44ES JOURNÉES DE LA SOCIÉTÉ FRANÇAISE DE SÉNOLOGIE ET DE PATHOLOGIE MAMMAIRE

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SFSPM

Carcinome Canalaire In Situ
Hormonothérapie recommandée aux US / sélective en Europe ?

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DISCLOSURES

- **Consulting fees:** Astra Zeneca (institutional), Gilead (personal), Novartis (institutional), Lilly (institutional), MSD (institutional), Daiichi-Sankyo (institutional/personal).
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- **Travel support:** MSD; Gilead, Daiichi-Sankyo; Novartis

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General considerations

- DCIS represents a wide spectrum of lesions heterogeneous in grade, morphology, genomic profile and clinical presentation and represents almost 90% of all precursor breast cancers detected
- 20% of screen detected cancers are DCIS
- The proportion of DCIS which develop into IBC, untreated, is around 40%
- DCIS seems to be a real precursor of invasive cancer
- The type of treatment chosen, impacts recurrence but not survival
- The probability of dying from DCIS is very low

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Treatment considerations

- BCS is the most frequent form of treatment for DCIS
- Radiotherapy reduces LR by ±50%
- Hormonal treatment reduces ± LR by 30%
- The risk reduction of LR does not impact in survival

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Standard treatment options

- Mastectomy
- BCS alone
- BCS with RT
- BCS with HT
- BCS with RT and HT

Clinical Trials - Surveillance

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KEY Trials – Adjuvant Hormonal Therapy - SERMs

	Entry dates	Number randomised	Median follow-up (years)	HR (95% CI) for ipsilateral new breast events
Radiotherapy (50 Gy in 25 fractions recommended)				
NSABP B-17[7]	1985–90	818	10·7	RR 0·43 (p<0·0001)
EORTC 10853[9,17]	1986–96	1010	10·5	0·53 (0·40–0·70)
UK/ANZ[10]	1990–98	1030	12·7	0·32 (0·22–0·47)
Swedish[18]	1987–99	1067	8·0	0·40 (0·30–0·54)
Tamoxifen (20 mg for 5 years)				
NSABP B-24[14]	1991–94	1804	7·0	0·70 (0·50–0·98)
UK/ANZ[10]	1990–98	1576	12·7	0·71 (0·58–0·88)

HR=hazard ratio. RR=risk ratio.

Table 6: Trials of the treatment of ductal carcinoma in situ

At 10 years f-up

- Radiotherapy halves IL events IS and Invasive
- Tamoxifen reduces ipsilateral DCIS and contralteral tumours

Cuzick Lancet Oncology 2011

Cochrane systematic review – Adjuvant Tamoxifen

- *Tamoxifen* after surgery for DCIS *reduced*:
  - recurrence of ipsilateral DCIS (HR 0.75; 95% CI 0.61-0.92)
  - contralateral DCIS (RR 0.50; 95% CI 0.28-0.87).
  - contralateral invasive cancer (RR 0.57; 95% CI 0.39-0.83)

- There was a trend towards *decreased ipsilateral invasive cancer* (HR 0.79; 95% CI 0.62-1.01).

- The *number needed to treat* in order for tamoxifen to have a protective effect against all breast events is *15*.

- No reduction in risk of all-cause mortality

Staley, Breast, 2014

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KEY Trials – Adjuvant Hormonal Therapy - SERMs

Patiente Level Meta-analysis 2013 – SERMs as Breast Cancer Prevention

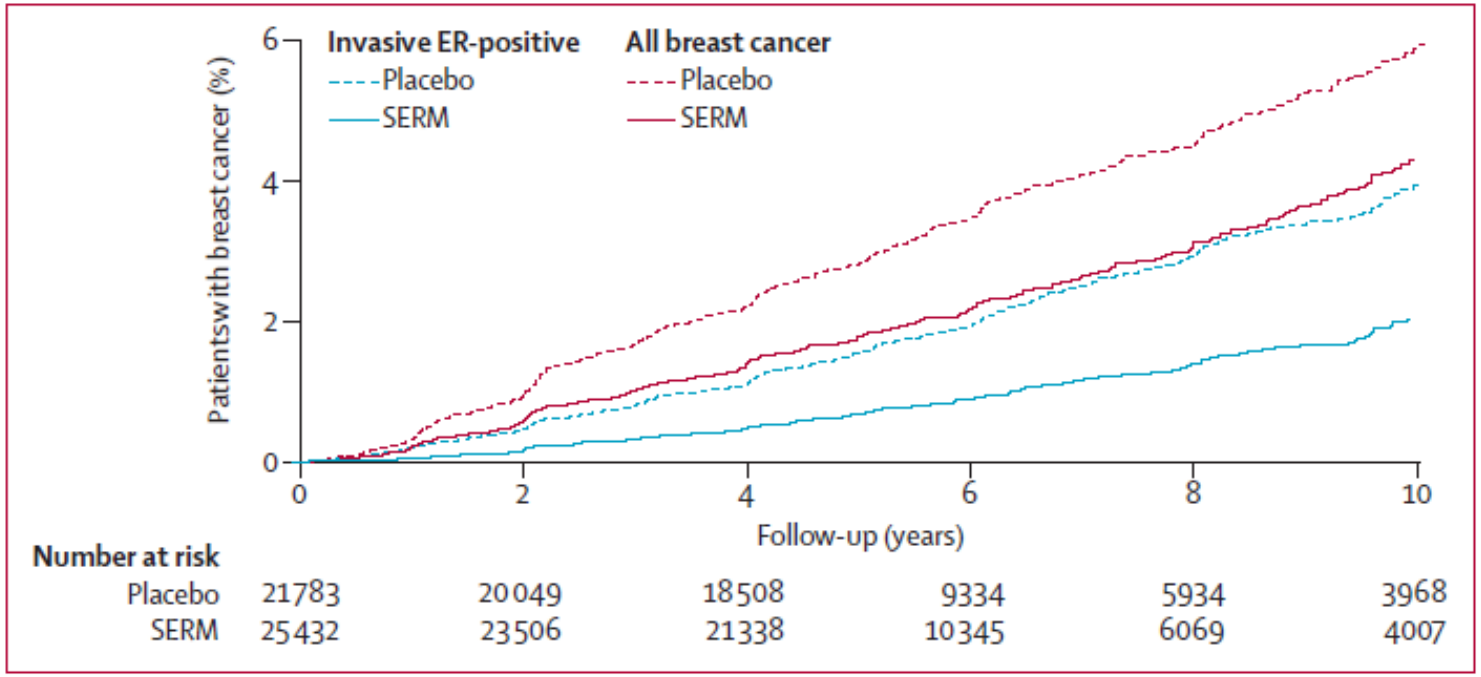

Figure 1: Cumulative incidence for all breast cancer (including ductal carcinoma in situ) and all ER-positive invasive cancers in years 0–10 according to treatment allocation
SERM=selective oestrogen receptor modulator. ER=oestrogen receptor.

