GRUPPO C

3 - QUESITO GRADE: Nelle pazienti in premenopausa con carcinoma mammario operato, recettori ormonali positivi o negativi, e candidate a chemioterapia adiuvante, è raccomandabile iniziare un trattamento con LHRHa prima della chemioterapia al fine di preservare la funzionalità ovarica?

JENNIFER FOGLIETTA
ONCOLOGIA MEDICA- PERUGIA

23/04/2016

DEFINIZIONE DEL QUESITO CLINICO

- P (POPOLAZIONE TARGET): PAZIENTI CON CARCINOMA MAMMARIO OPERATO HR+/HR– IN PREMENOPAUSA CANDIDATE A CHEMIOTERAPIA ADIUVANTE
- I (INTERVENTO): LHRH ANALOGO SEGUITO DA LHRH ANALOGO + CHEMIOTERAPIA ADIUVANTE
- C (CONFRONTO): CHEMIOTERAPIA ADIUVANTE
- O (OUTCOME): BENEFICIO: PRESERVAZIONE DELLA FUNZIONALITÀ OVARICA, TASSO DI GRAVIDANZA, SOPRAVVIVENZA LIBERA DA MALATTIA (DFS)

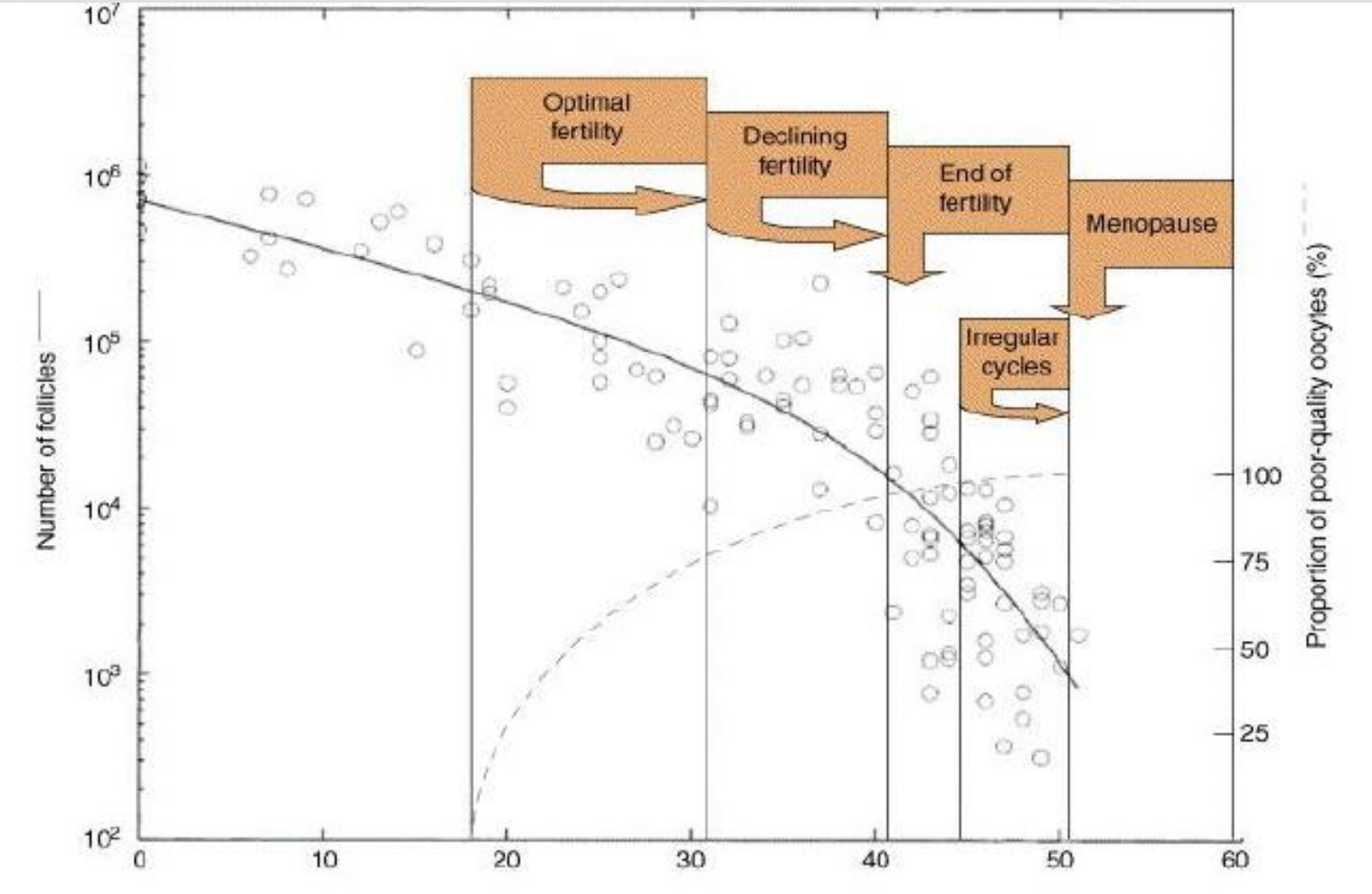
  DANNO: SOPRAVVIVENZA LIBERA DA MALATTIA (DFS) TROMBOEMBOLISMO, SINTOMI VASOMOTORI

CLASSIFICAZIONE DEGLI OUTCOME POSITIVI (BENEFICI) E NEGATIVI (RISCHI)

