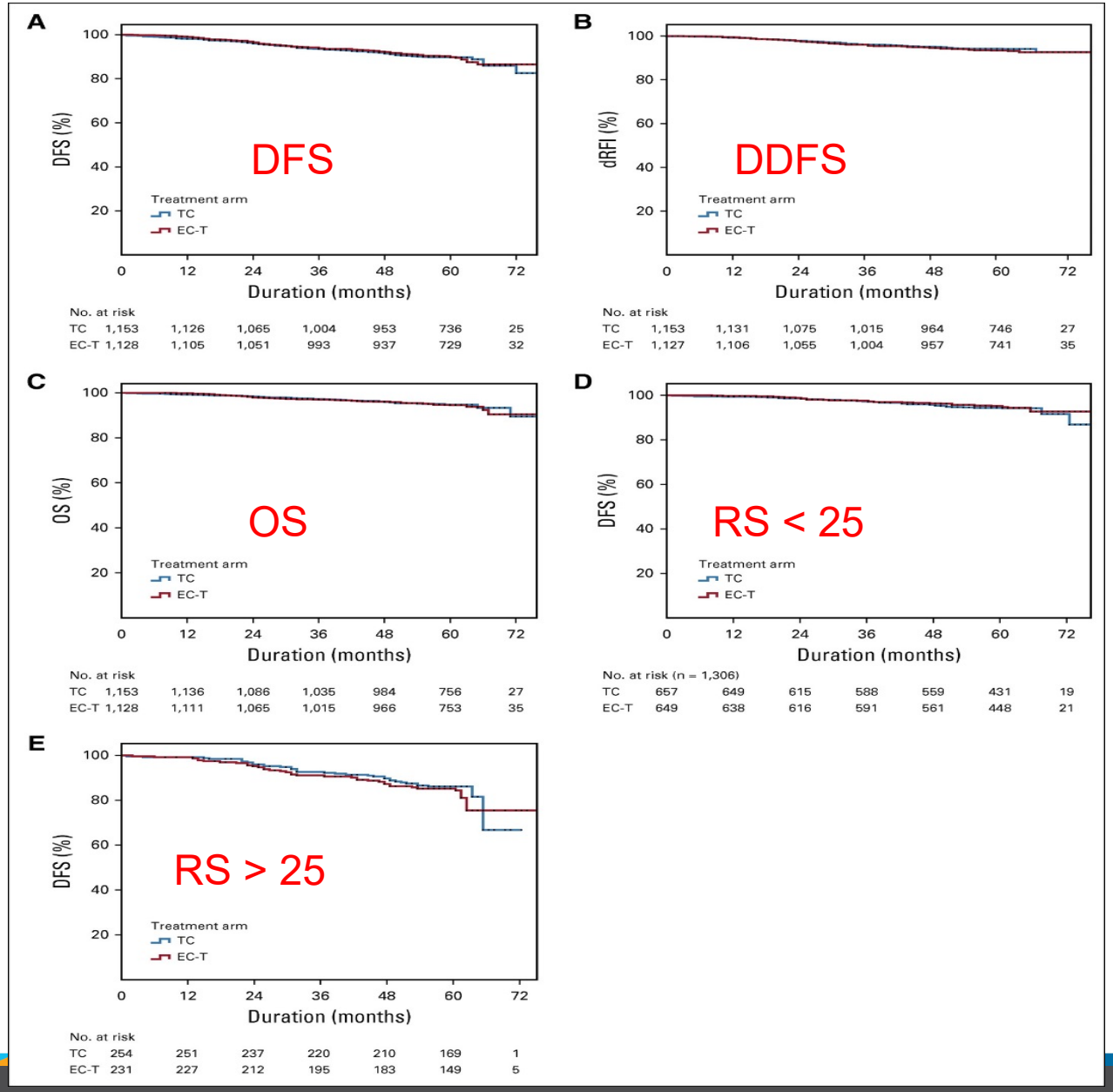
Anthracyclines in Early Breast Cancer
The ABC Trials—USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49





Blum JL, et al. J Clin Oncol 2017;35:2647-55.