38% reduction in BC incidence [[HR] 0·62, 95% CI 0·56-0·69)

Cuzick et al, Lancet 2013

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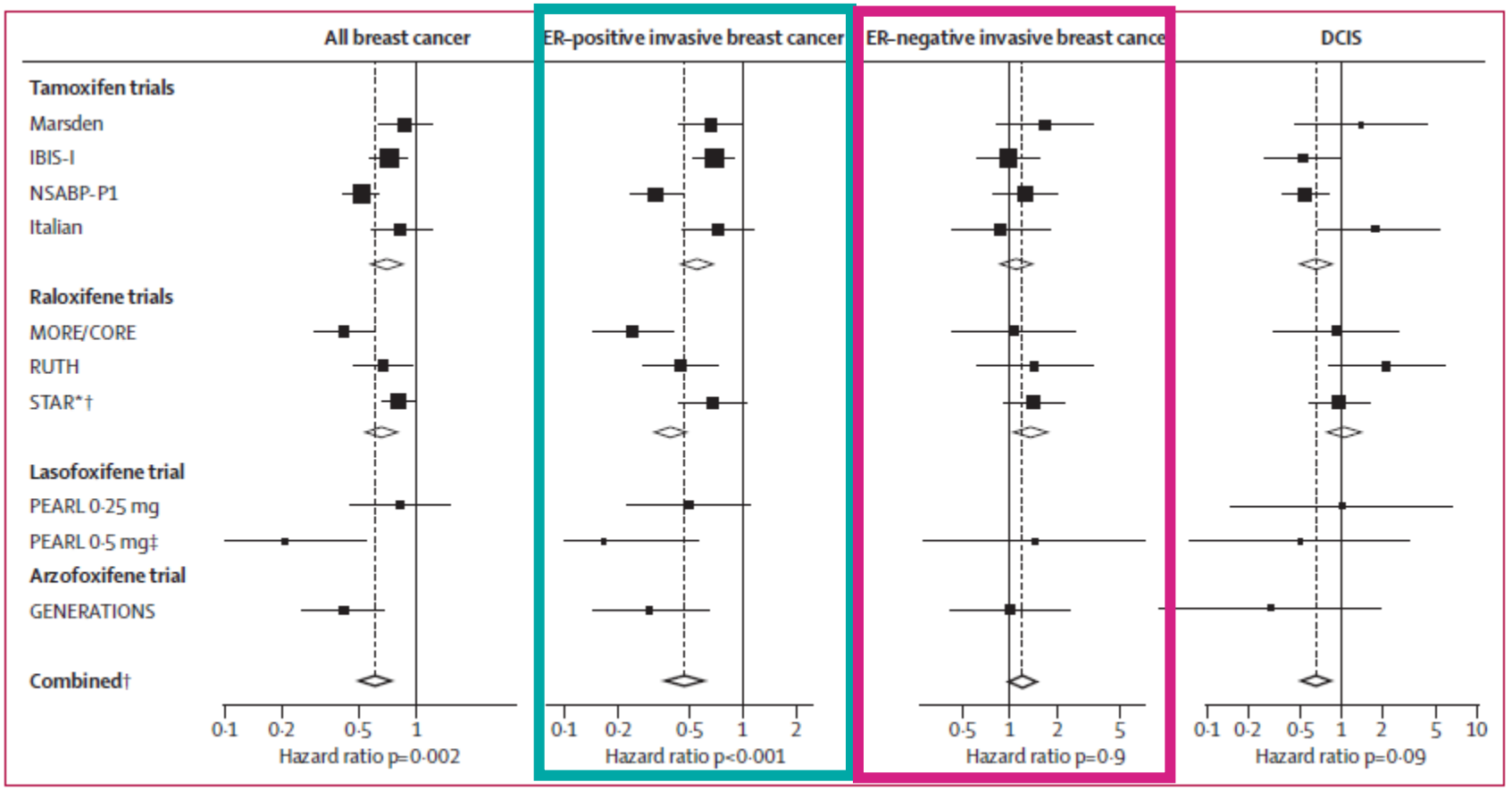

Figure 3: All breast cancers, invasive breast cancer, and DCIS in years 0–10

NNT = 42

Cuzick et al Lancet 2013

KEY Trials – Adjuvant Hormonal Therapy - SERMs

Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Recurrence in Breast Noninvasive Neoplasia: A 10-Year Follow-Up of TAM-01 Study

- N=500
- Reduction invasive BC recurrence: invasive (77%) and ipsilateral (59%)

  [HR: 0.58; 95% CI, 0.35 to 0.95; log-rank *P* = .03]
- No between-group difference in the incidence of serious adverse events

