Neoadjuvant therapy – a new pathway to registration?

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Themes

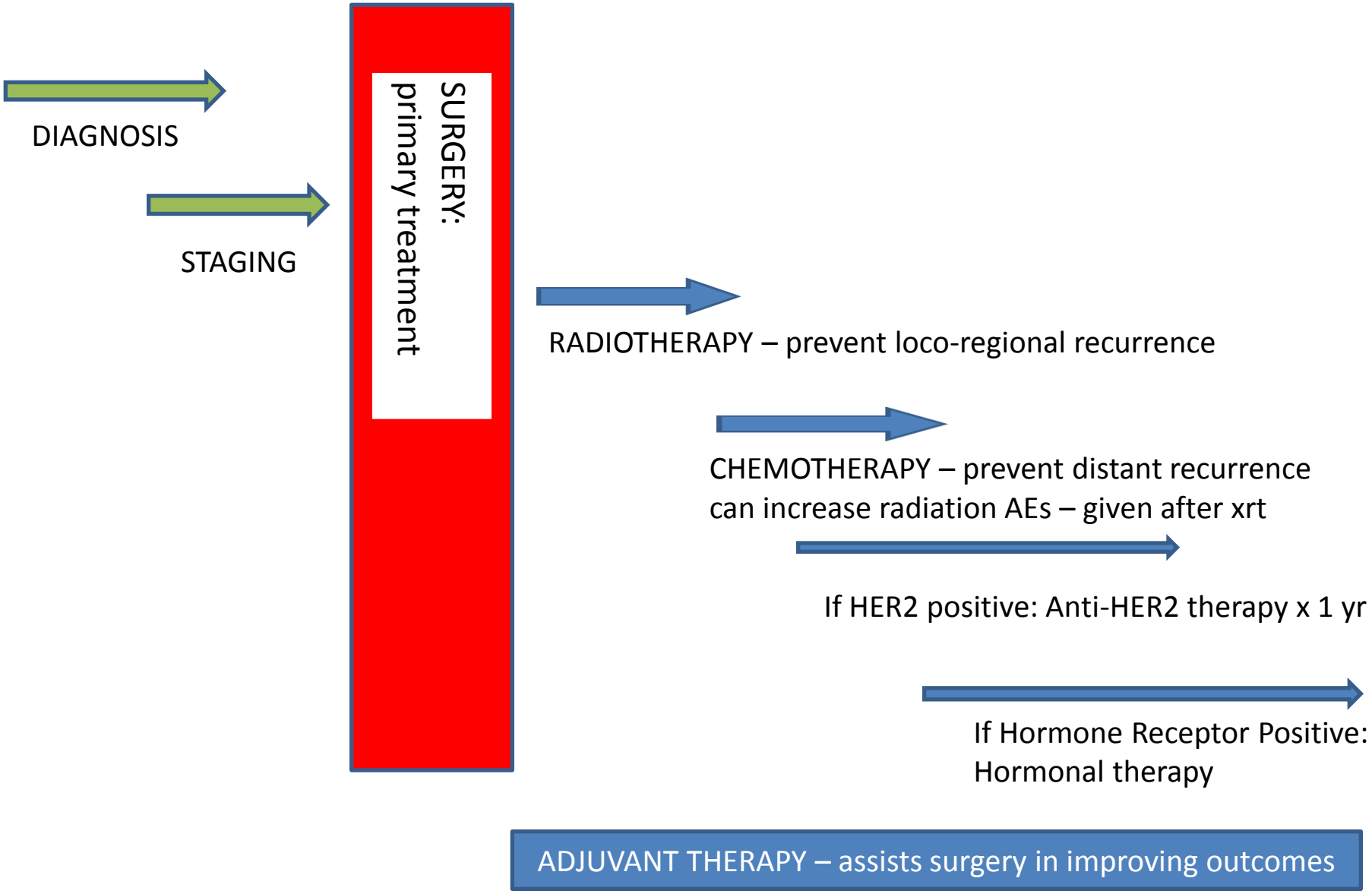
Neoadjuvant therapy

Pathological Complete Response

