



Carcinomes canaux in situ: y-a-t-il une place pour un traitement systémique?

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Plan

- Contexte
- Données récentes et controverses
- Recommandations nationales et internationales

Contexte

- Incidence croissante des CIS
- Taux de mastectomie élevé
- Polémique sur surdiagnostic et sur-traitement
- Pas de pression industrielle

Attention: dans ce topo, surveiller les critères de jugement:

- **survie sans rechute locale**
- **survie sans rechute**
- **évènements ipsi/controlatéraux, infiltrants ou pas**
- **survie spécifique**
- **survie globale**

Plan

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Pronostic des in-situ

EORTC 10853- à 15 ans

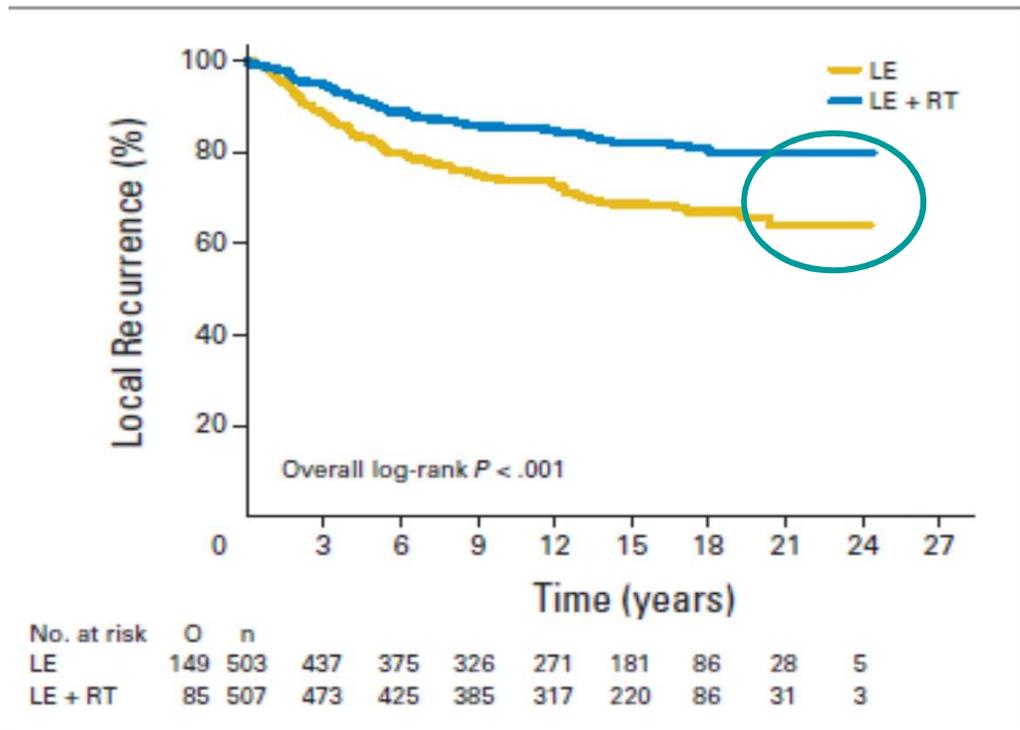


Fig 2. Time to local recurrence by treatment arm. LE, local excision; n, number

23% rechute locale,
1/2 invasive, 1/2 in situ

Risque de DC identique
dans les 2 bras:

BCSS: HR = 1.07

OS: HR = 1.02

Pronostic des in-situ

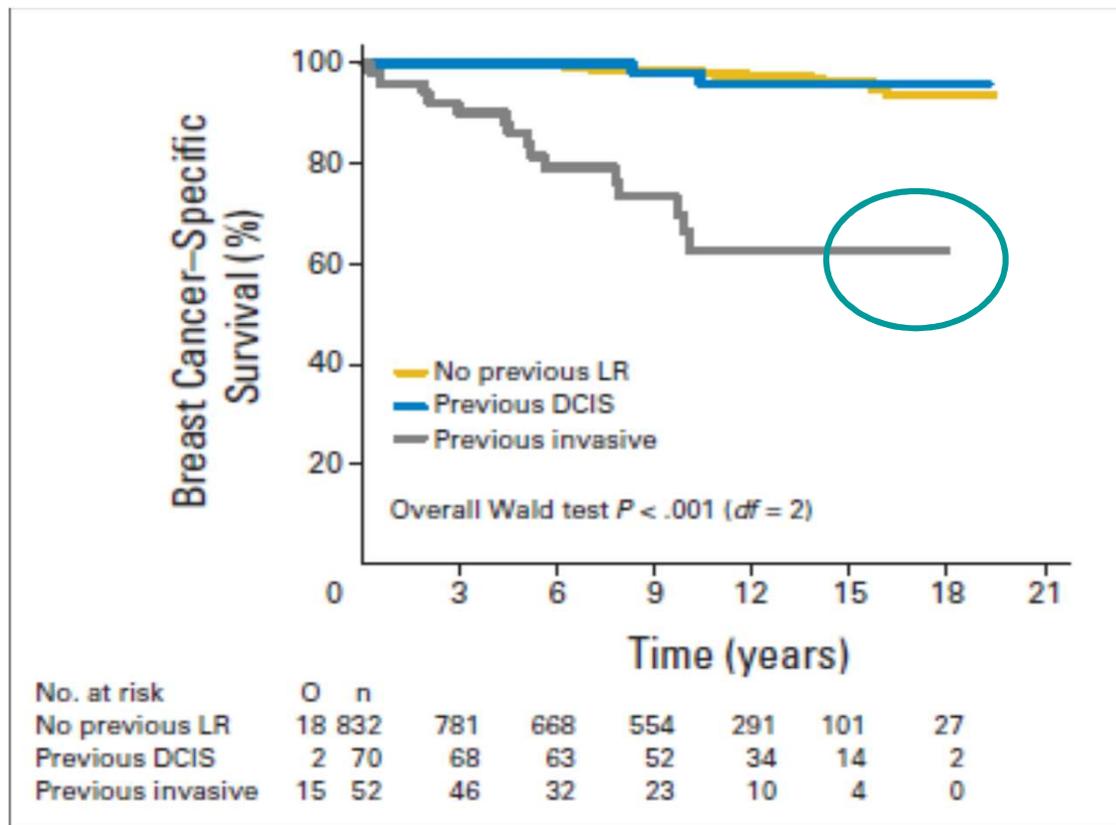


Fig 4. Breast cancer-specific survival after a local recurrence (LR) 5 years after random assignment. DCIS, ductal carcinoma in situ; n, number of patients; O, observed.

Mais...
après une rechute
invasive:
OS: HR 5.17 (vs
pas de rechute)

