GRANDANGOLO IN RADIOTERAPIA ONCOLOGICA

8 Novembre 2014

NEOPLASIA MAMMARIA

Icro Meattini

Radioterapia Oncologica
Azienda Ospedaliero-Universitaria Careggi Firenze

OVERVIEW

Surgical margins

Sentinel lymph node(s)

Nodal regions radiotherapy

Partial Breast Irradiation

Endocrine therapy

Target therapy

OVERVIEW

Surgical margins

Sentinel lymph node(s)

Nodal regions radiotherapy

Partial Breast Irradiation

Endocrine therapy

Target therapy

ADJUVANT BREAST CANCER
Final Surgical Margins

The SSO/ASTRO guideline concluded that the use of **no ink on tumor** *(ie, no cancer cells adjacent to any inked edge/surface of the specimen)* as the **standard for an adequate margin in invasive cancer** in the era of multidisciplinary therapy is associated with low rates of ipsilateral breast tumor recurrence and has the potential to **decrease re-excision rates**, **improve cosmetic outcomes**, and **decrease health care costs**

Buchholz TA, JCO, 2014

Final Surgical Margins

Table 1. Summary of SSO/ASTRO Clinical Practice Guideline Recommendations

Clinical Question	Recommendation	Level of Evidence
What is the absolute increase in risk of IBTR with a positive margin? Can the use of radiation boost, systemic therapy, or favorable tumor biology mitigate this increased risk?	A positive margin, defined as ink on invasive cancer or DCIS, is associated with at least a two-fold increase in IBTR; this increased risk in IBTR is not nullified by delivery of a boost, delivery of systemic therapy (endocrine, chemotherapy, biologic therapy), or favorable biology	Meta-analysis, secondary data from prospective trials and retrospective studies
Do margin widths wider than no ink on tumor cells reduce the risk of IBTR?	Negative margins (no ink on tumor) optimize IBTR; wider margin widths do not significantly lower this risk; the routine practice to obtain wider negative margin widths than ink on tumor is not indicated	Meta-analysis, retrospective studies
What are the effects of endocrine or biologically targeted or systemic chemotherapy on IBTR? Should a patient who is not receiving any systemic treatment have wider margin widths?	Rates of IBTR are reduced with the use of systemic therapy; in the uncommon circumstance of a patient not receiving adjuvant systemic therapy, there is no evidence suggesting that margins wider than no ink on tumor are needed	Multiple randomized trials, meta-analysis
Should unfavorable biologic subtypes (such as triple-negative breast cancers) require wider margins (than no ink on tumor)?	Margins wider than no ink on tumor are not indicated based on biologic subtype	Multiple retrospective studies
Should margin width be taken into consideration when determining WBRT delivery techniques?	Choice of WBRT delivery technique, fractionation, and boost dose should not be dependent on the margin width	Retrospective studies
Is the presence of LCIS at the margin an indication for re-excision? Do invasive lobular carcinomas require a wider margin (than no ink on tumor)? What is the significance of pleomorphic LCIS at the margin?	Wider negative margins than no ink on tumor are not indicated for invasive lobular cancer; classic LCIS at the margin is not an indication for re-excision; significance of pleomorphic LCIS at the margin is uncertain	Retrospective studies
Should increased margin widths (wider than no ink on tumor) be considered for patients of young age (< 40 years)?	Young age (≤ 40 years) is associated with both increased IBTR after BCT as well as increased local relapse on the chest wall after mastectomy and is also more frequently associated with adverse biologic and pathologic features; there is no evidence that increased margin width nullifies the increased risk of IBTR in young patients	Secondary data from prospective randomized trials and retrospective studies
What is the significance of an EIC in the tumor specimen, and how does this pertain to margin width?	EIC identifies cases that may have a large residual DCIS burden after lumpectomy; there is no evidence of an association between increased risk of IBTR when margins are negative	Retrospective studies

Abbreviations: ASTRO, American Society for Radiation Oncology; BCT, breast-conserving therapy; DCIS, ductal carcinoma in situ; EIC, extensive intraductal component; IBTR, ipsilateral breast tumor recurrence; LCIS, lobular carcinoma in situ; SSO, Society of Surgical Oncology; WBRT, whole-breast radiation therapy.

Buchholz TA, JCO, 2014

Final Surgical Margins

Table 1. Summary of SSO/ASTRO Clinical Practice Guideline Recommendations

Clinical Question	Recommendation	Level of Evidence
What is the absolute increase in risk of IBTR	A positive margin, defined as ink on invasive cancer or DCIS, R; this boost, py.	Meta-analysis, secondary data from prospective trials and retrospective studies
D	der e ths	Meta-analysis, retrospective studies
W systemic treatment have wider margin widths?	erapy; iving gesting that margins wider than no ink on tumor are needed	Multiple randomized trials, meta-analysis
S	based	Multiple retrospective studies
S	boost	Retrospective studies
Is	the ce of	Retrospective studies
S	sed the ently ures; lifies	Secondary data from prospective randomized trials and retrospective studies
W specimen, and how does this pertain to margin width?	S burden after lumpectomy; there is no evidence of an association between increased risk of IBTR when margins are negative	Retrospective studies

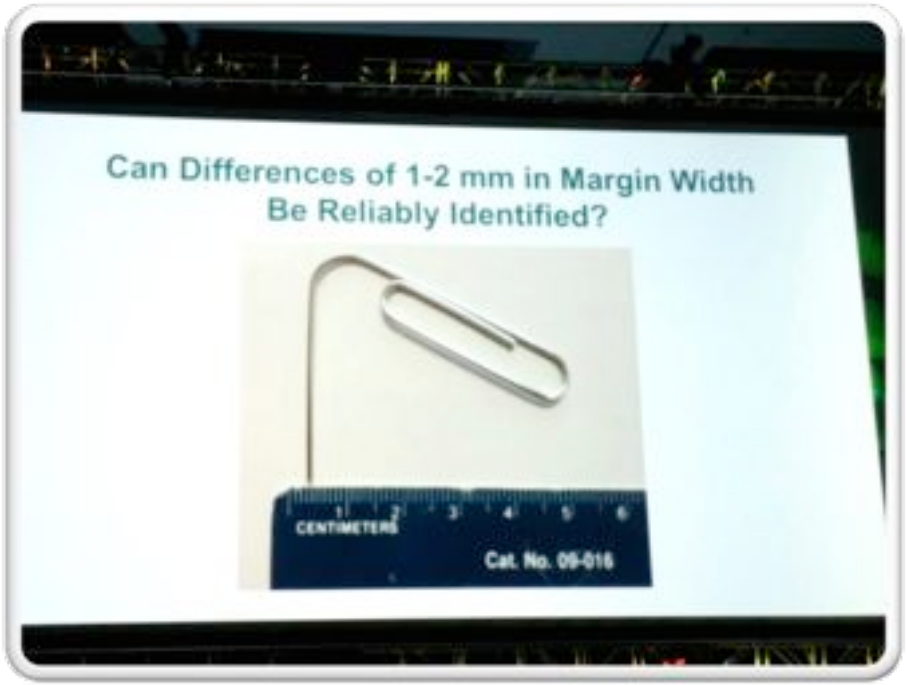
Abbreviations: ASTRO, American Society for Radiation Oncology; BCT, breast-conserving therapy; DCIS, ductal carcinoma in situ; EIC, extensive intraductal component; IBTR, ipsilateral breast tumor recurrence; LCIS, lobular carcinoma in situ; SSO, Society of Surgical Oncology; WBRT, whole-breast radiation therapy.

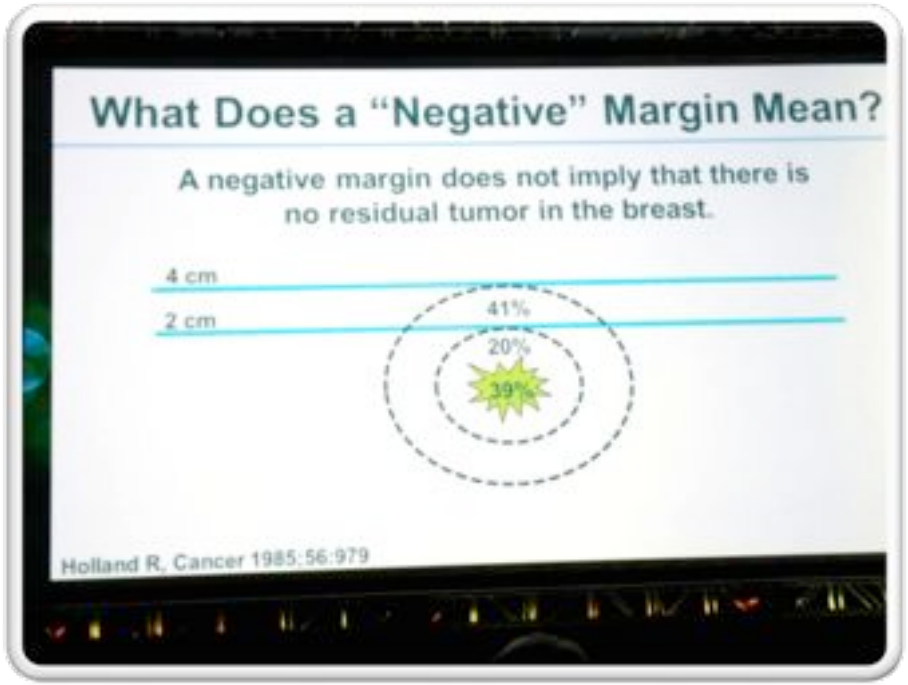
Positive margins increase IBTR risk
Wider margins do not lower IBTR risk
Systemic therapy do not influence IBTR

Unfavorable biologic subtypes
WBRT delivery, dose, fractionation techniques
Histological variants
Patients age
Extensive intraductal component

