QUESITO GRADE
Gruppo di lavoro 2

Coordinatori
Massimo Di Maio, Mimma Rizzo

Presentatori
Marta Bonotto, Caterina Fontanella, Marta Pestrin

Special guest:
Giovanni L. Pappagallo

Pz di 72 anni,
Vive in famiglia assieme alla figlia
Nota per intolleranza glucidica, ipertensione arteriosa controllata farmacologicamente, calcolosi renale

Riscontro accidentale di lesioni epatiche (almeno 3) ad una ecografia addominale eseguita a seguito di una colica renale

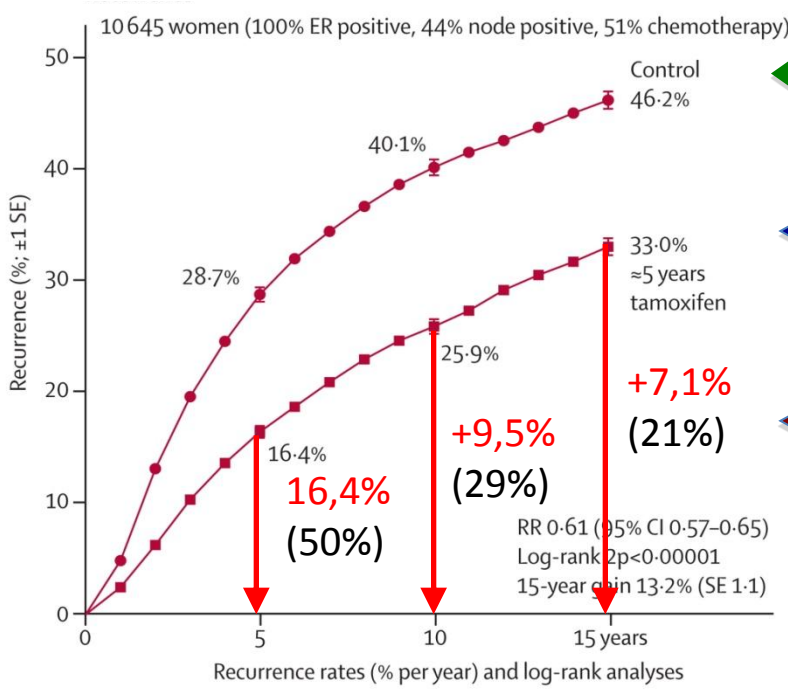
Anamnesi oncologica:

-01.2013 intervento di quadrantectomia destra + linfoadenoctomia omolaterale per un CDI di G2 con associate espressione di CDIS di G3, coinvolgente 2 dei 7 linfonodi ascellari esaminati. Margini chirurgici indenni. Invasione vascolare focalmente presente. ER: 80%; PgR: 20%; HER2: negativo; Ki67: 15%. pT2 (2.5 cm) N1

-La paziente rifiutava il trattamento chemioterapico, dal 03.2013 ha avviato trattamento ormonale adiuvante con letrozolo 2.5 mg 1cp/die e veniva inviata ai colleghi della radioterapia per la presa in carico per la RT complementare sul seno residuo

-Dal 03.2013 esegue regolari controlli oncologici e senologici

Timing of adjuvant endocrine treatment failure



	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	3·74 (891/23 819)	2·62 (454/17 315)	2·06 (220/10 657)	1·75 (88/5034)
Control	6·71 (1466/21 862)	3·46 (499/14 420)	2·11 (182/8620)	1·76 (71/4045)
Rate ratio	0·53 (SE 0·03)	0·68 (SE 0·06)	0·97 (SE 0·10)	0·88 (SE 0·16)
(O–E)/V	−343·3/535·1	−82·5/217·5	−3·3/93·3	−4·4/35·5

46% of patients do not need Rx !!