EC/T vs TC x 6
West German PlanB Trial



Nitz U et al. J Clin Oncol 2019;

Adjuvant Chemotherapy for ER+ breast cancer

- Recurrence score testing is the norm for node-negative tumors and tumors with limited (e.g. 1 or 2 + SLN)
- Data limited for extremes of stage
  - Tumors < 1 cm
  - Tumors > 5 cm
  - Multi LN positive
- Unlikely that there is substantial chemo benefit when genomic tests are in very low range

monarchE Study Design

HR+, HER2-, high risk early breast cancer

High risk defined as:

- ≥4 positive axillary lymph nodes (ALN) OR
- 1-3 ALN and at least 1 of the below:
  - Tumor size ≥5 cm
  - Histologic grade 3
  - Centrally tested Ki67 ≥20%

N = 5637[a]

R
1:1

Stratified for:
- Prior chemotherapy
- Menopausal status
- Region

Abemaciclib (150mg twice daily for up to 2 years[b])
+ Standard of Care Endocrine Therapy
(5 to 10 years as clinically indicated)

Standard of Care Endocrine Therapy[b]
(5 to 10 years as clinically indicated)

Endocrine therapy of physician's choice

Other criteria:
- Women or men
- Pre-/ postmenopausal
- With or without prior adjuvant/neoadjuvant chemotherapy
- No distant metastases

Primary Objective: Invasive disease-free survival (STEEP criteria)
Key Secondary Objectives: Distant relapse-free survival, Overall survival, Safety, Patient reported outcomes, and Pharmacokinetics

[a] Recruitment from July 2017 to August 2019; [b] Treatment period = first 2 years on study treatment after randomization

High Risk Disease Characteristics

		Abemaciclib + ET N = 2808, n (%)	ET Alone N = 2829, n (%)
Number of positive lymph nodes	0	7 (0.2)	7 (0.2)
	1-3	1119 (39.9)	1143 (40.4)
	≥4 or more	1680 (59.8)	1679 (59.3)
Histological grade	Grade 1	209 (7.4)	215 (7.6)
	Grade 2	1373 (48.9)	1395 (49.3)
	Grade 3	1090 (38.8)	1066 (37.7)
Primary tumor size by pathology following definitive surgery	<2 cm	780 (27.8)	765 (27.0)
	2-5 cm	1369 (48.8)	1419 (50.2)
	≥5 cm	610 (21.7)	612 (21.6)
Central Ki-67	<20%	953 (33.9)	973 (34.4)
	≥20%	1262 (44.9)	1233 (43.6)
	Unavailable	593 (21.1)	623 (22.0)
Progesterone receptor status	Positive	2421 (86.2)	2453 (86.7)
	Negative	298 (10.6)	294 (10.4)

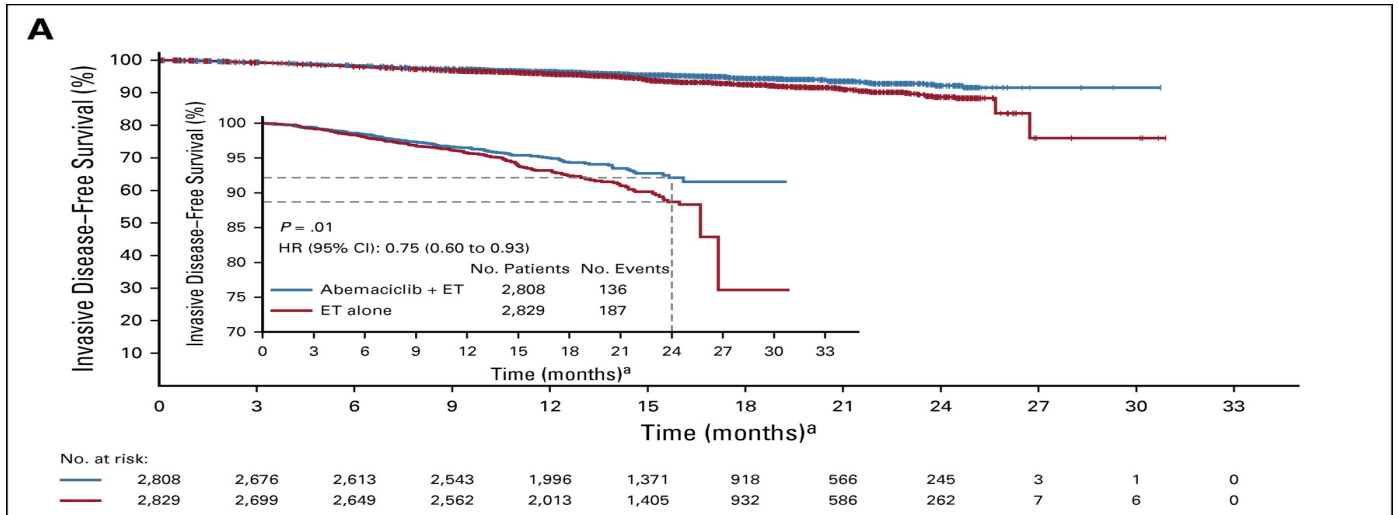
Note: where values do not add up to 100%, remaining data are missing, unavailable or could not be assessed

