Cancers du sein HER2 neg, RH pos

référentiels en phase métastatique

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The Breast

journal homepage: www.elsevier.com/brst

Original article

1st International consensus guidelines for advanced breast cancer (ABC 1)

F. Cardoso [a,*], A. Costa [b], L. Norton [c], D. Cameron [d], T. Cufer [e], L. Fallowfield [f], P. Francis [g], J. Gligorov [h], S. Kyriakides [i], N. Lin [j], O. Pagani [k], E. Senkus [l], C. Thomssen [m], M. Aapro [n], J. Bergh [o], A. Di Leo [p], N. El Saghir [q], P.A. Ganz [r], K. Gelmon [s], A. Goldhirsch [t], N. Harbeck [u], N. Houssami [v], C. Hudis [w], B. Kaufman [x], M. Leadbeater [y], M. Mayer [z], A. Rodger [aa], H. Rugo [bb], V. Sacchini [cc], G. Sledge [dd], L. van't Veer [ee], G. Viale [ff], I. Krop [gg], E. Winer [gg]

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Chemotherapy and Targeted Therapy for Women With Human Epidermal Growth Factor Receptor 2–Negative (or unknown) Advanced Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Ann H. Partridge, R. Bryan Rumble, Lisa A. Carey, Steven E. Come, Nancy E. Davidson, Angelo Di Leo, Julie Gralow, Gabriel N. Hortobagyi, Beverly Moy, Douglas Yee, Shelley B. Brundage, Michael A. Danso, Maggie Wilcox, and Ian E. Smith

Published online ahead of print at www.jco.org on September 2, 2014.

6èmes

Recommandations pour la Pratique Clinique

J Gligorov, M Piccart, M Namer

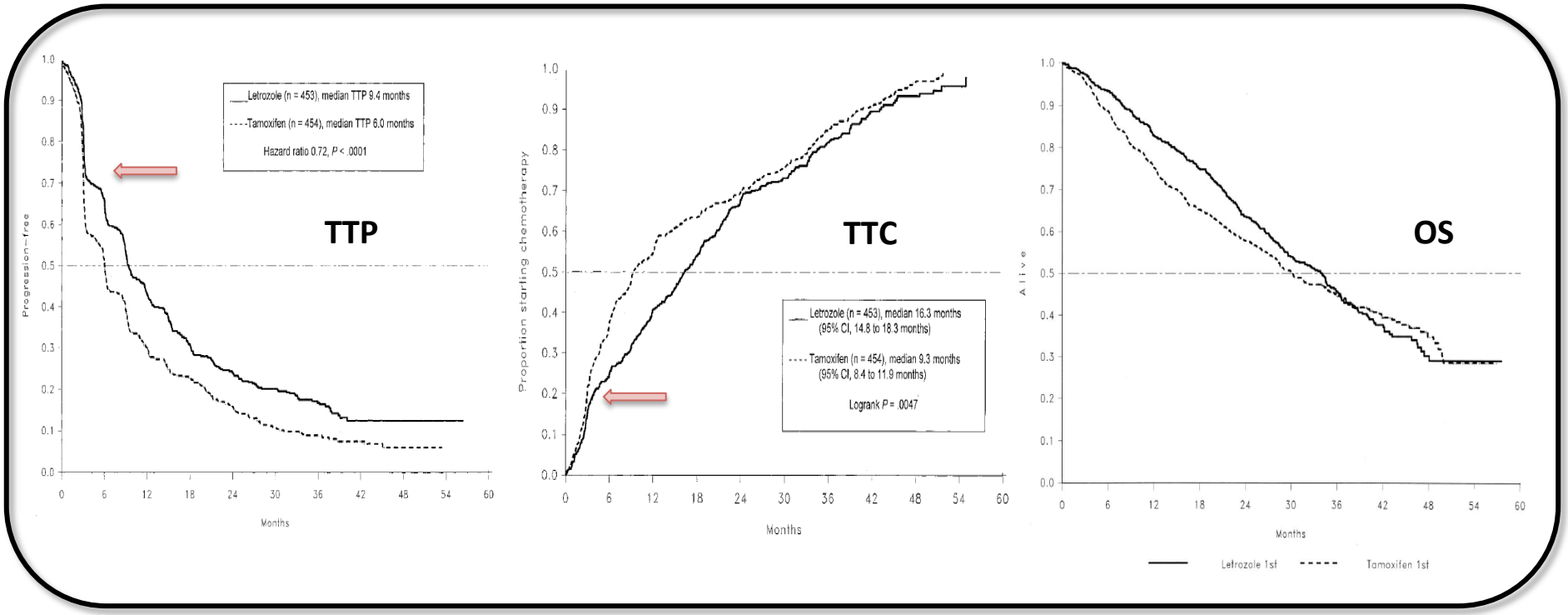
CHOIX STRATÉGIQUES DANS LA POPULATION RH+