Absolute benefit in 13% of patients

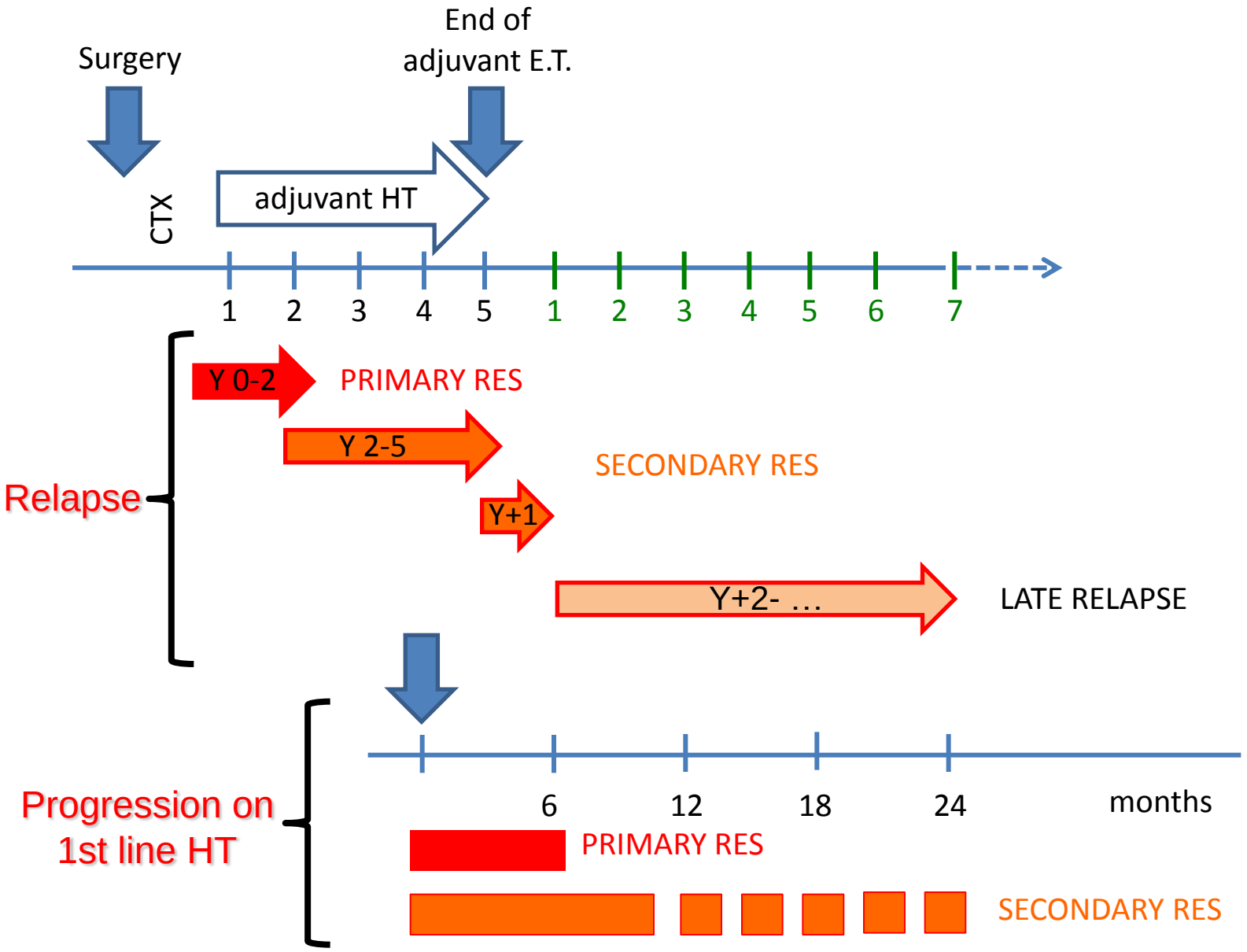
Recurrence in 33% of patients in spite Rx

Primary or Acquired Resistance

- Half of the patients who will recur, will do so within 5 years from surgery
- In the first 2 years we see as many recurrences as in years 10-15

EBCTCG, *Lancet* 2011

Clinical definition of “Endocrine resistance”



Current Guidelines for Endocrine Therapy in MBC

National Comprehensive Cancer Network®

NCC
Inva

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

ENDOCRINE THERAPY FOR RECURRE

Premenopausal patients with **…opausal guidelines**

Postmenopausal Patients
- **Non-steroidal aromatase inh**
- **Steroidal aromatase inactiva**
- **Exemestane + everolimus[1]**
- **Palbociclib + letrozole[2]**
- **Fulvestrant**
- **Tamoxifen or to**
- **Megestrol aceta**
- **Fluoxymesteron**
- **Ethinyl estradio**

A		**a forte**
B		**debole**
A	Nelle pazienti con carcinoma mammario metastatico ER-positivo e/o PgR positivo in postmenopausa, pretrattate in adiuvante o in fase metastatica con inibitore delle aromatasi non steroideo, deve essere preso in considerazione un trattamento con everolimus ed exemestane[30].	**Positiva forte**

…gressed within 12 mo or on non-
…nts with ER-positive, HER2-negative

Guideline statements	LoE	Consensus
The preferred first-line ET for postmenopausal patients is an aromatase inhibitor or tamoxifen, depending on the type and duration of	IA	83.3% (30) yes 16.6% (6) abstain (36 voters)

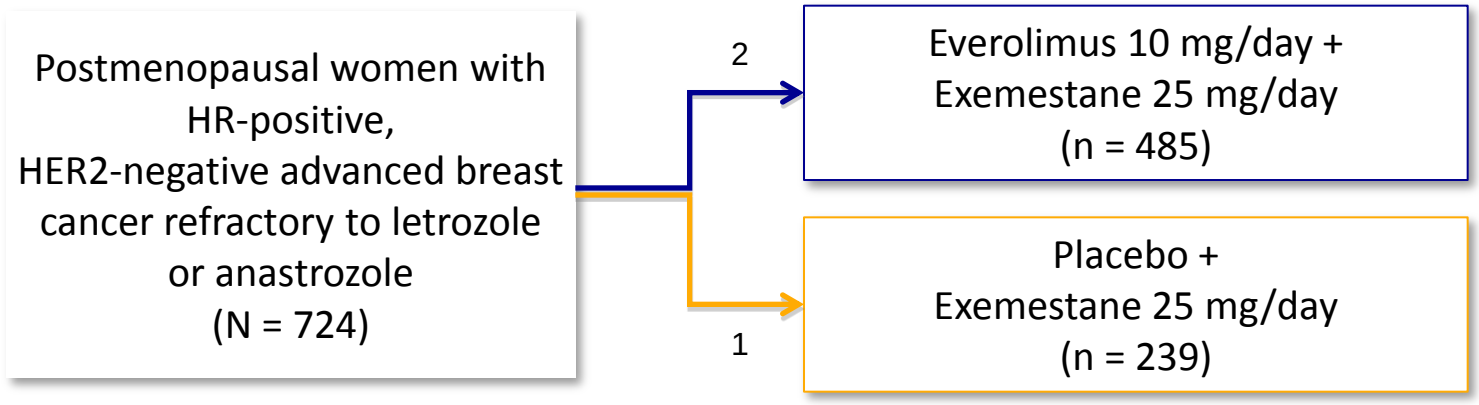
LoE: available level of evidence; consensus: percentage of panel members in agreement with the statement; ET: endocrine therapy; PFS: progression-free survival.