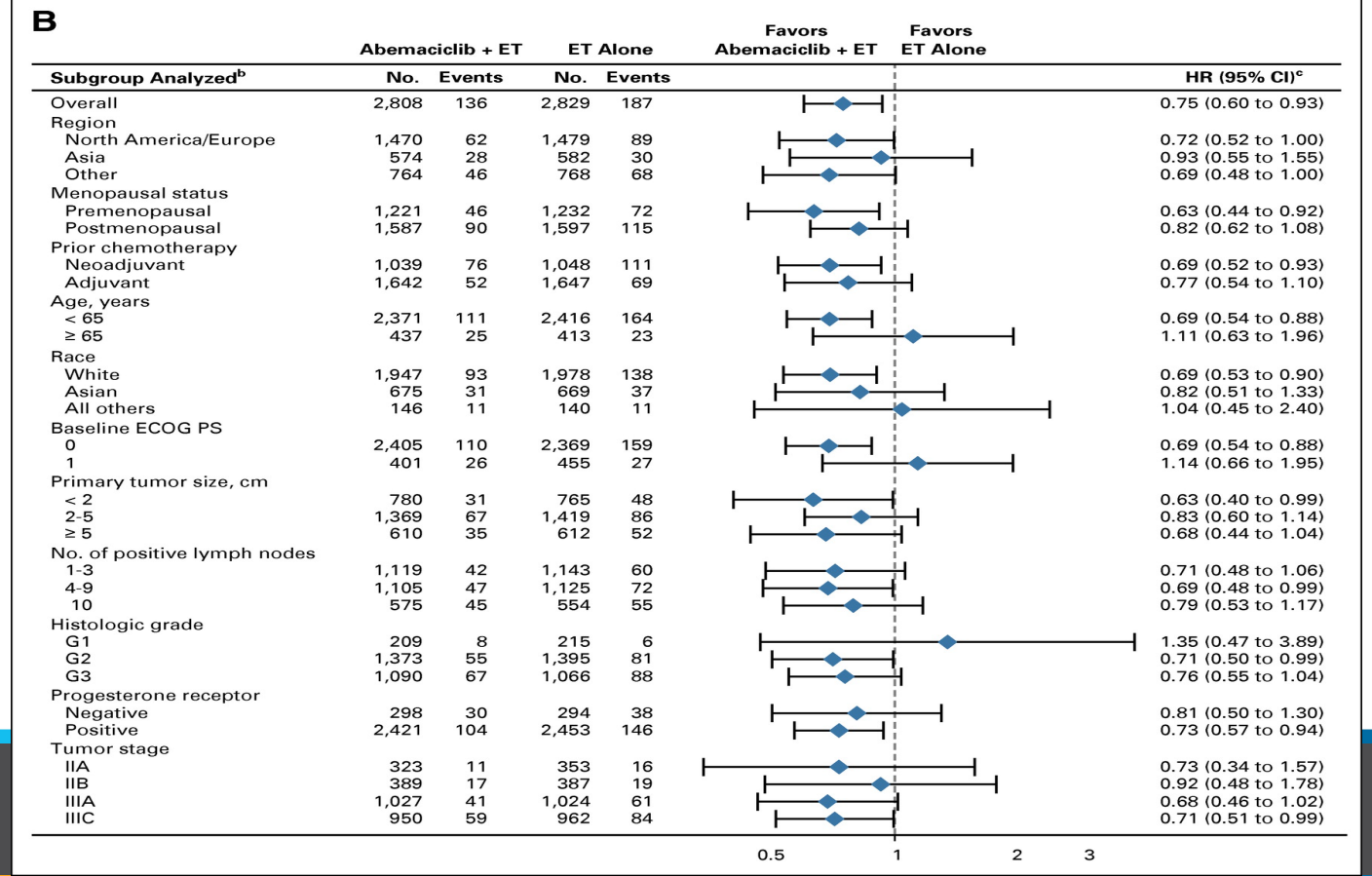
Additional high risk eligibility criteria for patients with 1-3 nodes	Abemaciclib + ET N = 2808, n (%)	ET Alone N = 2829, n (%)
Tumor size ≥5 cm (pathology) [a]	249 (8.9)	236 (8.3)
Tumor size ≥5 cm (imaging) [a, b]	152 (5.4)	158 (5.6)
Histologic grade 3 [a]	629 (22.4)	618 (21.8)
Central Ki-67 ≥20% only [c]	216 (7.7)	237 (8.4)