Recommandation 1:
Traitement antihormonal d'abord chez les RH+

1. Endocrine therapy, rather than chemotherapy, should be offered as the standard first-line treatment for patients with hormone receptor–positive advanced/metastatic breast cancer, except for immediately life threatening disease or if there is concern regarding endocrine resistance.
   A. The main benefit is less toxicity and better quality of life for the patient associated with endocrine therapy compared with chemotherapy (potential benefit: high). The harm is that metastatic disease could progress rapidly and prove fatal if there is no response, but the risk of this is low (potential harm: low).
   B. The quality of the evidence is intermediate, and is based on the NCCC systematic review.
   C. The strength of this recommendation is strong and is supported by the evidence and expert consensus.

- *Qualifying statement: It should be noted that the basis for this recommendation is the relative likelihood of response to chemotherapy versus endocrine therapy and not the rapidity of response, for which there are no good data*

Letrozole vs Tamoxifen



Mouridsen et al. JCO 2003

ER POSITIVE / HER-2 NEGATIVE MBC

The preferred 1st line ET for postmenopausal patients is an aromatase inhibitor or tamoxifen, depending on type and duration of adjuvant ET. (LoE: 1 A)

Fulvestrant HD is also an alternative option. (LoE: 1 B)

AI + everolimus is also an option after progression on a non-steroidal AI. (LoE: 1 B)

Total number of votes: 36

1. **YES: 83,3% (30)**
2. **NO: 0%**
3. **ABSTAIN: 16,6% (6)**

VISCERAL CRISIS is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.

Visceral crisis is not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.

(LoE: Expert opinion).

Total number of votes: 40

1. **YES: 95,0% (38)**
2. **NO: 0%**
3. **ABSTAIN: 5,0% (2)**

PRIMARY ENDOCRINE RESISTANCE is defined as:

Relapse while on the first 2 years of adjuvant ET

PD within first 6 ms of initiating 1st line ET for MBC, while on ET

SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE is defined as:

Relapse while on adjuvant ET but after the first 2 years

Relapse within 12 months of completing adjuvant ET

PD ≥ 6 months after initiating ET for MBC, while on ET

(LoE: Expert opinion)

Total number of votes: 33

1. **YES: 66,6% (22)**
2. **NO: 12,1% (4)**
3. **ABSTAIN: 21,2% (7)**

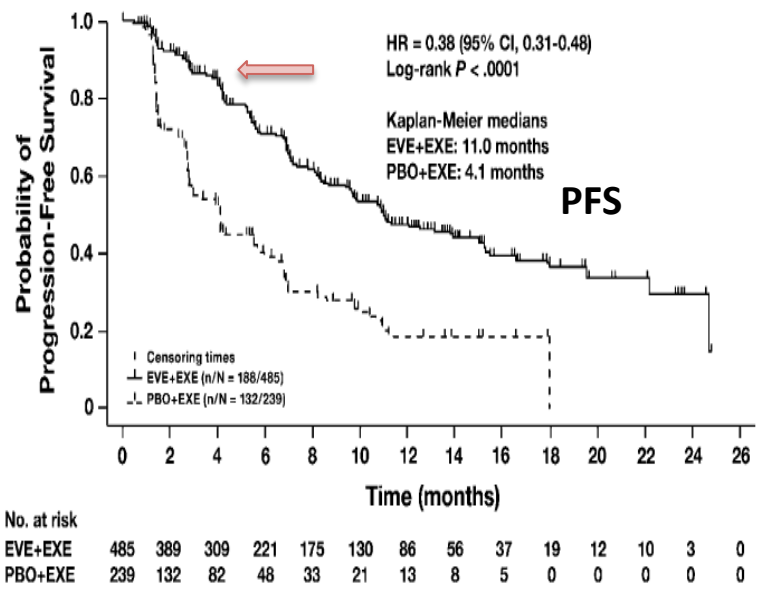
The addition of everolimus to an AI is a valid option for some post-menopausal patients with disease progression after a non-steroidal AI, since it provides a significant benefit in PFS (about 5 months). However, data on OS are still awaited and decision must balance the increased toxicity associated. (LoE: 1 B)

