Existe-t-il un traitement médical protecteur de la fonction ovarienne?

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Impact de la chimiothérapie

Famille	Drogues
Alkylants	Cyclophosphamide
	Ifosfamide
	Nitrosourées
	Chlorambucil
	Melphalan
	Busulphan
Vinca-alcaloïdes	Vinblastine
Antimétabolites	Cytarabine
Sels de platine	Cisplatine
Autres	Procarbazine

Cyclophosphamide
500 mg/m² soit 0,8 g par cure (1,6m²)

3 FEC 100 + 3 Taxotere
Adjuvant, N+
Néoadjuvant
Total : 2,4 g

4 à 6 FEC 100
Adjuvant
N-
Total : 3,2 à 4,8 g

Taux d'aménorrhée	< 40 ans	> 40 ans
CMF	30-80%	60-96%
AC	13-30%	57-63%
FEC/FAC	10-25%	80-90%
AC+Taxanes	15-52%	66-77%

Stroud, Fertil Steril 2009;92:417-27.

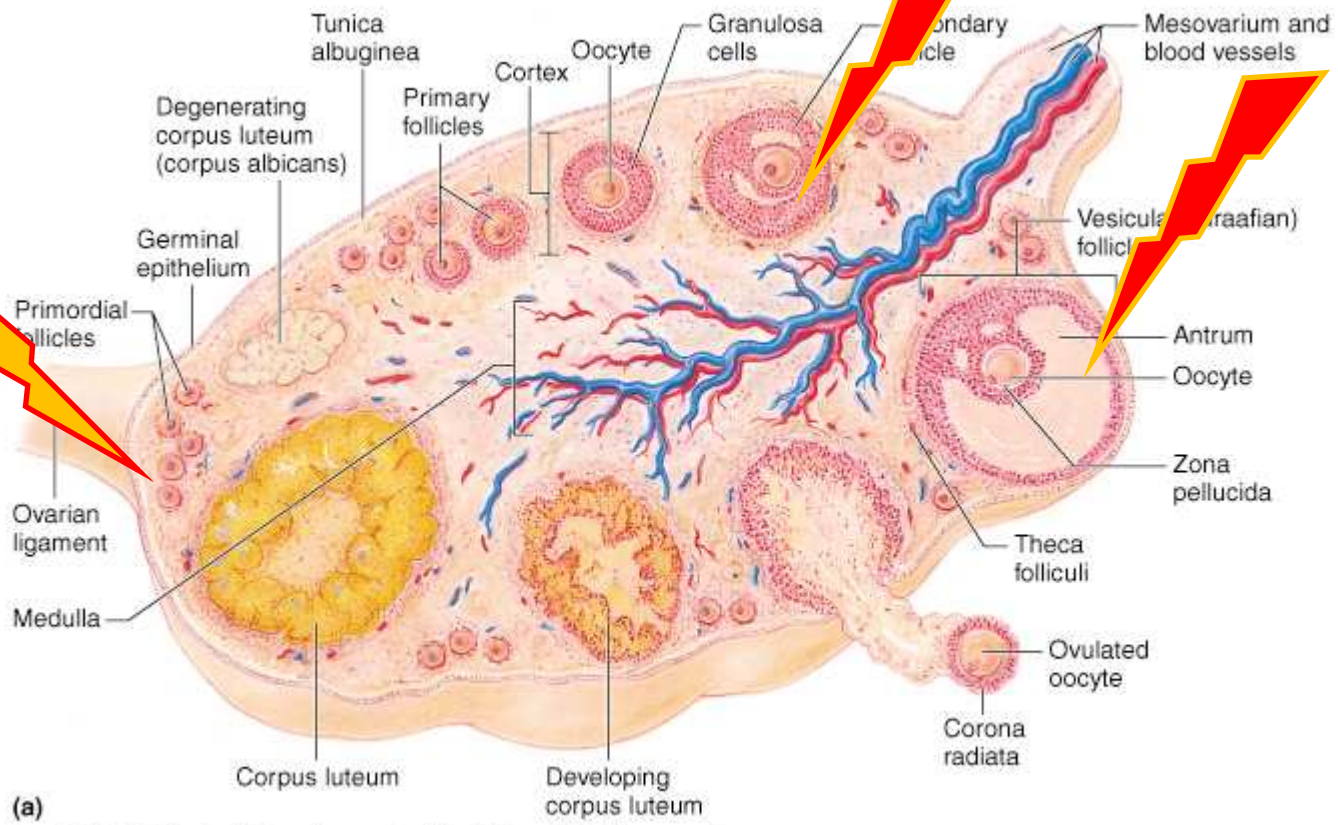
Stearns, Nat Rev Cancer 2006;6:886-93.

Drogue / Dose / Age

Fonction endocrine
Aménorrhée

Reproduction
Grossesse

?



Analogues de la LH-RH

↓

Désensibilisation de l'axe gonatrope

↓

Suppression de la maturation folliculaire
Hypovascularisation ovarienne
Protection des cellules indifférenciées
Activation protéines anti-apoptotiques

Proc. Natl. Acad. Sci. USA
Vol. 82, pp. 2975–2979, May 1985
Medical Sciences

D-Tryptophan-6 analog of luteinizing hormone-releasing hormone as a protective agent against testicular damage caused by cyclophosphamide in baboons

(chemotherapeutic agents/prevention of gonadal damage/subhuman primates)

RONALD W. LEWIS*†, KEITH J. DOWLING*†, AND ANDREW V. SCHALLY‡§

Proc. Natl. Acad. Sci. USA
Vol. 84, pp. 851–855, February 1987
Medical Sciences

Protective effects of analogs of luteinizing hormone-releasing hormone against x-radiation-induced testicular damage in rats

(luteinizing hormone-releasing hormone agonists and antagonists/gonadal radioprotectors)

ANDREW V. SCHALLY*†‡, JOSE I. PAZ-BOUZA†, JOSEPH V. SCHLOSSER§, TSUYOSHI KARASHIMA†, LUCIANO DEBELJUK†, BRUCE GANDLE§, AND MARTHA SAMPSON†