Buchholz TA, JCO, 2014

Final Surgical Margins

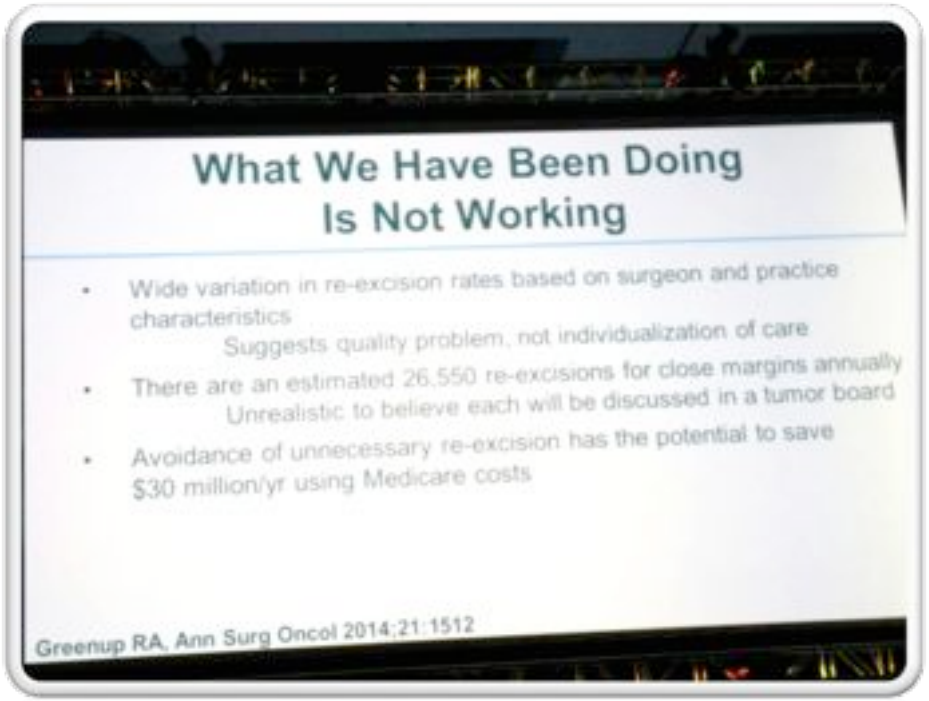


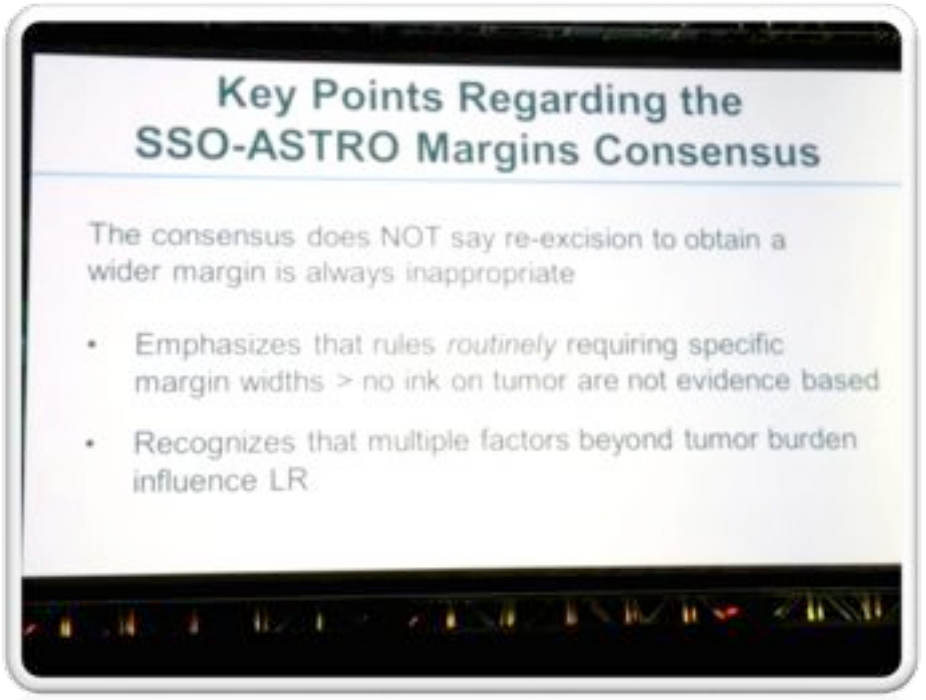


Morrow M, ASTRO 2014, San Francisco

ASTRO TARGETING CANCER CARE

Final Surgical Margins





Morrow M, ASTRO 2014, San Francisco

SURGICAL MARGINS


Radiotherapy and Oncology 108 (2013) 273–278

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Breast cancer radiotherapy

Radiotherapy boost dose-escalation for invasive breast cancer after breast-conserving surgery: 2093 Patients treated with a prospective margin-directed policy

Lorenzo Livi [a], Icro Meattini [a,*], Davide Franceschini [a], Calogero Saieva [b], Fiammetta Meacci [a], Livia Marrazzo [c], Elena Gerlain [b], Isacco Desideri [a], Vieri Scotti [a], Jacopo Nori [d], Luis Jose Sanchez [e], Lorenzo Orzalesi [e], Pierluigi Bonomo [a], Daniela Greto [a], Simonetta Bianchi [f], Giampaolo Biti [a]

Our experience showed that a **margin-directed** policy of RT **boost dose-escalation** seems to **reduce the negative impact of FMS on LR**, but it is not able to overcome the unfavorable effect of higher nuclear grade, higher T stage and triple negative subtype

FMS	BOOST DOSE
> 5 mm	10 Gy
5 – 2 mm	16 Gy
< 2 mm	20 Gy

SURGICAL MARGINS

17 year results of the randomized boost versus no boost EORTC 22881-10882 trial in early breast cancer

H. Bartelink, P. Maingon, P.M. Poortmans, C. Weltens, A. Fourquet, J.J. Jager, D.A.X. Schinagl, C.C. Rodenhuis, S. Collette, L. Collette

A **boost dose of 16 Gy** reduced the **local recurrence** rate from **13.1% to 8.8% at 15 years** and from **16.4% to 12.0% at 20 years** (HR: 0.65)

This relative reduction is seen in all age groups, the largest absolute benefit (12%) was observed in **younger breast cancer patients**

Bartelink H, ESTRO 2014, Vienna

OVERVIEW

Surgical margins

Sentinel lymph node(s)

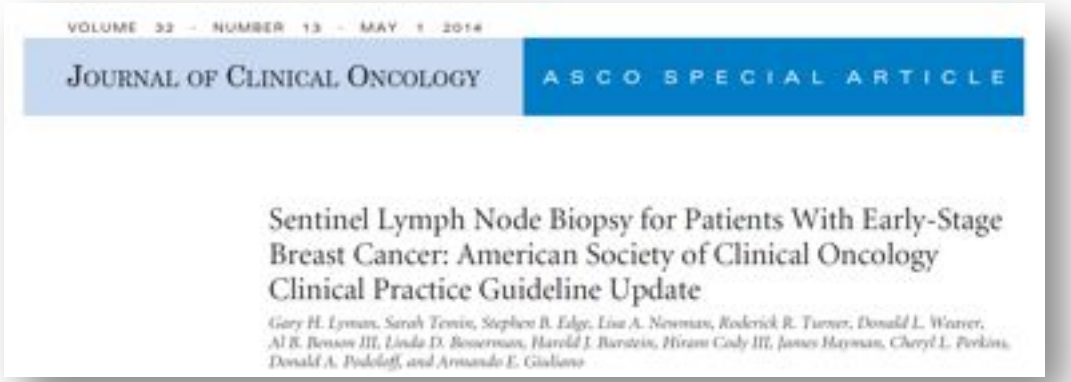
Nodal regions radiotherapy

Partial Breast Irradiation

Endocrine therapy

Target therapy

Sentinel lymph node(s)



Recommendation based on randomized controlled trials

Recommendations

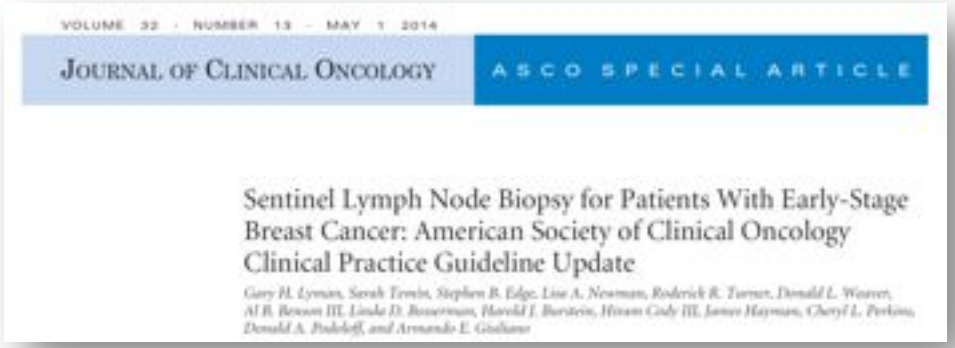
Women **without** sentinel lymph node (SLN) metastases **should not receive axillary lymph node dissection** (ALND).

Women with **one to two metastatic SLNs** planning to undergo **breast-conserving surgery with whole-breast radiotherapy** should not undergo ALND (in most cases).

Women with **SLN metastases** who will undergo **mastectomy** should be **offered ALND**.

Lyman GH, et al, JCO, 2014

Sentinel lymph node(s)


VOLUME 32 · NUMBER 13 · MAY 1 2014

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Clinical question: Is ALND necessary for all patients with metastatic findings on SNB?

Rationale

ACOSOG Z0011 trial

Non inferiority trial (OS)

Both studies closed early due to failure to meet their accrual target

Giuliano AE, et al, JAMA, 2011

IBCSG 23-01 trial

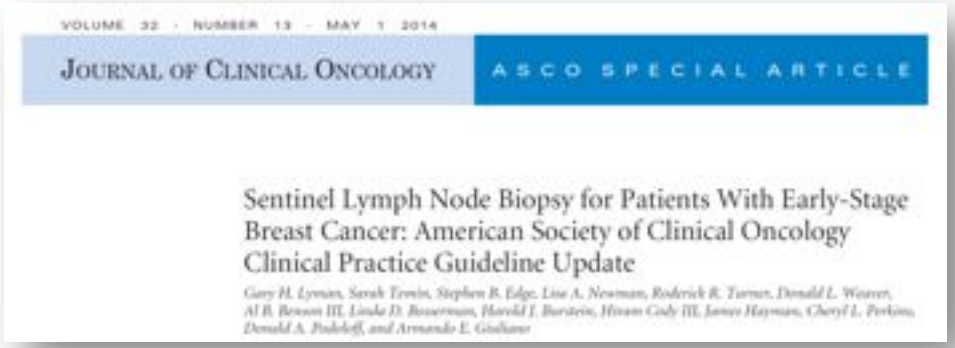
Non inferiority (DFS)

SN micrometastases

964 patients

Galimberti V, et al, Lancet Oncol, 2013

Sentinel lymph node(s)


VOLUME 32 · NUMBER 13 · MAY 1 2014

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Clinical question: Is ALND necessary for all patients with metastatic findings on SNB?

Results

No apparent negative impact omitting ALND in **mortality**

Non-inferiority in DFS *(underpowered)*

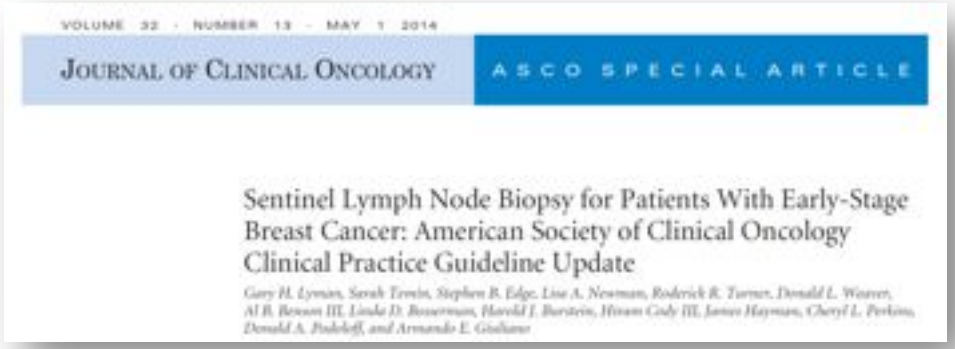
No significant **differences** in terms of **recurrences**

Statistically significant **higher surgical adverse events** in **ALND** groups

Giuliano AE, et al, JAMA, 2011

Galimberti V, et al, Lancet Oncol, 2013

Sentinel lymph node(s)


VOLUME 32 · NUMBER 13 · MAY 1 2014

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Clinical question: Is ALND necessary for all patients with metastatic findings on SNB?