- SOPPRESSIONE PREMATURA DELLA FUNZIONALITÀ OVARICA (POF)
  - POF COME AMENORREA A 12 M DALLA CHEMIO
  - GRAVIDANZE
  - DFS
  - TROMBOSI
  - SINTOMI VASOMOTORI

Rating (mediana del voto)	Importanza	Incluso in
7 8 9	Outcome importanti ed essenziali: POF GRAVIDANZE AMENORREA DOPO 12 M DA CHEMIO	Tabelle sulla qualità delle prove:si Raccomandazione:si
4 5 6	Outcome importanti ma non essenziali: DFS	Tabelle sulla qualità delle prove:si Raccomandazione:no
1 2 3	Outcome non importanti TROMBOSI SINTOMI VASOMOTORI	Tabelle sulla qualità delle prove:no Raccomandazione:no

RIDUZIONE QUANTITATIVA E QUALITATITIVA DEGLI OVOCITI CON ETA'



Broekmans FJ et al. 2007

CHEMIOTERAPIA E RISCHIO DI INFERTILITA'

Treatment	Age <30	Age 30-40	Age>40
AC x 4	--	13	57-63
CMF x 6	19	31-38	76-96
CAF/CEF x 6	23-47		80-89
TAC x 6	51		
AC x 4 -> T x 4	38 (15% age <40)		

(Goodwin et al., JCO 1999; Burstein, H. J. et al. NEJM 2000; Nabholtz et al., ASCO 2002; Parulekar et al., JCO 2005; Fornier et al., Cancer 2005; Petrek et al, JCO 2006)

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Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies

M. Lambertini[1], M. Ceppi[2], F. Poggio[1], F. A. Peccatori[3], H. A. Azim Jr[4], D. Ugolini[5], P. Pronzato[1], S. Loibl[6,7], H. C. F. Moore[8], A. H. Partridge[9], P. Bruzzi[2] & L. Del Mastro[10*]

Table 1. Main characteristics of the randomized studies included in the present meta-analysis

Authors	Year	Patients randomized, *n* (control/experimental)	Median age (control/experimental)	Hormone receptor status, *n* (pos/neg)	Use of endocrine therapy	Type of LHRHa used	Definition of POF	Timing of POF evaluation
Li et al. [44]	2008	32/31	NR	NR	NR	Goserelin	No resumption of menses	NR
Badawy et al. [31]	2009	39/39	29.2/30	NR	NR	Goserelin	No resumption of menses and ovulation	8 months
Sverrisdottir et al. [32]	2009	66/57	45–45/45–46	NR	Yes (tamoxifen)	Goserelin	No resumption of menses	36 months
Del Mastro et al. [34] Lambertini et al. [40]	2011 2014	133/148	39/39	226/51	Yes (tamoxifen)[a]	Triptorelin	No resumption of menses and postmenopausal levels of FSH and E_2	12 months
Gerber et al. [33]	2011	30/30	38.5/35.0	0/60	No	Goserelin	No resumption of two consecutive menstrual periods	6 months
Sun et al. [42]	2011	50/50	33/32	NR	NR	Goserelin	No resumption of menses	NR
Munster et al. [35]	2012	22/27	38/39	16/20	Yes (tamoxifen)	Triptorelin	No resumption of menses	12 months
Elgindy et al. [36]	2013	50/50	32.3–32.8/33.2–33.0	0/100	No	Triptorelin	No resumption of menses	12 months
Song et al. [37]	2013	94/89	40.3/42.1	150/33	Yes (tamoxifen)[b]	Leuprolide	Postmenopausal levels of FSH and E_2 in the absence of menstrual activity	12 months
Karimi-Zarchi et al. [38]	2014	21/21	37	0/42	No	Diphereline	No resumption of menses	6 months
Li et al. [43]	2014	108/108	39/37.5	216/0	Yes (tamoxifen)	Goserelin	Amenorrhea for the prior 12 months and postmenopausal levels of FSH	12 months
Moore et al. [39]	2015	113/105	38.7/37.6	0/218	No	Goserelin	Amenorrhea for the prior 6 months and postmenopausal levels of FSH	24 months

CHEMOTHERAPY: NUMBER OF CYCLES, TYPE AND DOSE

Authors	Year	Type of chemotherapy	Cycles, *n*	Patients treated with anthracycline, *n* (control/experimental)	Patients treated with taxane, *n* (control/experimental)	Patients treated with cyclophosphamide, *n* (control/experimental)	Median dose of cyclophosphamide (control/experimental)
Li et al. [44]	2008	AC or AC → D	4	32/31	NR	63	NR
Badawy et al. [31]	2009	FAC	6	39/39	0/0	39/39	NR
Sverrisdottir et al. [32]	2009	CMF	6	0/0	0/0		NR
Del Mastro et al. [34] Lambertini et al. [40]	2011 2014	CMF or E → CMF or EP → CMF or ED → CMF or AC or EC or FEC or AC → D or EC → D or EC → P or FEC → P or FEC → D or ED	4–8	122/143	64/87	125/142	4008/4080
Gerber et al. [33]	2011	FEC → T or EC → T or FEC or FAC or TAC or FEC → GEM	6–8	30/30	16/16	30/30	NR
Sun et al. [42]	2011	NR	NR	NR	NR	NR	NR
Munster et al. [35]	2012	AC or AC → P or FEC or FAC	4–8	22/27	5/8	22/27	NR
Elgindy et al. [36]	2013	FAC	6	50/50	0	50/50	5.680–5.528/5.564–5.536
Song et al. [37]	2013	AC or AC → D	4–6	94/89	25/32	94/89	3217.0/3094.5
Karimi-Zarchi et al. [38]	2014	TAC	NR	42	42	42	NR
Li et al. [43]	2014	NR	NR	NR	NR	NR	NR
Moore et al. [39]	2015	AC or CAF or TAC or CEF or AC → T or CMF	NR	102/96	NR	113/105	NR