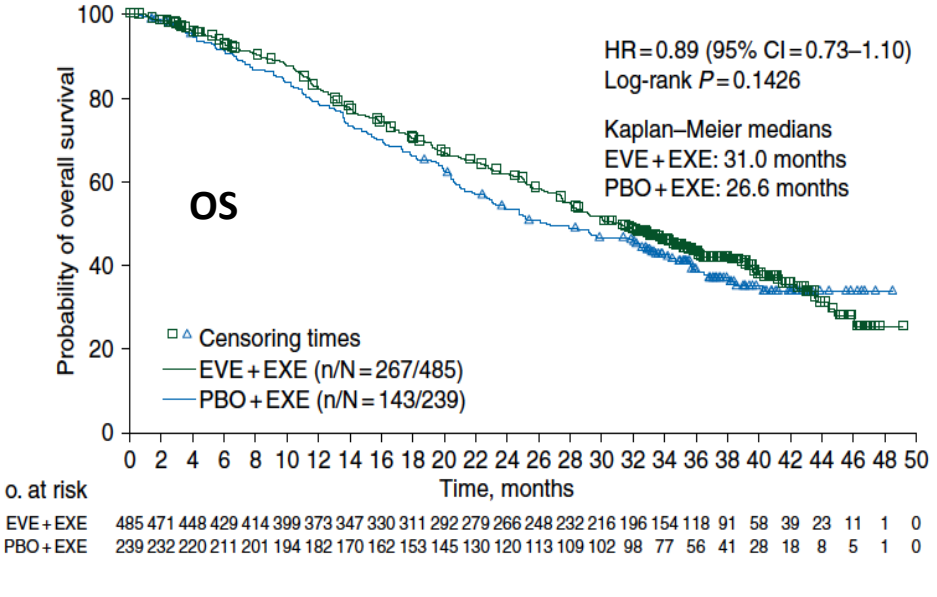
At present, no predictive biomarker exists to identify those patients who benefit from this approach.

Total number of votes: 40

1. **YES: 90,0% (36)**
2. **NO: 2,5% (1)**
3. **ABSTAIN: 7,5% (3)**

Exemestane vs Exemestane + Everolimus





Poststudy Treatment Anticancer Therapies

Therapy Type	Everolimus + Exemestane (n = 485), %	Placebo + Exemestane (n = 239), %
Any posttreatment therapy	84	90
Chemotherapy	53	63
Hormonal therapy	47	44
Targeted therapy	10	11
Radiation therapy	9	11
Surgery	1	1
Immunotherapy	<1	0
Other	2	1
Chemotherapy	53	63
Taxane	28	36
Capecitabine	24	28
Anthracyclines	13	15
Cyclophosphamide	9	9
Vinorelbine	7	13
Platinum-based regimens	4	2
Gemcitabine	4	5

10% more patients in placebo arm received chemotherapy compared with the everolimus arm.