BCSS: HR 17.7

Tendances américaines des traitements et effets

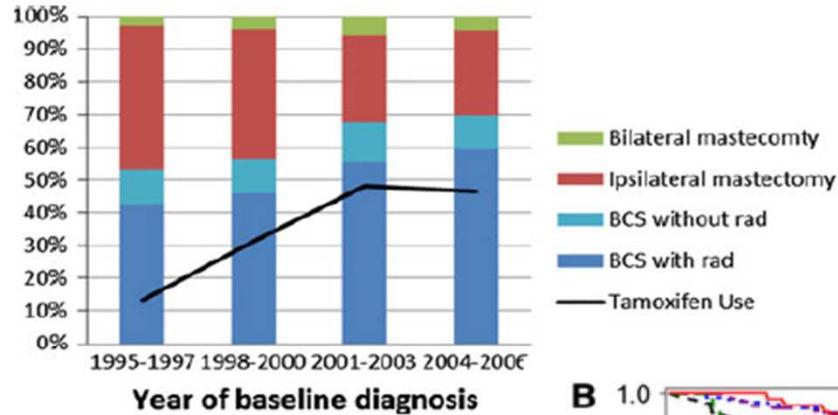
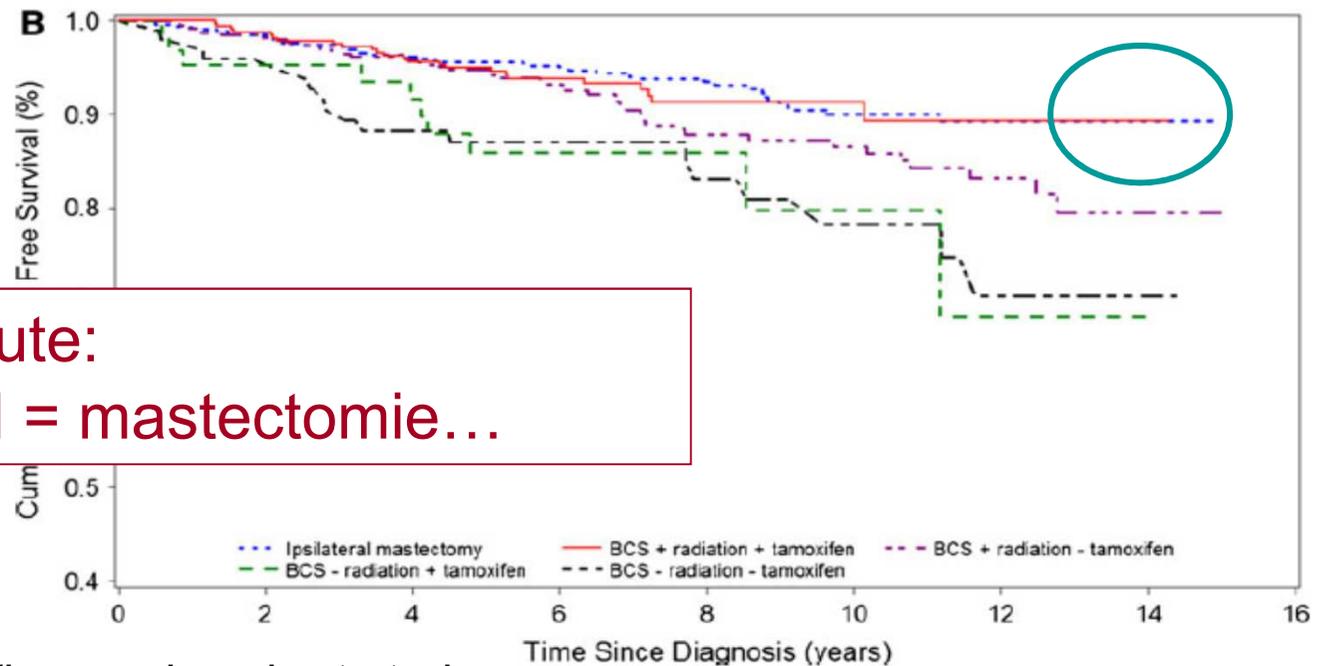
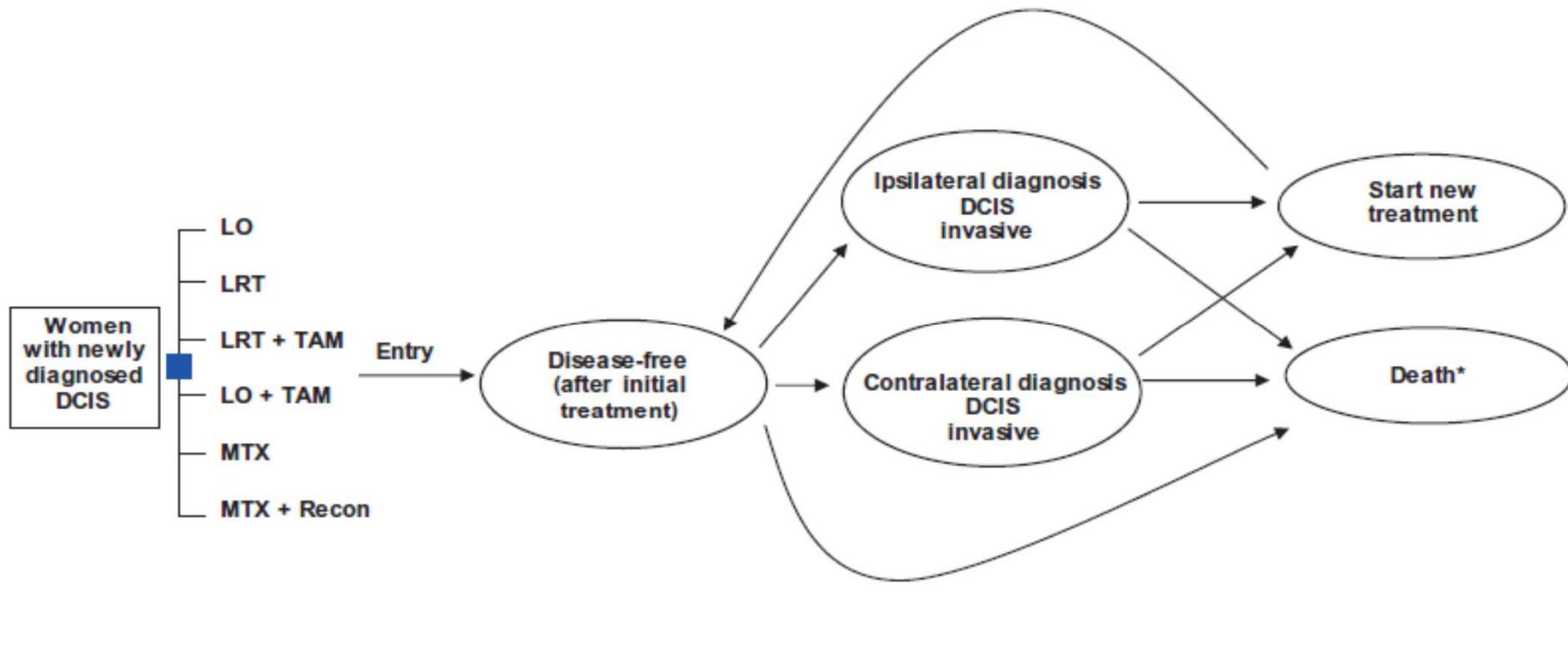


Fig. 2 Surgical treatment, radiation, and diagnosis, Wisconsin DCIS, cases ($n = 1,100$)



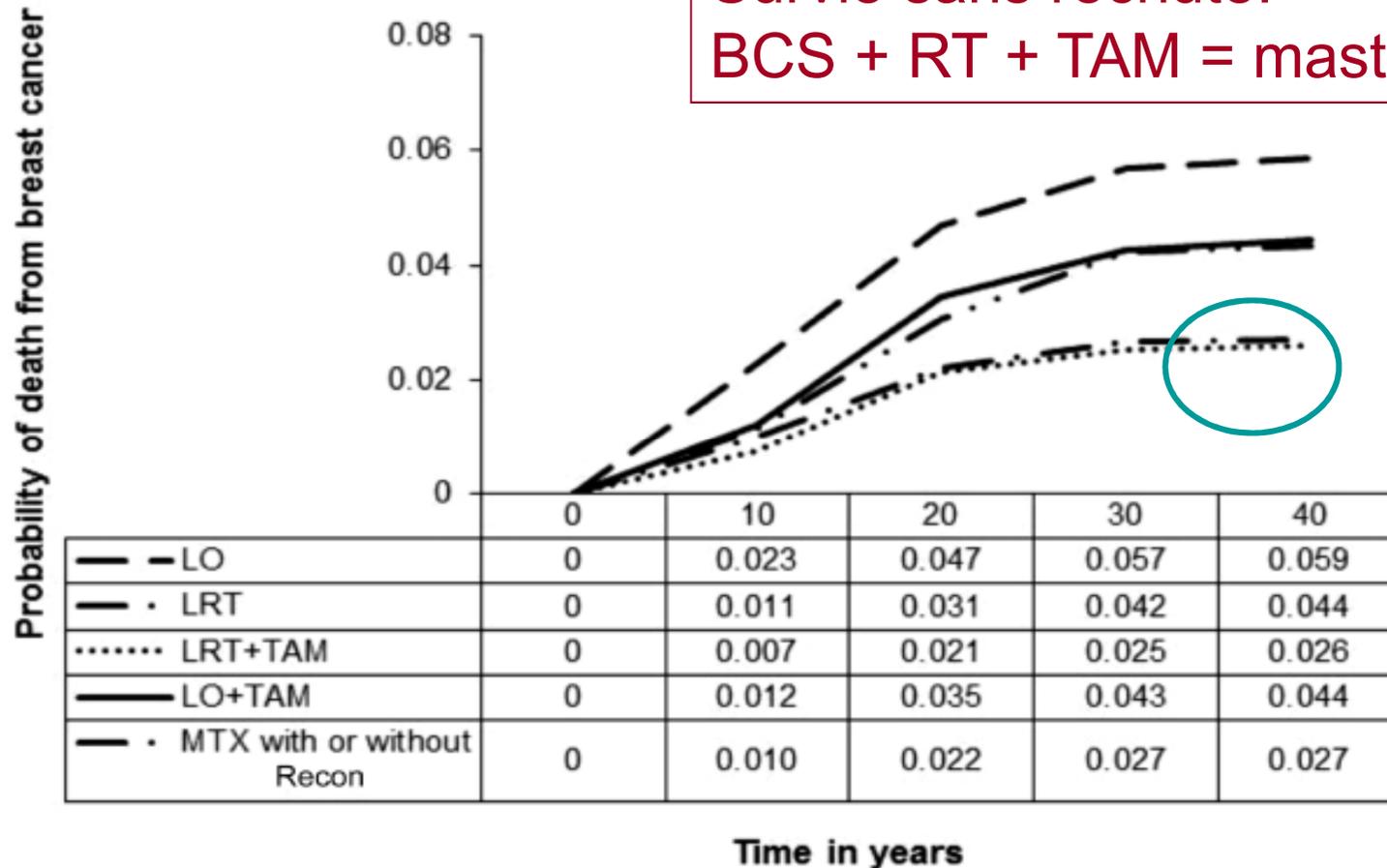
Survie sans rechute:
BCS + RT + TAM = mastectomie...