Lambertini M et al. Annals of Oncol 2015:26:2408-2419

Effect of the Gonadotropin-Releasing Hormone Analogue Triptorelin on the Occurrence of Chemotherapy-Induced Early Menopause in Premenopausal Women With Breast Cancer

A Randomized Trial

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Teresa Gamucci, MD
Nina Olmeo, MD
Stefania Gori, MD
Monica Giordano, MD
Ornella Garrone, MD
Paolo Pronzato, MD
Claudia Bighin, MD
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Sara Giraudi, MD
Nicola Cresti, MD
Emanuela Magnolfi, MD
Tiziana Scotto, MD
Carlo Vecchio, MD
Marco Venturini, MD

Context Premenopausal patients with breast cancer are at high risk of premature ovarian failure induced by systemic treatments, but no standard strategies for preventing this adverse effect are yet available.

Objective To determine the effect of the temporary ovarian suppression obtained by administering the gonadotropin-releasing hormone analogue triptorelin during chemotherapy on the incidence of early menopause in young patients with breast cancer undergoing adjuvant or neoadjuvant chemotherapy.

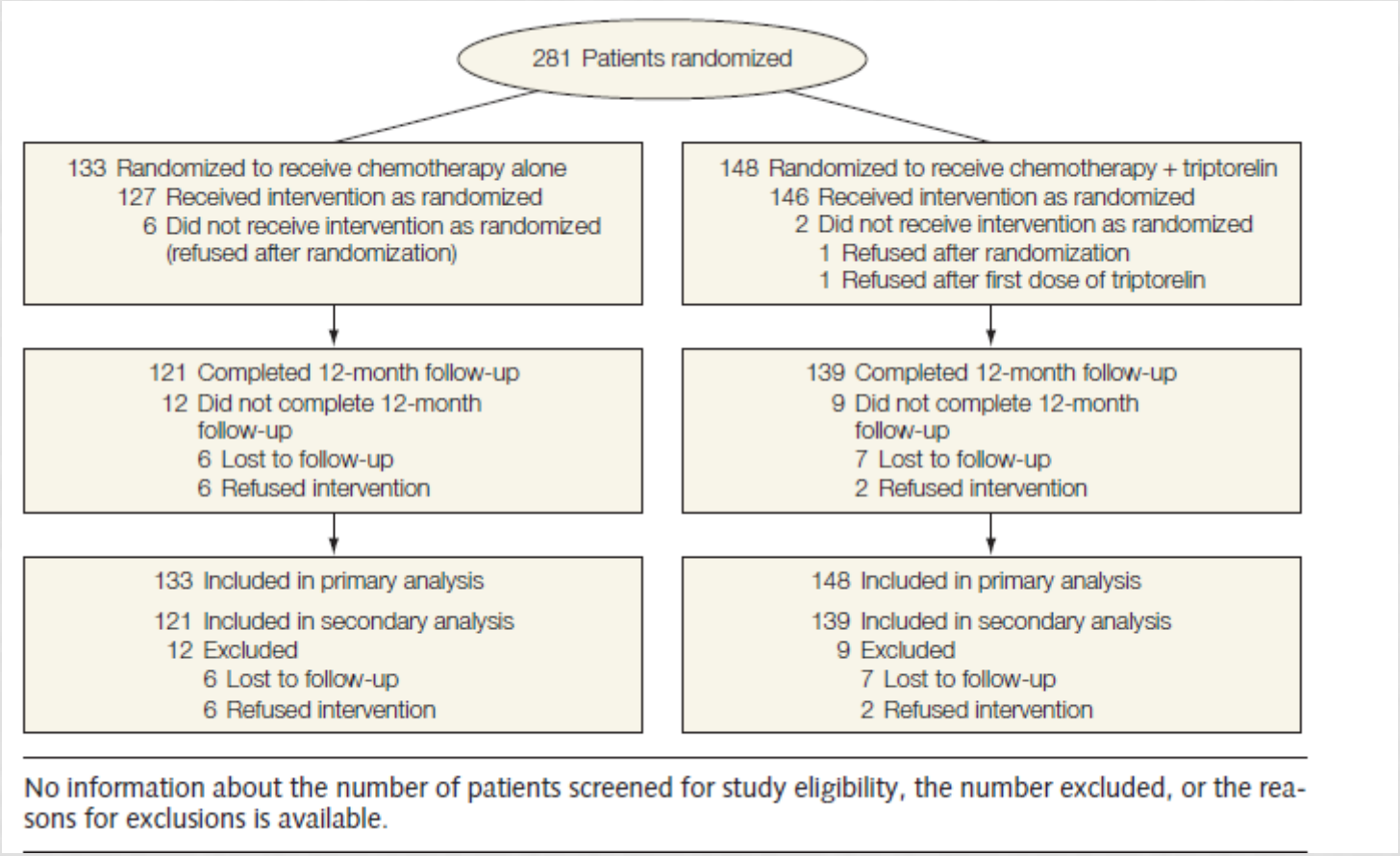
Design, Setting, and Patient The PROMISE-GIM6 (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients–Gruppo Italiano Mammella 6) study, a parallel, randomized, open-label, phase 3 superiority trial, was conducted at 16 sites in Italy and enrolled 281 patients between October 2003 and January 2008. The patients were premenopausal women with stage I through III breast cancer who were candidates for adjuvant or neoadjuvant chemotherapy. Assuming a 60% rate of early menopause in the group treated with chemotherapy alone, it was estimated that 280 patients had to be enrolled to detect a 20% absolute reduction in early menopause in the group treated with chemotherapy plus triptorelin. The intention-to-treat analysis was performed by including all randomized patients and using imputed values for missing data.