TREAMENT OPTIONS:

- Exemestane-everolimus
- Exemestane
- Fulvestrant HD
- Tamoxifene

2 - QUESITO GRADE: Nelle pazienti in postmenopausa con carcinoma mammario HR+/HER2- in assenza di malattia viscerale sintomatica, con recidiva di malattia durante o entro 1 anno dal termine del trattamento adiuvante includente un antiaromatasico non steroideo, il trattamento con exemestane+everolimus è raccomandabile rispetto al solo exemestane?

BOLERO-2: study design



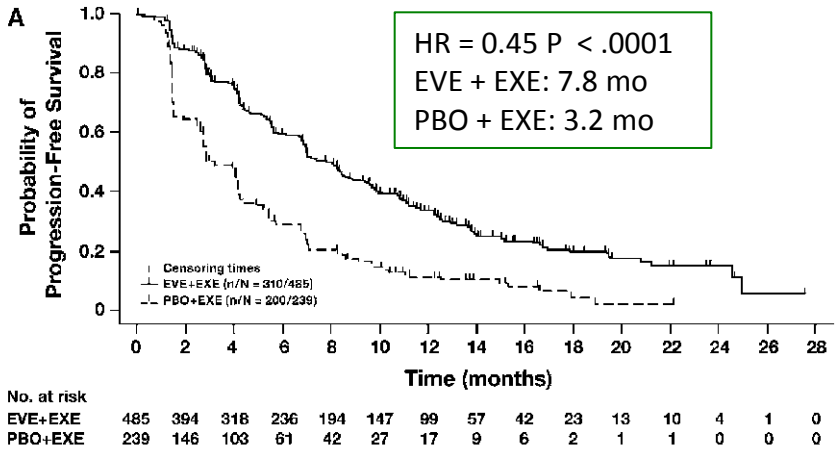
- Refractory to therapy:
  - Recurrence during or within 12 mos of end of adjuvant treatment
  - Progression during or within 1 mo after end of treatment for advanced disease
- Stratification:
  - Sensitivity to previous hormonal therapy
  - Presence of visceral disease
- No crossover allowed
- Primary endpoint: PFS
  - Secondary endpoints: OS, ORR, CBR, safety, QoL, bone markers

Baselga J, et al. N Engl J Med. 2012;366:520-529

BOLERO-2: patient characteristics and results

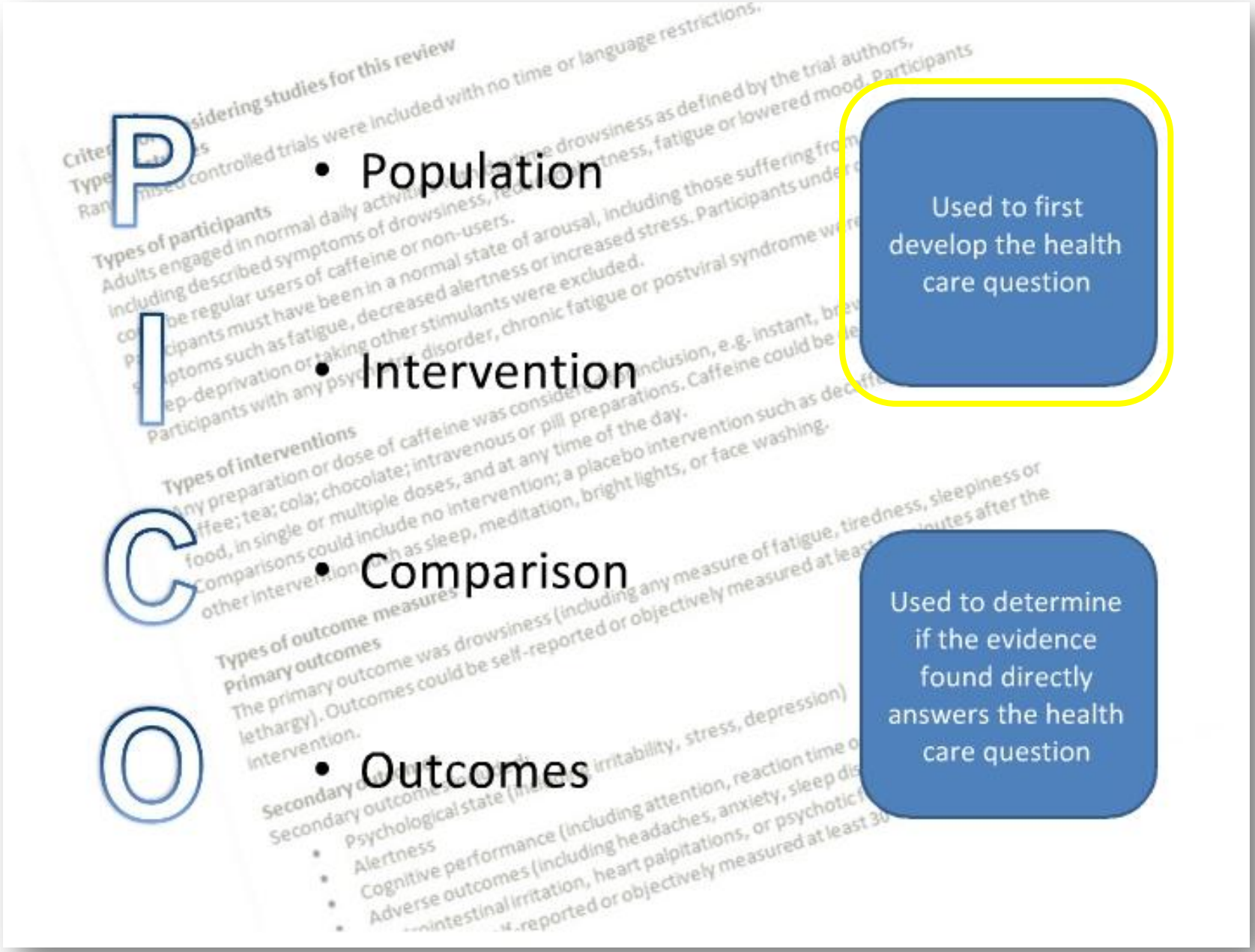
		Everolimus + Exemestane (N=485) %	Placebo + Exemestane (N=239) %
Sensitivity to prior hormonal therapy		84	84
Disease free interval			
	< 12 months	2	4
	12-24 months	5	6
	>24 months	56	54
Last treatment			
	Adjuvant	21	15
	Metastatic	79	85