Modélisation des risques



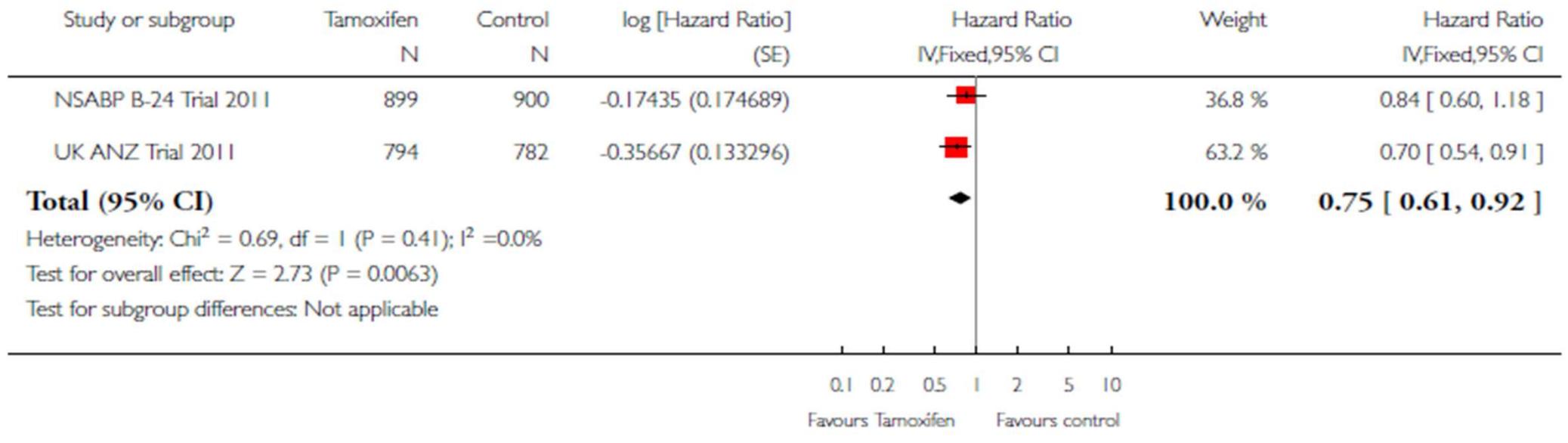
Modélisation des risques

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BCS + RT + TAM = mastectomie...



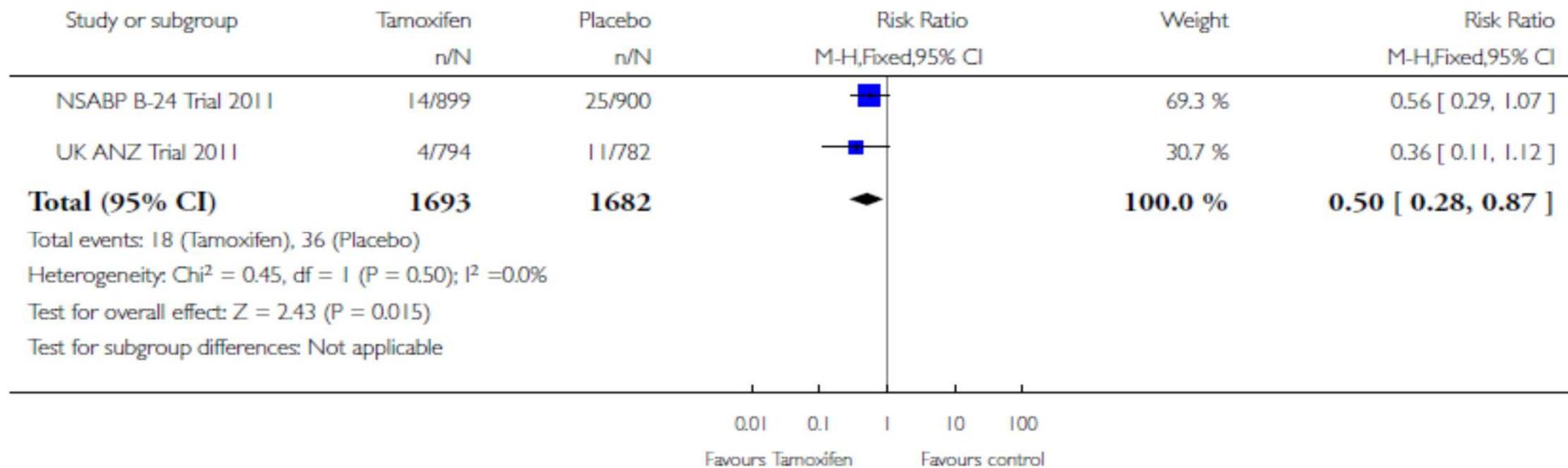
Cochrane 2012: Méta-analyse des 2 essais randomisés

CIC Ipsilateral



Cochrane 2012: Méta-analyse des 2 essais randomisés

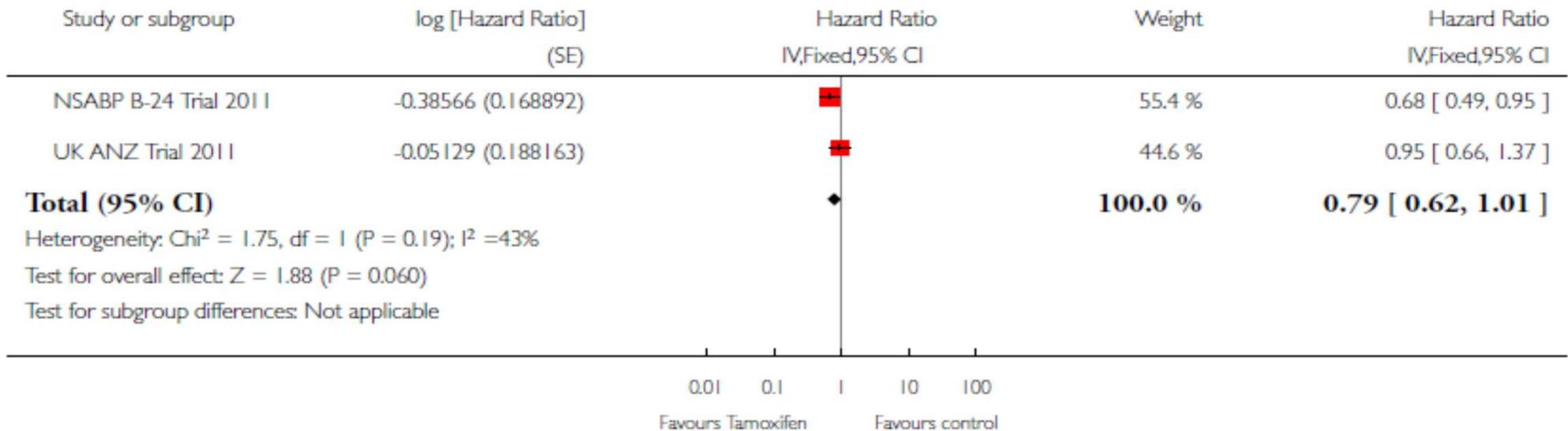
CIC controlateral



Cochrane 2012: Méta-analyse des 2 essais randomisés

Invasif ipsilateral

NSBAP B24. When data for those with clear margins were analyzed, there was no significant benefit of tamoxifen in reducing ipsilateral breast cancer events (11.27 per 1,000 patients with tamoxifen versus 14.52 per 1,000 patients on placebo, RR 1.00).