Proc. Natl. Acad. Sci. USA
Vol. 85, pp. 2329–2333, April 1988
Medical Sciences

Protective effects of analogs of luteinizing hormone-releasing hormone against chemotherapy-induced testicular damage in rats

(luteinizing hormone-releasing hormone agonists and antagonists/gonadal chemoprotectors)

TSUYOSHI KARASHIMA*, ATTILA ZALATNAI*, AND ANDREW V. SCHALLY*†‡

Br. J. Cancer (1990), **61**, 861–865

Protective effects of D-Trp⁶-luteinising hormone-releasing hormone microcapsules against cyclophosphamide-induced gonadotoxicity in female rats

L. Bokser, B. Szende & A.V. Schally

Les premières études comparatives

Auteur	Patientes, âge	Etude	LH-RHa	Chimio	IOP	Suivi (ans)
Blumenfeld, 2000	LED	Prosp.	Tripto.	Cyclo 4-26g	Amen. / FSH>25	2-15
Pereyra, 2001	Leucémie ado	Prosp.	Leupro.	Polychimio	Aménorrhée	5-6
Petri, 2004	LED < 40	Prosp.	Leupro.	Cyclo dose var.	FSH > 25	ND
Somers, 2005	LED < 32	Prosp.	Leupro.	Cyclo	Amen. / FSH>40	3-9
Dann, 2005	LMNH < 40	Prosp.	Tripto.	Polychimio	Cycles, FSH	2-8
Blumenfeld, 2005	Lymphome	Prosp.	Tripto.	Polychimio	Amen. / FSH>25	ND
Castelo, 2007	Hodgkin < 45	Prosp.	Tripto.	Polychimio	Cycles irrégul.	ND
Loverro, 2007	Hodgkin 24	Random.	Tripto.	Polychimio	Aménorrhée	2-6

- 9 études, 366 patientes
- Préservation fonction ovarienne : 93% vs 48%, RR=1,7 (1,3-2,1)
- Grossesses : 22% vs 14%, RR=1,6 (1,0-2,6)

Clowse, J Women Health 2009;18:311-8

THE COCHRANE COLLABORATION®

- 4 essais randomisés: 154 Hodgkin/sein < 38-46 ans
- Fonction endocrine : cycles, règles
- Reproduction : FSH/LH, CFA, grossesses

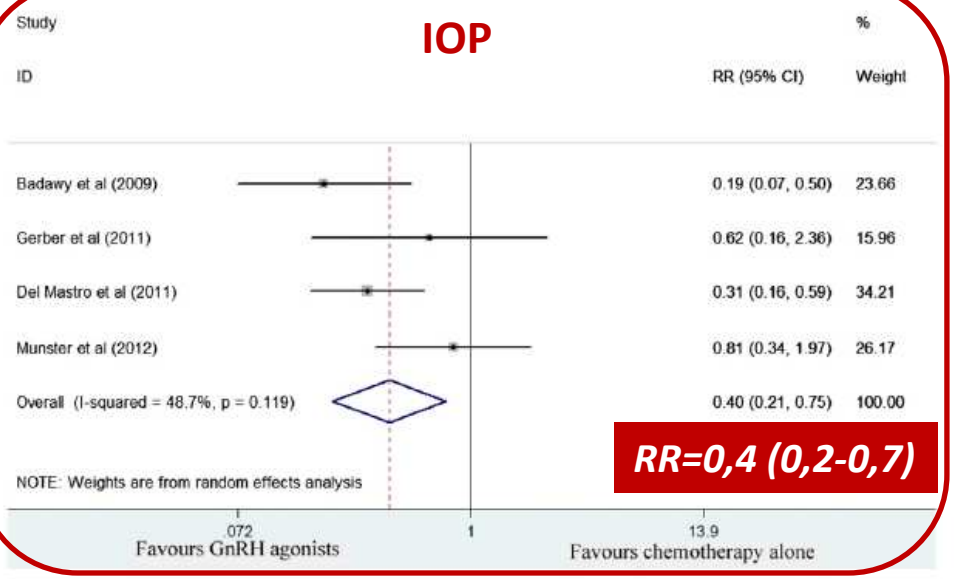
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resumed menses	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Intramuscularly or subcutaneously	3	137	Risk Ratio (IV, Random, 95% CI)	1.90 [1.33, 2.70]
1.2 Intranasally	1	17	Risk Ratio (IV, Random, 95% CI)	0.75 [0.33, 1.72]
2 Amenorrhoea	2	59	Risk Ratio (IV, Random, 95% CI)	0.08 [0.01, 0.58]
3 Ovulation	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1 Intramuscularly or subcutaneously	1	78	Risk Ratio (IV, Random, 95% CI)	2.7 [1.52, 4.79]
3.2 Intranasally	1	17	Risk Ratio (IV, Random, 95% CI)	1.13 [0.20, 6.24]
4 Pregnancy	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1 Intramuscularly or subcutaneously	1	29	Risk Ratio (IV, Random, 95% CI)	0.21 [0.01, 4.09]
4.2 Intranasally	1	18	Risk Ratio (IV, Random, 95% CI)	0.41 [0.02, 8.84]
5 FSH (mUI/L)	1	29	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-1.03, 0.44]
6 FSH < 20 mIU/mL	1	30	Risk Ratio (IV, Random, 95% CI)	1.48 [1.02, 2.13]
7 LH (mUI/L)	1	29	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [1.00, 0.47]
8 LH < 20 mIU/L	1	30	Risk Ratio (IV, Random, 95% CI)	1.48 [1.02, 2.13]
9 Estradiol > 20 pg/mL	1	30	Risk Ratio (M-H, Random, 95% CI)	3.44 [1.57, 7.58]
10 Inhibin B	1	29	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.67, 0.78]
11 AMH (pmol/L)	1	29	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.78, 0.68]
12 AFC	1	29	Std. Mean Difference (IV, Random, 95% CI)	1.11 [0.32, 1.90]

Chen, Cochrane 2011;11:CD008018.