SECONDARY RESISTANCE POPULATION



AE G 3/4	EVE + Exe (N=482) %	PBO + Exe (N=238) %
Stomatitis	8	1
Anemia	6	<1
Dyspnea	4	1
Hyperglycemia	4	<1
Pneumonitis	3	0

Baselga J, et al. N Engl J Med. 2012;366:520-529
Yardley DA, et al. Adv.Ther 2013; 30: 870-84


P
• Population
I
• Intervention
C
• Comparison
O
• Outcomes
Used to first develop the health care question
Used to determine if the evidence found directly answers the health care question

GRADE and PICO

QUESITO GRUPPO B:

Nelle pazienti in post-menopausa con carcinoma mammario HR+/HER2- in assenza di malattia viscerale sintomatica, con recidiva di malattia durante o entro 1 anno dal termine del trattamento adiuvante includente un antiaromatasico non steroideo, è raccomandabile il trattamento con Everolimus+Exemestane rispetto al solo Exemestane?

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carcinoma mammario HR+/HER2-
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I.

C.

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I. Everolimus in associazione a Exemestane

C. Exemestane

O. **di beneficio:** **OS, PFS (local), PFS (central), progressive disease in bone, ORR (local), ORR (central), time to QOL deterioration**
di danno: **stomatitis, fatigue, hyperglicaemia, pneumonitis**

OUTCOMES

- **Outcomes of benefit**
  - Overall Survival (9) (8) (7) (6) (5) (4) (3) (2) (1)
  - PFS (local assessment) (9) (8) (7) (6) (5) (4) (3) (2) (1)
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  - time to QOL deterioration (9) (8) (7) (6) (5) (4) (3) (2) (1)

- **Outcomes of harm**
  - stomatitis (9) (8) (7) (6) (5) (4) (3) (2) (1)
  - fatigue (9) (8) (7) (6) (5) (4) (3) (2) (1)
  - hyperglicaemia (9) (8) (7) (6) (5) (4) (3) (2) (1)
  - pneumonitis (9) (8) (7) (6) (5) (4) (3) (2) (1)
  - AEs leading to discontinuation (9) (8) (7) (6) (5) (4) (3) (2) (1)

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OUTCOMES

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  - Overall Survival
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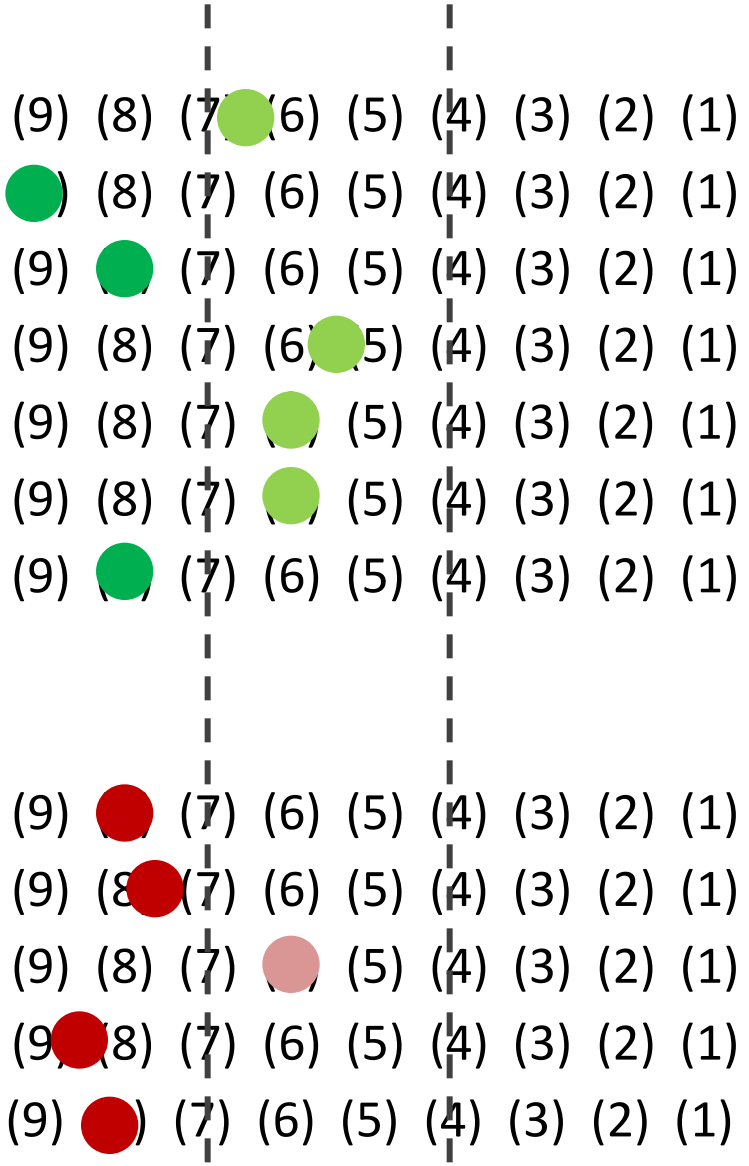