Interventions Before beginning chemotherapy, patients were randomly allocated to receive chemotherapy alone or combined with triptorelin. Triptorelin was administered intramuscularly at a dose of 3.75 mg at least 1 week before the start of chemotherapy and then every 4 weeks for the duration of chemotherapy.

Main Outcome Measure Incidence of early menopause (defined as no resump-

Del Mastro L, Boni L, Michelotti A et al JAMA 2011

GIM6/PROMISE STUDY FLOW



Del Mastro L, Boni L, Michelotti A et al JAMA 2011

GIM6/PROMISE: RESULTS

281 premenopausal women with stage I to III HR-positive or HR-negative breast cancer

	CT alone	CT+tritorelin	HR	P value
Early menopause* (1)	25.9%	8.9%	0.28 [95% CI, 0.14-0.59]	<0.001
Pregnancy # (2)	1.6%	2,1%	2.56 [95% CI, 0.68-9.60]	*0* .14

* Defined as no resumption of menstrual activity and postmenopausal levels of FSH and estradiol 1 year after the last cycle of chemotherapy

Median follow-up: 7.3 ys

1 Del Mastro L et al JAMA 2011
2 Lambertini M et al JAMA 2015

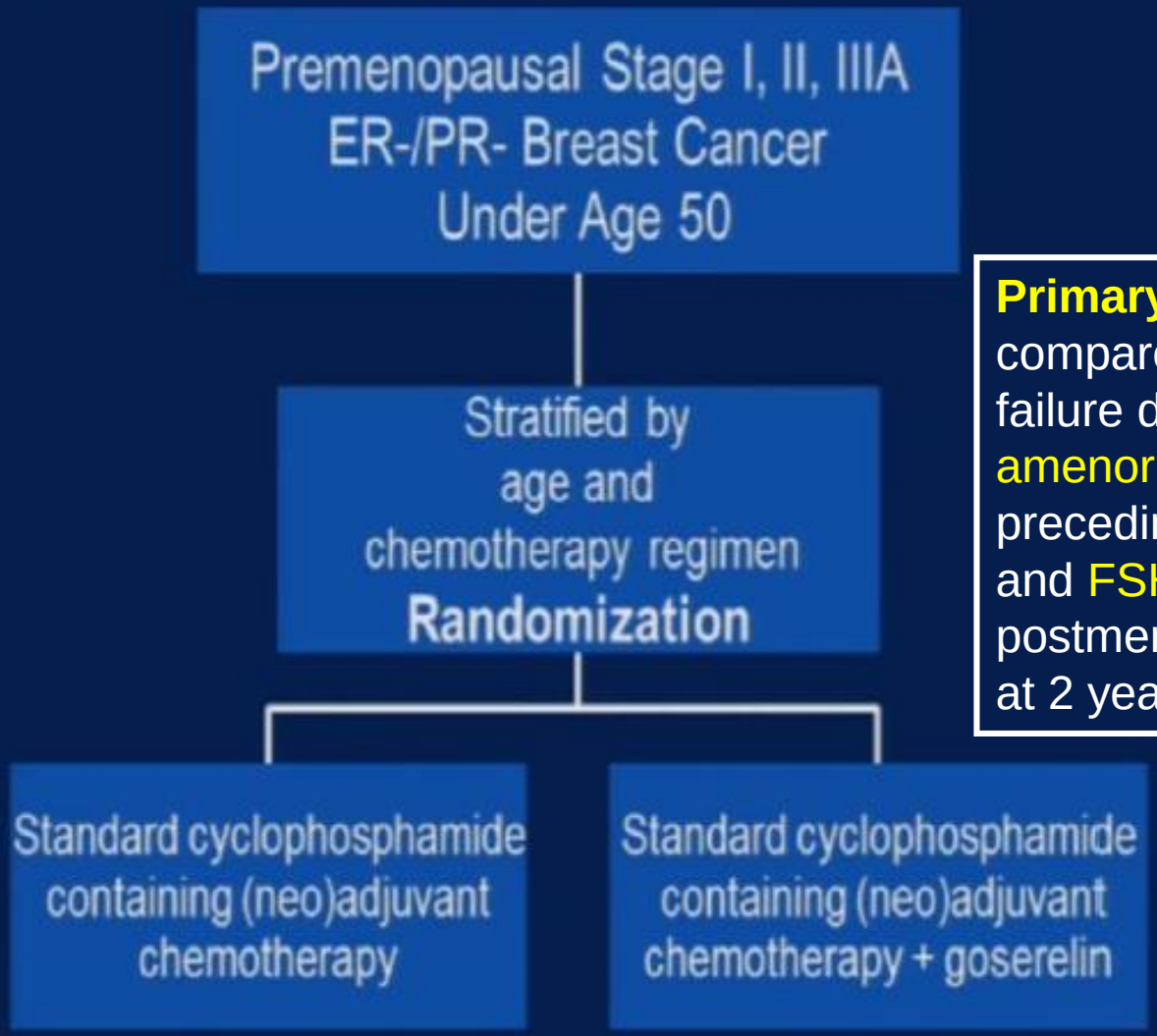
ORIGINAL ARTICLE

Goserelin for Ovarian Protection during Breast-Cancer Adjuvant Chemotherapy

Halle C.F. Moore, M.D., Joseph M. Unger, Ph.D., Kelly-Anne Phillips, M.D., Frances Boyle, M.B., B.S., Ph.D., Erika Hitre, M.D., David Porter, M.D., Prudence A. Francis, M.D., Lori J. Goldstein, M.D., Henry L. Gomez, M.D., Carlos S. Vallejos, M.D., Ann H. Partridge, M.D., M.P.H., Shaker R. Dakhil, M.D., Agustin A. Garcia, M.D., Julie Gralow, M.D., Janine M. Lombard, M.D., John F. Forbes, M.B., B.S., Silvana Martino, D.O., William E. Barlow, Ph.D., Carol J. Fabian, M.D., Lori Minasian, M.D., Frank L. Meyskens, Jr., M.D., Richard D. Gelber, Ph.D., Gabriel N. Hortobagyi, M.D., and Kathy S. Albain, M.D., for the POEMS/S0230 Investigators

Moore H, Unger J, Phillips KA et al NEJM 2015

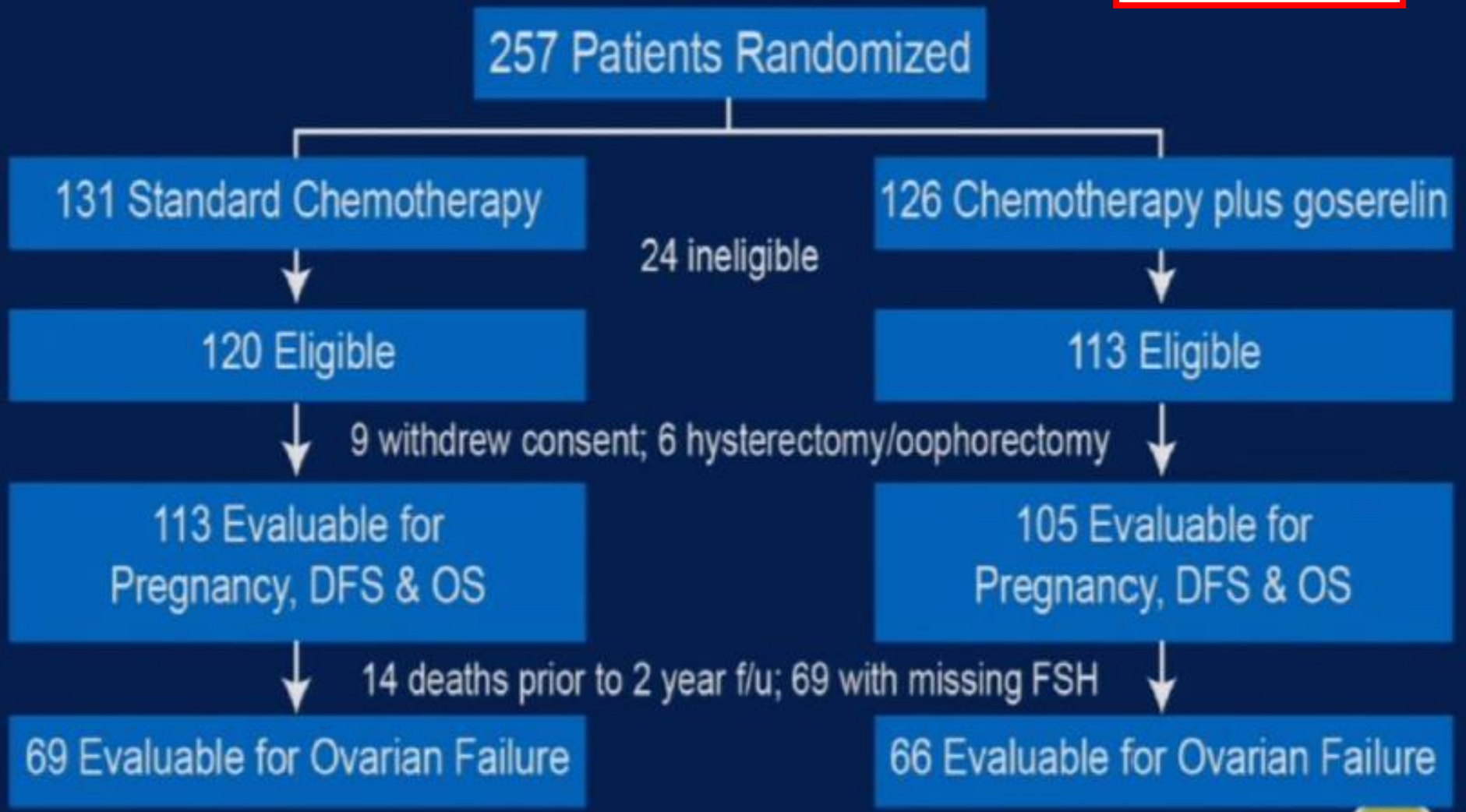
POEMS/S0230 Schema



Primary objective: compare rate of ovarian failure defined as amenorrhea for the preceding 6 months and FSH levels in the postmenopausal range at 2 years