NNT = 22/14

Lazzeroni M et al JCO 2023

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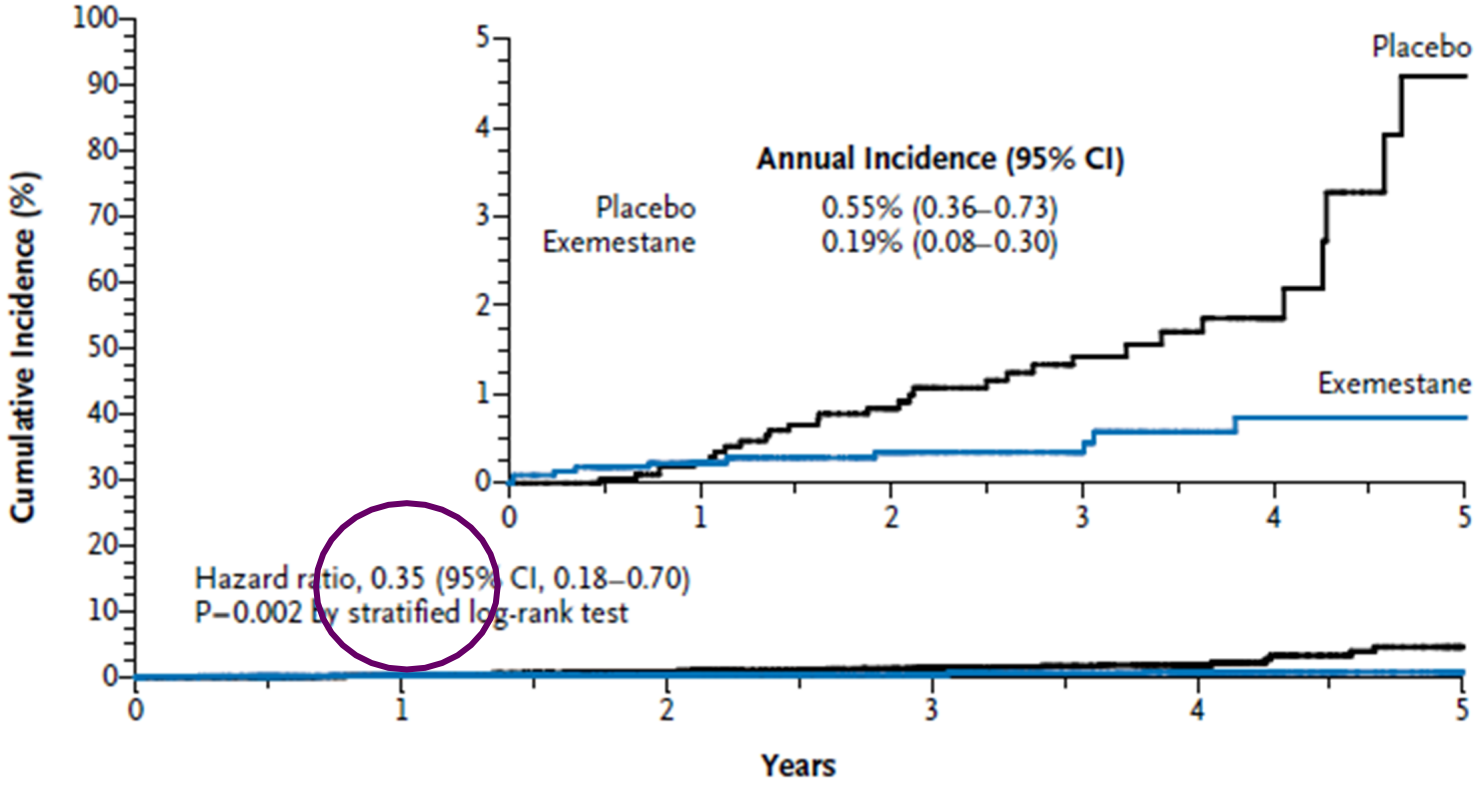
KEY Trials – AIs as breast cancer prevention - -> MAP.3 Trial

High risk women, exemestane versus placebo, 5 years (Fup: 35 months)



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

Goss NEJM 2013

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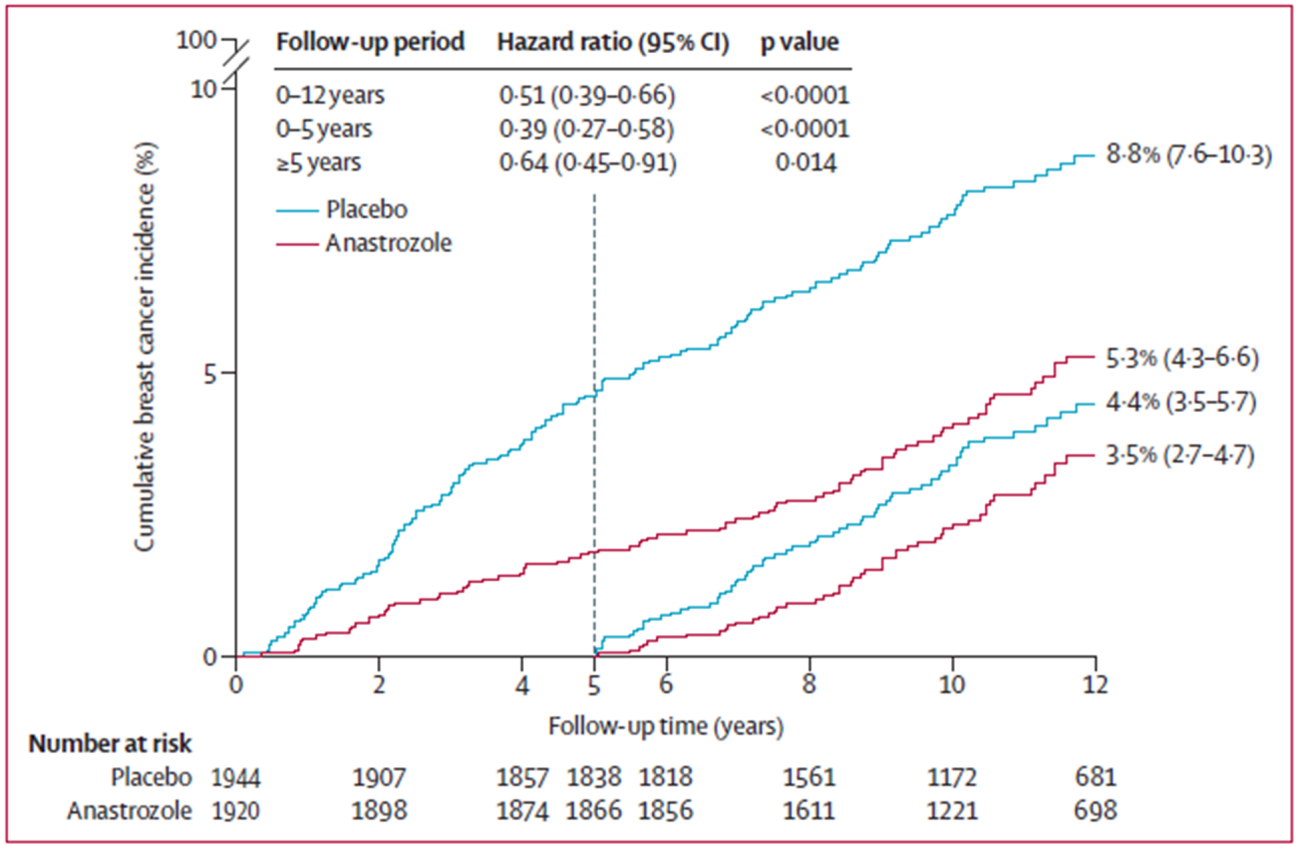