Pathways to registration of new active agents in Breast Cancer

Standard treatment for early breast cancer

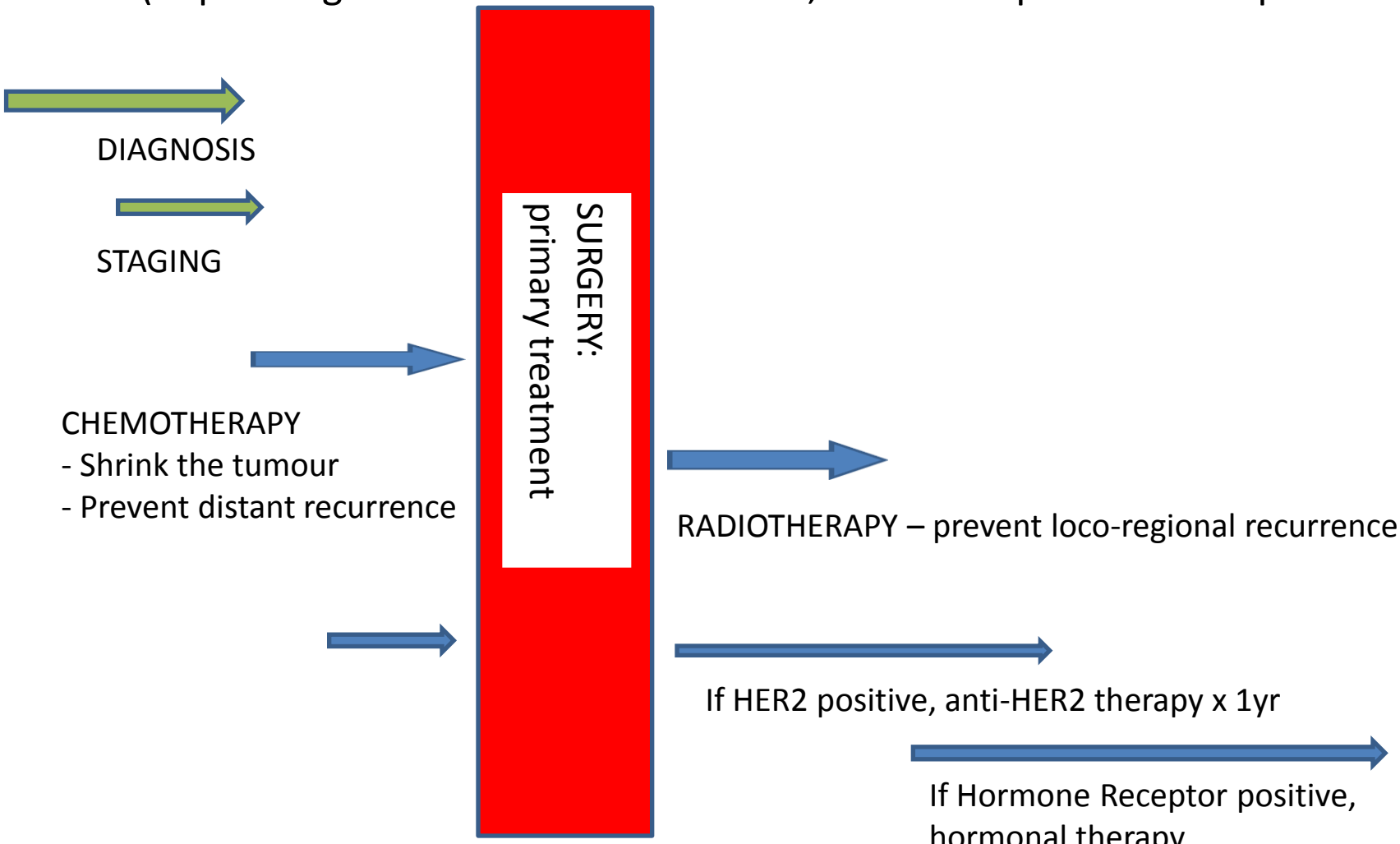
(depending on tumour characteristics, risk of relapse and local practice)



What is neoadjuvant therapy?