Yardley et al. BCRT 2013
Piccart et al. Ann Oncol 2014

Nice St Paul de Vence 2015

Cancers du sein
Cancers de l'ovaire
Soins de support

Prise en charge des cancers du sein RH+

14. Un traitement anti-hormonal doit toujours être le premier choix thérapeutique en cas de rechute métastatique d'un cancer du sein RE+ ; Her2- en l'absence de crise viscérale. (accord d'experts)

	Jury	Salle
1. Oui, je suis d'accord avec la proposition	64%	88%
2. Non, je ne suis pas d'accord avec la proposition	33%	12%
3. Je m'abstiens	3%	0%

Nice St Paul de Vence 2015
Cancers du sein
Cancers de l'ovaire
Soins de support

Prise en charge des cancers du sein RH+

15. En cas d'hormono-résistance secondaire à 1 traitement par IA, l'association de everolimus à une hormonothérapie est une option valide. (niveau 1B)

	Jury	Salle
1. Oui, je suis d'accord avec la proposition	92%	100%
2. Non, je ne suis pas d'accord avec la proposition	4%	0%
3. Je m'abstiens	4%	0%

Conclusions 2

- Le traitement antihormonal reste le choix initial privilégier en situation métastatique chez les patientes RH + mais:
  - Il est essentiel de définir une population qui doit bénéficier d'une chimiothérapie première
  - Il est important de considérer que la définition de la résistance aux traitements antihormonaux est une définition de consensus et non biologique
  - Que l'association everolimus-exemestane est le choix préférentiel à ce jour après une résistance aux IA non stéroidiens
  - Mais que la « sous-exposition » à une chimiothérapie peut éventuellement impacter la survie globale

CHOIX DU TRAITEMENT DE CHIMIOTHÉRAPIE

Recommandation 2:
préférer la chimiothérapie séquentielle à la polychimiothérapie concomittante

2. Sequential single-agent chemotherapy rather than combination therapy should be offered, although combination regimens may be considered for immediately life-threatening disease for which time may allow only one potential chance for therapy.
   A. The benefit is less toxicity and better quality of life (potential benefit: high). The potential harm is for rapidly progressing, life-threatening disease to escape control if response to a single agent isn't achieved (potential harm: high). The main benefit is there is less toxicity and better quality of life for the patient associated with sequential single agent chemotherapy compared with combination chemotherapy (potential benefit: high). The harm is that metastatic disease could progress rapidly if there is no response, but the risk of this is low (potential harm: low).
   B. The evidence quality is high, and includes a large RCT.
   C. The strength of this recommendation is strong.

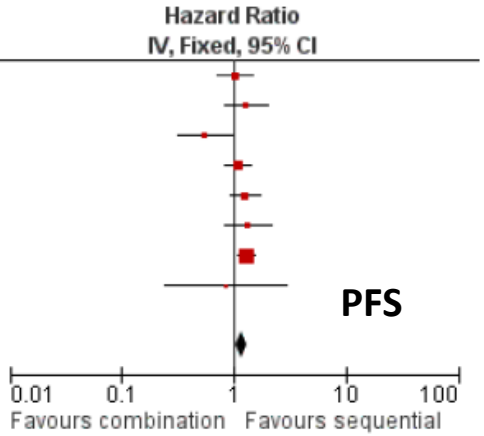
Both combination and sequential single agent CT are reasonable options. Based on the available data, we recommend sequential monotherapy as the preferred choice for MBC. Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control (LoE: 1 B).

Total number of votes: 26

1. **YES: 96% (25)**
2. **NO: 0%**
3. **ABSTAIN: 4% (1)**

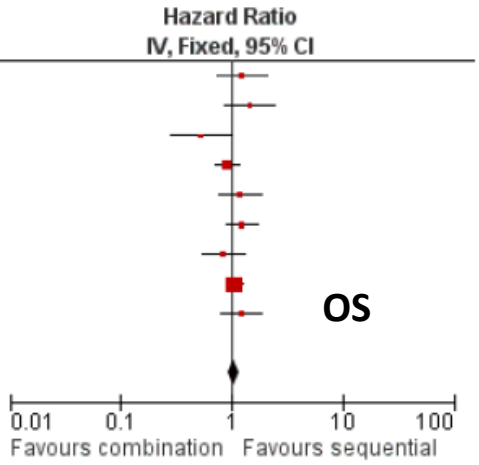
Study or Subgroup	log[Hazard Ratio]	SE	Combination Total	Sequential Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Alba 2004	0.0296	0.1827	69	75	10.7%	1.03 [0.72, 1.47]
Baker 1974	0.239	0.2295	46	30	6.8%	1.27 [0.81, 1.99]
Beslija 2006	-0.6033	0.2865	50	50	4.3%	0.55 [0.31, 0.96]
Conte 2004	0.0862	0.139	106	92	18.5%	1.09 [0.83, 1.43]
Fountzilas 2001	0.2151	0.1579	90	93	14.3%	1.24 [0.91, 1.69]
Park 2010	0.2776	0.2429	41	40	6.0%	1.32 [0.82, 2.12]
Sledge 2003	0.2469	0.0962	230	453	38.5%	1.28 [1.06, 1.55]
Tomova 2010	-0.1625	0.6415	46	53	0.9%	0.85 [0.24, 2.99]
Total (95% CI)			**678**	**886**	**100.0%**	**1.16 [1.03, 1.31]**