- Méta-analyse, 5 essais randomisés: **528 K. sein**; 38 ans (21-47); Gosereline/Triptoreline; CMF/FAC; suivi : 8-24 mois; **IOP : définition variable**!

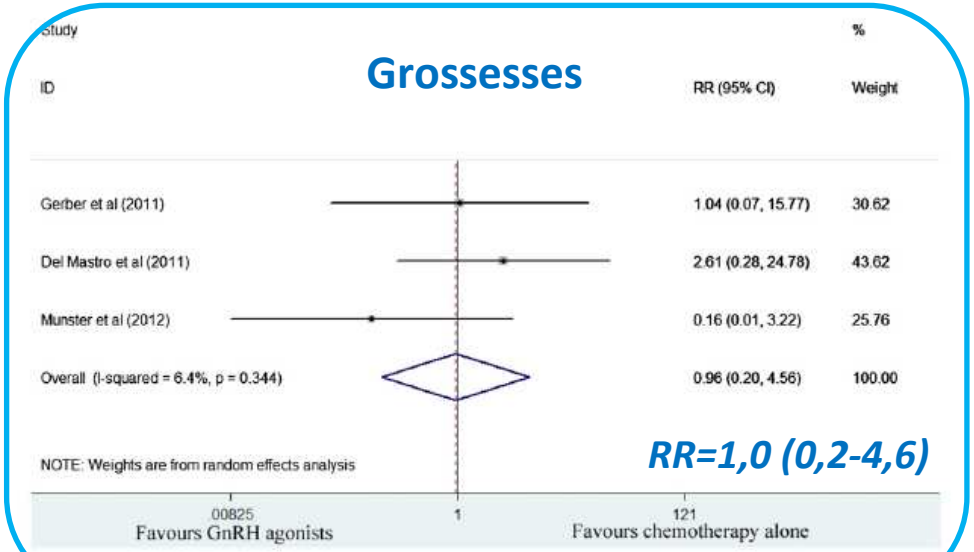
Yang, Breast 2013; 22:150-7.

IOP



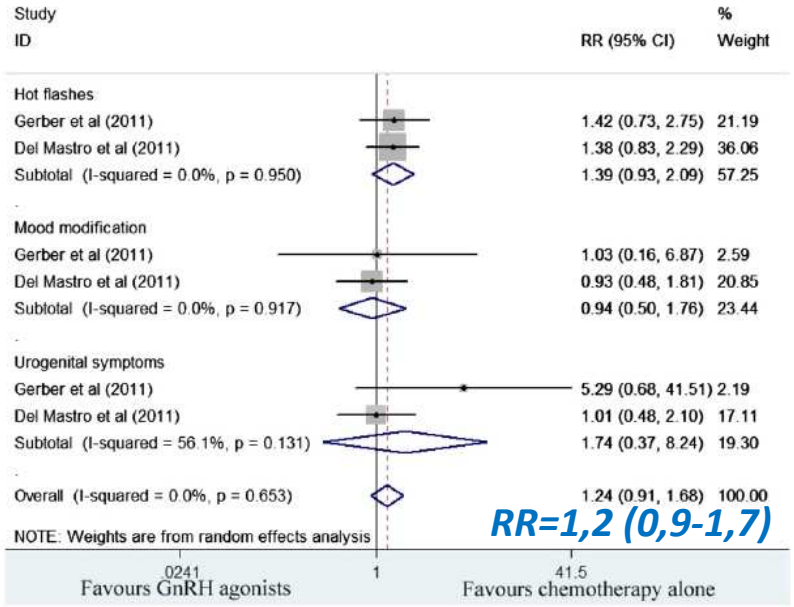
RR=0,4 (0,2-0,7)

Grossesses



RR=1,0 (0,2-4,6)