Figure 1: **Cumulative incidence for all breast cancer by treatment allocation and follow-up period**

	Anastrozole, N=1920, all years (>5 years)	Placebo, N=1944, all years (>5 years)	Odds ratio (95% CI), all years
Fractures	380 (182)	373 (186)	1·04 (0·88–1·22)
Myocardial infarction	16 (8)	14 (8)	..
Deep vein thrombosis*	13 (6)	17 (5)	..
Pulmonary embolism	17 (11)	12 (7)	..
Transient ischaemic attack†	24 (14)	20 (9)	..
Stroke	23 (15)	17 (9)	..

*In the absence of pulmonary embolism. †In the absence of stroke. Numbers in parentheses refer to events occurring in the post-treatment period (>5 year follow-up).

Table 3: **Major adverse events**

Goss NEJM 2013

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KEY Trials – AIs as breast cancer prevention - -> IBIS-II DCIS Trial

Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial

John F Forbes, Ivana Sestak, Anthony Howell, Bernardo Bonanni, Nigel Bundred, Christelle Levy, Gunter von Minckwitz, Wolfgang Eiermann, Patrick Neven, Michael Stierer, Chris Holcombe, Robert E Coleman, Louise Jones, Ian Ellis, Jack Cuzick, on behalf of the IBIS-II investigators*

Results Between March 3, 2003, and Feb 8, 2012, we enrolled 2980 postmenopausal women from 236 centres in 14 countries and randomly assigned them to receive anastrozole (1449 analysed) or tamoxifen (1489 analysed). Median follow-up was 7·2 years (IQR 5·6–8·9), and 144 breast cancer recurrences were recorded. We noted no statistically significant difference in overall recurrence (67 recurrences for anastrozole *vs* 77 for tamoxifen; HR 0·89 [95% CI 0·64–1·23]). The non-inferiority of anastrozole was established (upper 95% CI <1·25), but its superiority to tamoxifen was not (p=0·49). A total of 69 deaths were recorded (33 for anastrozole *vs* 36 for tamoxifen; HR 0·93 [95% CI 0·58–1·50], p=0·78), and no specific cause was more common in one group than the other. The number of women reporting any adverse event was similar between anastrozole (1323 women, 91%) and tamoxifen (1379 women, 93%); the side-effect profiles of the two drugs differed, with more fractures, musculoskeletal events, hypercholesterolaemia, and strokes with anastrozole and more muscle spasm, gynaecological cancers and symptoms, vasomotor symptoms, and deep vein thromboses with tamoxifen.

Conclusions No clear efficacy differences were seen between the two treatments. Anastrozole offers another treatment option for postmenopausal women with hormone-receptor-positive DCIS, which may be be more appropriate for some women with contraindications for tamoxifen. Longer follow-up will be necessary to fully evaluate treatment differences.

Forbes J, Lancet, 2016

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Prevention trials

			Breast Cancer Incidence			Deaths From Breast Cancer		
Trial	**N**	**Follow-up[a]**	**Tamoxifen**	**Placebo**	**RR (95% CI)**	**Tamoxifen**	**Placebo**	
Royal Marsden[b]	2,494	13.2 years	82	104	0.78 (0.58 to 1.04)	12	9	Not reported
			Tamoxifen	**Placebo**	**HR (95% CI)**	**Tamoxifen**	**Placebo**	**OR (95% CI)**
NSABP P-1	13,388	74 months (mean)	145	250	0.57 (0.46 to 0.70)	12	11	Not reported
			Tamoxifen	**Placebo**	**HR (95% CI)**	**Tamoxifen**	**Placebo**	**OR (95% CI)**
IBIS-1	7,154	16.0 years (median)	251	350	0.71 (0.60 to 0.83)	31	26	1.19 (0.68 to 2.10)
			Anastrozole	**Placebo**	**HR (95% CI)**	**Anastrozole**	**Placebo**	
IBIS-II	3,864	131 months (median)	85	165	0.51 (0.39 to 0.66)	2	3	Not reported
			Exemestane	**Placebo**	**HR (95% CI)**	**Exemestane**	**Placebo**	**HR (95% CI)**
MAP.3	4,560	35 months (median)	11	32	0.35 (0.18 to 0.70)	1	0	Not reported
			Low-fat	**Control**	**HR (95% CI)**	**Low-fat**	**Control**	**HR (95% CI)**
WHI DM	48,835[a]	19.6 years (median)	1,299 (0.44%)	2,075 (0.46%)	0.95 (0.89 to 1.02)	132 (0.037%)	251 (0.047%)	0.79 (0.64 to 0.97)
			CEE	**Placebo**	**HR (95% CI)**	**CEE**	**Placebo**	**HR (95% CI)**
WHI CEE-alone	10,739	20.3 years (median)	238 (0.30%)	296 (0.37%)	0.78 (0.65 to 0.93)	30 (0.031%)	46 (0.046%)	0.60 (0.37 to 0.97)