Original Study

Safety and Efficacy of Everolimus With Exemestane vs. Exemestane Alone in Elderly Patients With HER2-Negative, Hormone Receptor—Positive Breast Cancer in BOLERO-2

Adv Ther (2013) 30:870–884
DOI 10.1007/s12325-013-0060-1

ORIGINAL RESEARCH

Rugo,[4]
öszi,[8]
12

Everolimus Plus Exemestane i
Patients with HR+ Breast Can
Progression-Free Survival Ana

original articles

Incidence and time course adverse events in postmen hormone receptor-positive advanced breast cancer: insights from BOLERO-2

H. S. Rugo[1*], K. I. Pritchard[2], M. Gnant[3], S. Noguchi[4], M. Piccart[5], G. Hortobagyi[6], J. Baselga[7], A. Perez[8], M. Geberth[9], T. Csoszi[10], E. Chouinard[11], V. Srimuninnimit[12], P. Puttawibul[13], J. Eakle[14], W. Feng[15], H. Bauly[16], M. El-Hashimy[15], T. Taran[15] & H. A. Burris, III[17]

Breast Cancer Res Treat (2014) 143:459–467
DOI 10.1007/s10549-013-2814-5

CLINICAL TRIAL

Everolimus plus exemestane as first-line therapy in HR+, HER2− advanced breast cancer in BOLERO-2

J. Thaddeus Beck · Gabriel N. Hortobagyi · Mario Campone · Fabienne Lebrun · Ines Deleu · Hope S. Rugo · Barbara Pistilli · Norikazu Masuda · Lowell Hart · Bohuslav Melichar · Shaker Dakhil · Matthias Geberth · Martina Nunzi · Daniel Y. C. Heng · Thomas Brechenmacher · Mona El-Hashimy · Shyanne Douma · Francois Ringeisen · Martine Piccart

OUTCOMES OF BENEFIT

Author(s):
Date: 04.08.2015
Question: Everolimus+ Exemestane compared to Exemestane for 1st line metastatic disease
Setting: HR-pos, HER2-neg, advanced breast cancer
Bibliography (systematic reviews): Piccart M et al, Ann Oncol 2014; Yardley D, et al, Adv Ther 2013; Beck JT et al, Breast Cancer Res Treat 2013; Burris HA et al, Cancer 2013; Gnant M et al, JNCI 2013; Rugo H et al, Ann Oncol 2014

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№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Everolimus+ Exemestane	Exemestane	Relative (95% CI)	Absolute (95% CI)		
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1	randomised trials	not serious	not serious	very serious [1]	serious [2]	none	267/485 (55.1%)	143/239 (59.8%)	**HR 0.89** (0.73 to 1.10)	4 fewer per 100 (from 4 more to 11 fewer)	⊕◯◯◯ VERY LOW	
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1	randomised trials	not serious	not serious	very serious [1]	not serious	none	300/485 (61.9%)	210/239 (87.9%)	**HR 0.45** (0.38 to 0.54)	27 fewer per 100 (from 20 fewer to 33 fewer)	⊕⊕○○ LOW	
Progression Free Survival (local assessment) (Beck et al, 2013) (follow up: median 17.7; assessed with: Kaplan-Meier estimate; HR)												
1	randomised trials	very serious [3]	not serious	not serious	not serious	none	58/100 (58.0%)	32/37 (86.5%)	**HR 0.39** (0.26 to 0.62)	32 fewer per 100 (from 15 fewer to 46 fewer)	⊕⊕○○ LOW	
Progression Free Survival (central assessment) (Yardley et al, 2013) (follow up: median 17.7 months; assessed with: Kaplan-Meier estimate; HR)												
1	randomised trials	not serious	not serious	very serious [1]	not serious	none	185/485 (38.1%)	135/239 (56.5%)	**HR 0.38** (0.31 to 0.48)	29 fewer per 100 (from 24 fewer to 34 fewer)	⊕⊕○○ LOW	
Progression Free Survival (central assessment) (Beck et al, 2013) (follow up: median 17.7 months; assessed with: Kaplan-Meier estimate; HR)												
1	randomised trials	very serious [3]	not serious	not serious	not serious	none	36/100 (36.0%)	21/37 (56.8%)	**HR 0.32** (0.18 to 0.57)	33 fewer per 100 (from 19 fewer to 43 fewer)	⊕⊕○○ LOW	