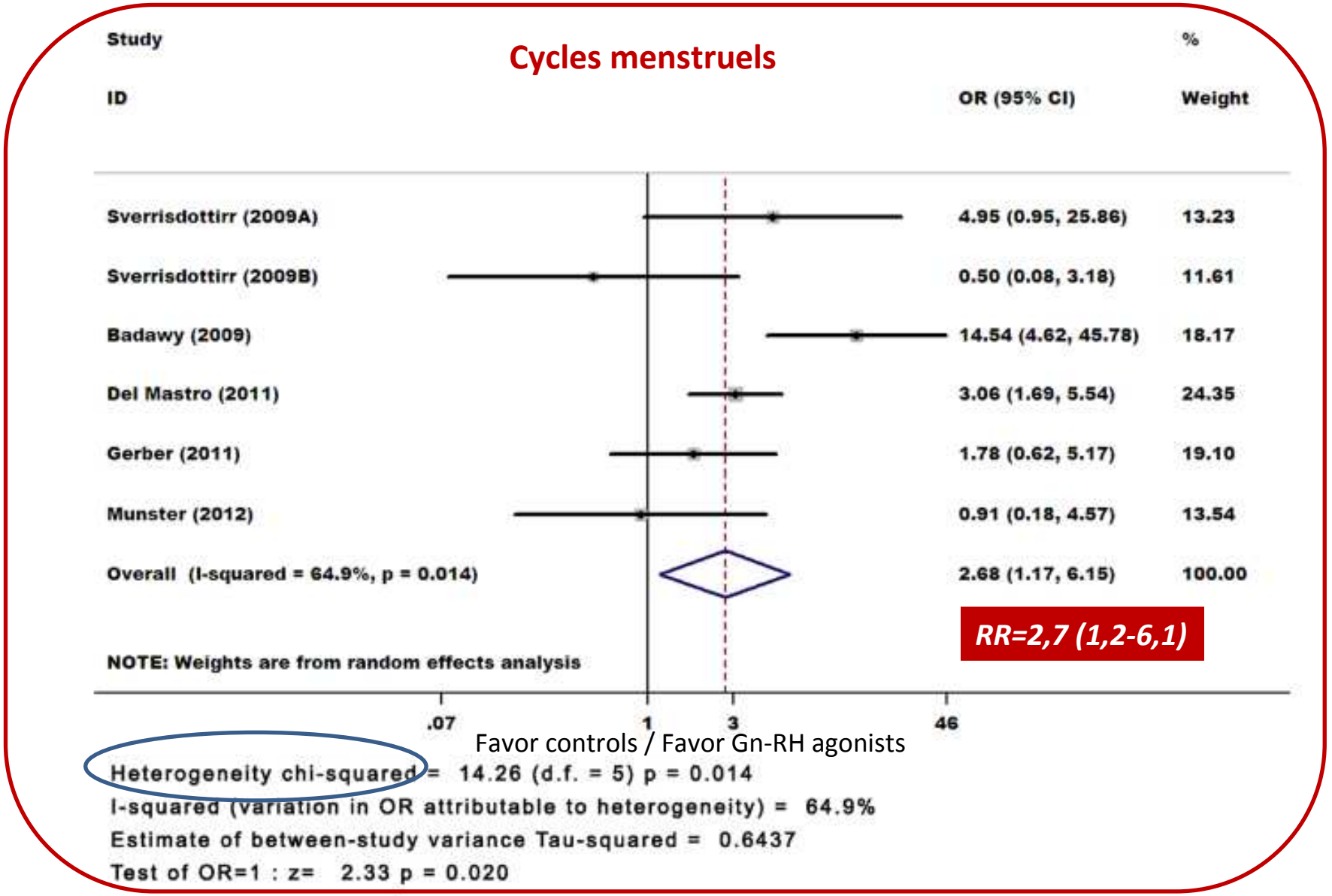
Effets secondaires



RR=1,2 (0,9-1,7)

- Méta-analyse, 7 essais randomisés: **677 K. sein**; 38 ans (21-47); Gosereline/Triptoreline; CMF/FAC; suivi : 8-24 mois; **IOP ≈ retour des règles**!

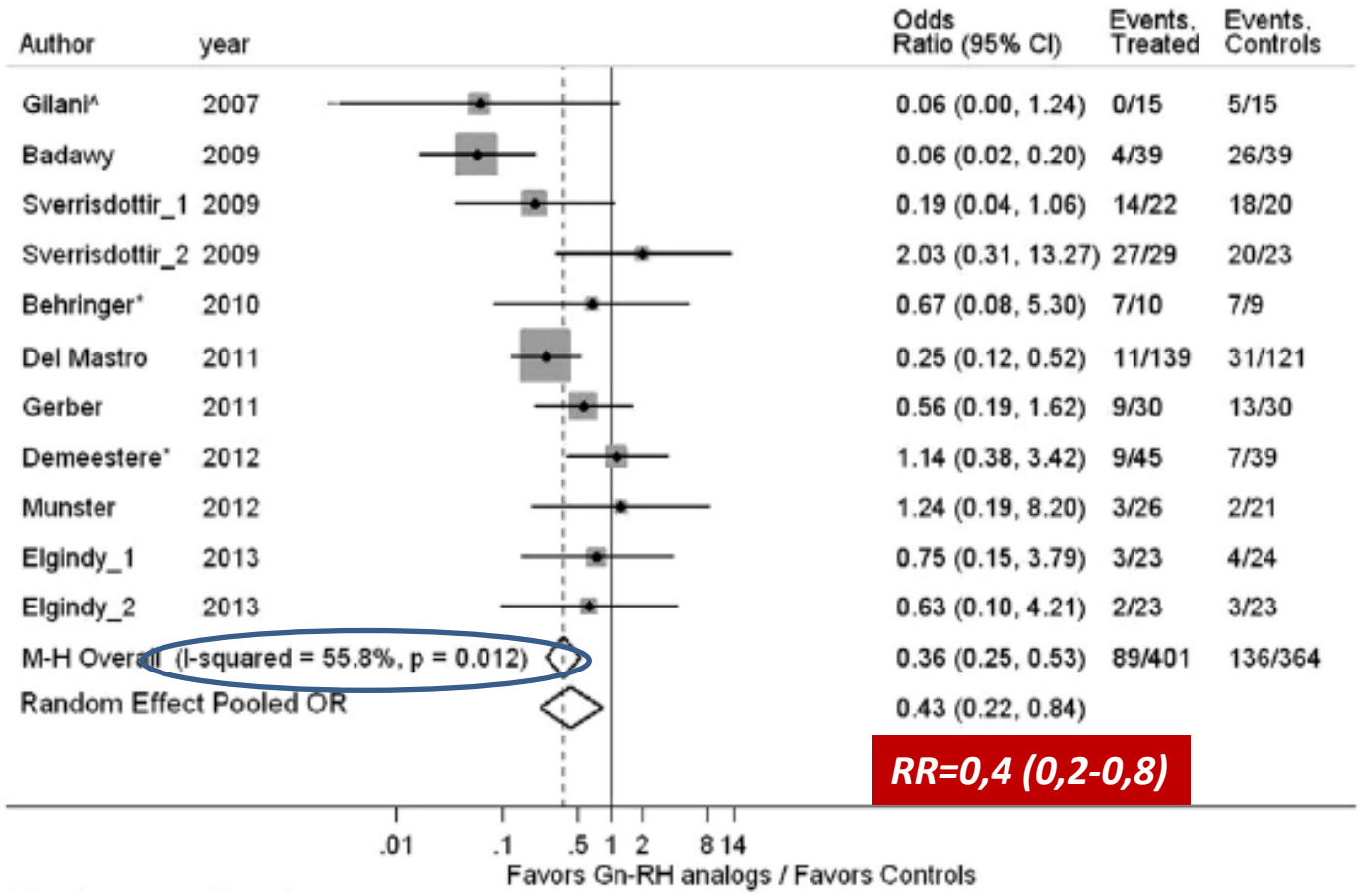
Wang, PLOs one 2013;8:e66360.



- Méta-analyse, 9 essais randomisés: 765 **K. sein, ovaire, Hodgkin**; Gosereline /Triptoreline; suivi : 6-36 mois; **IOP ≈ aménorrhée secondaire**

Del Mastro, Cancer Treat Rev 2014;40:675-83.