Interpretation

In the experts opinion ALND can be avoided in case of **BCS**, but **only when WBI is planned with conventional fractionation**

Consider ALND in case of:

- **axillary fine-needle aspiration;**
- **large or bulky metastatic axillary SLNs;**
- **gross extranodal tumor extension**

Giuliano AE, et al, JAMA, 2011

Galimberti V, et al, Lancet Oncol, 2013

EORTC 10981-22023 AMAROS

The Lancet Oncology, Volume 15, Issue 12, Pages 1303 - 1310, November 2014
doi:10.1016/S1470-2045(14)70460-7 Cite or Link Using DOI
This article can be found in the following collections: Oncology (Breast cancer)
Published Online: 16 October 2014

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial

Mila Donker MD a, Geertjan van Tienhoven MD c, Marieke E Straver MD a, Philip Meijnen MD b, Prof Cornelis J H van de Velde MD d, Prof Robert E Mansel MD e, Prof Luigi Catalisotti MD f, A Helen Westenberg MD g, Prof Jean H G Klinkenbijl MD h, Lorenzo Orzalesi MD f, Willem H Bouma MD i, Huub C J van der Mijle MD j, Grard A P Nieuwenhuijzen MD k, Sanne C Veltkamp MD l, Leen Slaets PhD m, Nicole J Duez MSc m, Peter W de Graaf MD n, Thijs van Dalen MD o, Andreas Marinelli MD p, Herman Rijna MD q, Prof Marko Snoj MD r, Prof Nigel J Bundred MD s, Jos W S Merkus MD t, Prof Yazid Belkacemi MD u, Prof Patrick Petignat MD v, Dominic A X Schinagl MD w, Corneel Coens MSc x, Carlo G M Messina MD x, Jan Bogaerts PhD x, Prof Emiel J T Rutgers MD a

16 October 2014
Published online

Patients with T1—2 primary breast cancer and no palpable nodes
2001-2010
4823 patients
34 centers

2402 patients ALND vs 2404 axillary radiotherapy
1425 patients with a **positive sentinel node**
744 ALND vs 681 axillary radiotherapy

THE LANCET Oncology

EORTC 10981-22023 AMAROS

Median **follow-up** was **6.1 years** for the patients with positive sentinel lymph nodes

Axillary recurrence occurred in **four** of **744** patients in the ALND group and **seven** of **681** in the axillary RT group.

5-year axillary recurrence was **0.43%** (95% CI 0·00—0·92) after ALND versus **1.19%** (0·31—2·08) after axillary RT.

The planned non-inferiority test was underpowered because of the low number of events.

ALND and axillary RT after a positive sentinel node provide **excellent and comparable** axillary control for patients with T1—2 primary breast cancer and no palpable lymphadenopathy.

THE LANCET Oncology

AMAROS trial
Is it a practice changing study?

The extremely **low rate** of **axillary recurrence** in both study arms does not allow to draw any definitive conclusions.

The trial do not take in account all **the very low-risk patients** (probably a not negligible rate) that could reasonably **not undergo any intervention.**

We have to consider the **suboptimal dose** delivered in adjuvant setting in case of presence of **residual** axillary disease, and the technical challenge of **re-irradiation** in case of recurrence in already irradiated patients.

We do need to continue evaluating results of the contemporary **multidisciplinary approach** in breast cancer to evaluate the final outcome, including **survival** and **toxic effects**.

Axillary RT should be a **valid option** in case of no indication to lymphadenectomy, and it will represent **one more tool** in the hand of the oncologist.

THE LANCET Oncology

Sentinel Lymph Node(s)

Fu Y. *Chung D, Cao MA, Apple S, Chang H.* ***Ann Surg Oncol****. 2014 Aug 1.*

Is Axillary Lymph Node Dissection Necessary After Sentinel Lymph Node Biopsy in Patients with Mastectomy and Pathological N1 Breast Cancer?

This is a **retrospective study of 214 patients** diagnosed with primary invasive breast cancer who were treated by mastectomy and lymph node staging surgery (SLNB or ALND) at the Revlon/ UCLA Breast Center between January 2002 and December 2010. Patients with **pathological N1 disease** were separated by their first nodal surgery into SLNB (subgroups: observation, radiation, and additional ALND with or without radiation) and ALND groups (subgroups: ALND with or without radiation).

After a **median follow-up of 43.6 months**, the OS and systemic **relapse-free survival (RFS)** rate of the **radiation group** and additional **ALND group** were **significantly better than the observation group** ($p = 0.031$ and 0.046, respectively).

Radiation was as effective as ALND in patients with mastectomy and N1 disease for OS and RFS rates, yet radiation after SLNB had fewer side effects than ALND. **SLNB followed by radiation could replace ALND** in patients with mastectomy and pathological N1 breast cancer identified by SLNB

FINAL TREND
The published literature seems to follow the STRONGEST DISCIPLINE, NOT the STRONGEST DATA

OVERVIEW

Final surgical margins

Sentinel lymph node(s)

Nodal regions radiotherapy

Partial Breast Irradiation

Endocrine therapy

Target therapy

Nodal regions radiotherapy

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

*EBCTCG (Early Breast Cancer Trialists' Collaborative Group)**

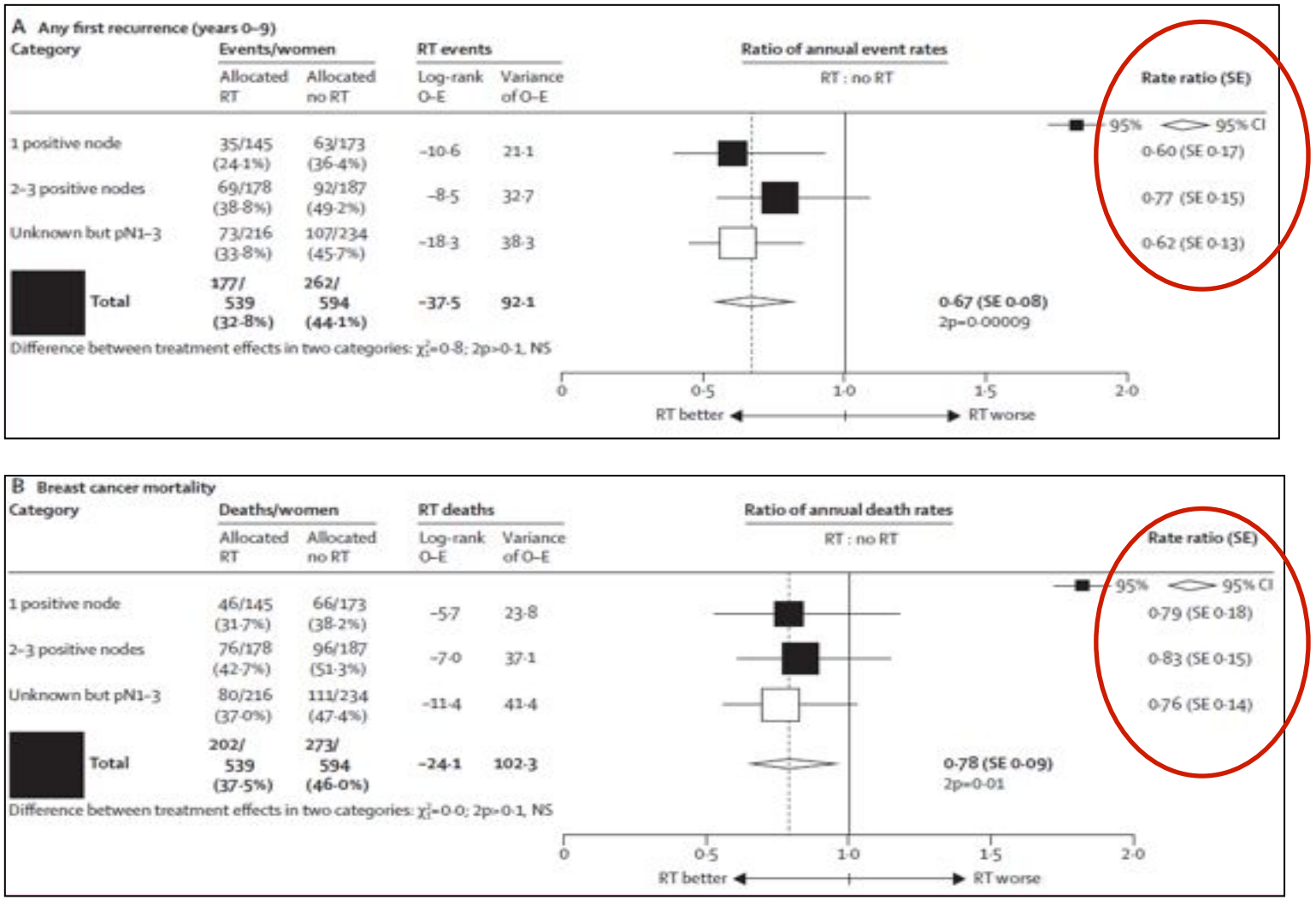
Meta-analysis of individual data for **8135** women randomly assigned to treatment groups during *1964–86* in ***22 trials*** of **radiotherapy to the chest wall and regional lymph nodes** after mastectomy and axillary surgery **versus** the same surgery but **no radiotherapy**

Analyses were stratified by trial, individual follow-up year, age at entry, and pathological nodal status

Follow-up lasted 10 years for **recurrence** and to Jan 1, 2009, for mortality

EBCTCG, Lancet Oncol, 2014

Nodal regions radiotherapy



EBCTCG, Lancet Oncol, 2014

Nodal regions radiotherapy

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

*EBCTCG (Early Breast Cancer Trialists' Collaborative Group)**

Radiotherapy reduced both recurrence and breast cancer mortality in the women with one to three positive lymph nodes in these trials even when <u>systemic therapy</u> was given

Study period: 1964-1986

No sentinel lymph node biopsy procedure used

Out-of-date systemic therapies (CMF schedule and tamoxifen)

Absolute benefits from postmastectomy radiotherapy today are likely to be **smaller** than those reported here

EBCTCG, Lancet Oncol, 2014

Nodal regions radiotherapy

Postmastectomy radiation in breast cancer with one to three involved lymph nodes: ending the debate

Overall, **postmastectomy radiotherapy improves locoregional disease-free survival**, overall disease-free survival, and breast-cancer-specific survival, irrespective of the number of involved lymph nodes and of administration of adjuvant systemic therapy

We need to **continue evaluating results** of the contemporary **multidisciplinary approach in breast cancer** to better understand the complex interaction between respective contributions of **systemic and locoregional treatments** to the final outcome, including **survival** and **toxic effects**

Philip Poortmans
Department of Radiation Oncology, Institute Verbeeten, Tilburg, LA 5000, Netherlands

www.thelancet.com Vol 383 June 21, 2014

Nodal regions radiotherapy

The **one in four rule** from earlier EBCTCG meta-analyses **cannot be generalized** to all patient groups

Radiotherapy can increase the rate of **deaths not related to breast cancer**, mainly by inducing **cardiac diseases** and **secondary cancers**

This outcome **lowers** the **benefit** of **radiotherapy** on breast cancer mortality after longer follow-up

However, **modern radiotherapy techniques** allow the non-intended dose to organs at risk to be **decreased**, while at the same time **improving** target coverage

Continued follow-up is needed to understand fully the ultimate influence of radiotherapy on breast-cancer-related mortality and on late toxic effects

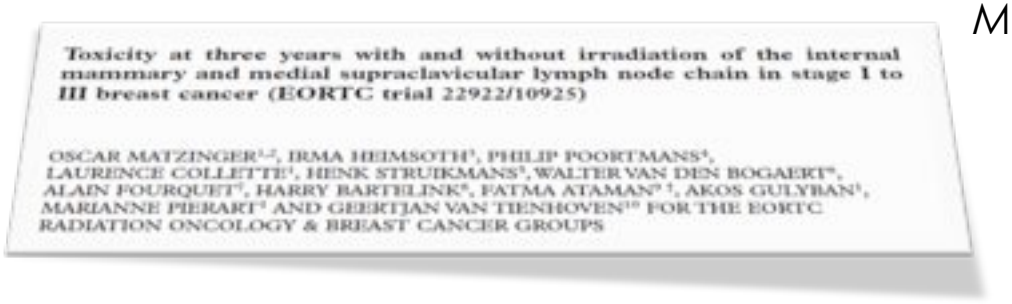
The results of this EBCTCG meta-analysis clearly **confirm** that postmastectomy radiotherapy **should be considered equally** for patients with one to three involved axillary lymph nodes **as** it should be for patients with four or more affected **axillary lymph nodes**

Philip Poortmans
Department of Radiation Oncology, Institute Verbeeten, Tilburg, LA 5000, Netherlands

www.thelancet.com Vol 383 June 21, 2014

EORTC 22922/10925

- EORTC 22922/10925 trial investigated the potential survival benefit and toxicity of **elective irradiation of the internal mammary and medial supraclavicular nodes.**
- Between 1996 and 2004, **4004** patients from 43 centres participated, of which 55.6% had involved axillary lymph nodes.
- **Nearly all node-positive (99.0%) and 66.3% of node-negative patients received adjuvant systemic treatment.**
- Initial **3-year** report showed **no relevant toxicity** following regional node irradiation.


Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925)

OSCAR MATZINGER[1,2], IRMA HEIMSOTH[3], PHILIP POORTMANS[4], LAURENCE COLLETTE[5], HENK STRUIKMANS[6], WALTER VAN DEN BOGAERT[6], ALAIN FOURQUET[7], HARRY BARTELINK[8], FATMA ATAMAN[9,1], AKOS GULYBAN[1], MARIANNE PIERART[5] AND GEERTJAN VAN TIENHOVEN[10] FOR THE EORTC RADIATION ONCOLOGY & BREAST CANCER GROUPS

Matzinger O, et al, Acta Oncologica, 2010

EORTC 22922/10925

10-years Results

- Overall survival **at 10 years** was 82.3% with and 80.7% without radiation therapy to the internal mammary and medial supraclavicular lymph nodes
- The causes of death were similar except for breast cancer (259 vs. 310).
- **DFS and DMFS** were **greater** after lymph node **irradiation**.
- The rate of **lung** and **skin** toxicity was **slightly higher** in the regionally irradiated group.
- **No increase** in **cardiac events** or lethal complications was observed.

Poortmans, et al, Presidential ECC 2013
Poortmans, et al, ESTRO 2014
Struikmans, et al, EBCC 2014

OVERVIEW

Final surgical margins

Sentinel lymph node(s)

Nodal regions radiotherapy

Partial Breast Irradiation

Endocrine therapy

Target therapy

Partial Breast Irradiation

- APBI demonstrated durable and acceptable local control in **biological** low risk cases (i.e. *luminal A case*):

  Stage I; ER positive; > 50 years old

- **Outcome** from randomized trials are still needed

- Question **not addressed** by trials:

- Optimal **fractionation**
- **Dose**
- **Methodology** to minimize variation in cosmetic outcome

White J, ASTRO 2014

ASTRO TARGETING CANCER CARE

AIRO

Partial Breast Irradiation

Phase 3 Trial Design

ACCELERATED IMRT TO TREAT THE INDEX QUADRANT
30 Gy in 5 fractions (6 Gy/fr in 2 weeks)

versus

STANDARD WHOLE BREAST RADIOTHERAPY
50 Gy + boost 10 Gy in 30 fractions (2 Gy/fr in 6 weeks)

*AFTER CONSERVING SURGERY IN HIGHLY **SELECTED** EARLY BREAST CANCER **PATIENTS***

Livi L, et al, IJROBP, 2010

Partial Breast Irradiation

Low rate of events at *5-year* median follow-up

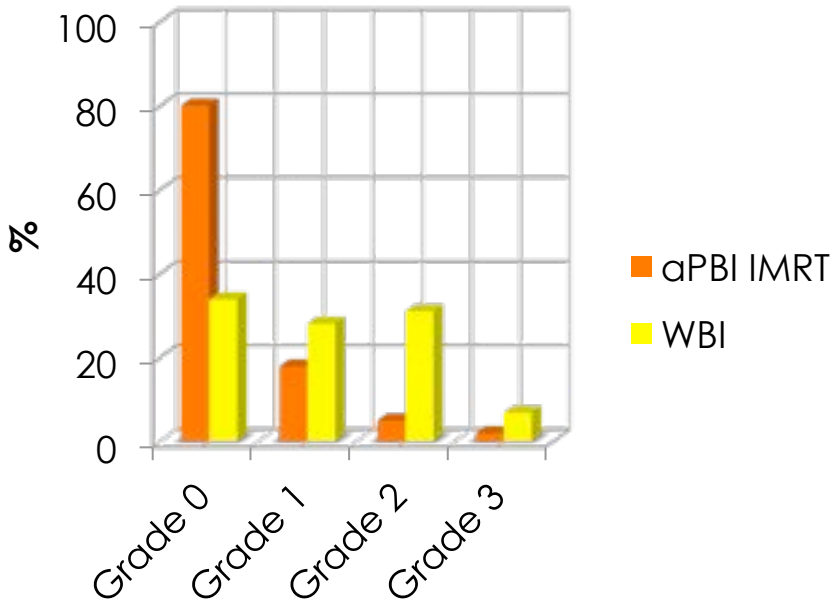
10 locoregional relapses
(4 APBI *vs* 6 WBI arm)

10 Contralateral breast cancer
(3 APBI *vs* 7 WBI)

	WBI (n:274)		APBI (n:246)	
Events	**n**	**%**	**n**	**%**
Contralateral breast cancer	7	2.6	3	1.2
Distant metastasis	4	1.5	3	1.2
Total deaths	9	3.3	3	1.2
Breast cancer	4	1.5	2	0.8

Accepted as oral presentation at San Antonio Breast Cancer Symposium
L. Livi, et al
San Antonio, Texas, 8-13 December, 2014

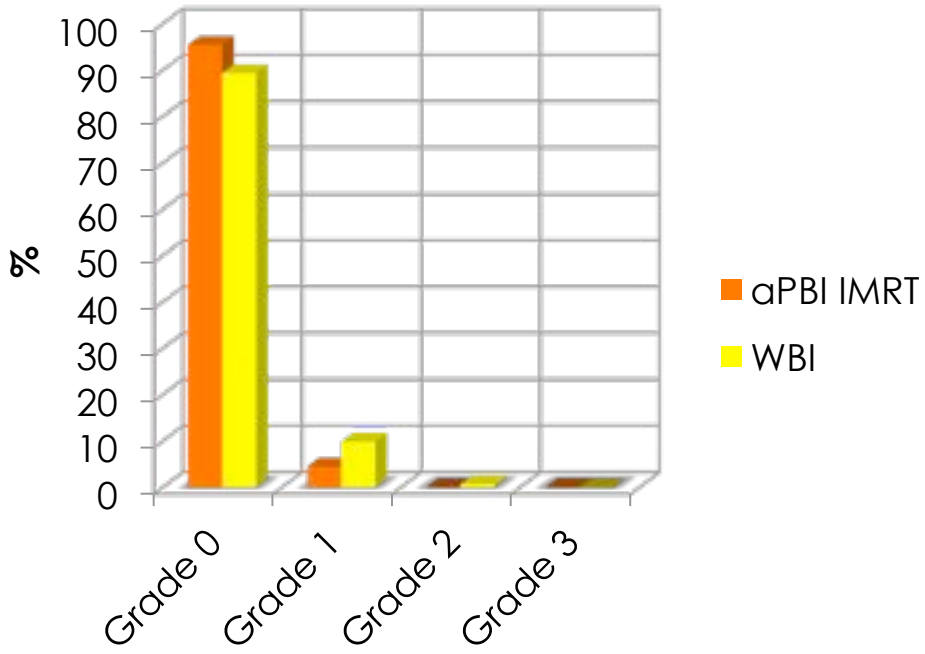
Partial Breast Irradiation



	WBI (n:274) N	%	APBI (n:246) N	%	p-value
Any skin toxicity					
None	93	33.9	197	80.1	
Yes, any Grade	181	66.1	49	19.9	**0.0001**
None	93	33.9	197	80.1	
Grade 1	77	28.1	44	17.9	
Grade 2	85	31.1	5	2.0	
Grade 3	19	6.9	0	0	
Grade 4	0	0	0	0	**0.0001**
Grade 0-1	170	62.0	241	98.0	
Grade ≥2	104	38.0	5	2.0	**0.0001**
Erythema					
None	93	33.9	197	80.1	
Grade 1-2	162	59.2	49	19.9	
Grade 3-4	19	6.9	0	0	
Breast edema					
None	225	82.1	246	100	
Grade 1-2	44	16.1	0	0	
Grade 3-4	5	1.8	0	0	

Meattini I, et al, ESTRO 2014, Vienna

Partial Breast Irradiation



	WBI (n:274) N	%	APBI (n:246) N	%	p-value
Late skin toxicity					
None	245	89.4	235	95.5	
Yes, any Grade	29	10.6	11	4.5	**0.013**
None	245	89.4	235	95.5	
Grade 1	27	9.9	11	4.5	
Grade 2	2	0.7	0	0	
Grade 3	0	0	0	0	
Grade 4	0	0	0	0	**0.024**
Grade 0-1	272	99.3	246	100.0	
Grade ≥2	2	0.7	0	0	0.50
Fibrosis					
None	245	89.4	235	95.5	
Grade 1-2	29	10.6	11	4.5	
Grade 3-4	0	0	0	0	
Telangiectasia					
None	267	97.4	244	99.2	
Grade 1-2	7	2.6	2	0.8	
Grade 3-4	0	0	0	0	

Meattini I, et al, ESTRO 2014, Vienna

Partial Breast Irradiation

	All patients n=520		>12 months FU n=487		>24 months FU n=457		>36 months FU n=407		>48 months FU n=337	
Cosmetic result	*APBI n=246*	*WBI n=274*	*APBI n=221*	*WBI n=266*	*APBI n=198*	*WBI n=259*	*APBI n=182*	*WBI n=225*	*APBI n=154*	*WBI n=183*
Excellent	234 (95.1)	247 (90.1)	209 (94.6)	239 (89.8)	186 (93.9)	232 (89.6)	172 (94.5)	200 (88.9)	144 (93.5)	162 (88.5)
Good	12 (4.9)	25 (9.1)	12 (5.4)	25 (9.4)	12 (6.1)	25 (9.7)	10 (5.5)	23 (10.2)	10 (6.5)	19 (10.4)
Fair	0	2 (0.8)	0	2 (0.8)	0	2 (0.8)	0	2 (0.9)	0	2 (1.1)
Poor	0	0	0	0	0	0	0	0	0	0

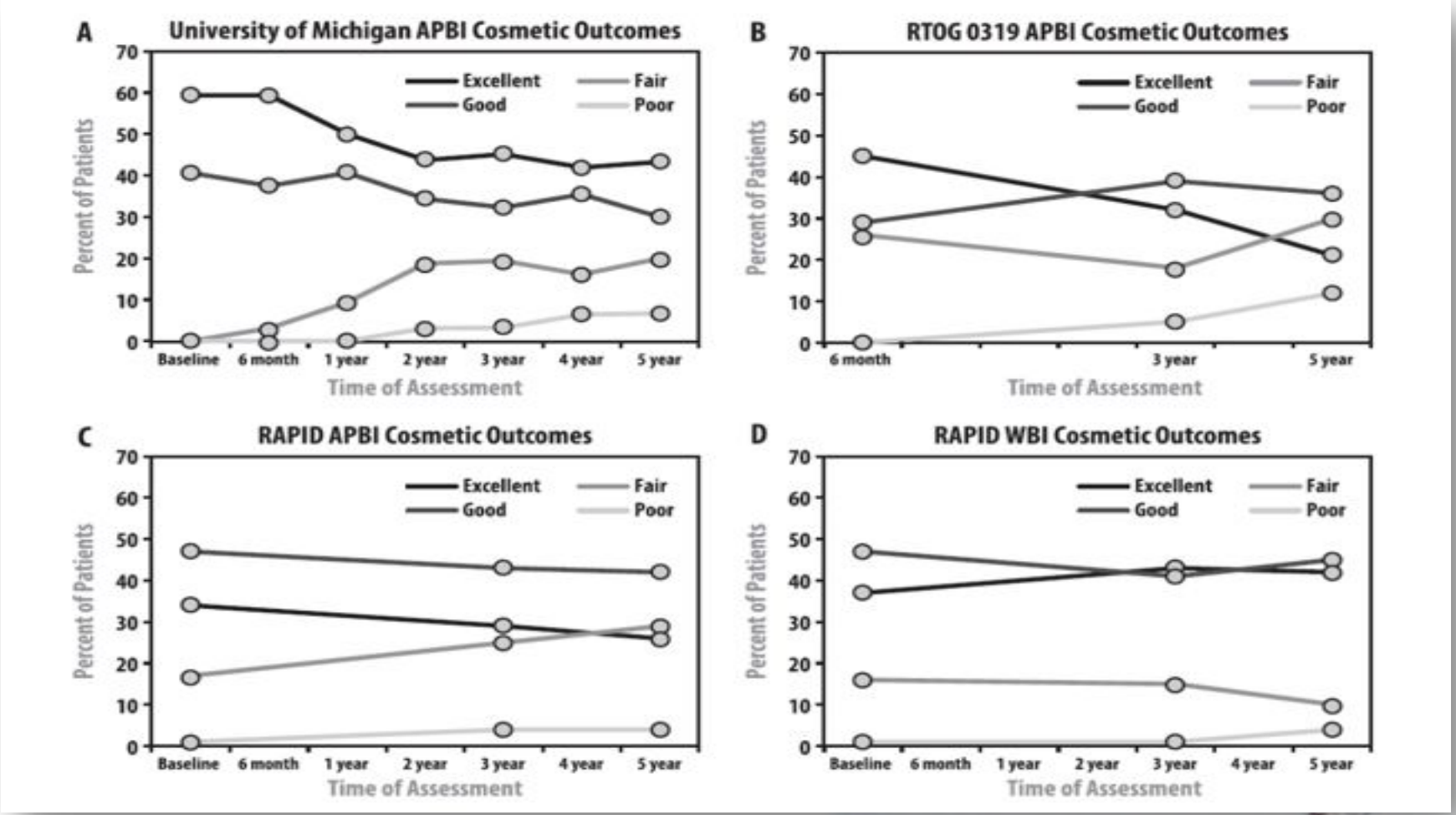
-337 patients **(64.8%)** had a cosmetic evaluation with a **minimum follow-up of 48 months**