1. only 19% of Bolero-2 patients entered the trial having received (neo) adjuvant therapy as their last systemic treatment
2. 95% confidence limits consistent with conflicting recommendations
3. not pre-planned, not a stratification factor

OUTCOMES OF BENEFIT

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Everolimus+ Exemestane	Exemestane	Relative (95% CI)	Absolute (95% CI)		
Progressive disease in bone (Gnant et al, 2013) (follow up: median 17.7 months; assessed with: Kaplan-Meier estimate; HR)												
1	randomised trials	very serious [3]	not serious	very serious [1]	not serious	none	60/371 (16.2%)	43/185 (23.2%)	**HR 0.43** (0.35 to 0.53)	12 fewer per 100 (from 10 fewer to 14 fewer)	⊕○○○ VERY LOW	
Overall Response Rate (local assessment) (Yardley et al, 2013) (assessed with: 2x2 frequency table; RR)												
1	randomised trials	not serious	not serious	very serious [1]	serious [2]	none	61/485 (12.6%)	4/239 (1.7%)	**RR 7.51** (2.76 to 20.42)	11 more per 100 (from 3 more to 33 more)	⊕○○○ VERY LOW	
Overall Response Rate (central assessment) (Yardley et al, 2013) (assessed with: 2x2 frequency table; RR)												
1	randomised trials	not serious	not serious	very serious [1]	serious [2]	none	61/485 (12.6%)	5/239 (2.1%)	**RR 6.01** (2.45 to 14.76)	10 more per 100 (from 3 more to 29 more)	⊕○○○ VERY LOW	
Time to QoL deterioration (5% change of EORTC QLQ-C30 GHS from baseline) (Burris et al, 2013) (follow up: median 17.7 months; assessed with: Kaplan-Meier estimate; HR)												
1	randomised trials	serious [4]	not serious	very serious [1]	not serious	none	254/485 (52.4%)	113/239 (47.3%)	**HR 0.74** (0.58 to 0.95)	10 fewer per 100 (from 2 fewer to 16 fewer)	⊕○○○ VERY LOW	
Time to QoL deterioration (10-point (MCID) change of EORTC QLQ-C30 GHS from baseline) (Burris et al, 2013) (follow up: median 17.7 months; assessed with: Kaplan-Meier estimate; HR)												
1	randomised trials	serious [4]	not serious	very serious [1]	serious [2]	none	202/485 (41.6%)	84/239 (35.1%)	**HR 0.80** (0.61 to 1.06)	6 fewer per 100 (from 2 more to 12 fewer)	⊕○○○ VERY LOW	

1. only 19% of Bolero-2 patients entered the trial having received (neo) adjuvant therapy as their last systemic treatment
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4. attrition bias (unbalanced missing questionnaires)

OUTCOMES OF BENEFIT

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Everolimus+ Exemestane	Exemestane	Relative (95% CI)	Absolute (95% CI)		
Progressive disease in bone (Gnant et al, 2013) (follow up: median 17.7 months; assessed with: Kaplan-Meier estimate; HR)												
1	randomised trials	very serious [3]	not serious	very serious [1]	not serious	none	60/371 (16.2%)	43/185 (23.2%)	**HR 0.43** (0.35 to 0.53)	12 fewer per 100 (from 10 fewer to 14 fewer)	⊕○○○ VERY LOW	
Overall Response Rate (local assessment) (Yardley et al, 2013) (assessed with: 2x2 frequency table; RR)												
1	randomised trials	not serious	not serious	very serious [1]	serious [2]	none	61/485 (12.6%)	4/239 (1.7%)	**RR 7.51** (2.76 to 20.42)	11 more per 100 (from 3 more to 33 more)	⊕○○○ VERY LOW	
Overall Response Rate (central assessment) (Yardley et al, 2013) (assessed with: 2x2 frequency table; RR)												
1	randomised trials	not serious	not serious	very serious [1]	serious [2]	none	61/485 (12.6%)	5/239 (2.1%)	**RR 6.01** (2.45 to 14.76)	10 more per 100 (from 3 more to 29 more)	⊕○○○ VERY LOW	
Time to QoL deterioration (5% change of EORTC QLQ-C30 GHS from baseline) (Burris et al, 2013) (follow up: median 17.7 months; assessed with: Kaplan-Meier estimate; HR)												
1	randomised trials	serious [4]	not serious	very serious [1]	not serious	none	254/485 (52.4%)	113/239 (47.3%)	**HR 0.74** (0.58 to 0.95)	10 fewer per 100 (from 2 fewer to 16 fewer)	⊕○○○ VERY LOW	
Time to QoL deterioration (0-point (MCID) change of EORTC QLQ-C30 GHS from baseline) (Burris et al, 2013) (follow up: median 17.7 months; assessed with: Kaplan-Meier estimate; HR)												
1	randomised trials	serious [4]	not serious	very serious [1]	serious [2]	none	202/485 (41.6%)	84/239 (35.1%)	**HR 0.80** (0.61 to 1.06)	6 fewer per 100 (from 2 more to 12 fewer)	⊕○○○ VERY LOW	

1. only 19% of Bolero-2 patients entered the trial having received (neo) adjuvant therapy as their last systemic treatment
2. 95% confidence limits consistent with conflicting recommendations
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4. attrition bias (unbalanced missing questionnaires)