Heterogeneity: Chi² = 9.41, df = 7 (P = 0.22); I² = 26%
Test for overall effect: Z = 2.52 (P = 0.01)



Study or Subgroup	log[Hazard Ratio]	SE	Combination Total	Sequential Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Alba 2004	0.2151	0.2634	69	75	4.5%	1.24 [0.74, 2.08]
Baker 1974	0.3716	0.2606	46	30	4.6%	1.45 [0.87, 2.42]
Beslija 2006	-0.6387	0.3182	50	50	3.1%	0.53 [0.28, 0.99]
Chlebowski 1989	-0.1054	0.1282	129	93	19.2%	0.90 [0.70, 1.16]
Conte 2004	0.174	0.2355	106	92	5.7%	1.19 [0.75, 1.89]
Fountzilas 2001	0.1989	0.1667	90	93	11.3%	1.22 [0.88, 1.69]
Park 2010	-0.1744	0.235	41	40	5.7%	0.84 [0.53, 1.33]
Sledge 2003	0.0488	0.0901	230	453	38.8%	1.05 [0.88, 1.25]
Tomova 2010	0.1989	0.211	46	53	7.1%	1.22 [0.81, 1.84]
Total (95% CI)			**807**	**979**	**100.0%**	**1.04 [0.93, 1.16]**

Heterogeneity: Chi² = 10.54, df = 8 (P = 0.23); I² = 24%
Test for overall effect: Z = 0.76 (P = 0.45)



Dear et al. Cochrane Review 2013

Place du bévacizumab

3. With regard to targeted agents, the role of bevacizumab is controversial, and this therapy should be considered (where available) with single-agent chemotherapy only when there is immediately life-threatening disease or severe symptoms, in view of improved response rates (similar to Recommendation 2 regarding the use of combination chemotherapy). It is recognized that there is not currently an approved indication for bevacizumab in the United States because the weight of evidence shows no significant survival benefit. Other targeted agents should not be used either in addition to, or as a replacement for, chemotherapy in this setting outside of a trial
   A. The benefit is improved disease control (potential benefit: moderate). The potential harms are unique toxicity, increased costs, and barriers to access (potential harm: high)
   B. The quality of the evidence is high and Is supported by multiple trials.
   C. The strength of the recommendation Is moderate and is based on both evidence and expert consensus.