Cochrane 2012: Méta-analyse des 2 essais randomisés

Invasif controlateral

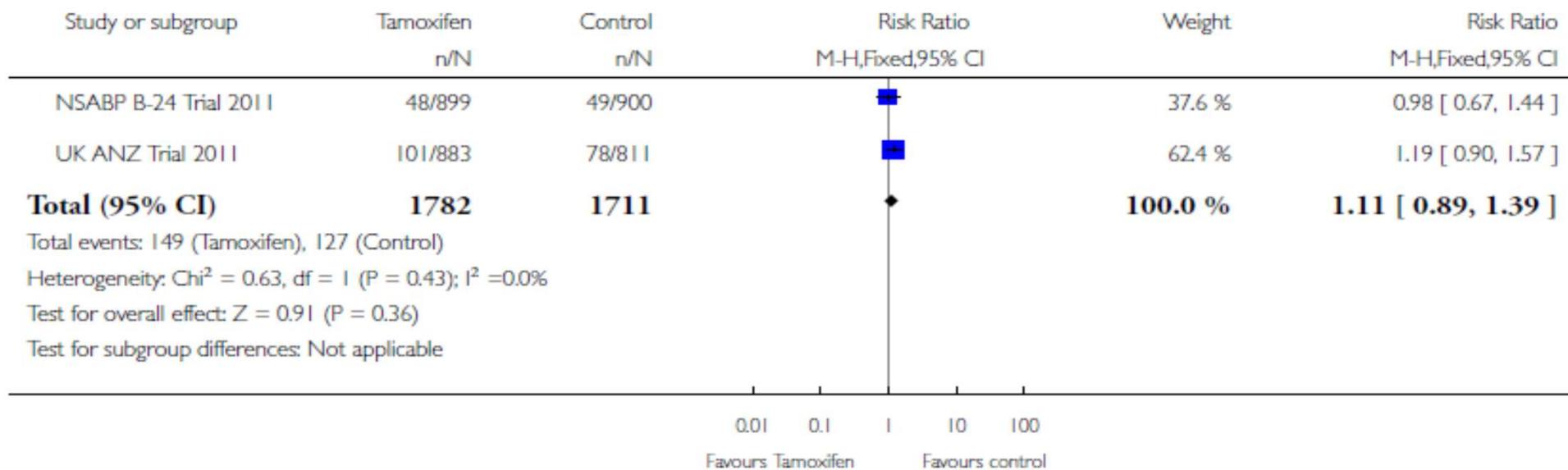
Study or subgroup	Tamoxifen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
NSABP B-24 Trial 2011	30/899	48/900		65.6 %	0.63 [0.40, 0.98]
UK ANZ Trial 2011	12/794	25/782		34.4 %	0.47 [0.24, 0.93]
Total (95% CI)	1693	1682		100.0 %	0.57 [0.39, 0.83]

Total events: 42 (Tamoxifen), 73 (Placebo)
Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² = 0.0%
Test for overall effect: Z = 2.93 (P = 0.0034)
Test for subgroup differences: Not applicable

Message de fond:
Il faut traiter 15 femmes pour éviter un évènement mammaire

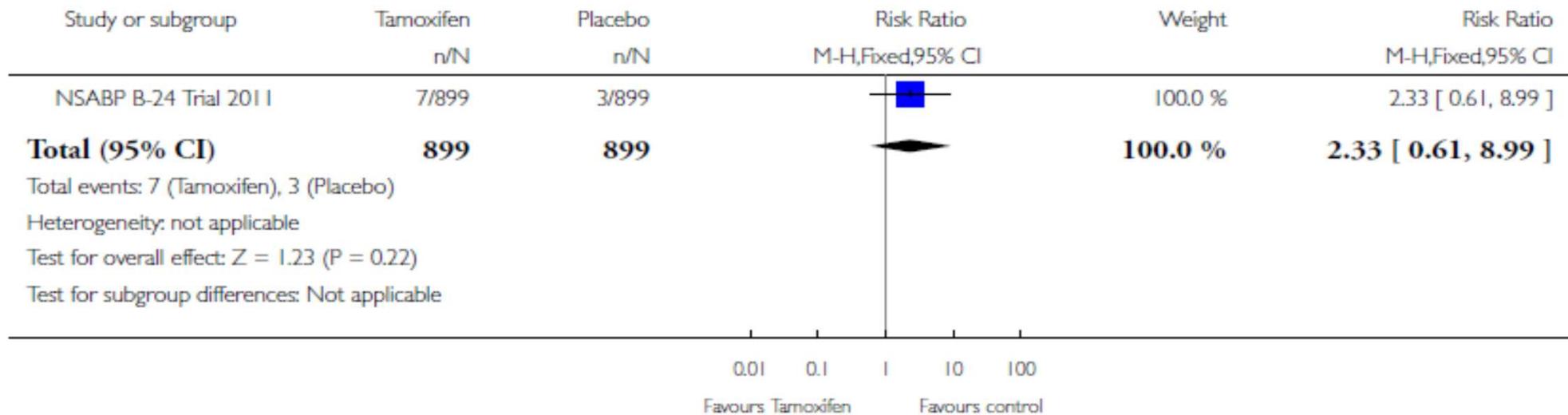
Cochrane 2012: Méta-analyse des 2 essais randomisés

Mortalité



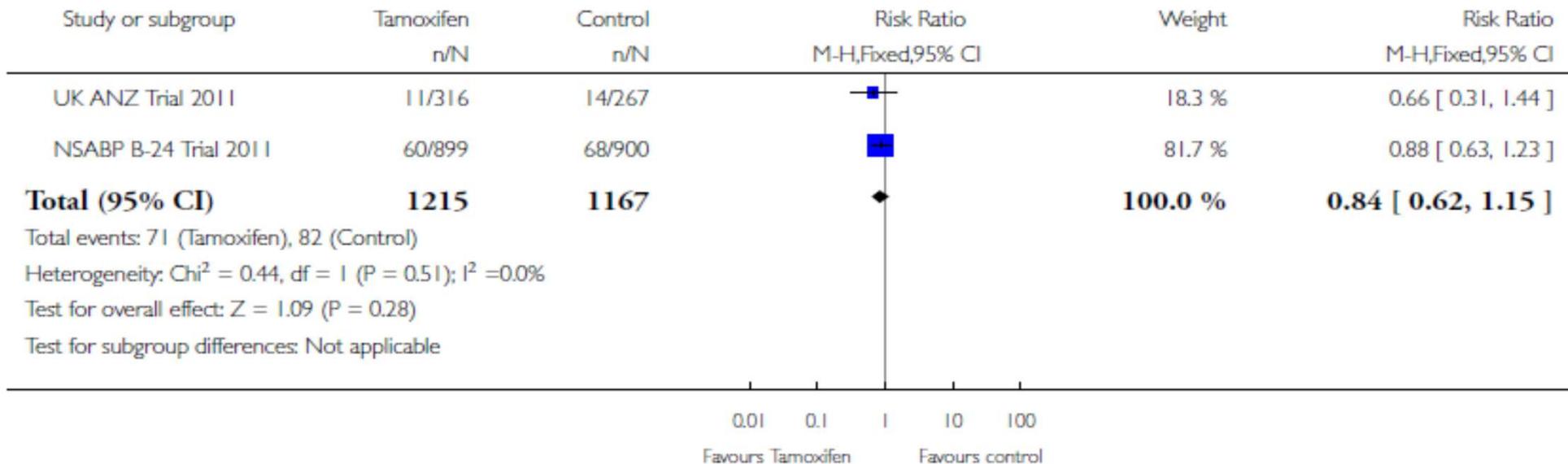
Cochrane 2012: Méta-analyse des 2 essais randomisés

Cancer de l'endomètre



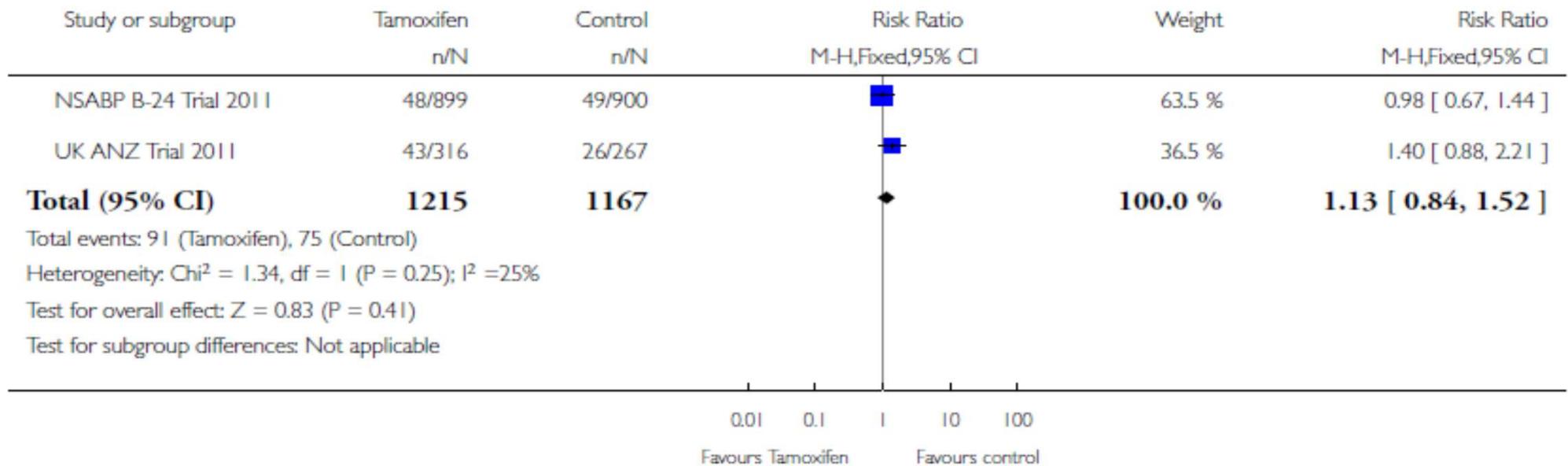
Cochrane 2012: Méta-analyse des 2 essais randomisés