Part or all of the adjuvant therapy is given ***prior*** to surgery

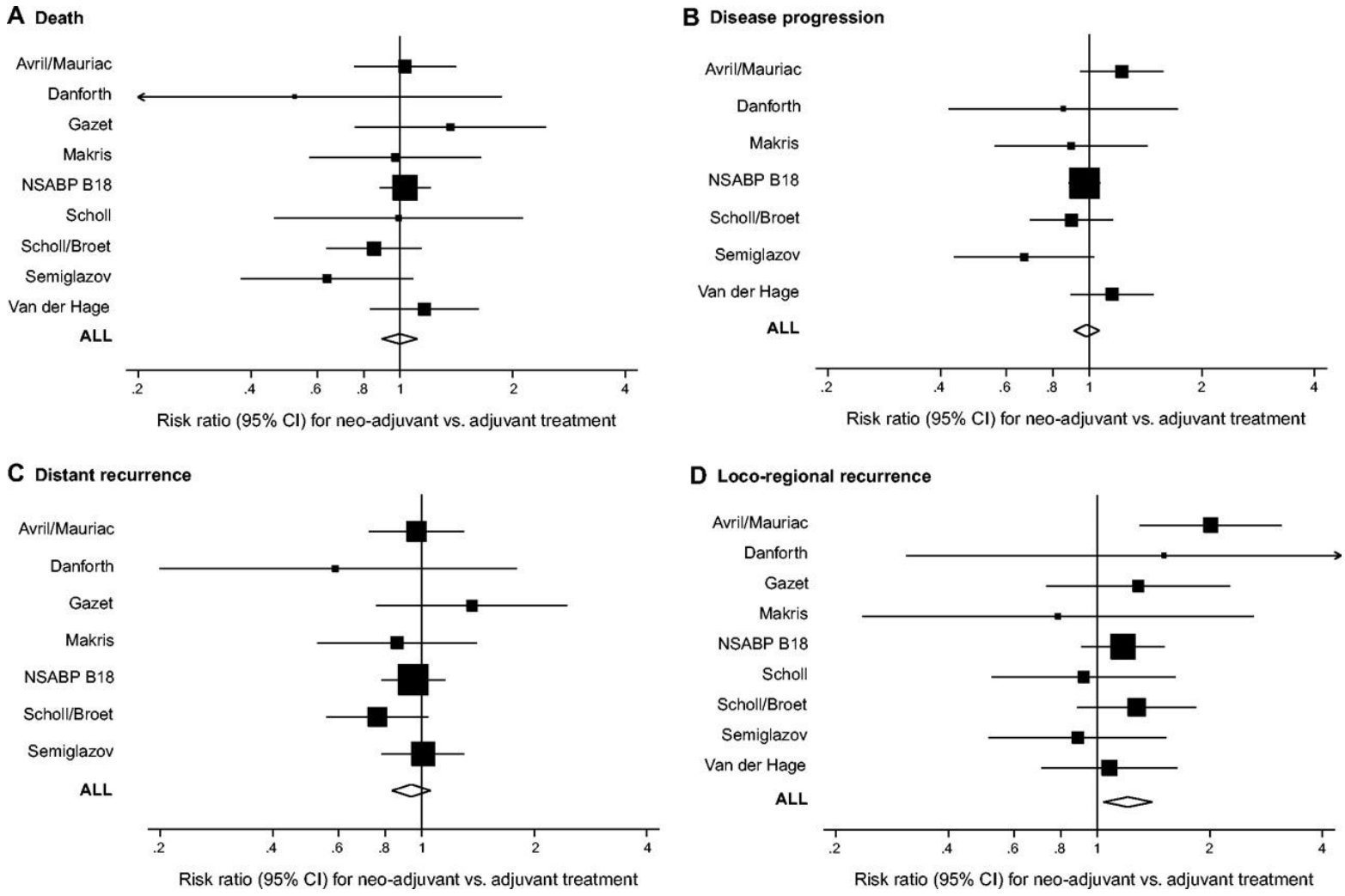
(depending on tumour characteristics, risk of relapse and local practice)



NEO-ADJUVANT THERAPY

ADJUVANT THERAPY – assists surgery in improving outcomes

Mauri Meta-analysis: IF THE SAME TREATMENT IS GIVEN BEFORE OR AFTER SURGERY THE OUTCOMES ARE THE SAME



Mauri D et al. JNCI J Natl Cancer Inst 2005;97:188-194

JNCI

What are the potential advantages of neoadjuvant therapy?