POEMS Consort Diagram

Original target: 416 pts

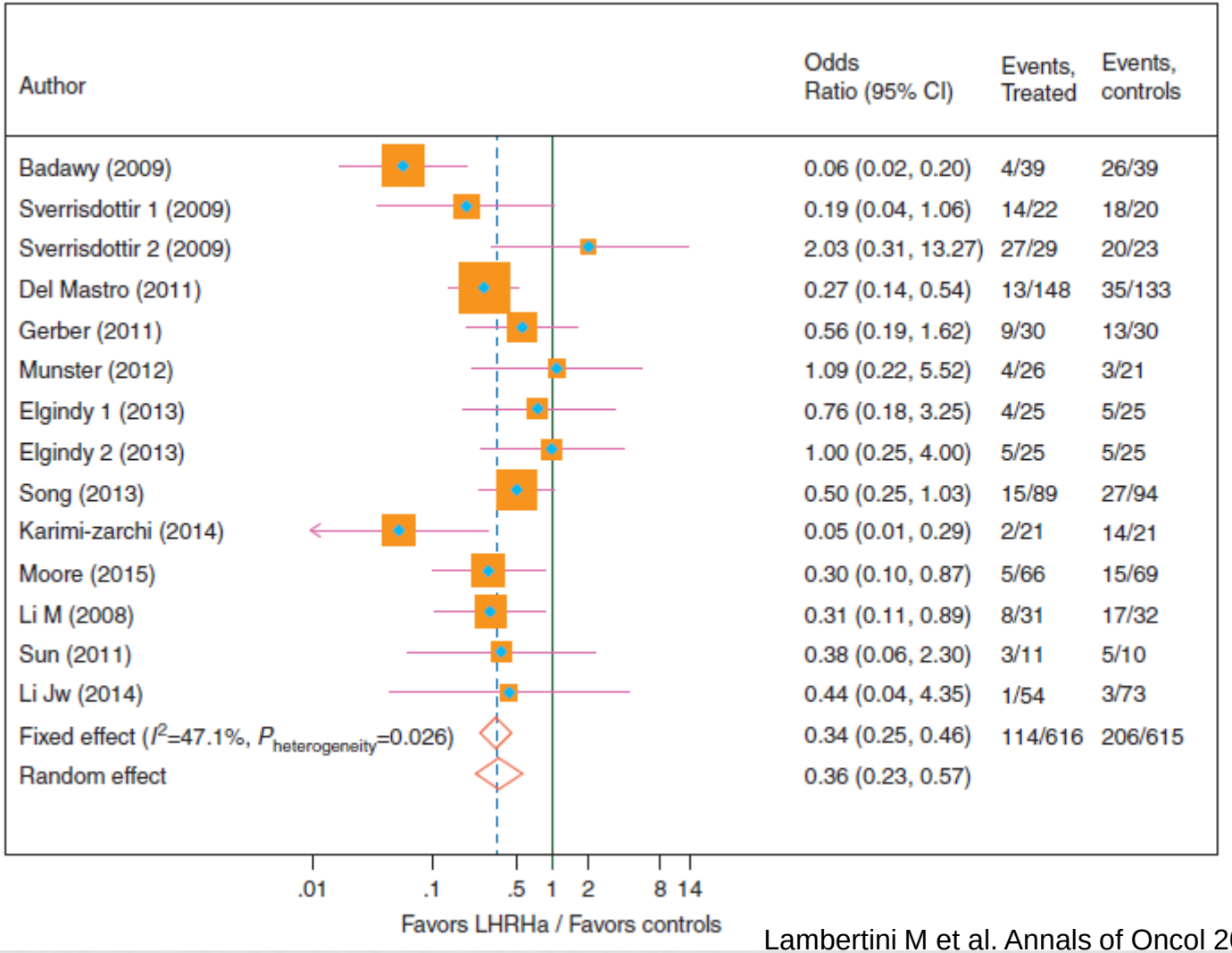


POEMS: RESULTS

	Standard chemo	Chemo + goserelin	HR	P value
Ovarian failure at 2 years	22/67 (33%)	9/36 (14%)	0.35	0.03
Pregnancy achieved	12 (11%)	22 (21%)	2.45	0.03