-In both treatment groups the cosmetic result was rated as **excellent/ good** for more than **90%** of patients

Meattini I, et al, ESTRO 2014, Vienna

Partial Breast Irradiation

International Journal of Radiation Oncology biology • physics
www.redjournal.org



Liss AL, et al, IJROBP, 2014

Partial Breast Irradiation

- The **hypofractionated schedule** commonly used for external beam APBI and prescribed by the ongoing phase 3 trials **may be suboptimal**
- **3.85 Gy bid in 5 days** could be a **too high dose**
- The **V50 and V100** of the breast reference volume seem correlated with cosmetic outcome
- **Stricter limits** may be appropriate in this setting

Liss AL, et al, IJROBP, 2014
Olivotto IA, et al, JCO, 2013

OVERVIEW

Surgical margins

Sentinel lymph node(s)

Nodal regions radiotherapy

Partial Breast Irradiation

Endocrine therapy

Target therapy

Endocrine therapy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 10, 2014 VOL. 371 NO. 2

Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer

Olivia Pagani, M.D., Meredith M. Regan, Sc.D., Barbara A. Walley, M.D., Gini F. Fleming, M.D., Marco Colleoni, M.D., István Láng, M.D., Henry L. Gomez, M.D., Carlo Tondini, M.D., Harold J. Burstein, M.D., Edith A. Perez, M.D., Eva Ciruelos, M.D., Vered Stearns, M.D., Hervé R. Bonnefoi, M.D., Silvana Martino, D.O., Charles E. Geyer, Jr., M.D., Graziella Pinotti, M.D., Fabio Puglisi, M.D., Diana Crivellari, M.D., Thomas Ruhstaller, M.D., Eric P. Winer, M.D., Manuela Rabaglio-Poretti, M.D., Rudolf Maibach, Ph.D., Barbara Ruepp, Pharm.D., Anita Giobbie-Hurder, M.S., Karen N. Price, B.S., Jürg Bernhard, Ph.D., Weixiu Luo, M.S., Karin Ribi, Ph.D., Giuseppe Viale, M.D., Alan S. Coates, M.D., Richard D. Gelber, Ph.D., Aron Goldhirsch, M.D., and Prudence A. Francis, M.D., for the TEXT and SOFT Investigators and the International Breast Cancer Study Group*

Adjuvant therapy with an aromatase inhibitor improves outcomes, as compared with tamoxifen, **in postmenopausal women** with hormone-receptor–positive breast cancer.

In two phase 3 trials, we randomly assigned premenopausal women with hormone receptor–positive early breast cancer to the **aromatase inhibitor exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for a period of 5 years**.

The primary analysis combined data from **4690 patients** in the two trials.

Pagani O, et al, NEJM, 2014

Endocrine therapy

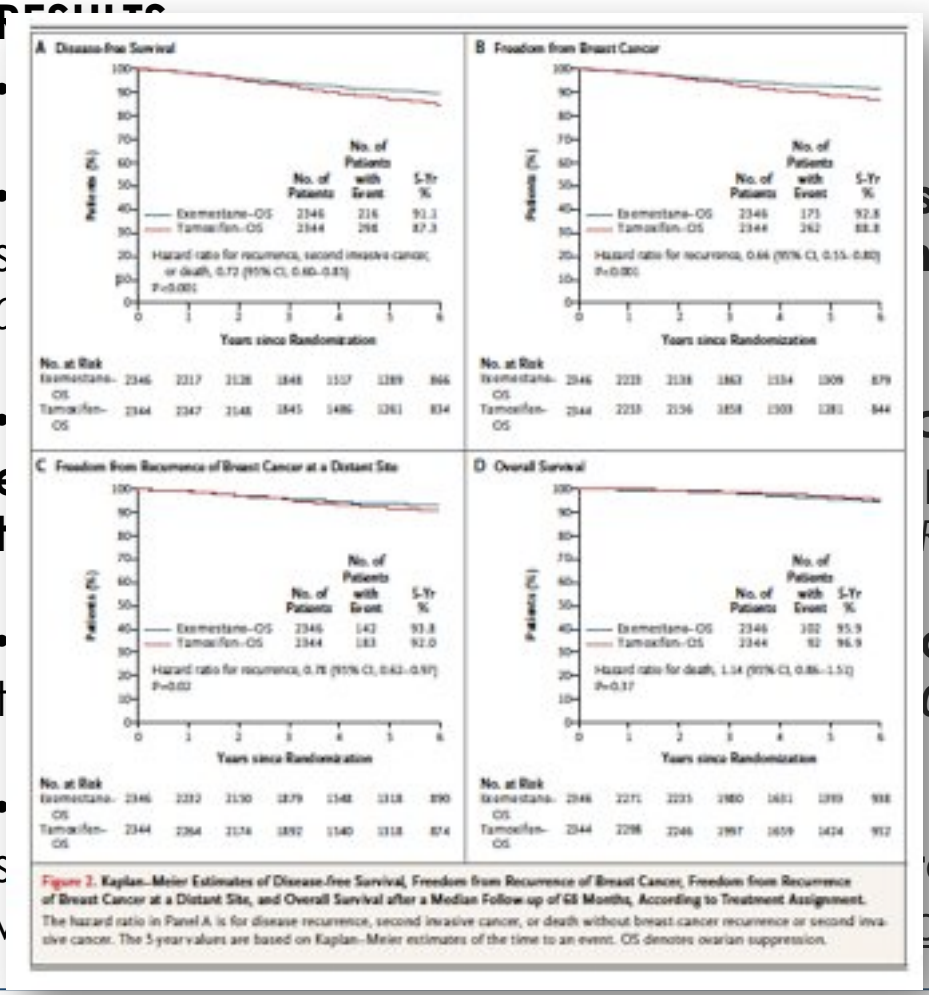


Figure 2. Kaplan–Meier Estimates of Disease-free Survival, Freedom from Recurrence of Breast Cancer, Freedom from Recurrence of Breast Cancer at a Distant Site, and Overall Survival after a Median Follow-up of 68 Months, According to Treatment Assignment.
The hazard ratio in Panel A is for disease recurrence, second invasive cancer, or death without breast cancer recurrence or second invasive cancer. The 5-year values are based on Kaplan–Meier estimates of the time to an event. OS denotes ovarian suppression.

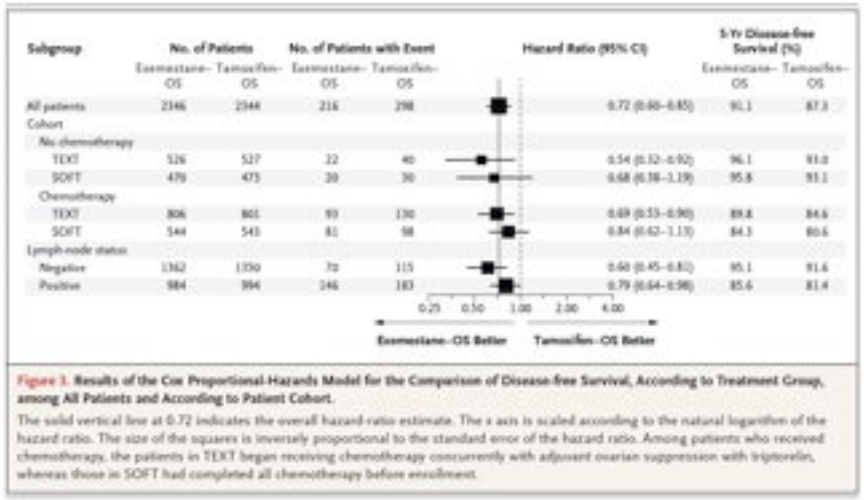


Figure 3. Results of the Cox Proportional-Hazards Model for the Comparison of Disease-free Survival, According to Treatment Group, among All Patients and According to Patient Cohort.
The solid vertical line at 0.72 indicates the overall hazard-ratio estimate. The x axis is scaled according to the natural logarithm of the hazard ratio. The size of the squares is inversely proportional to the standard error of the hazard ratio. Among patients who received chemotherapy, the patients in TEXT began receiving chemotherapy concurrently with adjuvant ovarian suppression with triptorelin, whereas those in SOFT had completed all chemotherapy before enrollment.

- **30.6%** for the **exemestane**–ovarian
- **amoxifen**–ovarian suppression group,
- ppausal women.

Pagani O, et al, NEJM, 2014

Endocrine therapy

CONCLUSIONS

In **premenopausal** women with hormone-receptor–positive early breast cancer, adjuvant treatment with exemestane plus ovarian suppression, as compared with tamoxifen plus ovarian suppression, significantly **reduced recurrence**

Premenopausal women who receive ovarian suppression may now benefit from an **aromatase inhibitor**, a class of drugs that **until now has been recommended only for postmenopausal women.**

TEXT and SOFT ClinicalTrials.gov numbers, NCT00066703 and NCT00066690

Pagani O, et al, NEJM, 2014

Medical News & Perspectives

New Practice-Changing Study Findings Presented at ASCO

Kate O'Rourke

Clifford Hudis, MD, chief of the breast cancer medicine service at Memorial Sloan Kettering Cancer Center (MSKCC) in New York City.

Should premenopausal women with hormone-positive breast cancer have their ovaries shut off as part of treatment, and if they are shut off, do patients do better when an aromatase inhibitor is substituted for tamoxifen?

Joint analysis answers the question, with aromatase inhibitors performing better than tamoxifen.

"What is unanswered here, and this is important, is whether the people who got tamoxifen alone [without OFS] might have done just as well. But for the moment, there is a benefit seen with the aromatase inhibitor therapy, only in terms of disease control."

For some people, such as **those with high-risk disease**, "the extra toxicity from being made menopausal will feel worth it," Hudis said. "Others will say, 'Without a difference in survival right now, I'm not sure I want to go through this.'"