Aménorrhée

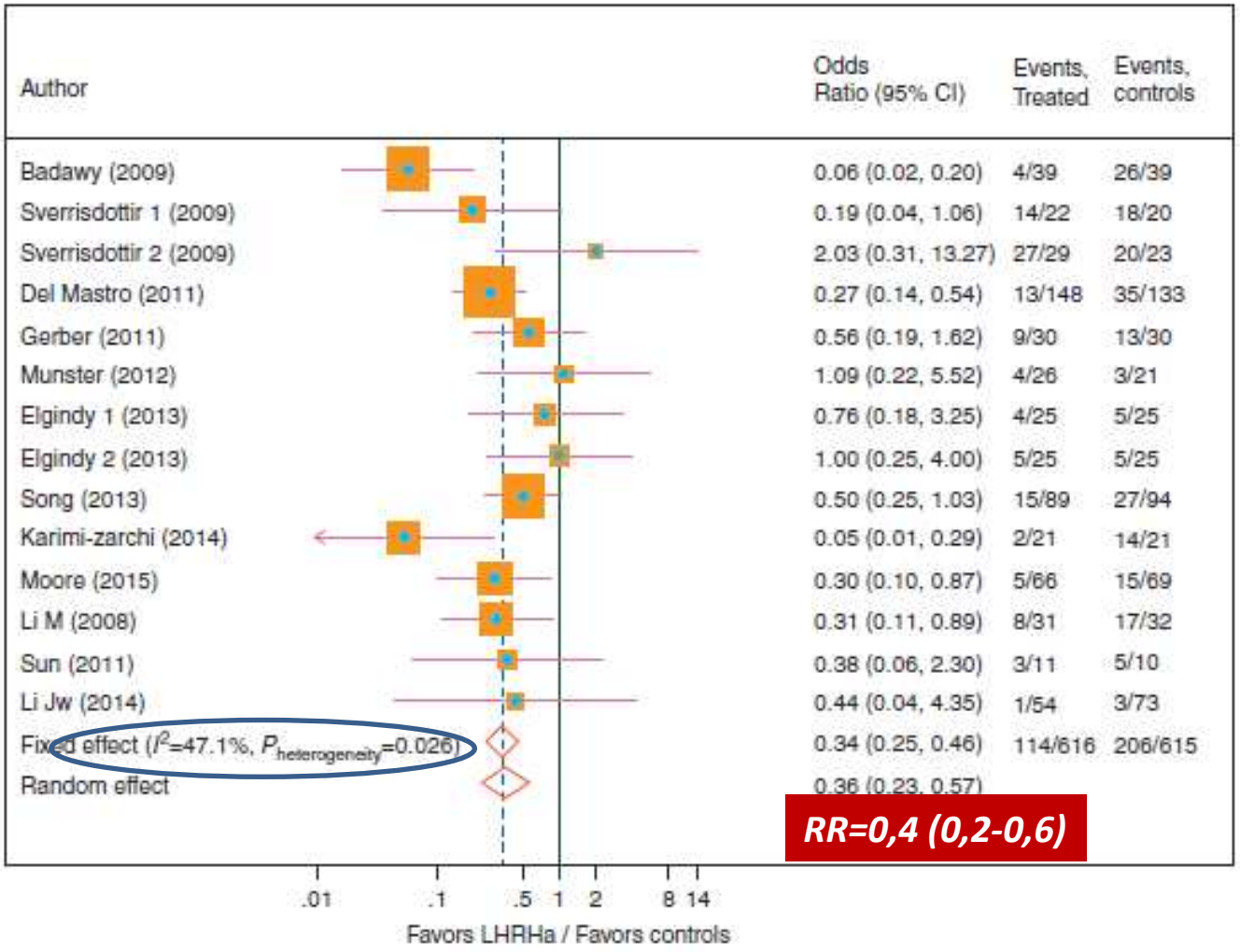


RR=0,4 (0,2-0,8)

- Méta-analyse, 12 essais randomisés: 1231 **K. sein**; CMF/FEC/TAC; Gose/Tripto/ Leupro; suivi : 6-36 mois; **IOP ≈ définition variable**

Lambertini, Ann Oncol 2015;26:2408-19.