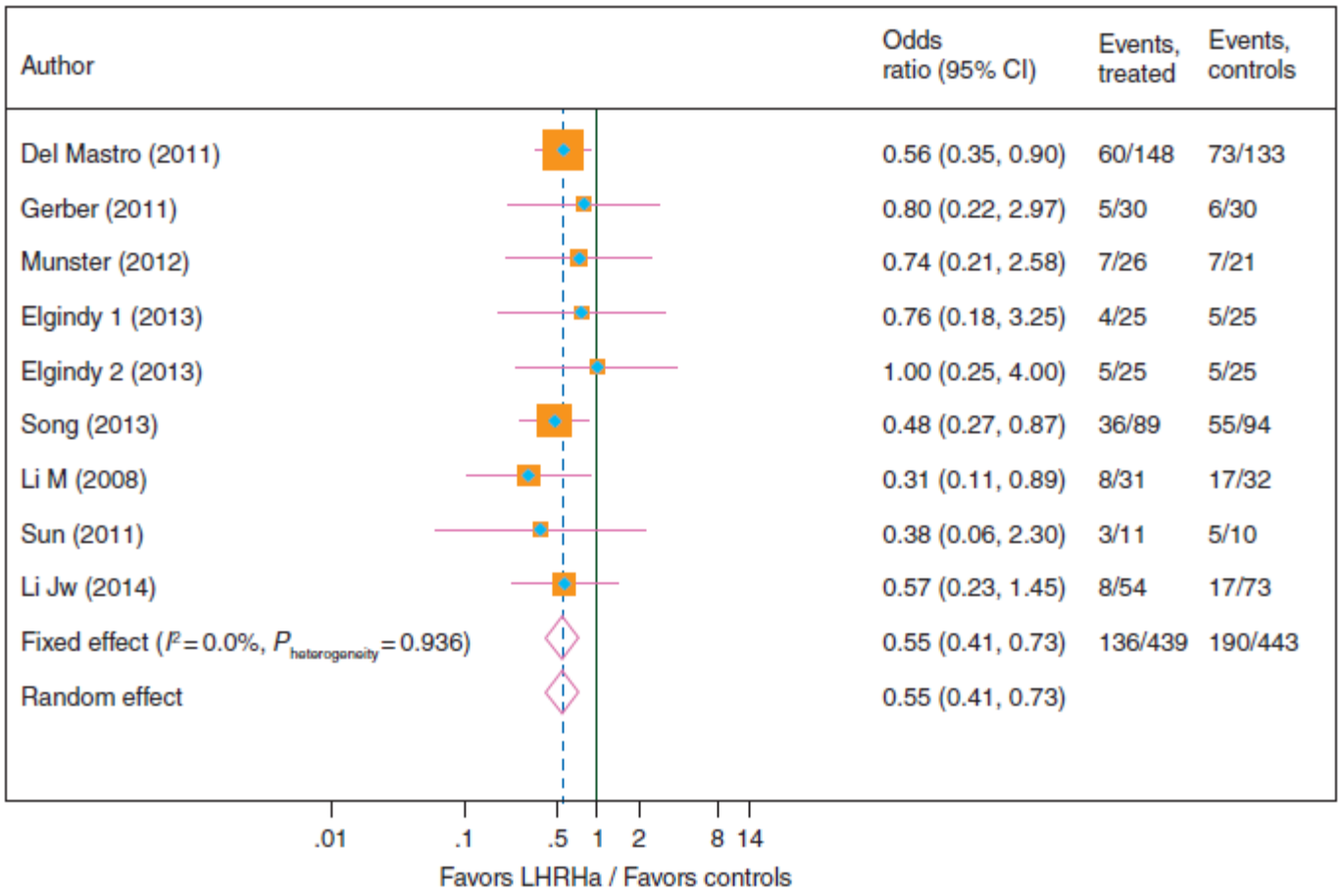
Moore H, Unger J, Phillips KA et al NEJM 2015

POF BY STUDY DEFINITION



Lambertini M et al. Annals of Oncol 2015:26:2408-2419

POF DEFINITA COME AMENORREA DOPO 12 MESI DALLA FINE DELLA CHEMIOTERAPIA



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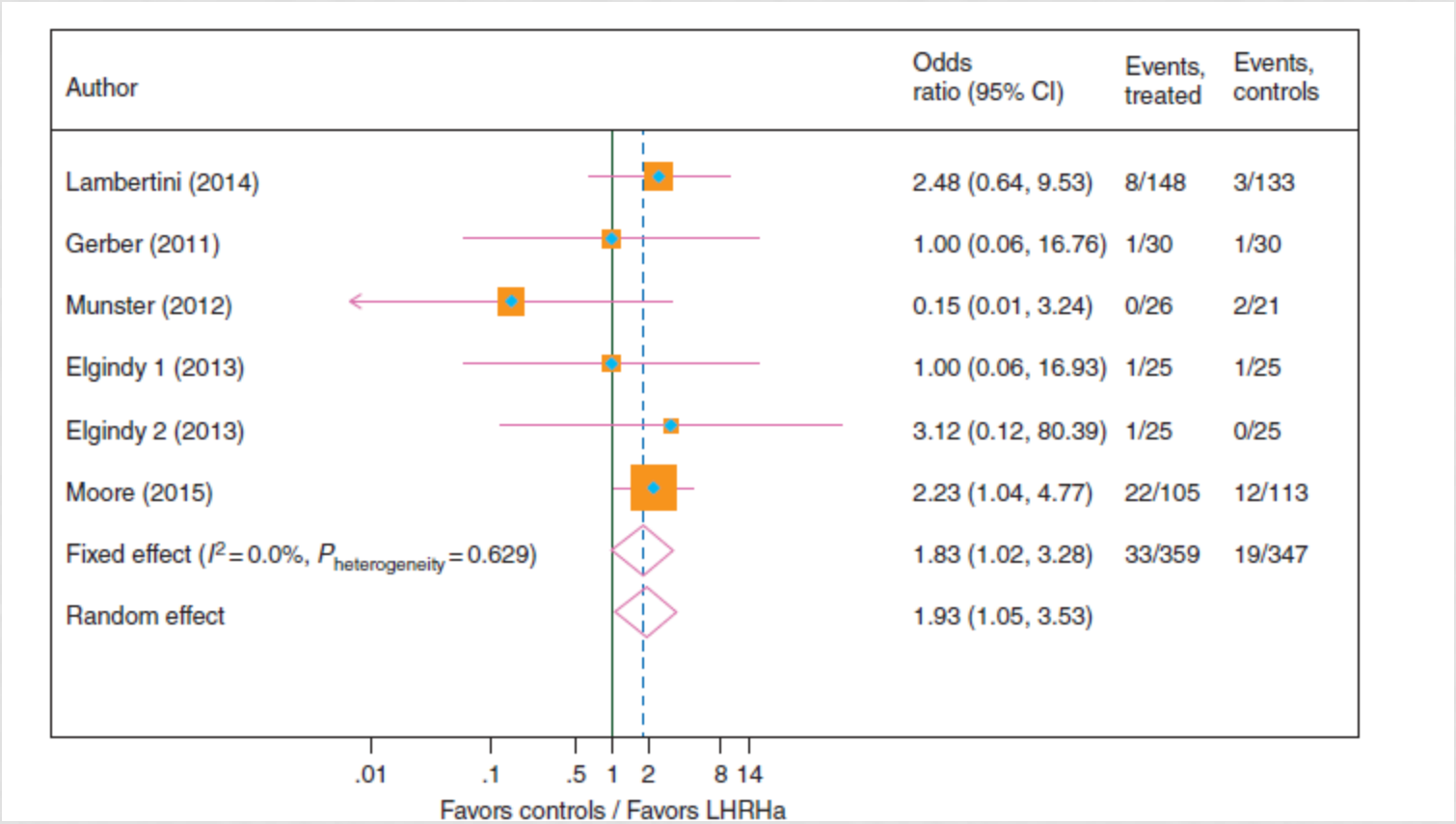
GRAVIDANZE