OVERVIEW

Surgical margins

Sentinel lymph node(s)

Nodal regions radiotherapy

Partial Breast Irradiation

Endocrine therapy

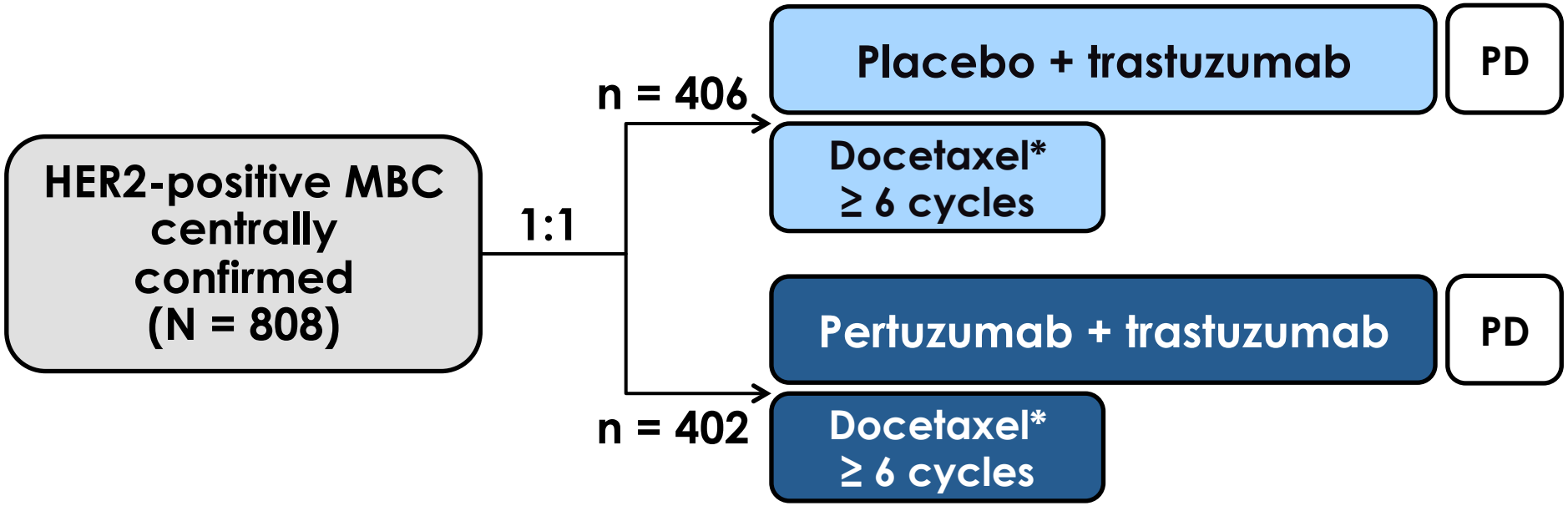
Target therapy

Target therapy

Final overall survival analysis from the CLEOPATRA study of first-line pertuzumab, trastuzumab, and docetaxel in patients with HER2-positive metastatic breast cancer

Sandra M. Swain, Sung-Bae Kim, Javier Cortés, Jungsil Ro, Vladimir Semiglazov, Mario Campone, Eva Ciruelos, Jean-Marc Ferrero, Andreas Schneeweiss, Sarah Heeson, Emma Clark, Graham Ross, Mark C. Benyunes, and José Baselga

CLEOPATRA Study Design

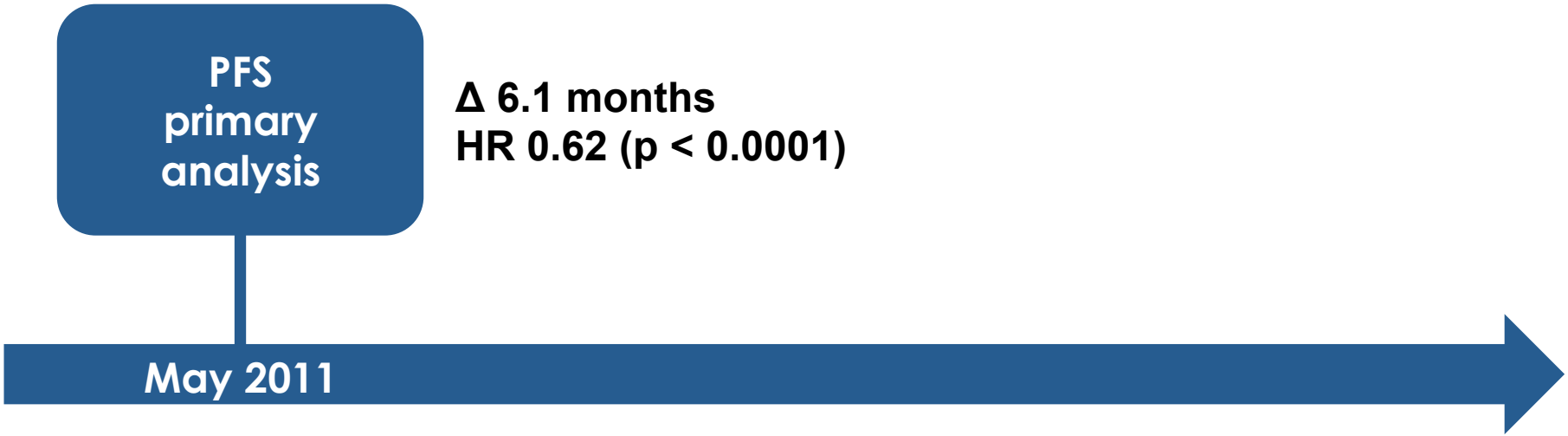


- **Randomization stratified by geographic region and neo/adjuvant chemotherapy**
- **Study dosing q3w:**
  - **Pertuzumab/placebo: 840 mg loading → 420 mg maintenance**
  - **Trastuzumab: 8 mg/kg loading → 6 mg/kg maintenance**
  - **Docetaxel: 75 mg/m^2 → 100 mg/m^2 escalation if tolerated**

* < 6 cycles allowed for unacceptable toxicity or PD; > 6 cycles allowed at investigator discretion.
HER2, human epidermal growth factor receptor 2;
MBC, metastatic breast cancer;
PD, progressive disease.

Baselga J, et al. N Engl J Med 2012; ***366:****109–119*

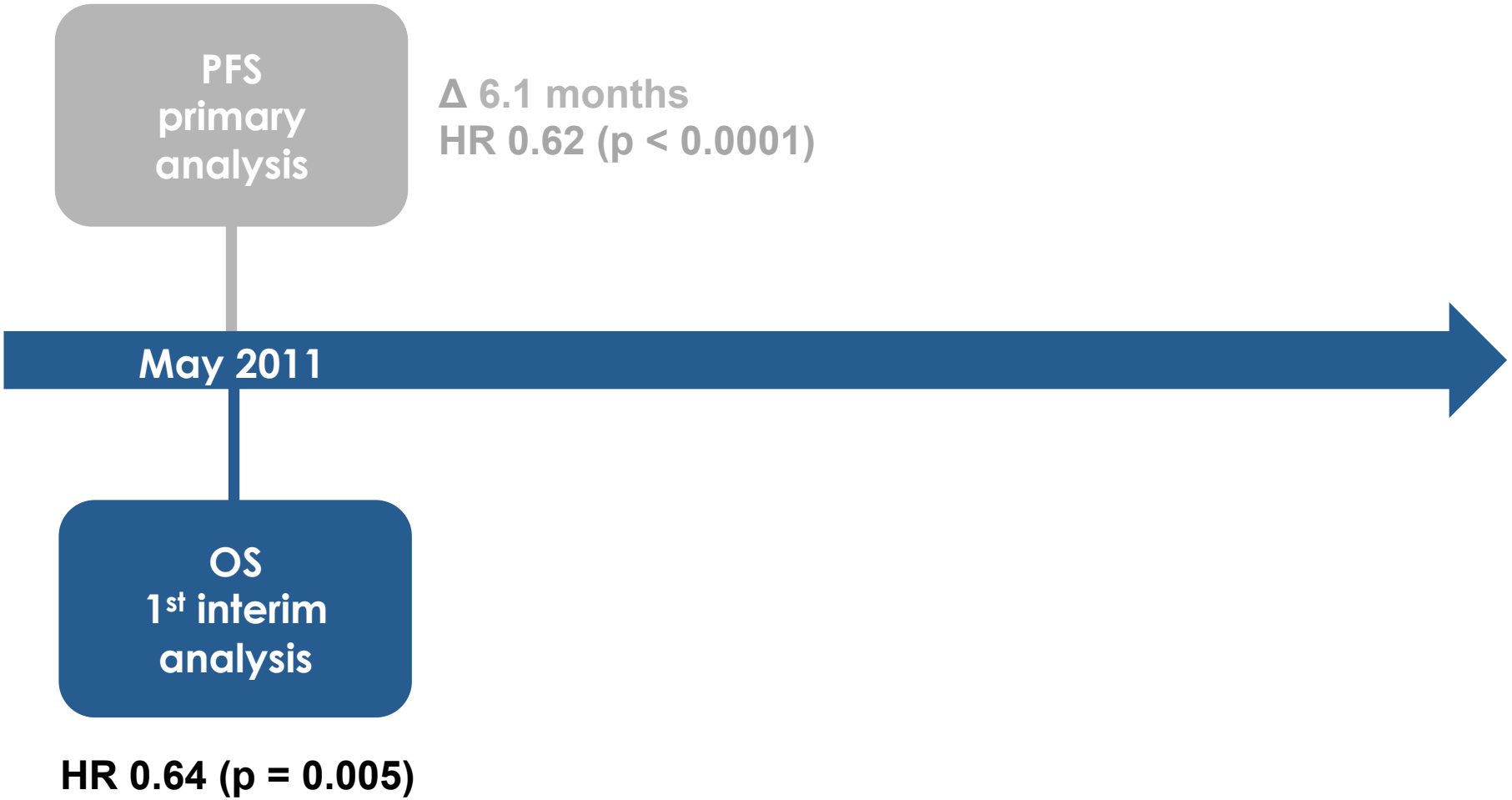
Efficacy Analysis Milestones



HR, hazard ratio.

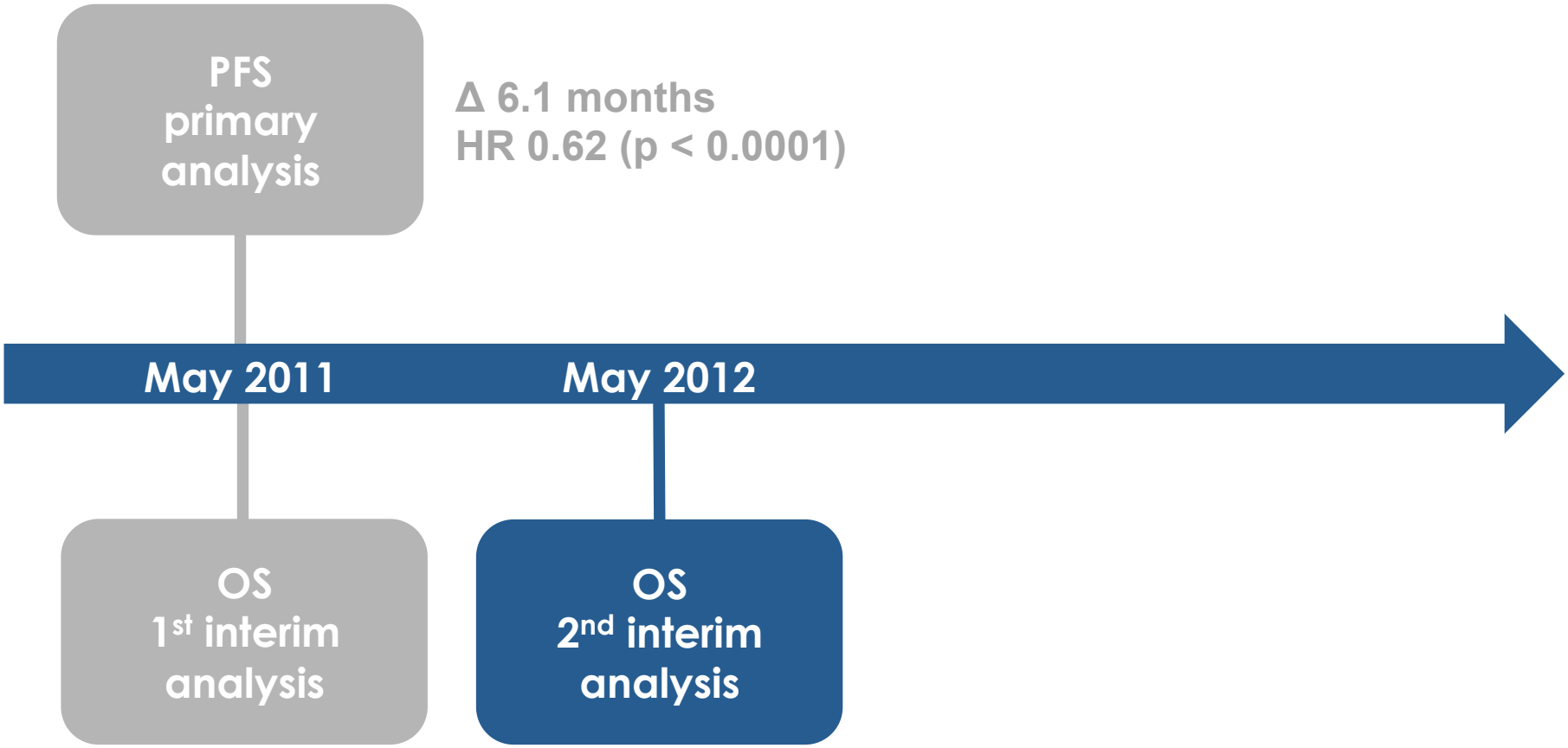
Baselga J, et al. N Engl J Med 2012; ***366:****109–119*