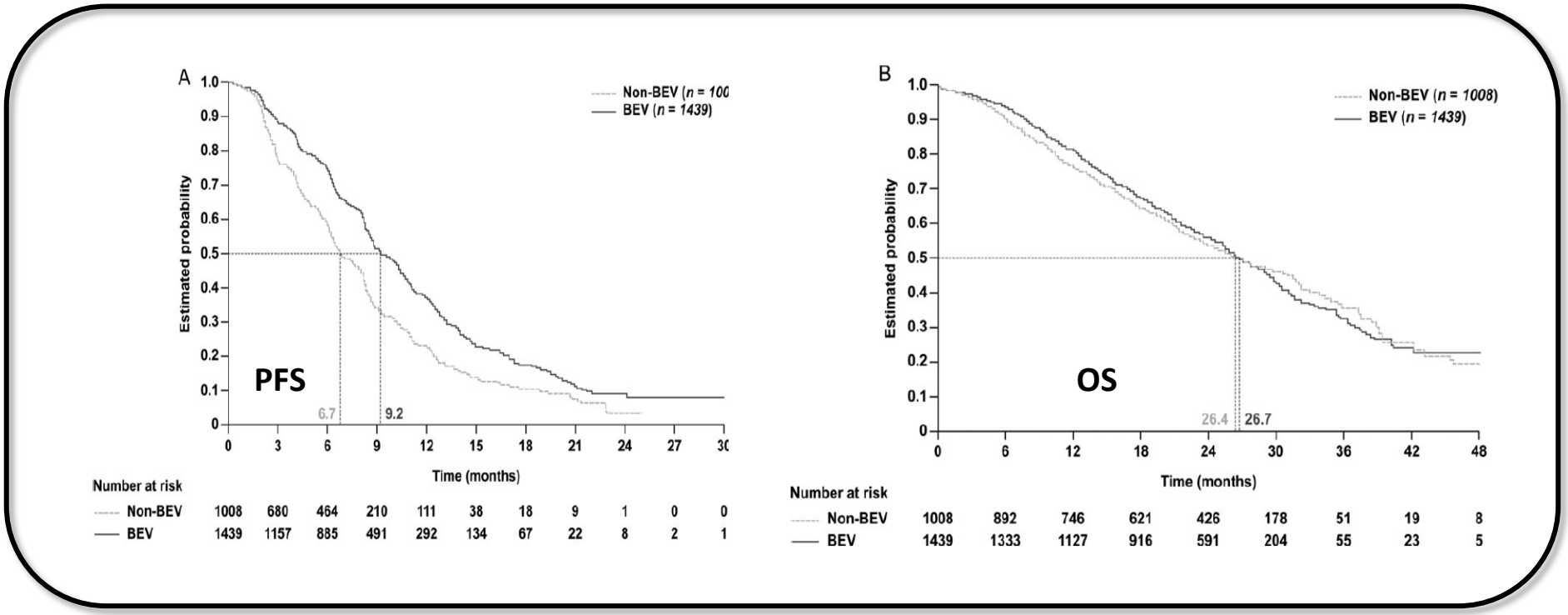
- *Qualifying statement: Bevacizumab added to single-agent chemotherapy improves response and progression-free survival but not overall survival*

Bevacizumab combined with a chemotherapy as 1st or 2nd line therapy for MBC provides only a moderate benefit in PFS and no benefit in OS. The absence of known predictive factors for bevacizumab efficacy renders recommendations on its use difficult. Bevacizumab can only therefore be considered as an option in selected cases in these settings and is not recommended after 1st/2nd line.

(LoE: 1 A).

Total number of votes: 23

1. **YES: 74% (17)**
2. **NO: 9% (2)**
3. **ABSTAIN: 17% (4)**



Miles et al. Ann Oncol 2013

Quelle chimiothérapie ?

4. No single agent has demonstrated superiority in the treatment of patients with advanced breast cancer, and there are several active agents appropriate for first-line chemotherapy. The evidence for efficacy is strongest for taxanes and anthracyclines. Other options include capecitabine, gemcitabine, platinum-based compounds, vinorelbine, and ixabepilone. Treatment selection should be based on previous therapy, differential toxicity, comorbid conditions, and patient preferences. Specifically, drugs for which clinical resistance has already been shown should not be reused
   A. The benefit is a patient-tailored approach with potential improvements in disease control and quality of life (potential benefit: high). The harm is the potential use of a less active agent (potential harm: low)
   B. The evidence quality supporting the activity of a number of single agents is high, but there is insufficient evidence to support superiority of any single agent.
   C. The strength of the recommendation is strong and is based on the available evidence and expert consensus

7. Second- and later-line therapy may be of clinical benefit and should be offered as determined by previous treatments, toxicity, coexisting medical conditions, and patient choice. As with first-line treatment, no clear evidence exists for the superiority of one specific drug or regimen. Active agents include those active in first-line treatment.
   A. The benefit is further chance of disease control and symptomatic improvement (potential benefit: high). The harm is toxicity (potential harm: high).
   B. The quality of the evidence ranges from high to low as reported in multiple randomized trials.
   C. The strength of the recommendation is strong and is based on expert consensus