IOP : absence de cycles menstruels après chimio

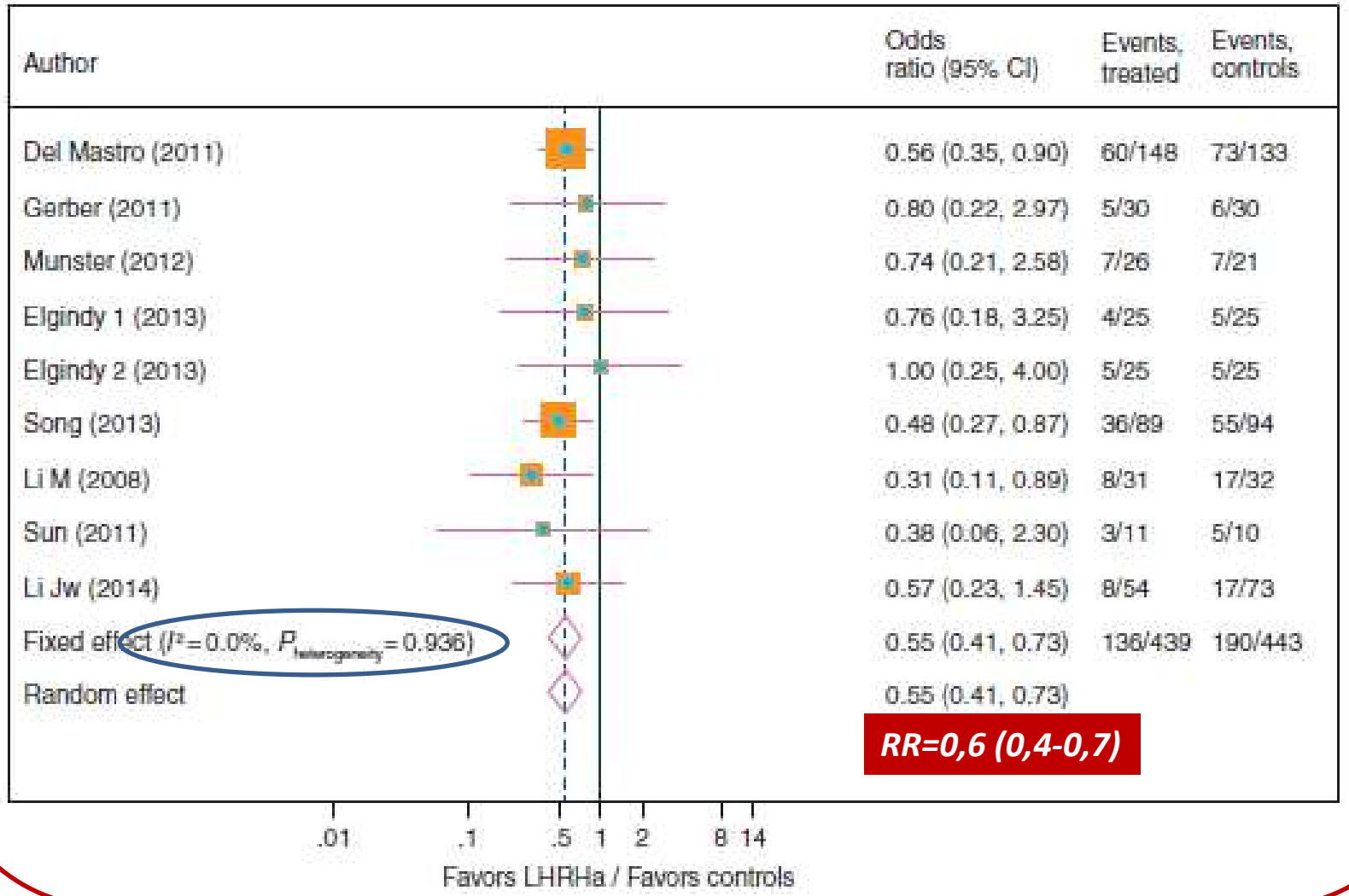


RR=0,4 (0,2-0,6)

- Méta-analyse, 12 essais randomisés: 1231 **K. sein**; Gosereline /Triptoreline/ Leuprolide; suivi : 6-36 mois; **IOP ≈ définition variable**

Lambertini, Ann Oncol 2015;26:2408-19.

IOP : aménorrhée secondaire > 12 mois

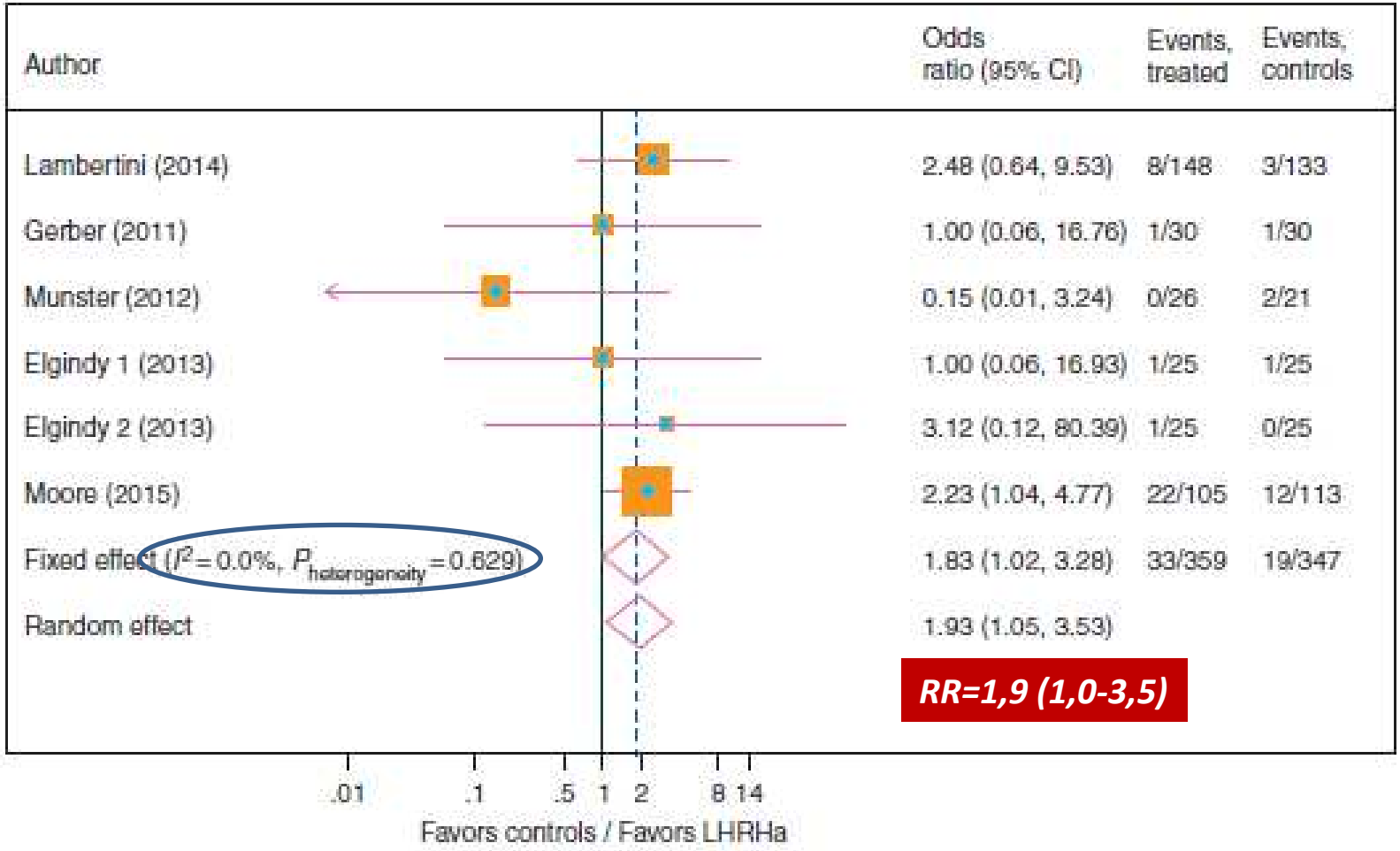


RR=0,6 (0,4-0,7)

- Méta-analyse, 12 essais randomisés: 1231 **K. sein**; Gosereline /Triptoreline/ Leuprolide; suivi : 6-36 mois; **IOP ≈ définition variable**

Lambertini, Ann Oncol 2015;26:2408-19.