CIC ipsilateral, patientes irradiées

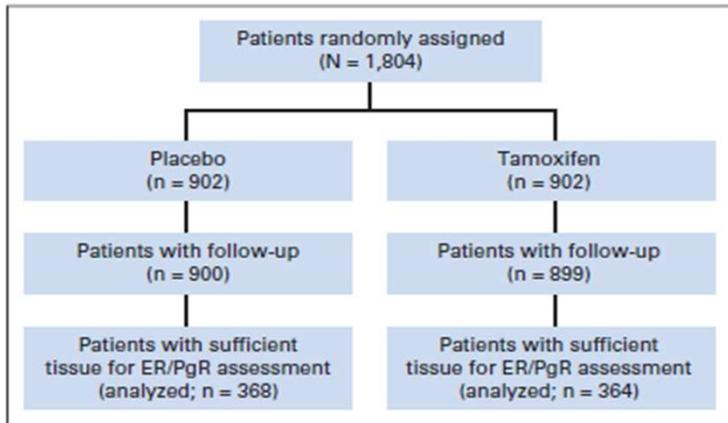


Cochrane 2012: Méta-analyse des 2 essais randomisés

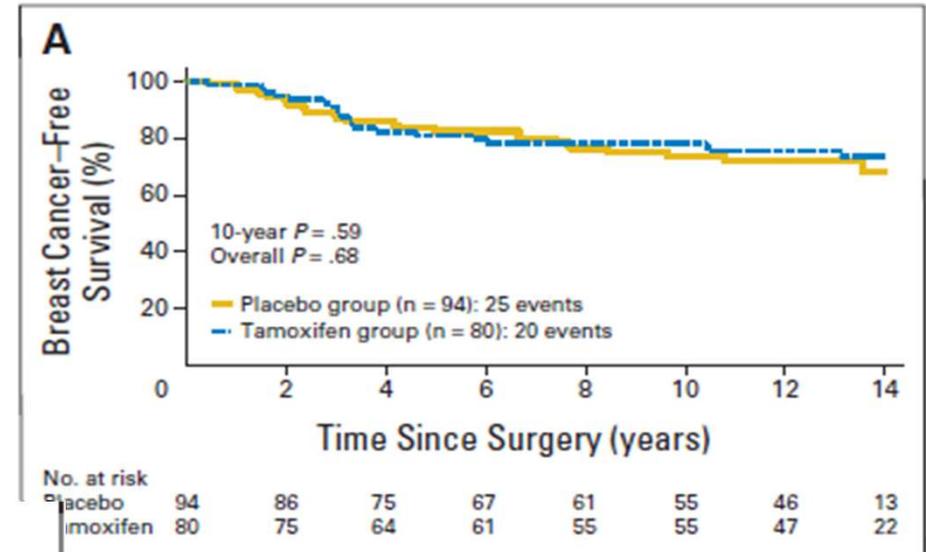
Mortalité, patientes irradiées



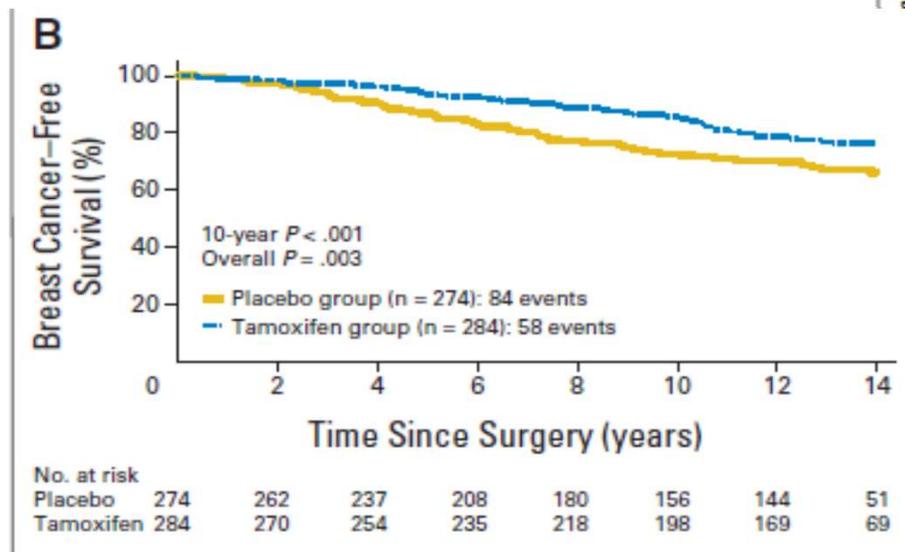
Bénéfice selon RE? NSABP B14



ER-



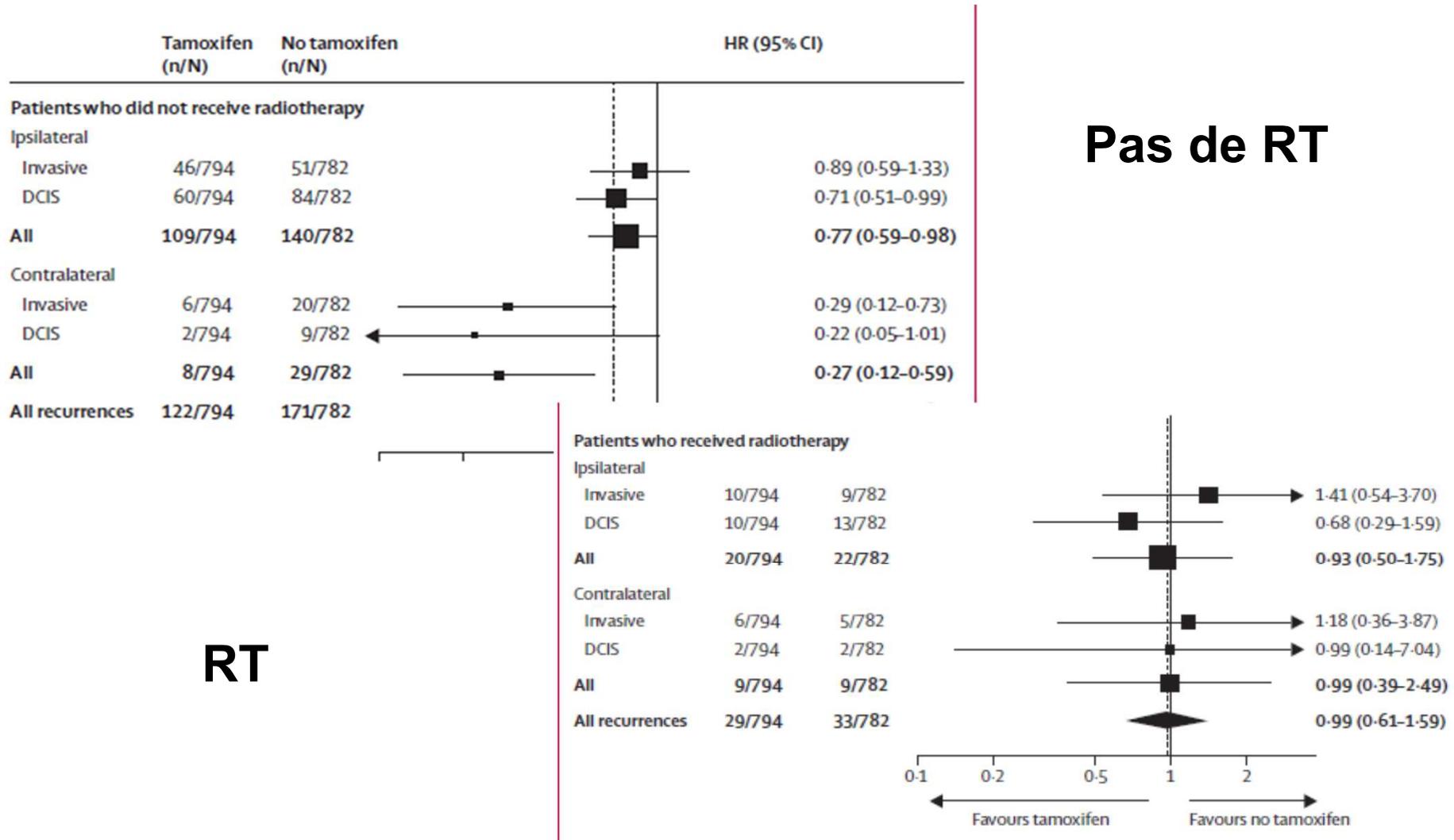
ER+



Mais...