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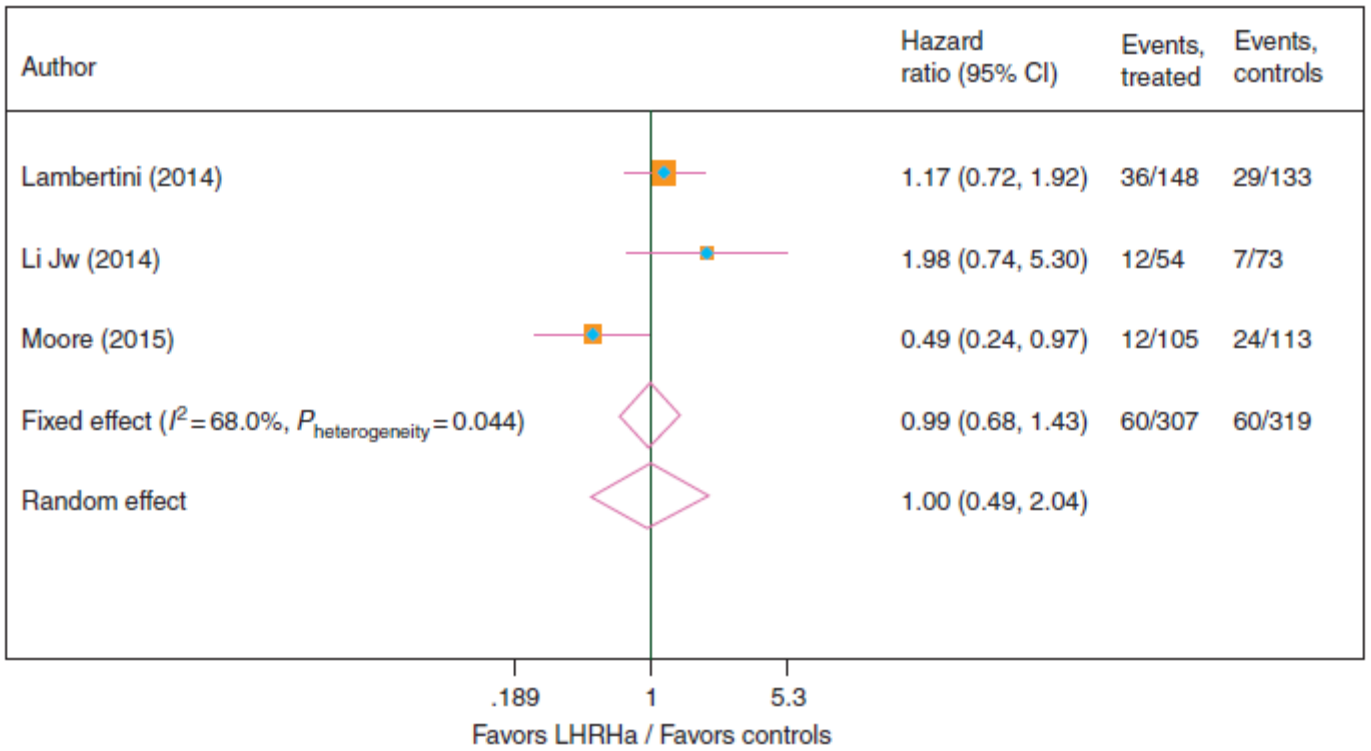
DISEASE FREE SURVIVAL (DFS)



Lambertini M et al. Annals of Oncol 2015:26:2408-2419