[a] Patients could be counted in more than one of the sub-categories under 1-3 positive lymph nodes; [b] Patients who received neoadjuvant chemotherapy may have been eligible based on imaging tumor size prior to receiving systemic therapy; [c] Patients not double counted; patients did not have tumor size ≥5 cm (either by pathology or imaging) or histologic grade 3

MONARCHe

iDFS





Number of IDFS events

Abemaciclib + ET	ET Alone
136	187

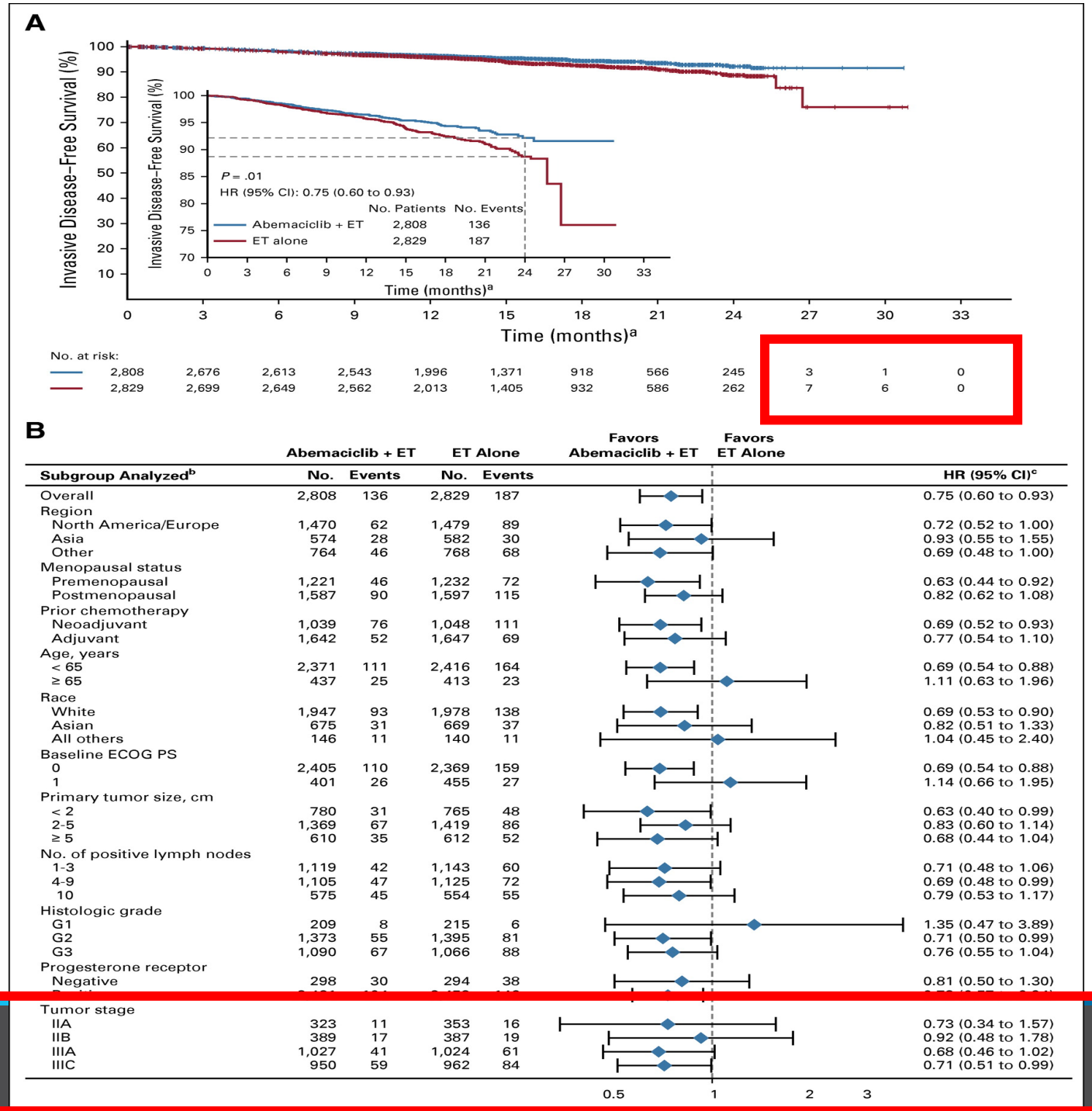
p = 0.0096 (2-sided)
HR (95% CI): 0.747 (0.598, 0.932)