Analyse à postériori
Gros pb de qualité des RE
etc

Bénéfice selon autres critères?



Bénéfice selon autres critères?

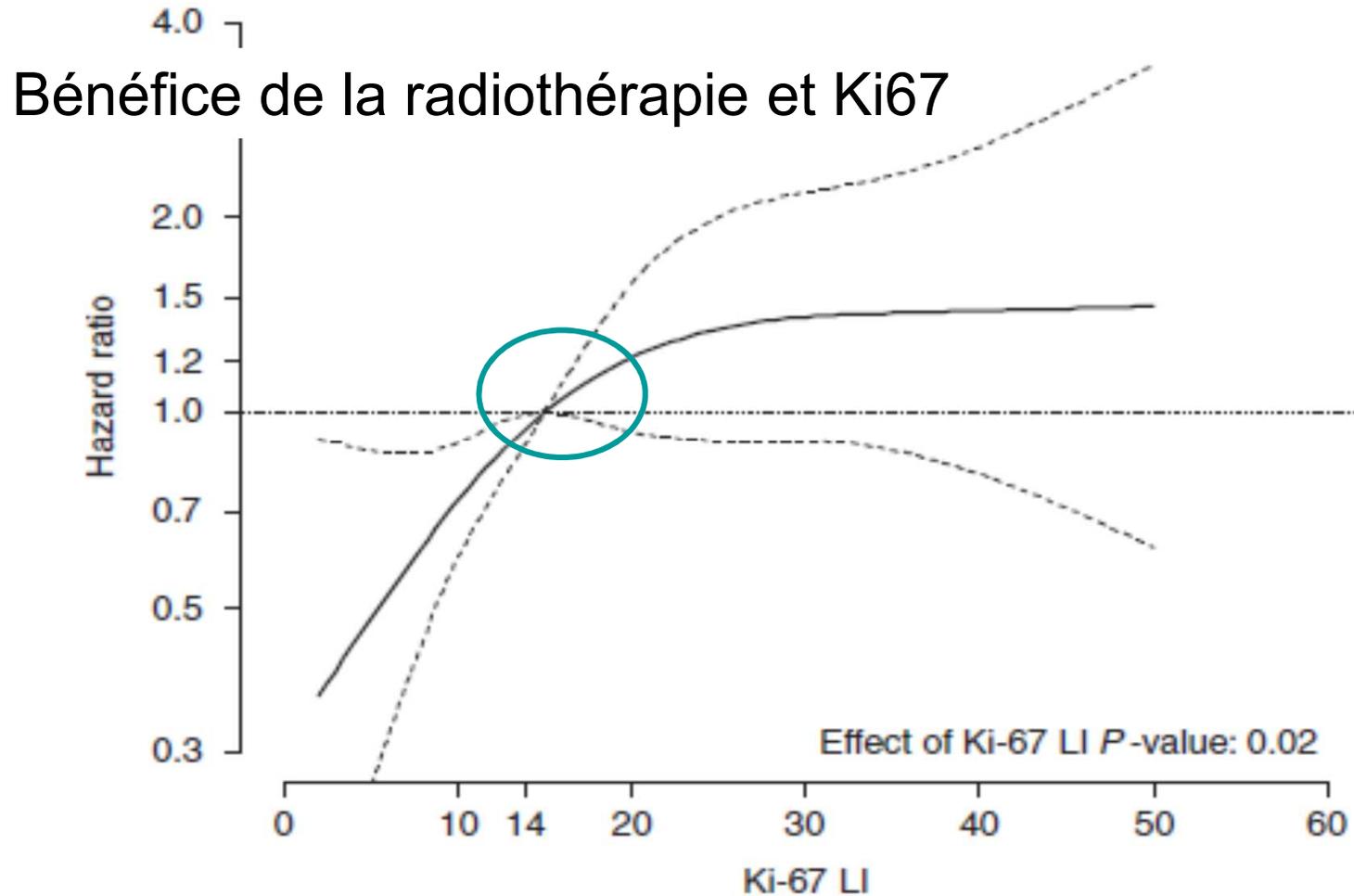
Grade?

	Randomised to tamoxifen	Randomised to no tamoxifen	Hazard ratio (95% CI)	Randomised to radiotherapy	Randomised to no radiotherapy	Hazard ratio (95% CI)
Grade						
Low (n=105)	2/50 (4%)	11/45 (24%)	0.15 (0.03-0.68)	3/33 (6%)	4/34 (12%)	0.78 (0.18-3.50)
Intermediate (n=267)	12/124 (9%)	24/125 (19%)	0.44 (0.22-0.90)	3/79 (4%)	19/83 (22%)	0.13 (0.04-0.51)
High (n=1014)	112/475 (22%)	138/467 (27%)	0.79 (0.62-1.02)	44/327 (12%)	87/294 (26%)	0.40 (0.27-0.58)
Age (years)						
<50 (n=160)	18/77 (22%)	27/69 (35%)	0.58 (0.32-1.07)	13/45 (27%)	16/56 (23%)	0.96 (0.45-2.03)
50-60 (n=919)	87/434 (19%)	102/425 (22%)	0.84 (0.63-1.12)	29/290 (9%)	74/275 (25%)	0.34 (0.22-0.52)
>60 (n=615)	46/283 (16%)	75/288 (25%)	0.59 (0.40-0.85)	18/187 (9%)	39/177 (20%)	0.39 (0.22-0.69)

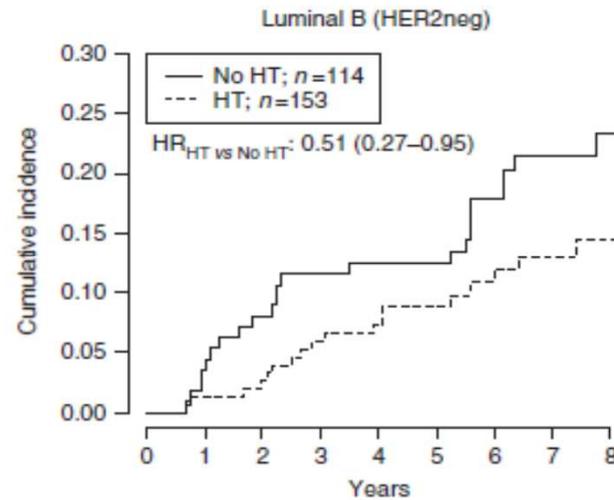
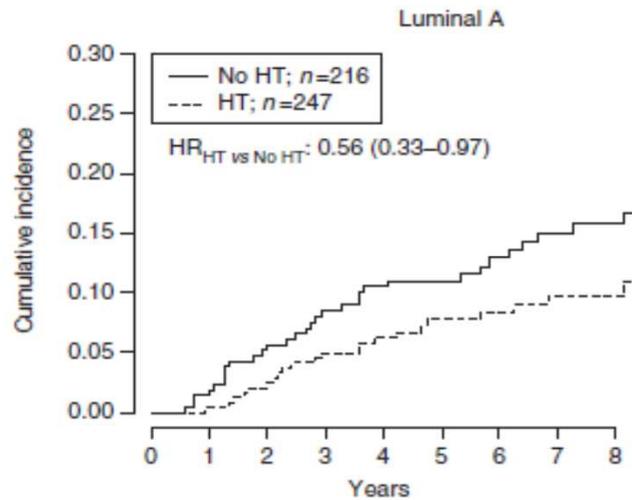
Data are n/N (%).

Table 4: All new breast events and 10-year estimates of percentages with an event in patients according to grade and age

Recherche de biomarqueurs prédictifs de bénéfice: Ki67, Her2?