OUTCOMES OF HARM

Author(s):
Date: 04.08.2015
Question: Everolimus+ Exemestane compared to Exemestane for 1st line metastatic disease
Setting: HR-pos, HER2-neg, advanced breast cancer
Bibliography (systematic reviews): Piccart M et al, Ann Oncol 2014; Yardley D, et al, Adv Ther 2013; Beck JT et al, Breast Cancer Res Treat 2013; Burris HA et al, Cancer 2013; Gnant M et al, JNCI 2013; Rugo H et al, Ann Oncol 2014

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Everolimus+ Exemestane	Exemestane	Relative (95% CI)	Absolute (95% CI)		
Adverse events leading to treatment discontinuation (Piccart et al, 2014) (assessed with: 2x2 frequency table; RR)												
1	randomised trials	not serious	not serious	very serious [1]	not serious	none	140/482 (29.0%)	12/238 (5.0%)	**RR 5.76** (3.26 to 10.17)	24 more per 100 (from 11 more to 46 more)	⊕⊕◯◯ LOW	
Stomatitis G3-G4 (Rugo et al, 2014) (assessed with: 2x2 frequency table; RR)												
1	randomised trials	not serious	not serious	very serious [1]	serious [2]	none	39/443 (8.8%)	2/236 (0.8%)	**RR 9.63** (2.34 to 39.54)	7 more per 100 (from 1 more to 33 more)	⊕◯◯◯ VERY LOW	
Fatigue G3-G4 (Rugo et al, 2014) (assessed with: 2x2 frequency table; RR)												
1	randomised trials	not serious	not serious	very serious [1]	not serious	none	32/450 (7.1%)	4/234 (1.7%)	**RR 3.95** (1.41 to 11.04)	5 more per 100 (from 1 more to 17 more)	⊕⊕◯◯ LOW	
Non infectious pneumonitis G3-G4 (Rugo et al, 2014) (assessed with: 2x2 frequency table; RR)												
1	randomised trials	not serious	not serious	very serious [1]	not serious	none	20/462 (4.3%)	0/-	not estimable	not estimable	⊕⊕◯◯ LOW	
Hyperglicaemia G3-G4 and new onset of DM (Rugo et al, 2014) (assessed with: 2x2 frequency table; RR)												
1	randomised trials	not serious	not serious	very serious [1]	not serious	none	28/454 (6.2%)	2/236 (0.8%)	**RR 6.92** (1.66 to 28.78)	5 more per 100 (from 1 more to 24 more)	⊕⊕◯◯ LOW	

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2. 95% confidence limits consistent with conflicting recommendations

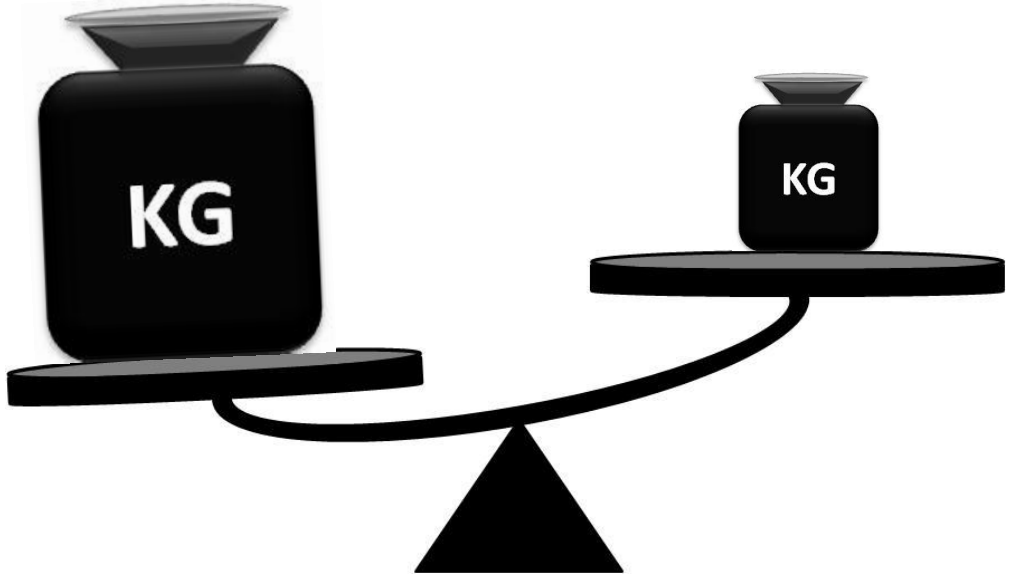

PFS
(central and local assessment)
QUALITY: LOW
Quality of Life
(- 5% and -10 points)
QUALITY: VERY LOW
Adverse Events
leading to treatment discontinuation
QUALITY: LOW
Stomatitis
grade 3-4
QUALITY: VERY LOW
Fatigue
grade 3-4
QUALITY: LOW
Non-infectious pneumonitis
grade 3-4
QUALITY: LOW