Risk of invasive disease reduced by 25.3%

Johnston S, JCO 2020
DOI: 10.1200/JCO.20.02514

MONARCHe

iDFS



Johnston S, JCO 2020
DOI: 10.1200/JCO.20.02524

TABLE 3. Safety Table

	Abemaciclib + ET (n = 2,791)			ET Alone (n = 2,800)		
≥ 10% in Either Arm	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any adverse event	2,731 (97.9)	1,200 (43.0)	70 (2.5)	2,410 (86.1)	335 (12.0)	19 (0.7)
Diarrhea	2,294 (82.2)	212 (7.6)	0	199 (7.1)	3 (0.1)	0
Neutropenia	1,246 (44.6)	501 (18.0)	18 (0.6)	141 (5.0)	16 (0.6)	3 (0.1)
Fatigue	1,073 (38.4)	78 (2.8)	0	433 (15.5)	4 (0.1)	0
Leukopenia	1,027 (36.8)	301 (10.8)	4 (0.1)	171 (6.1)	10 (0.4)	0
Abdominal pain	948 (34.0)	37 (1.3)	0	227 (8.1)	9 (0.3)	0
Nausea	779 (27.9)	13 (0.5)	0	223 (8.0)	1 (0.0)	0
Anemia	638 (22.9)	47 (1.7)	1 (0.0)	90 (3.2)	9 (0.3)	1 (0.0)
Arthralgia	571 (20.5)	6 (0.2)	0	876 (31.3)	18 (0.6)	0
Hot flush	393 (14.1)	3 (0.1)	0	587 (21.0)	8 (0.3)	0
Lymphopenia	372 (13.3)	140 (5.0)	2 (0.1)	94 (3.4)	13 (0.5)	0
Thrombocytopenia	341 (12.2)	25 (0.9)	6 (0.2)	40 (1.4)	1 (0.0)	2 (0.1)
Vomiting	455 (16.3)	13 (0.5)	0	117 (4.2)	2 (0.1)	0
Constipation	288 (10.3)	1 (0.0)	0	142 (5.1)	0	0
Upper respiratory tract infection	285 (10.2)	6 (0.2)	0	214 (7.6)	0	0
Urinary tract infection	284 (10.2)	13 (0.5)	0	170 (6.1)	6 (0.2)	0
Decreased appetite	312 (11.2)	15 (0.5)	0	54 (1.9)	1 (0.0)	0
Headache	482 (17.3)	6 (0.2)	0	359 (12.8)	3 (0.1)	0
Cough	337 (12.1)	1 (0.0)	0	193 (6.9)	0	0
Lymphedema	285 (10.2)	2 (0.1)	0	208 (7.4)	0	0
Additional adverse events of interest[a]						
Aspartate aminotransferase increase	257 (9.2)	43 (1.5)	3 (0.1)	106 (3.8)	13 (0.5)	0
Alanine aminotransferase increase	265 (9.5)	59 (2.1)	5 (0.2)	119 (4.3)	16 (0.6)	0
Alopecia	254 (9.1)	0	0	53 (1.9)	0	0
Venous thromboembolic event	63 (2.3)	27 (1.0)	6 (0.2)	14 (0.5)	4 (0.1)	0
Interstitial lung disease[b]	75 (2.7)	9 (0.3)	0	33 (1.2)	1 (0.0)	0