Fertilité : taux de grossesse

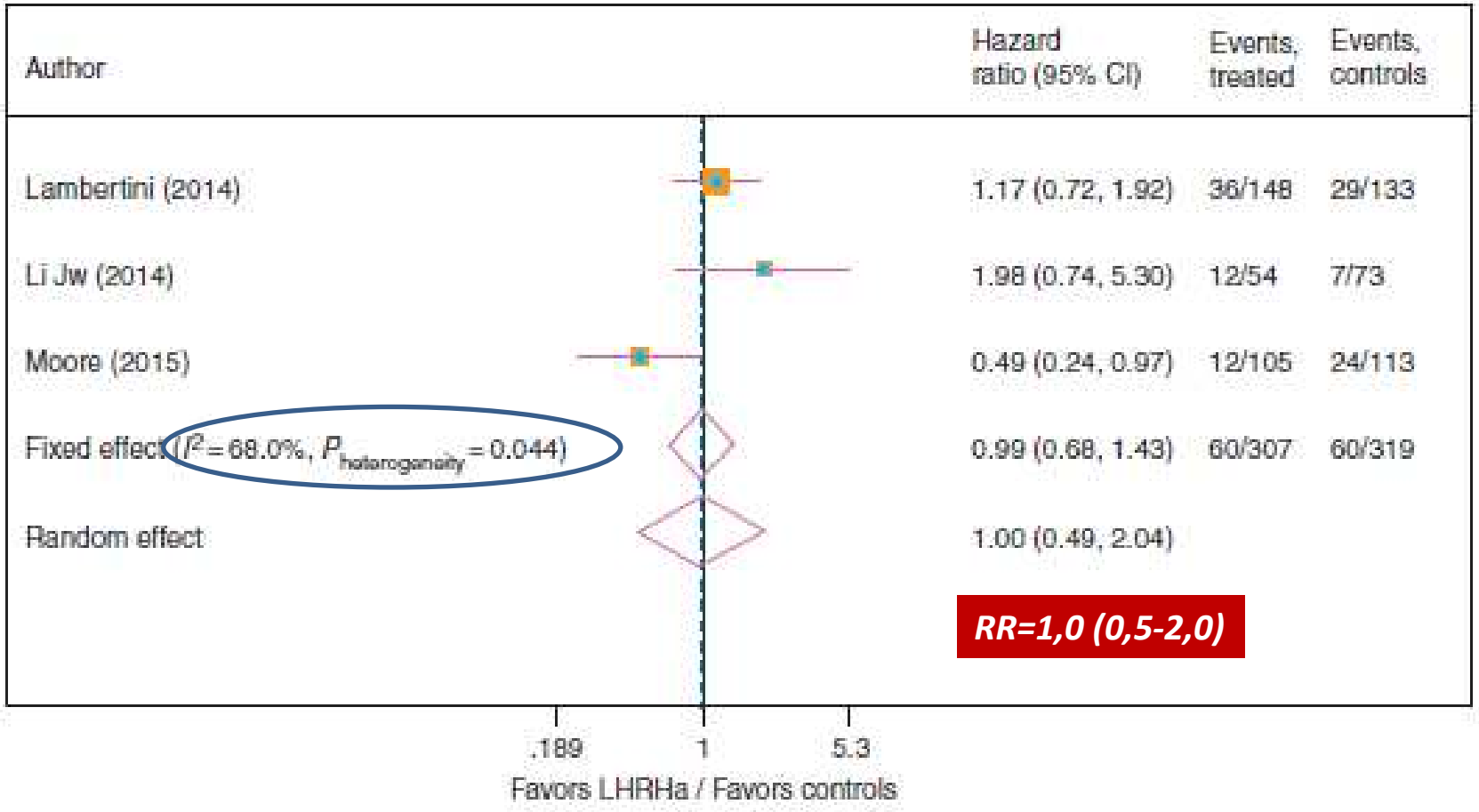


RR=1,9 (1,0-3,5)

- Méta-analyse, 12 essais randomisés: 1231 **K. sein**; Gosereline /Triptoreline/ Leuprolide; suivi : 6-36 mois; **IOP ≈ définition variable**

Lambertini, Ann Oncol 2015;26:2408-19.

Pronostic : taux de survie sans rechute



Sécurité & Tolérance

- Pas d'augmentation de la fréquence des effets secondaires type 3/4
- Pas d'impact délétère de la castration chimique concomitante à la chimiothérapie

Lambertini M, JAMA 2015;314:2632-40.

Toxicité	Grade 2	Grade 3	Grade 4
Chimio seule	24%	5%	0%
Chimio + LH-RHa	48%	6%	1%
P	*< 0,001*	*NS*	*NS*

Table 2. Grade 2 or Higher Toxic Effects.*

Adverse Event	Chemotherapy Alone (N=111)			Chemotherapy plus Goserelin (N=103)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Diarrhea	2	0	0	0	0	0
Fatigue	1	0	0	2	0	0
Hot flashes	14	3	0	29	4	0
Irregular menses	2	0	0	5	2	0
Decrease in libido	6	0	0	9	0	0
Agitation	4	1	0	6	0	0
Anxiety	4	0	0	9	0	0
Depression	3	0	0	8	1	0
Joint pain	1	1	0	0	0	0
Muscle pain	2	0	0	1	0	0
Headache	1	1	0	12	0	0
Sweating	7	0	0	10	0	0
Thromboembolism	0	0	0	0	0	1
Vaginal dryness	9	0	0	12	0	0

Moore HCF, NEJM 2015;372:923-32.