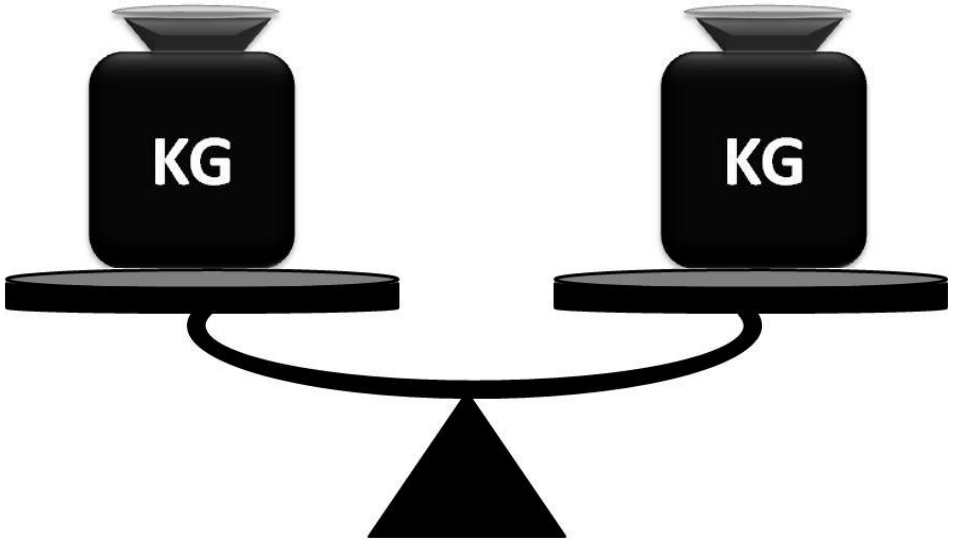
Bilancio tra benefici e danni e direzione della raccomandazione

La direzione a favore o contro l'uso del trattamento si dovrebbe basare sul bilancio tra gli effetti positivi (benefici) e negativi (effetti dannosi) dell'intervento.

In linea di principio, se gli **effetti positivi** vengono considerati **prevalenti rispetto a quelli negativi**, la **raccomandazione dovrebbe essere a favore** dell'intervento, viceversa dovrebbe essere contro.

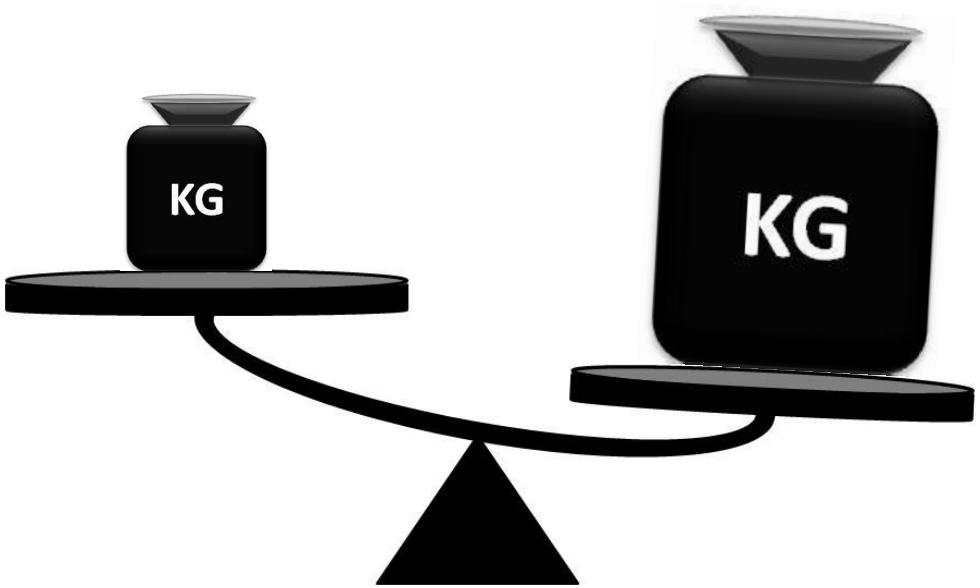
Chiaro beneficio





Nessun beneficio
né danno

Chiaro danno



Bilancio tra benefici e danni e forza della raccomandazione

- La forza della raccomandazione riflette la **misura in cui si ritiene che gli effetti benefici derivanti dal seguire la raccomandazione superino gli effetti indesiderabili** (o viceversa per raccomandazioni negative).

Bilancio tra benefici e danni e forza della raccomandazione

- La forza della raccomandazione riflette la **misura in cui si ritiene che gli effetti benefici derivanti dal seguire la raccomandazione superino gli effetti indesiderabili** (o viceversa per raccomandazioni negative).
- **4 categorie mutualmente esclusive**:
  - **FORTE o DEBOLE,**
  - **a FAVORE o CONTRO** uno specifico intervento

Forza / direzione delle raccomandazioni

GRADE

Grado	Definizione
FORTE a favore	definisce il trattamento in esame come opzione terapeutica di prima scelta (per rapporto beneficio/rischio favorevole)
DEBOLE a favore	indica la possibilità di considerare come prima opzione la strategia terapeutica analizzata, consapevoli però di avere a disposizione alternative che a seconda dei casi potrebbero offrire analoghi o più idonei benefici
DEBOLE a sfavore	non esclude il trattamento in oggetto, ma ne limita con forza l'utilizzo in casi selezionati, comportamento clinico che deve essere accompagnato da un'informazione approfondita data al paziente per coinvolgerlo consapevolmente nel percorso terapeutico
FORTE a sfavore	definisce il trattamento in esame come opzione terapeutica da evitare (causa rapporto beneficio/rischio sfavorevole o assenza di evidenze sperimentali)

Quesito: nelle pazienti in postmenopausa con carcinoma mammario HR+/HER2- in assenza di malattia viscerale sintomatica, con recidiva di malattia durante o entro 1 anno dal termine del trattamento adiuvante includente un antiaromatasico non steroideo, il trattamento con exemestane + everolimus è raccomandabile rispetto al solo exemestane?

Raccomandazione ?