NOTE. Data are presented as No. (%).

[a]Includes events of clinical significance and/or observed in earlier clinical studies of abemaciclib.

[b]Term is based on the Standard MedDRA Query.

PALLAS: Phase III open-label study of palbociclib and adjuvant endocrine therapy

Eligibility:

- Stage II-III HR+/HER2- breast cancer
- Completion of prior surgery, +/- chemo, RT
- Within 12 mo of diagnosis
- Within 6 mo of starting adjuvant endocrine treatment
- FFPE tumor block submitted

N=5,600

Stratification:

- **Stage** (IIA vs IIB/III)
- **Chemotherapy** (yes vs no)
- **Age** (≤50 vs >50)
- **Geographic region** (N. America vs Europe vs Other)

RANDOMIZE

1:1

Arm A
Palbociclib x 2 years
(125 mg qd, 3 wks on/1 wk off)
+
Endocrine Treatment*

Arm B
Endocrine Treatment

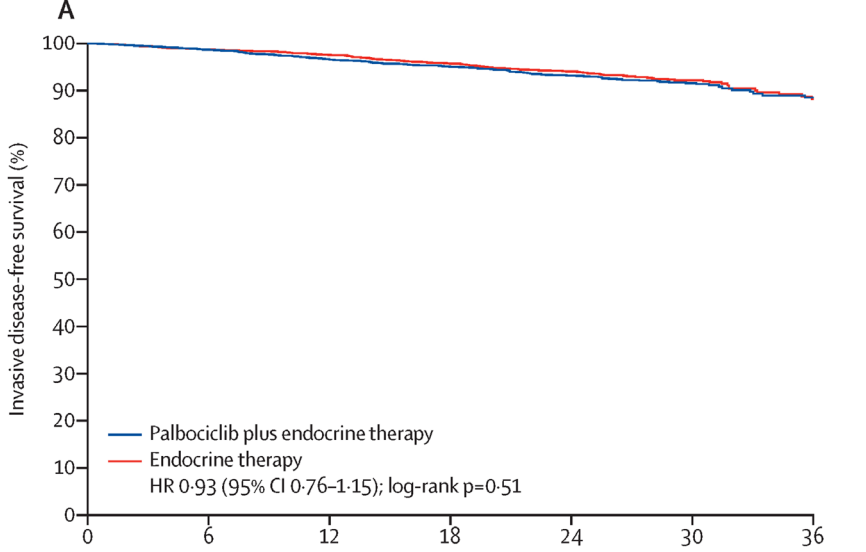
* Aromatase inhibitor or tamoxifen, +/- LHRH agonist

Primary Endpoint: invasive Disease-Free Survival (iDFS)