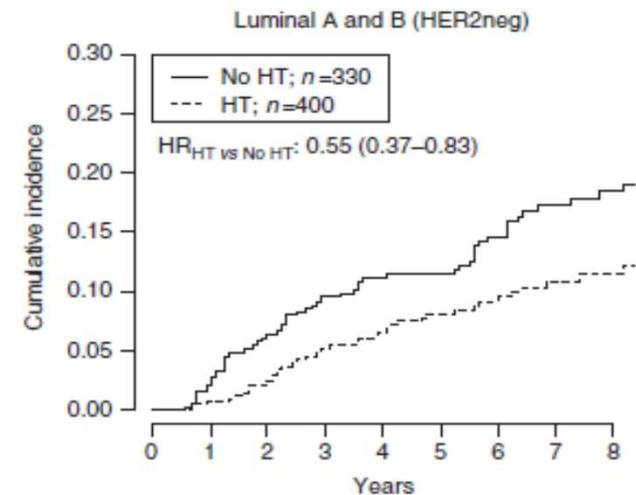
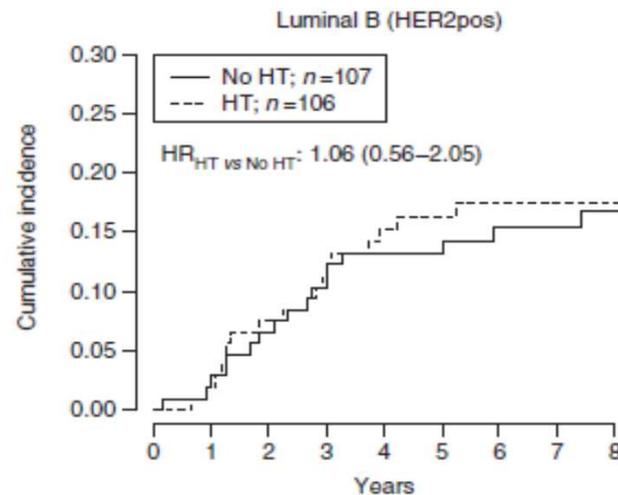


Recherche de biomarqueurs prédictifs de bénéfice: Ki67, Her2?

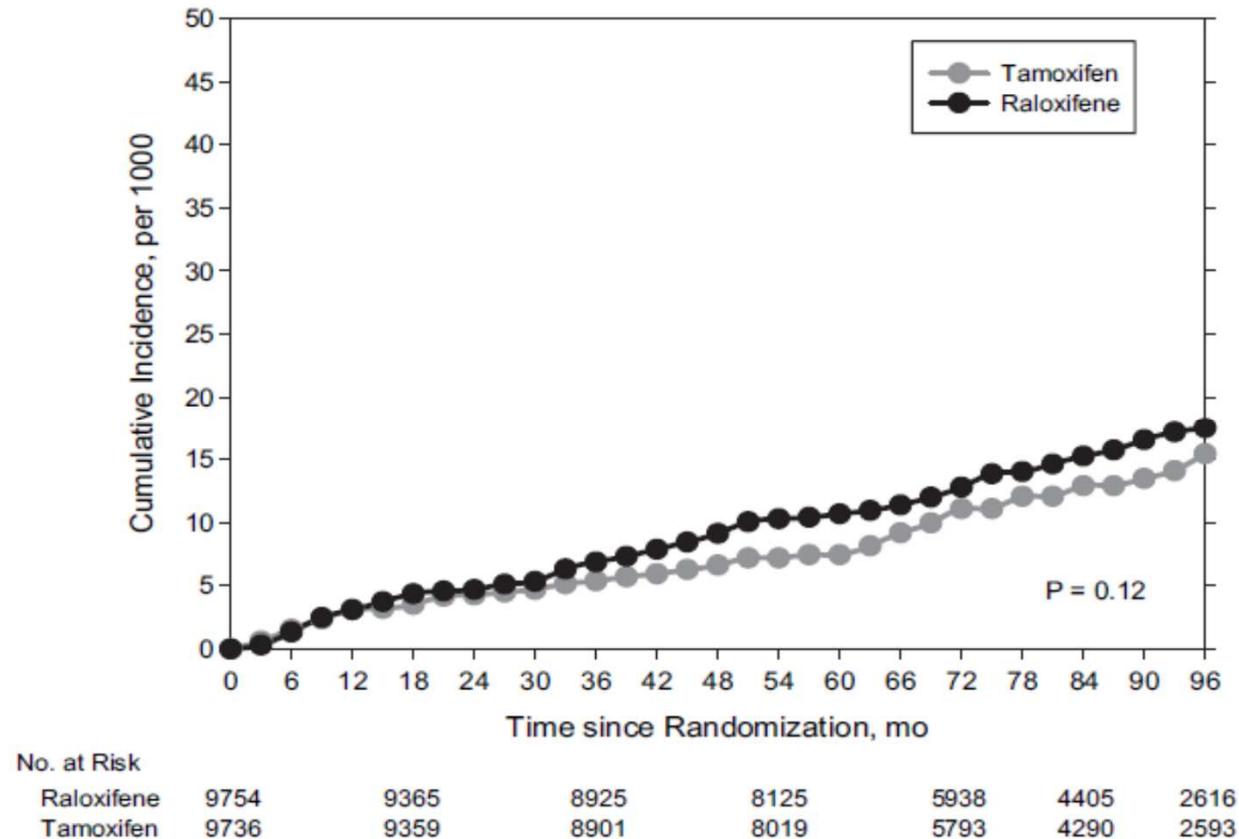


Bénéfice du TAM identique selon Ki

Différent selon Her2

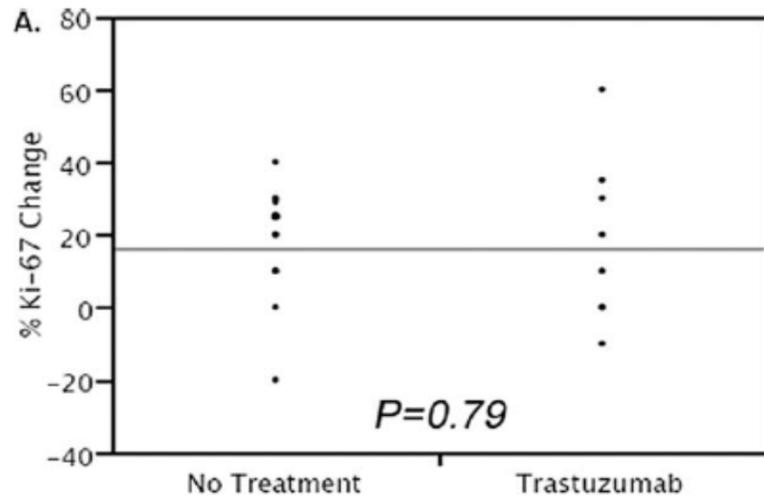


Prévention des CIS: tamoxifène versus raloxifène

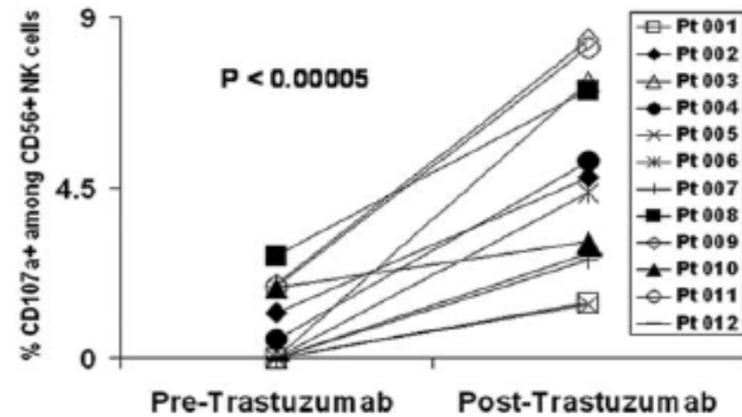


Traitements pré-opératoires: déceptions jusqu'alors

Quelques études dans les 15 dernières années (hormonothérapies, anti-Her2)



C



Etudes en attente

- NSABP B35 et IBIS II:
 - ER+ post meno, trt conservateur, RT
 - rando anastrozole versus tamoxifène

Plan

- Contexte
- Données récentes et controverses
- **Recommandations nationales et internationales**

Recommandations internationales

- NICE 2009: pas de tamoxifène
- NICE 2013: Tam ou raloxifène chez les femmes à haut risque/modéré (famille)
- NCCN 2013: considérer Tam 5 ans si trt conservateur RH+
- France: pas de trt médical adjuvant (Inca 2009)

DCIS POSTSURGICAL TREATMENT

SURVEILLANCE/FOLLOW-UP

Risk reduction therapy for ipsilateral breast following breast-conserving surgery:

Consider tamoxifenⁿ for 5 years for:

- Patients treated with breast-conserving therapy (lumpectomy) and radiation therapy^o (category 1), especially for those with ER-positive DCIS. The benefit of tamoxifen for ER-negative DCIS is uncertain
- Patients treated with excision alone^o

Risk reduction therapy for contralateral breast:

- Counseling regarding risk reductionⁿ
[See NCCN Guidelines for Breast Cancer Risk Reduction](#)

- Interval history and physical exam every 6-12 mo for 5 y, then annually
- Mammogram every 12 mo (and 6-12 mo postradiation therapy if breast conserved [category 2B])
- If treated with tamoxifen, monitor per [NCCN Guidelines for Breast Cancer Risk Reduction](#)

Merci!