Chlebowski et al, JOP 2021

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Adjuvant hormonal therapy

- The majority of trials reveal that, after surgery, adjuvant treatments reduce the rate of recurrent DCIS, and invasive recurrences
- OS in not improved by endocrine therapy

Indication	Metastases	Adjuvant	Prevention
Tamoxifen	+	+	+ USA
LH-RH agonists	+	+/-	-
SERD1 (Faslodex®)	+	-	-
SERDs 2nde G	+ (2022)		
SERM3 (Raloxifen…)	-	-	+ USA
Aromatase inhibitors	+++	+++	+ USA

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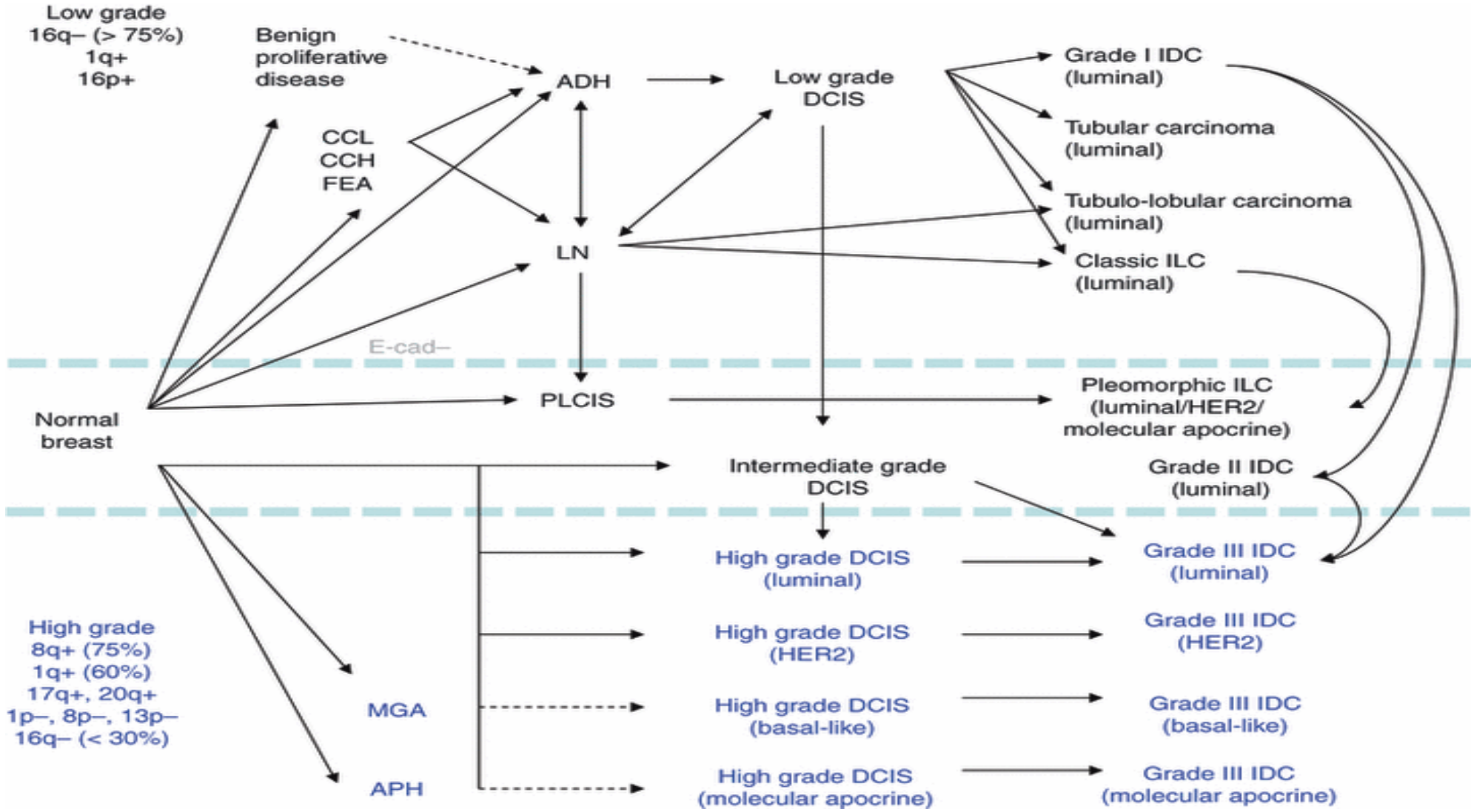
Adjuvant hormonal therapy



Chlebowski et al, JOP 2021

LORD Trial

Intergroup Study (EORTC-1401-BCG/BOOG 2014-04)
Management of low grade ductal carcinoma in situ (low-grade DCIS): a randomized, multicenter, non-inferiority trial, between standard therapy approach versus active surveillance