Efficacy Analysis Milestones



Baselga J, et al. N Engl J Med 2012; ***366:****109–119*

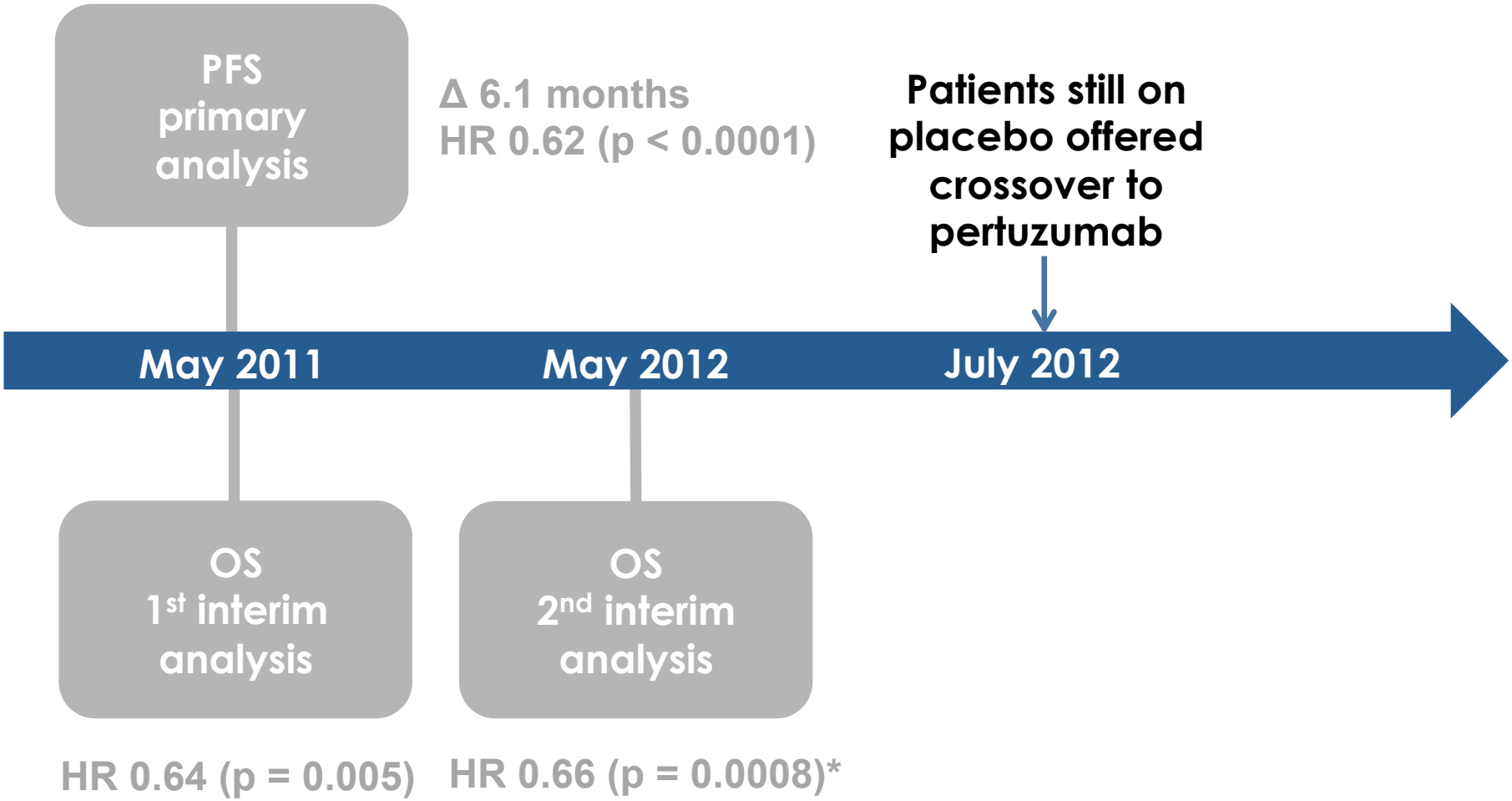
Efficacy Analysis Milestones



*** Crossed the prespecified O'Brien-Fleming stopping boundary (HR ≤ 0.739; p ≤ 0.0138)**

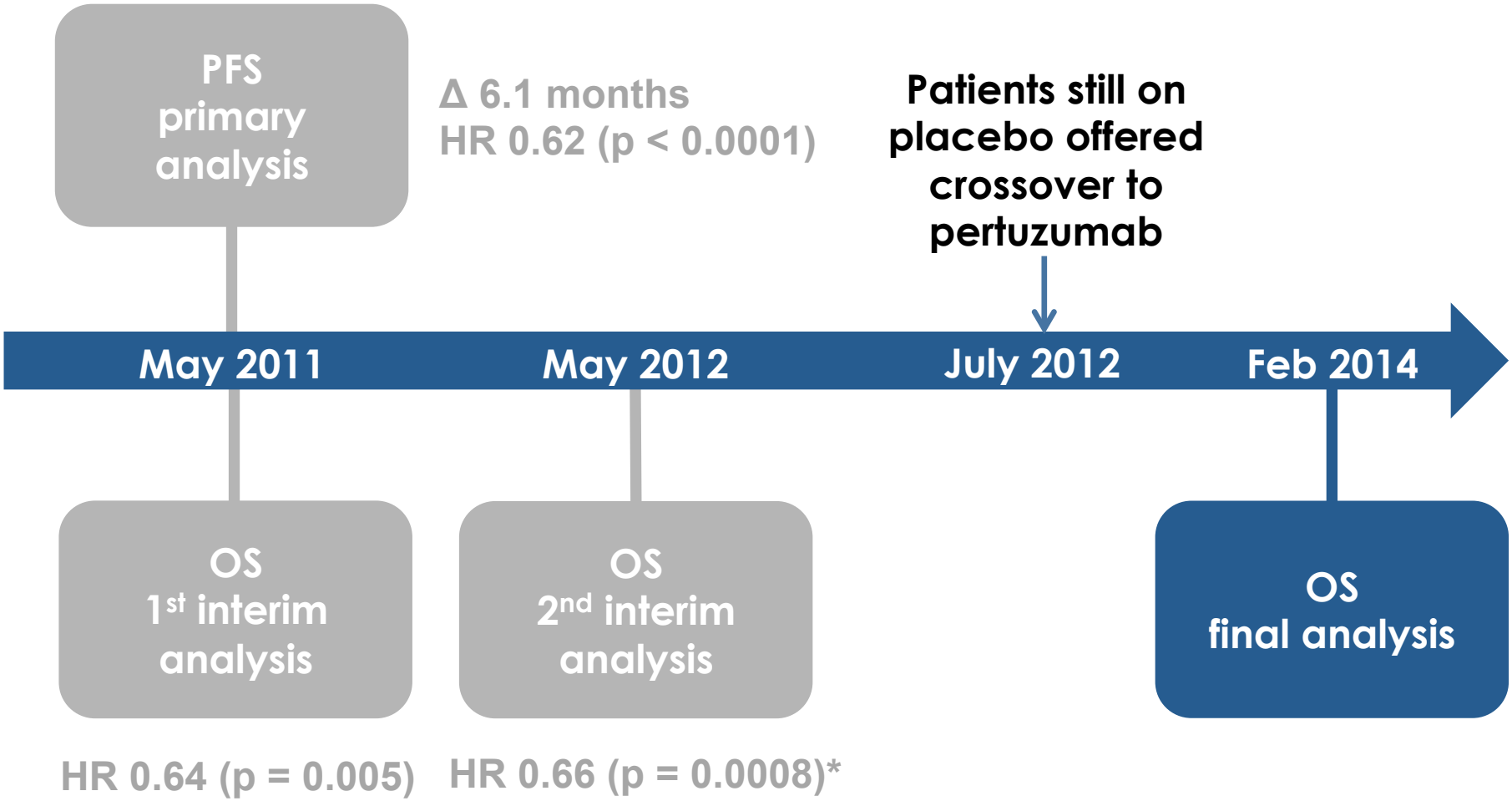
Swain SM, et al. Lancet Oncol 2013; ***14:****461–471*