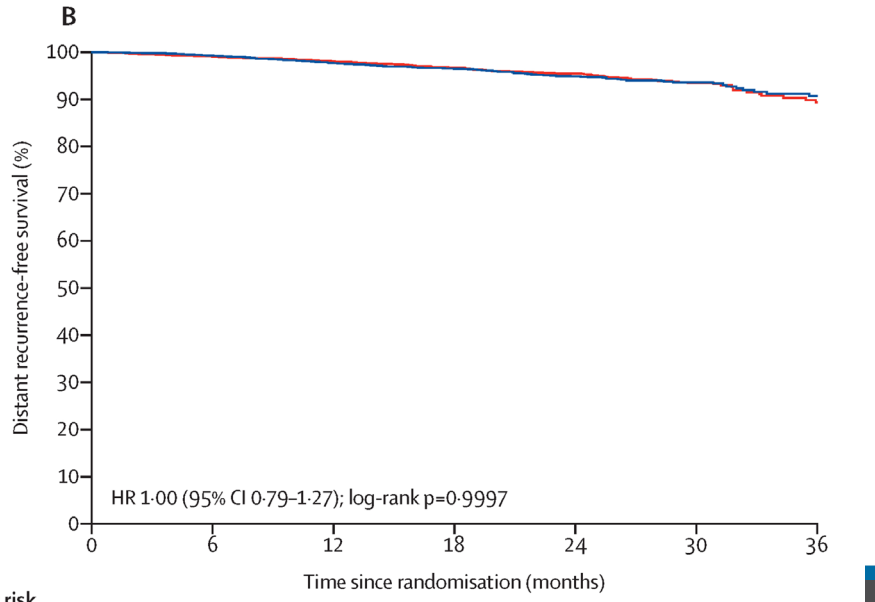
PALLAS: Patient Characteristics

- Between 9/2015 and 11/2018, 5,760 patients were randomized and included in the ITT set.
- The majority had higher stage disease and had received prior chemotherapy.
- 58·7% had high clinical risk disease, described as:
  - ≥4 nodes involved (≥N2), or
  - 1-3 nodes with either T3/T4 and/or G3 disease

Variable	Palbociclib + ET (N=2,883)	ET (N=2,877)
Age (y) – median (range)	52 (25 – 90)	52 (22 – 85)
Stage		
IIA	504 (17·5%)	509 (17·7%)
IIB	968 (33·6%)	951 (33·1%)
III	1402 (48·6%)	1408 (48·9%)
T-Stage		
T0/T1/Tis/TX	557 (19·3%)	500 (17·4%)
T2	1603 (55·6%)	1636 (56·9%)
T3/T4	722 (25·0%)	741 (25·8%)
N-Stage		
N0	367 (12·7%)	383 (13·3%)
N1	1427 (49·5%)	1415 (49·2%)
N2	703 (24·4%)	709 (24·6%)
N3	385 (13·4%)	370 (12·9%)
Histologic Grade		
G1	300 (10·4%)	313 (10·9%)
G2	1622 (56·3%)	1658 (57·6%)
G3	836 (29·0%)	767 (26·7%)
Prior Chemotherapy	2384 (82·7%)	2370 (82·4%)
Initial Adjuvant Endocrine Therapy		
Aromatase inhibitor	1954 (67·8%)	1918 (66·7%)
Tamoxifen	923 (32·0%)	949 (33·0%)
Concurrent Adjuvant LHRH Agonist	532 (18·5%)	604 (21.1%)



Number at risk (number censored)							
Palbociclib plus endocrine therapy	2883 (0)	2684 (163)	2563 (253)	1946 (827)	1257 (1488)	583 (2145)	163 (2554)
Endocrine therapy	2877 (0)	1649 (192)	2535 (250)	1953 (796)	1275 (1444)	574 (2131)	172 (2524)



Number at risk (number censored)							
Palbociclib plus endocrine therapy	2883 (0)	2692 (165)	2573 (256)	1956 (843)	1270 (1508)	588 (2172)	163 (2586)
Endocrine therapy	2877 (0)	1662 (195)	2554 (261)	1976 (811)	1288 (1473)	579 (2171)	175 (2567)

PALLAS trial

Mayer EL, et al.
Lancet Oncol 2021;22:212-222

PENELOPE^{B} Study Design

N=1250
- HR+/HER2- breast cancer
- no pCR after NACT
- CPS-EG score ≥3 or ≥2 with ypN+

Primary Endpoint: iDFS

Stratification factors
- Nodal status: ypN 0-1 vs ypN2-3
- Age: ≤50 vs >50 yrs
- Ki-67: >15% vs ≤ 15%
- Region: Asian vs non Asian
- CPS-EG Score: ≥3 vs 2 and ypN+