Primary endpoint: Ipsilateral invasive breast cancer free rate at 10 years

Biobanking for molecular analisys and translational research

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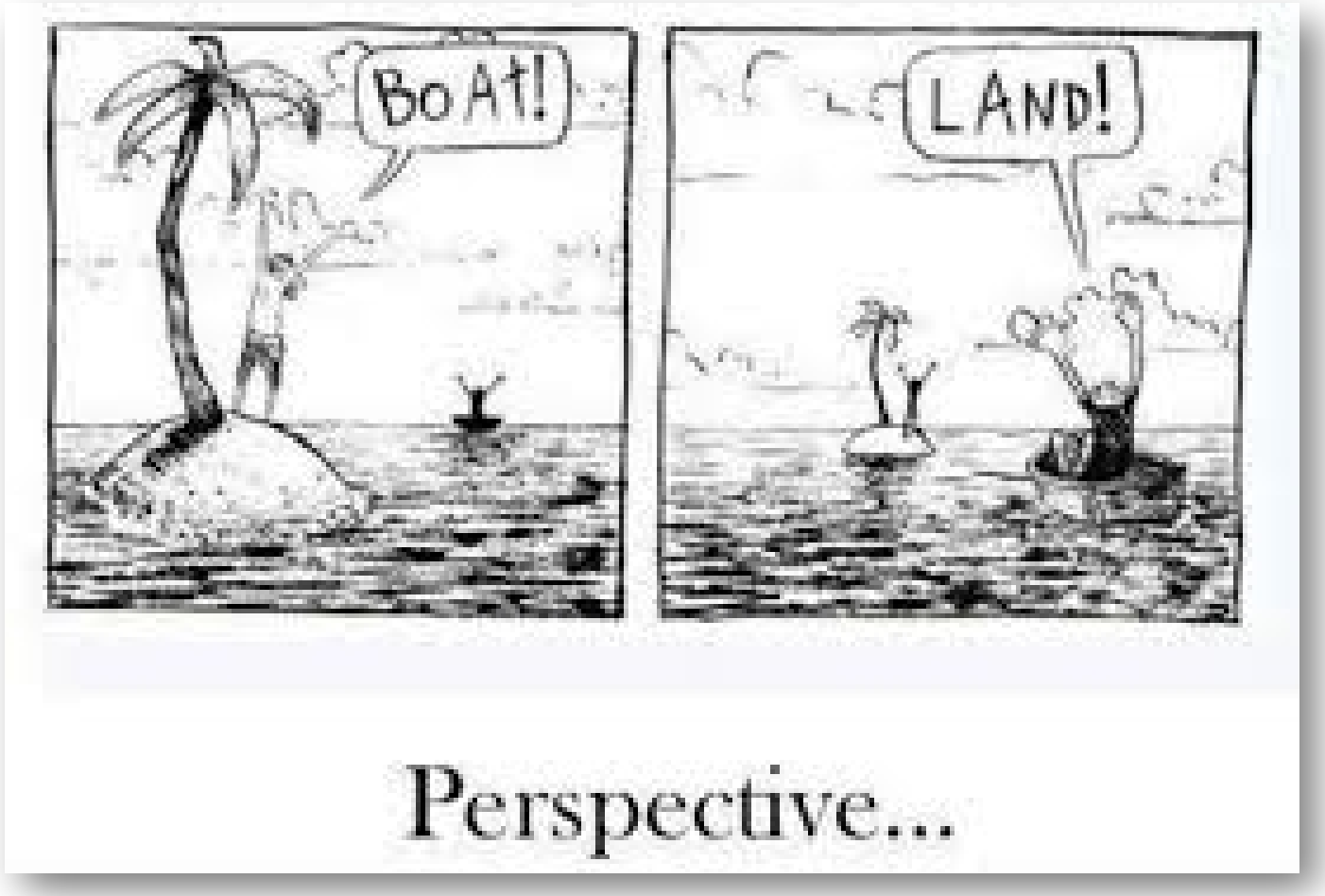
Adjuvant hormonal therapy



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St Gallen perspective

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Understanding breast cancer complexity to improve patient outcomes: The St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023

G. Curigliano[1,2*†], H. J. Burstein[3,4*†], M. Gnant[5,6], S. Loibl[7,8], D. Cameron[9], M. M. Regan[10], C. Denkert[11], P. Poortmans[12,13], W. P. Weber[14,15] & B. Thürlimann[16,17], St Gallen Consensus Conference Panelists 2023

Curigliano G et al, Annal Oncol 2023

- Adjuvant ET can further reduce the risk of recurrence in DCIS treated with breast conservation and RT, as well as reduce the risk of contralateral breast cancer.

- Both tamoxifen and AIs are options for adjuvant ET

[although the panelists generally lean towards tamoxifen owing to its favorable tolerability]

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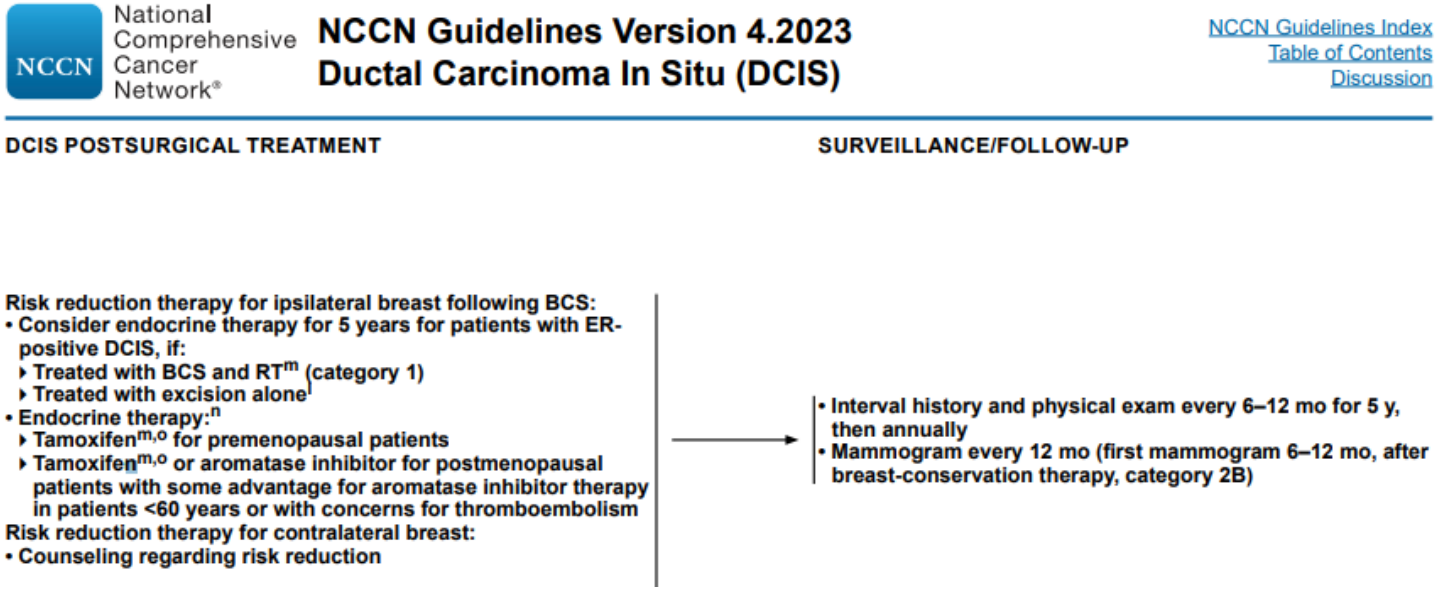
USA perspective