Efficacy Analysis Milestones



Swain SM, et al. Lancet Oncol 2013; ***14:****461–471*

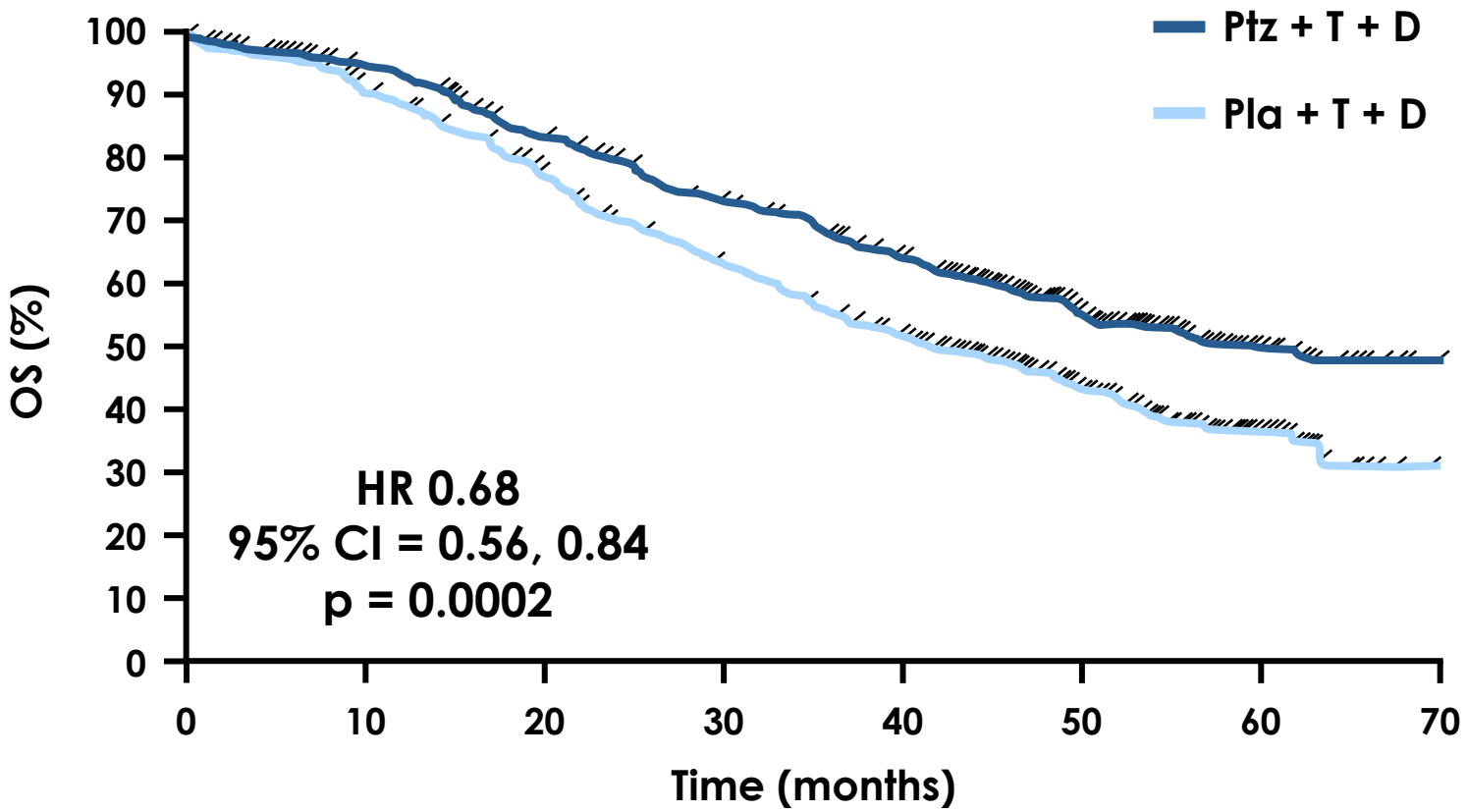
Efficacy Analysis Milestones



Swain SM, et al. ESMO 2014

Final OS Analysis

Median follow-up 50 months (range 0–70 months)



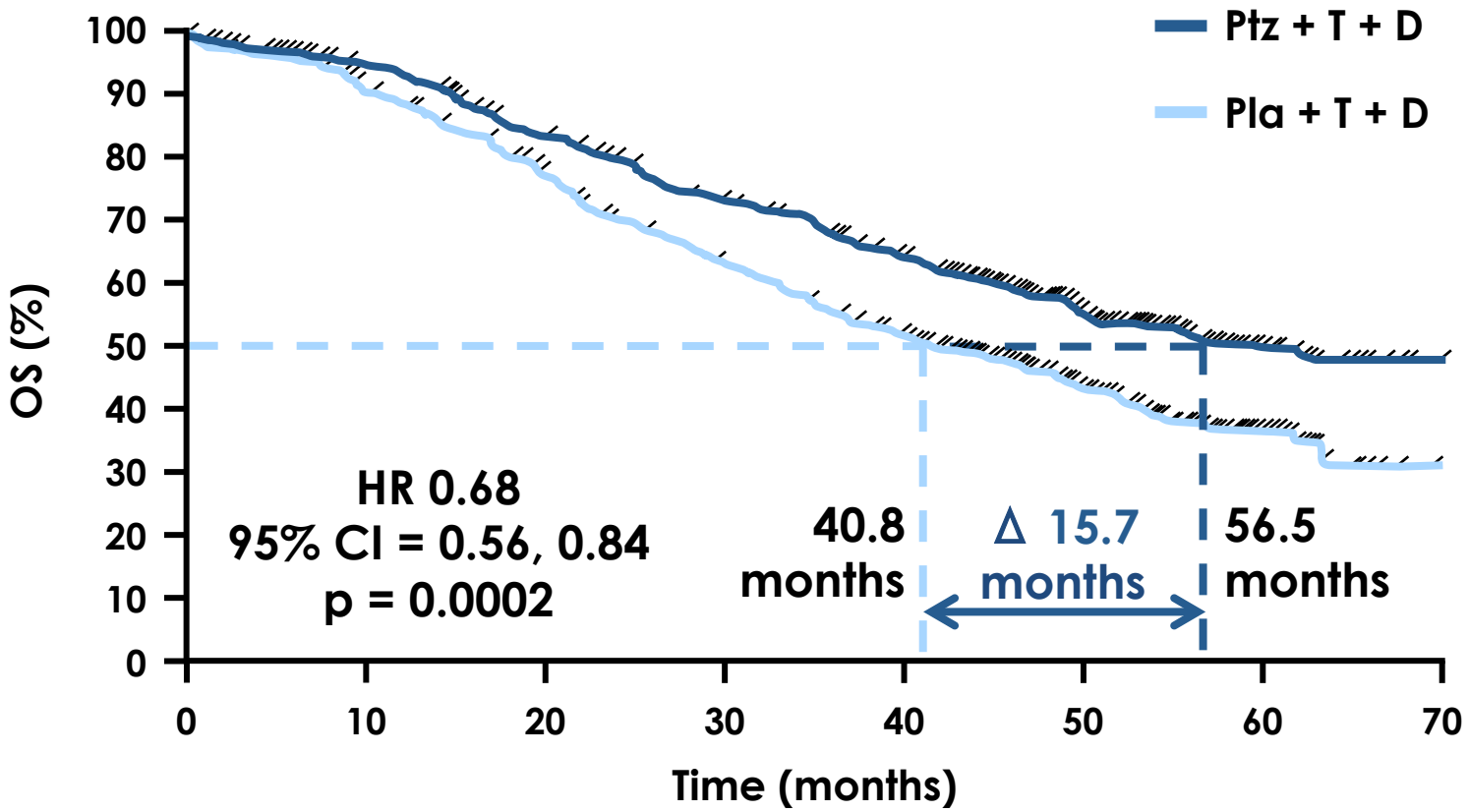
n at risk								
Ptz + T + D	402	371	318	268	226	104	28	1
Pla + T + D	406	350	289	230	179	91	23	0

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Swain SM, et al. ESMO 2014

Final OS Analysis

Median follow-up 50 months (range 0–70 months)



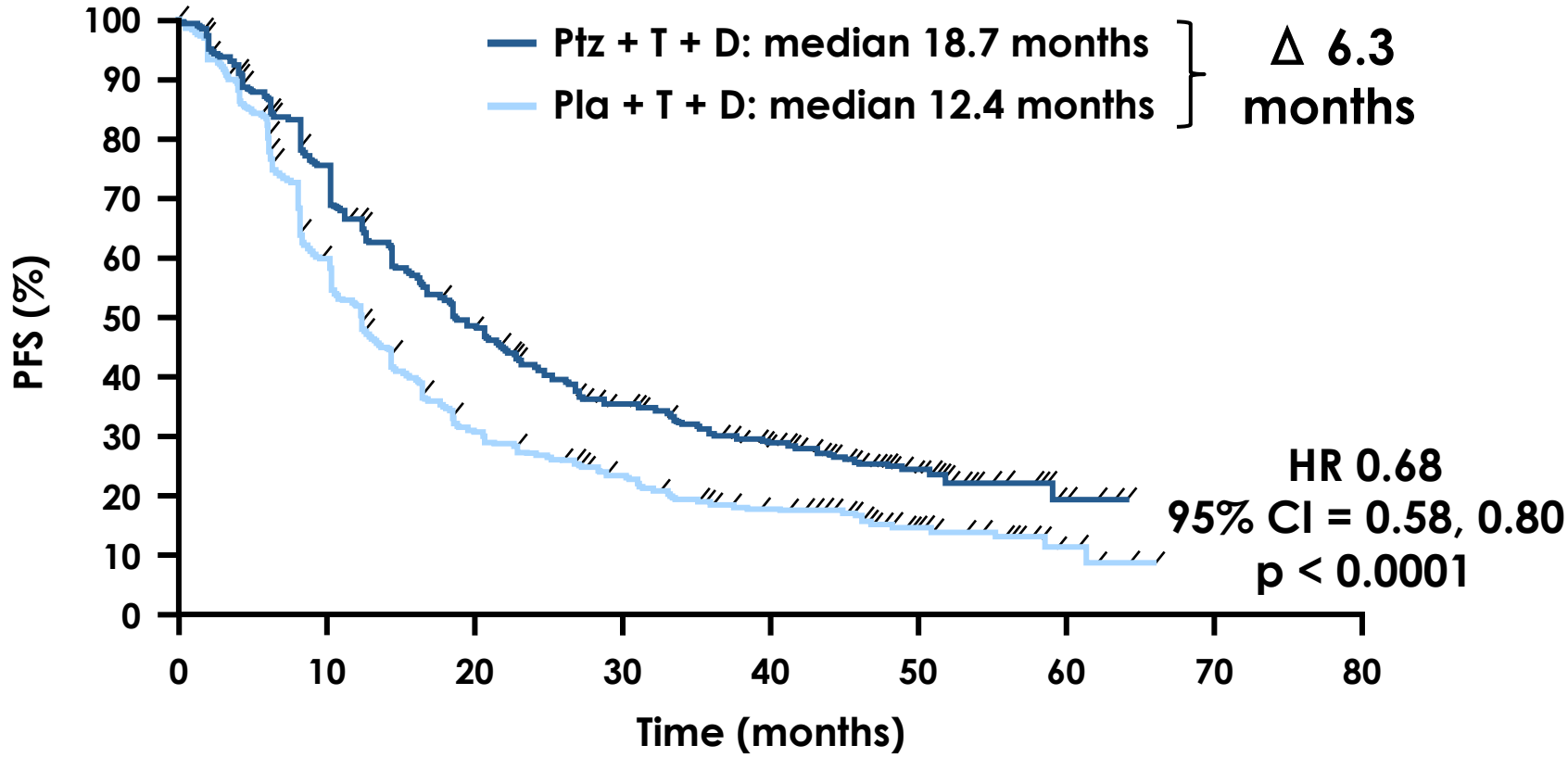
n at risk								
Ptz + T + D	402	371	318	268	226	104	28	1
Pla + T + D	406	350	289	230	179	91	23	0

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Swain SM, et al. ESMO 2014

Updated PFS

Investigator-Assessed



n at risk									
Ptz + T + D	402	284	179	121	87	37	6	0	0
Pla + T + D	406	223	110	75	51	21	6	0	0

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.

Swain SM, et al. ESMO 2014

CLEOPATRA Conclusions

- **The addition of pertuzumab to standard 1L therapy significantly improved median OS by 15.7 months**
  - **Benefit consistent across subgroups**
- **Investigator-assessed PFS benefit maintained**
- **No new safety concerns**
  - **Long-term cardiac safety maintained**

The 56.5-month median OS is unprecedented in this indication and confirms the pertuzumab regimen as first-line standard of care for patients with HER2-positive MBC

Swain SM, et al. ESMO 2014

Acknowledgments

Radiation-Oncology Unit, Careggi University Hospital, Florence, Italy
Head Department: ***Professor Lorenzo Livi***

Clinical Oncology Team

Benedetta Agresti
Pierluigi Bonomo
Carla De Luca Cardillo
Vittorio Cintolesi
Beatrice Detti
Alessandra Galardi
Daniela Greto
Monica Mangoni
Icro Meattini
Fabiola Paiar
Maria Grazia Papi
Maurizio Pertici
Silvia Scoccianti
Vieri Scotti
Gabriele Simontacchi
Susanna Sulprizio

Medical Physics Team

Professor Marta Bucciolini
Chiara Arilli
Marta Casati
Antonella Compagnucci
Livia Marrazzo
Stefania Pallotta
Cinzia Talamonti

GRANDANGOLO IN RADIOTERAPIA ONCOLOGICA

8 Novembre 2014

NEOPLASIA MAMMARIA

Icro Meattini

Radioterapia Oncologica
Azienda Ospedaliero-Universitaria Careggi Firenze