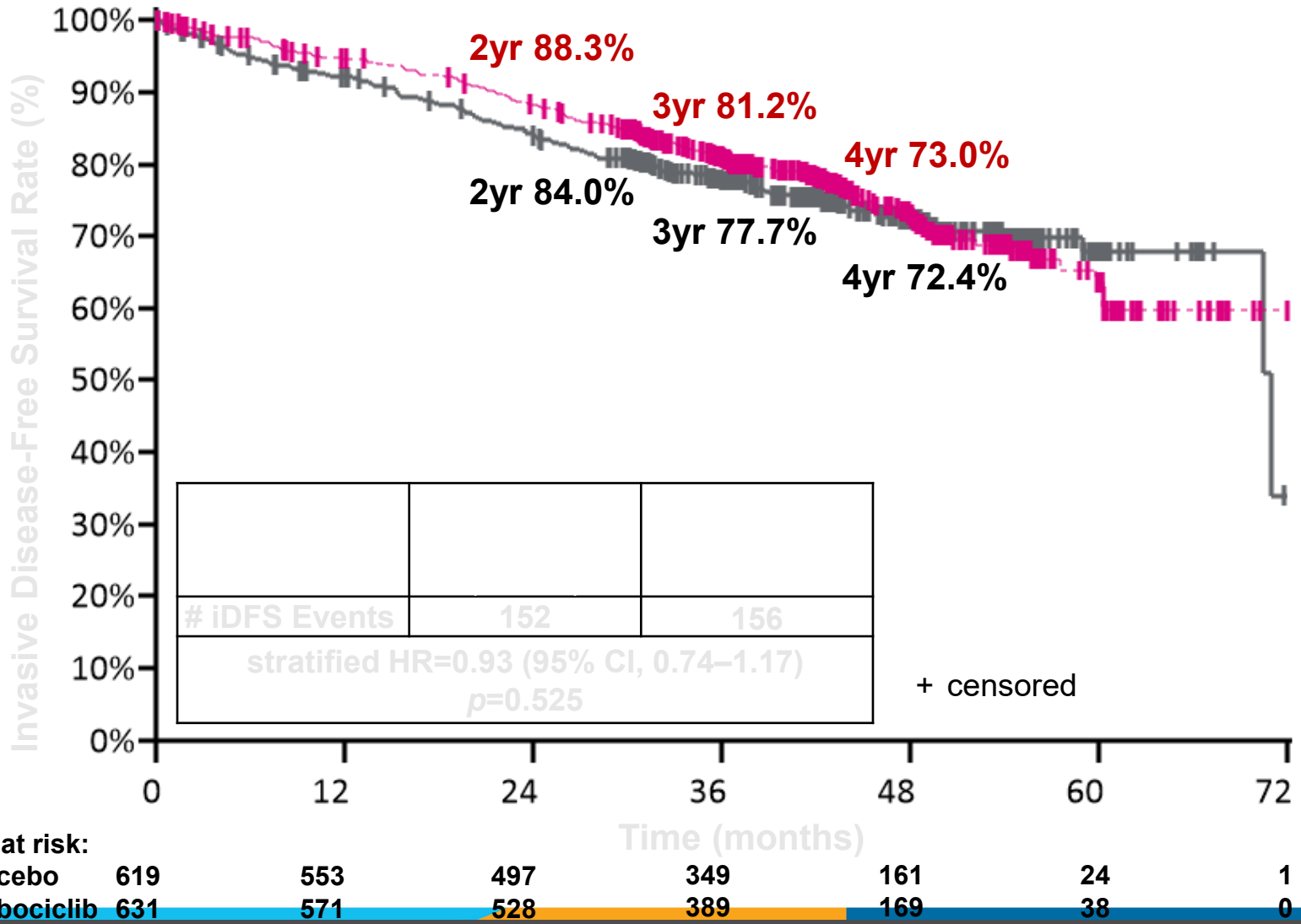
Neoadjuvant Chemotherapy → **Surgery +/- Radiotherapy** → **R 1:1**

Palbociclib
125 mg once daily p.o.
d1-21, q28d for 13 cycles

Placebo
d1-21, q28d for 13 cycles

All patients will receive concomitantly endocrine therapy according to local standards

Penelope-B: ClinicalTrials.gov NCT01864746



Patients at risk:

—	Placebo	619	553	497	349	161	24	1
—	Palbociclib	631	571	528	389	169	38	0

Median Follow-Up 42.8 Months

* Weighted log-rank test based on the CHW method, taking into account the adaptive sample size re-estimation and group-sequential nature of the design