- *Qualifying statement: The most convincing data are for eribulin based on survival superiority against best standard treatment in a recent large RCT, but there is a lack of good comparative data between these various agents.*

HER-2 NEGATIVE MBC

In patients pre-treated (in the adjuvant or metastatic setting) with anthracycline and taxanes and who do not need combination CT, capecitabine, vinorelbine or eribulin single agent are the preferred choices. Additional choices include gemcitabine, platinum, a taxane, liposomal anthracyclines.
Decision should be individualized and take into account different toxicity profile, previous exposure, patient preferences.
(LoE: 1 B)

Total number of votes: 35

1. **YES: 77,1% (27)**
2. **NO: 2,8% (1)**
3. **ABSTAIN: 20,0% (7)**

To include in manuscript: table with best options for 1st line, 2nd line, and beyond; mention that eribulin gives survival benefit in heavily pretreated pts

Conclusions 3

- Le choix de la chimiothérapie en première ligne métastatique reste « ouvert » entre anthracyclines/taxanes +/- bevacizumab

- Le choix après anthracyclines et taxanes se défini de façon plus claire avec deux options au moins équivalentes
  - Eribuline
  - Capecitabine

Doit-on adapter la chimiothérapie au profil biologique de la tumeur ?

6. Chemotherapy regimens should not be specifically tailored to different breast cancer subtypes (eg, triple negative, lobular) at the present time due to the absence of evidence proving differential efficacies. In addition, in vitro chemoresistance assays should not be used to select treatment
   A. The benefits are not omitting potentially efficacious treatment and cost-saving on in vitro assays (potential benefit: high)
   B. Current evidence shows no convincing basis for either of these approaches
   C. The strength of this recommendation is moderate, and is supported by expert consensus

BRCA-associated MBC

In patients with BRCA-associated triple negative or endocrine resistant MBC pre-treated with anthracycline and taxanes (in the adjuvant or metastatic setting) treatment with a platinum regimen may be considered, outside of a clinical trial. (LoE: 1 C)

All other treatment recommendations are similar to sporadic MBC.

Total number of votes: 40

1. **YES: 82,5% (33)**
2. **NO: 5% (2)**
3. **ABSTAIN: 12,5% (5)**

To include in manuscript: PARP inhibitors have shown significant activity in BRCA mutated tumors, in clinical trials.