Her2 et risque local

Table 3

Cox proportional hazards multivariate model for ipsilateral breast recurrence.

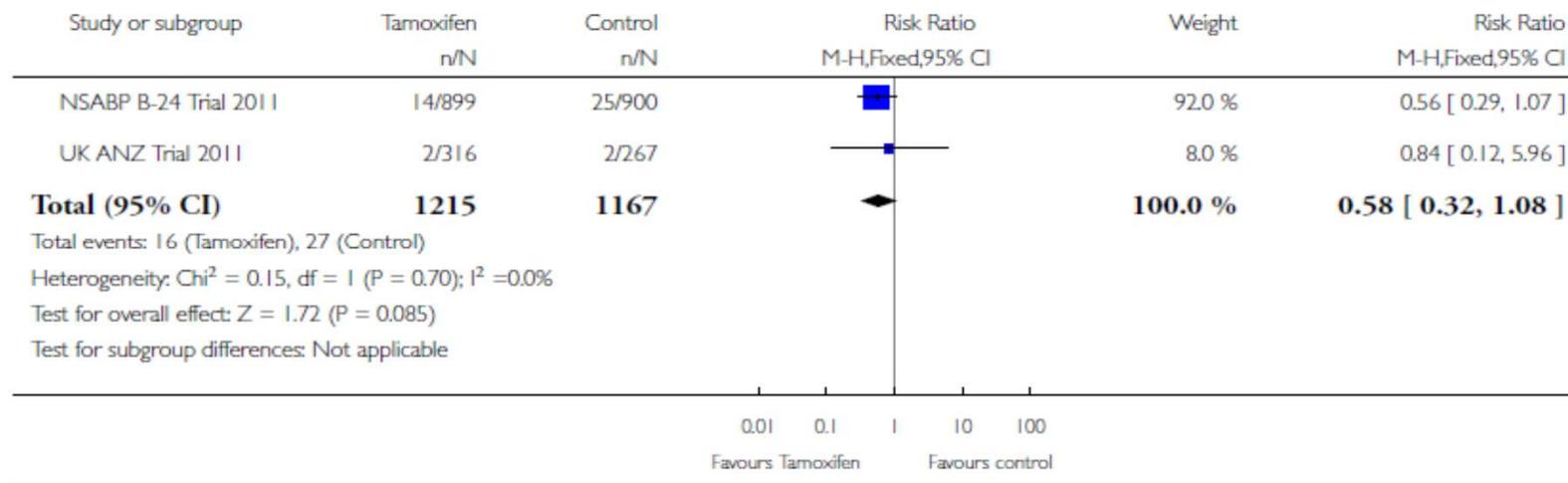
Variables	Ipsilateral breast recurrence		
	HR	95% CI	P
Age ≤ 40 years	1.176	0.813–1.702	0.3886
Size > 1.5 cm	1.133	0.405–3.166	0.8119
Multifocality	5.188	1.931–13.939	0.0011
Nuclear grade	0.906	0.573–1.433	0.6736
HER-2 overexpression	2.517	0.813–7.794	0.1094

Ipsilateral breast invasive recurrence			
	HR	95% CI	P
	1.281	0.790–2.076	0.3151
	0.376	0.073–1.933	0.2417
	5.103	1.304–19.979	0.0192
	0.691	0.329–1.454	0.3304
	3.495	0.794–15.385	0.0980

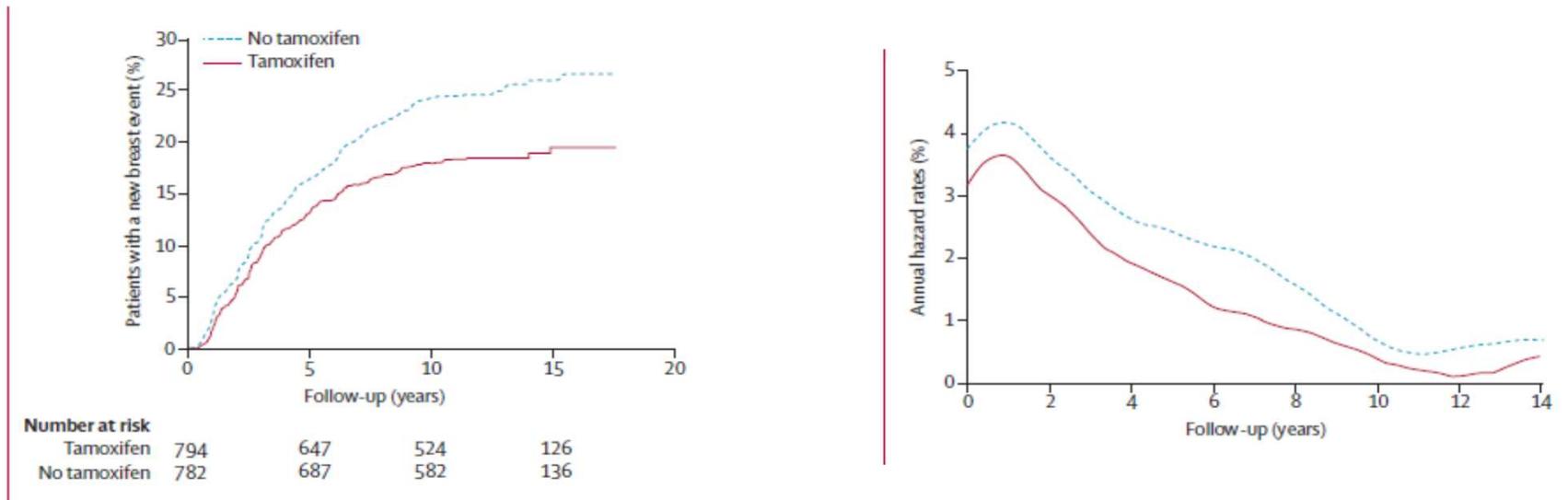
Noh et al The Breast 2013 Her2 n'est pas associé à un risque + élevé de rechute locale

Cochrane 2012: Méta-analyse des 2 essais randomisés

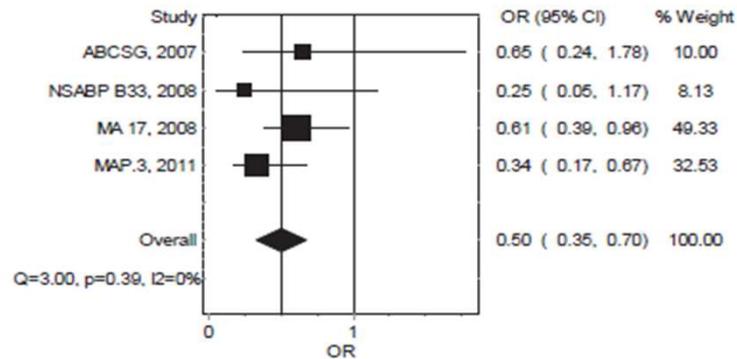
DCIS controlateral, patientes irradiées



Tamoxifen reduced the incidence of all new breast events (HR 0.71, 95% CI 0.58–0.88; p=0.002), reducing recurrent ipsilateral DCIS (0.70, 0.51–0.86; p=0.03) and contralateral tumours (0.44, 0.25–0.77; p=0.005), but having no effect on ipsilateral invasive disease (0.95, 0.66–1.38; p=0.8). No data on adverse events except cause of death were collected for this trial.



■ **Abstract:** For postmenopausal women with ductal carcinoma in situ (DCIS) where optimal local control or patient preference results in mastectomy, despite substantial risk of contralateral invasive breast cancer, tamoxifen is uncommonly prescribed based on unfavorable risk-benefit consideration. In the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) MAP.3 primary prevention trial, in postmenopausal women exemestane reduced invasive breast cancer incidence by 65% without increasing life-threatening side effects. In adjuvant breast cancer trials, the aromatase inhibitor exemestane as well as anastrozole and letrozole have all reduced new contralateral breast cancer incidence. Thus, aromatase inhibitors, and perhaps particularly exemestane, provide an option to address the risk of contralateral breast cancer in postmenopausal women with DCIS managed with mastectomy. ■



Study	Aromatase Inhibitor		Control	
	Events	Subjects	Events	Subjects
NSABP B33	2	799	8	799
MAP3	11	2285	32	2275
MA17	30	2583	49	2587
ABCSG	6	386	11	466

Figure 1. Risk of new invasive breast cancer events between aromatase inhibitors and control groups in randomized trials. New