Use of Endocrine Therapy for Breast Cancer Risk Reduction: ASCO Clinical Practice Guideline Update

Kala Visvanathan, MHS, MD[1]; Carol J. Fabian, MD[2]; Elissa Bantug, MHS[3]; Abenaa M. Brewster, MHS, MD[4]; Nancy E. Davidson, MD[5]; Andrea DeCensi, MD[6]; Justin D. Floyd, DO[7]; Judy E. Garber, MPH, MD[8]; Erin W. Hofstatter, MD[9]; Seema A. Khan, MD[10]; Maria C. Katapodi, PhD[11]; Sandhya Pruthi, MD[12]; Rachal Raab, MD[13]; Carolyn D. Runowicz, MD[14]; and Mark R. Somerfield, PhD[15]

Visvanathan K et al, JCO 2019



National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Ductal Carcinoma In Situ (DCIS)

NCCN Guidelines Index
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Discussion

DCIS POSTSURGICAL TREATMENT

Risk reduction therapy for ipsilateral breast following BCS:
- **Consider endocrine therapy for 5 years for patients with ER-positive DCIS, if:**
  - **Treated with BCS and RT[m] (category 1)**
  - **Treated with excision alone[l]**
- **Endocrine therapy:[n]**
  - **Tamoxifen[m,o] for premenopausal patients**
  - **Tamoxifen[m,o] or aromatase inhibitor for postmenopausal patients with some advantage for aromatase inhibitor therapy in patients <60 years or with concerns for thromboembolism**

Risk reduction therapy for contralateral breast:
- **Counseling regarding risk reduction**

→

SURVEILLANCE/FOLLOW-UP

- **Interval history and physical exam every 6–12 mo for 5 y, then annually**
- **Mammogram every 12 mo (first mammogram 6–12 mo, after breast-conservation therapy, category 2B)**

NCCN Guidelines Version 4.2023

A reduction in incidence of BC itself is an important end point

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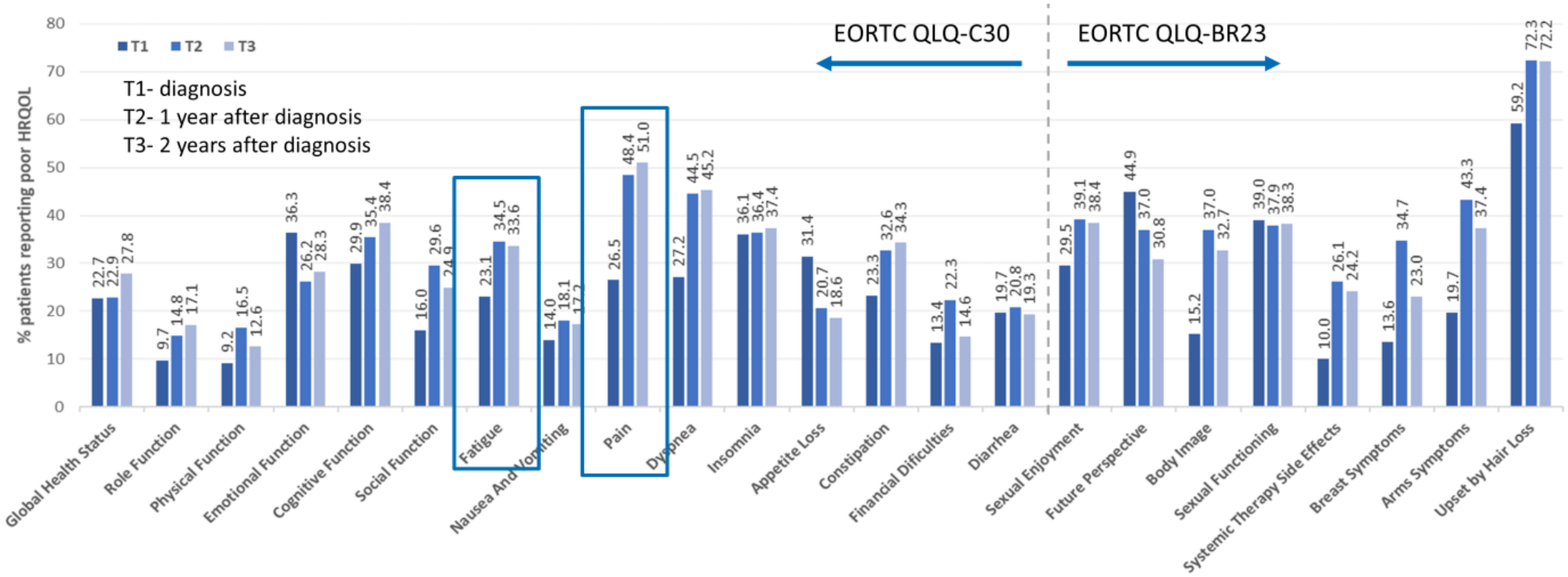
Adjuvant hormonal therapy

- The adverse medical, physical, psychosocial and health systems consequences of a breast cancer diagnosis and related therapies are well-documented.