Conclusions 4

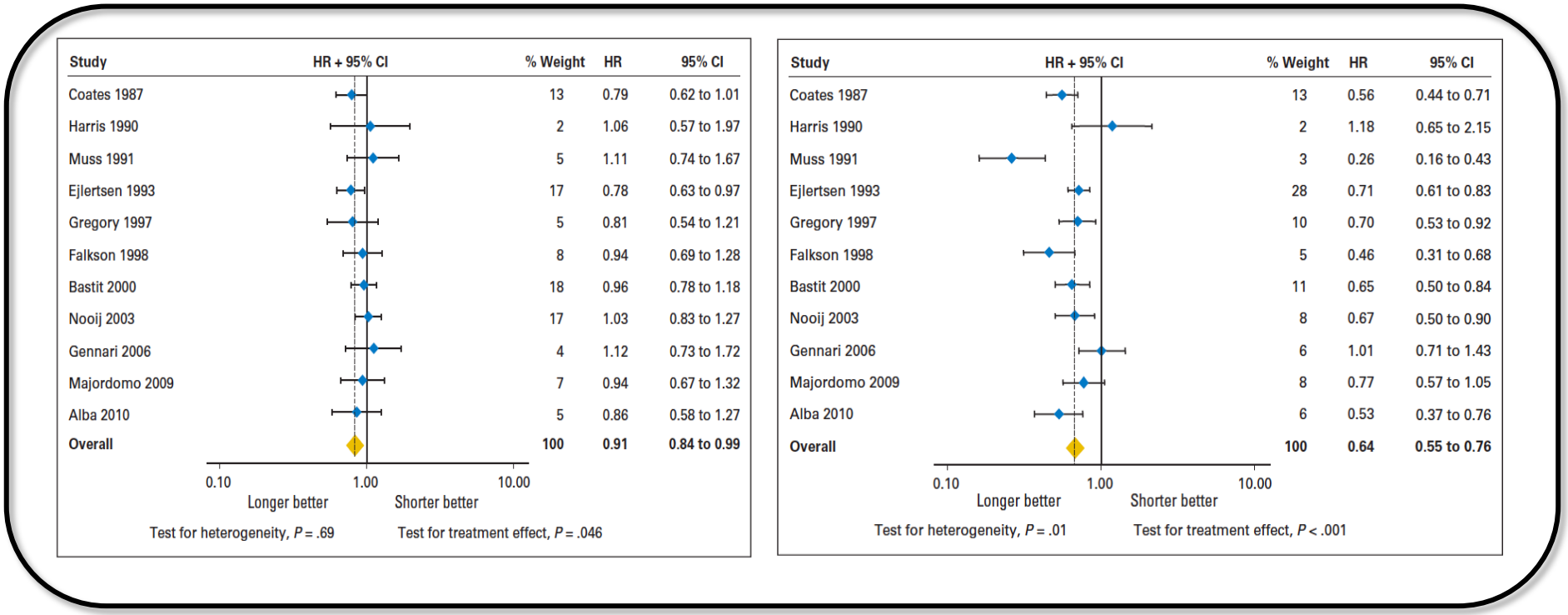
- En dehors de la population HER2 positive et de la population BRCA mutée, le choix de la chimiothérapie doit être orienté par le niveau de preuve des résultats cliniques

- La place des sels de platine reste à ce jour limitée en situation précoce aux populations BRCA mutée et non triples négatives en général

Quelle place pour la maintenance ?

5. Chemotherapy should be continued until progression of disease as tolerated because it modestly improves overall survival and substantially improves progression-free survival, but this has to be balanced against toxicity and quality of life. Short breaks, flexibility in scheduling, or a switch to endocrine therapy (in patients with hormone receptor–positive disease) may be offered to selected patients.
   A. The benefits are more time before disease-progression and modestly improved survival (potential benefit: high). The harm is more prolonged toxicity (potential harm: moderate).
   B. The evidence quality is high, and is based on a systematic review with meta-analysis.
   C. The strength of the recommendation is strong, and is supported by evidence and expert consensus.

- *Qualifying statement: It is recognized that the balance between continuing treatment to maintain disease control and coping with progressive AEs and/or toxicity is a difficult one. It will be influenced by many factors, including drug used (eg, long-term use of capecitabine is relatively easy, whereas docetaxel is severely limited by cumulative toxicity) and requires a continuing dialogue between doctor and patient.*



Gennariiet al. JCO 2011

ER POSITIVE MBC

Endocrine treatment after CT (maintenance ET) to maintain benefit is a reasonable option, though it has not been assessed in randomized trials (LoE: 1 C).

Total number of votes: 32

1. **YES: 88% (28)**
2. **NO: 3% (1)**
3. **ABSTAIN: 9% (3)**

Conclusions 5

- Le traitement de maintenance antihormonal est plus une habitude qu'un niveau de preuve démontré

- De nouvelles données viennent ouvrir des perspectives stratégiques avec des schémas de type « switch-maintenance »

En conclusion

- Recommandations ESO-ASCO proches avec quelques nuances
- Populations HER2 positives et probablement BRCA mutées dans l'avenir faisant l'objet de prises en charge spécifiques
- Choix stratégiques initiaux entre traitement antihormonal et chimiothérapie non encore élucidé mais attention à la « sous-exposition » à la chimiothérapie (STIC CTC)
- Indication d'une association d'un traitement antihormonal associé à un modulateur biologique en cas de progression sous IA non stéroidiens (everolimus)
- Anthracyclines ou taxanes +/- bevacizumab reste les traitements de référence en initiation (en l'absence de contre-indication
- Eribuline et capécitabine sont le choix stratégique après anthracyclines et taxanes

MERCI