Limites des méta-analyses

- Pas de données individuelles
- Impact non évalué
  - Âge
  - Chimiothérapie : type et dose
  - Récepteurs hormonaux
  - Tamoxifene

- Méta-analyse, 9 essais randomisés: 765 **K. sein, ovaire, Hodgkin**; Gosereline /Triptoreline; suivi : 6-36 mois; **IOP ≈ aménorrhée secondaire** Del Mastro, Cancer Treat Rev 2014;40:675-83.

Etude en sous groupes

Sous-groupe	RR (IC95%)	*P*
Cancer		
Sein	0,4 (0,2-0,8)	*0,016 **
Hodgkin	1,0 (0,4-2,7)	*NS*
Age		
< 35 ans	0,2 (0,1-1,5)	*NS*
> 35 ans	0,5 (0,2-1,0)	*0,057*
Evaluation IOP		
< 12 mois	0,4 (0,2-0,8)	*0,01 **
> 12 mois	0,7 (0,2-3,2)	*NS*

** P significatif pour l'hétérogénéité*

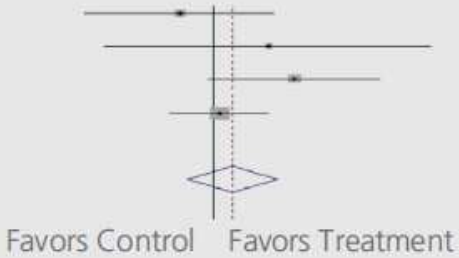
Méta-analyse restreinte aux K sein, RH négatifs, non traités par tamoxifene

Méta-analyse, 4 essais randomisés: 252 **K. sein**; Gosereline /Triptoreline; suivi : 12-36 mois; **IOP ≈ retour des règles**

Vitek WS. Fertil Steril 2014;102:808-15.

Forest plot of resumption of menses at 12–24 months after treatment in women with breast cancer who did not receive tamoxifen.

Study	Follow-up (mo)	GnRHa + chemo Events	GnRHa + chemo Total	Chemo alone Events	Chemo alone Total	Weight (%)	OR, random (95% CI)
Sverrisdottir et al. 2009	24	2	24	3	20	19.24	0.52 (0.08, 3.44)
Gerber et al. 2011	24	28	28	28	29	7.26	3.00 (0.12, 76.79)[a]
Del Mastro et al. 2011	12	27	29	16	22	22.82	5.06 (0.91, 28.15)
Elgnidy et al. 2013	12	41	50	40	50	50.68	1.14 (0.42, 3.10)
Munster et al. 2012	>24	7	7	6	6	0.00	Excluded
Total (95% CI)		105	138	93	127	100.00	1.47 (0.60, 3.62)



Note: $I^2 = 16.6\%$; $P = .308$.
[a] OR reflects 0 cell correction of 1/3.

RR=1,5 (0,6-3,6)

Essai randomisé sur tout K sein RH-, RH+

	RH négatifs			RH positifs		
Traitement	Chimio + aLHRH	Chimio seule	*P*	Chimio + aLHRH	Chimio seule	*P*
Retour des cycles	86% (75 - 99)	81% (66 - 99)	*NS*	69% (61 - 78)	61% (52 - 71)	*NS*
Survie sans rechute	62% (42 - 77)	76% (52 - 89)	*NS*	85% (77 - 90)	85% (77 - 90)	*NS*

Lambertini M, JAMA 2015;314:2632-40.

clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi160–vi170, 2013
doi:10.1093/annonc/mdt199
Published online 27 June 2013

Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The use of GNRH analogues concomitantly with chemotherapy should not be regarded as a reliable means of preserving fertility.

Embryo or oocyte cryopreservation is the main method to preserve female fertility.

Ann Oncol 2013;24:160-70.

NCCN Guidelines® Insights

Adolescent and Young Adult Oncology, Version 2.2014

Featured Updates to the NCCN Guidelines

Menstrual suppression with GnRH agonists is not recommended as an option for fertility preservation, because evidence showing that this procedure protects ovarian function during chemotherapy is inconclusive.

J Natl Compr Canc Netw 2014;12:21-32.

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

There is insufficent evidence regarding th effectiveness of ovarian suppression (Gn-RH analogs) as a fertility preservation method, and these agents should not be relied on to preserve fertility.

However, there may be other potential benefits such as inhibiting menses during intensive chemotherapy, thus preventing complications such as menorrhagia.

In emergency, rare, or extreme circumstances, where proven options are not available, providers may consider GnRHa an unproved option with special consideration of the patient's specific cancer and needs.

J Clin Oncol 2013;31:2500-10.

special articles

Annals of Oncology 26: 1533–1546, 2015
doi:10.1093/annonc/mdv221
Published online 4 May 2015

Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015

The Panel noted the value of an LHRH agonist given during chemotherapy for premenopausal women with ER-negative disease in protecting against premature ovarian failure and preserving fertility.

Ann Oncol 2015;26:1533-46.

Gyné Pôle

Bordeaux

Vendredi 1er et Samedi 2 Avril (matin) 2016

6ème Journée organisée par le Pôle d'Obstétrique Reproduction Gynécologie,
Centre Aliénor d'Aquitaine, CHU de Bordeaux

Université de Bordeaux,

Site de la Victoire (1er avril - Place de la Victoire, Bordeaux)

et Site Pey Berland (2 avril - Pôle juridique et judiciaire, Place Pey Berland, Bordeaux)

16.00 - 17.00	**Impact de l'environnement**	Dominique Dallay, Clément Jimenez
16.00	◆ Environnement et reproduction	Mohamed Benahmed *(Nice)*
16.20	◆ Environnement et périnatalité	Patrick Brochard
16.40	◆ Discussion	