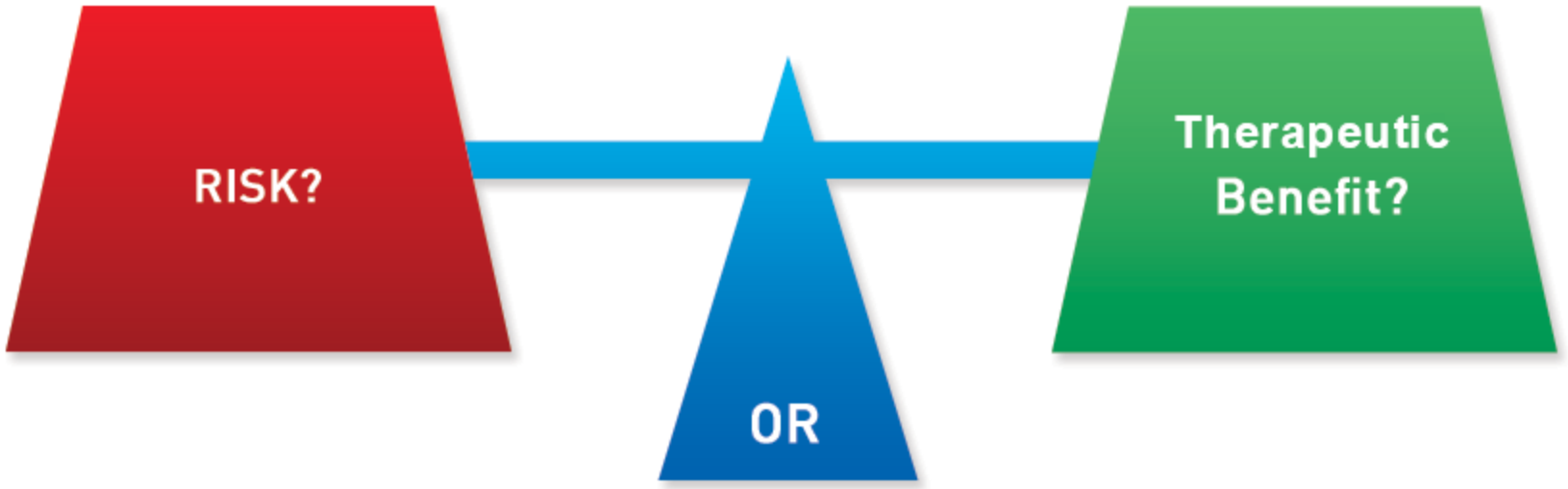


Patients reporting a severe dysfunction or sever symptom after diagnosis
Early-stage breast cancer, CANTO data

Ferreira AR, Ann Oncol 2019

Discussing uncertainties with patients: shared decision making

Shared Decision Making



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Discussing uncertainties with patients: shared decision making

Individual perceptions of risk and benefits

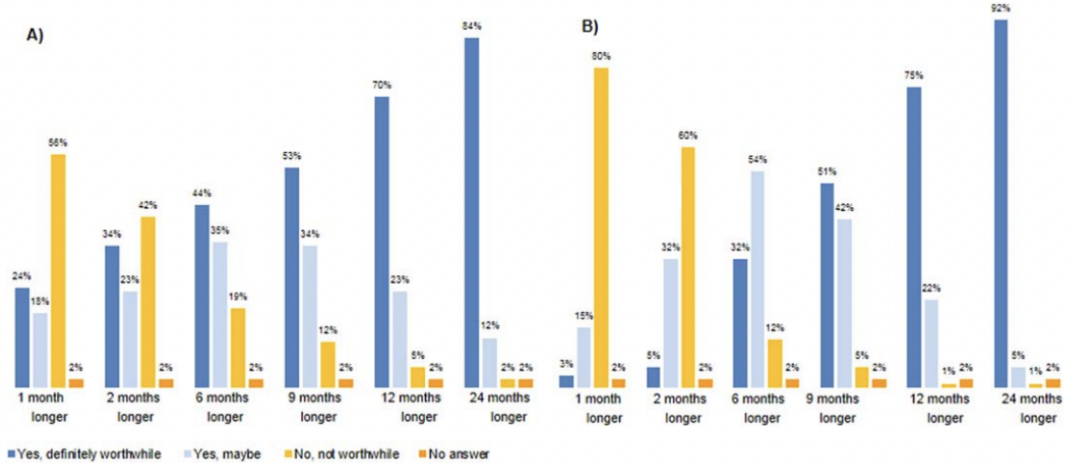
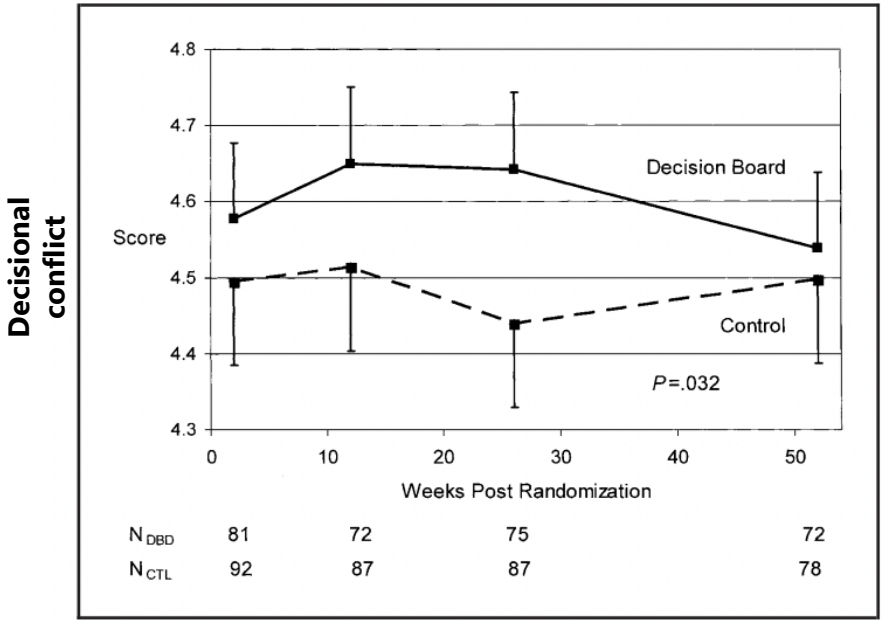


Figure 2. Trade-offs of survival benefit needed to consider chemotherapy worthwhile. (A) Patient preferences. (B) Physician ...s.

Vaz Luis I. Cancer 2017

Facilitating understanding and empowerment



Whelan T. JNCI 2003.

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Conclusion

- SERMs and AIs largely reduced ER-positive, PR-positive cancers and reduction in deaths from breast cancer has not been documented
- Toxicities with these agents are not negligible
- The adverse consequences of a breast cancer diagnosis and related therapies are well-documented.
- Patients emporement and Shared decision making is crucial

THANK YOU!!

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