The treatment of choice for inflammatory breast cancer

Facilitates the subsequent surgery:

increased breast conservation [Fisher, B-18, JCO, 1997]

might reduce the complications of surgery [Abt, JAMA Surgery, 2014]

appears to reduce the need for revision of the primary surgery
(revision typically about 20% [Javeen, BMJ, 2012, Morrow, JAMA Surgery 2014])

Enables early intervention with systemic therapy and response -adjusted therapy [von Minckwitz, JCO, 2012] and evaluation of biomarkers (eg Ki-67)

Ideal for research

In addition, for those patients who experience pathological response (pCR)

Is consistently associated with favourable long term outcomes (if we can increase the rate of pCR, one would reasonably expect that we will improve outcomes)

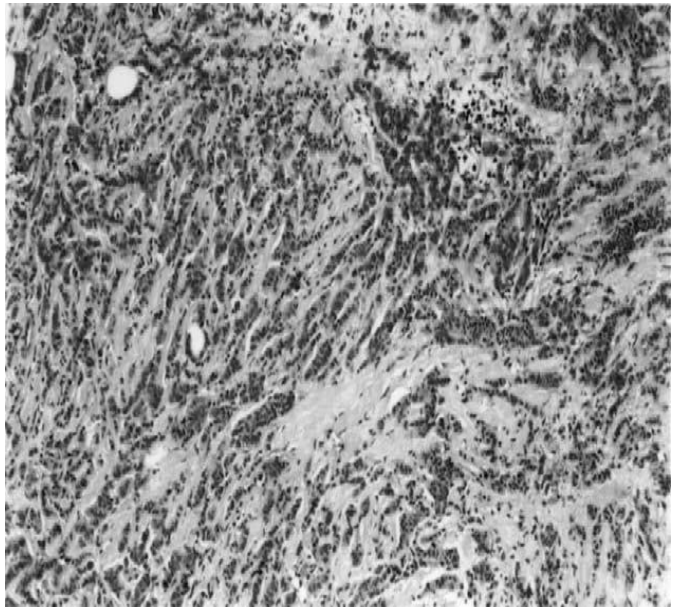
What does pathological Complete Response (pCR) look like?

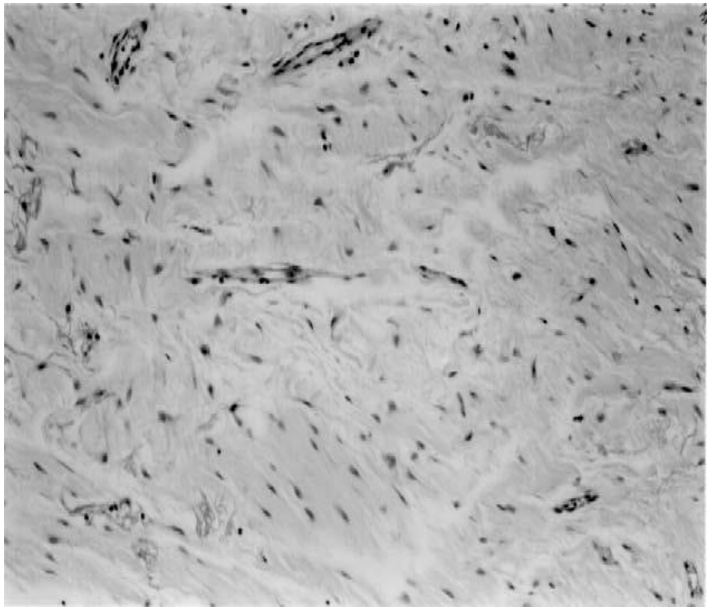
Ogston, Miller, Payne *et al*. The Breast, 2003 Vol 12, Issue 5, pp320-327

Miller-Payne Level 1 Response: no change
Sheets of malignant cells remain

Level 2 → Level 3 → Level 4

Miller-Payne Level 5 Response:
No malignant cells found

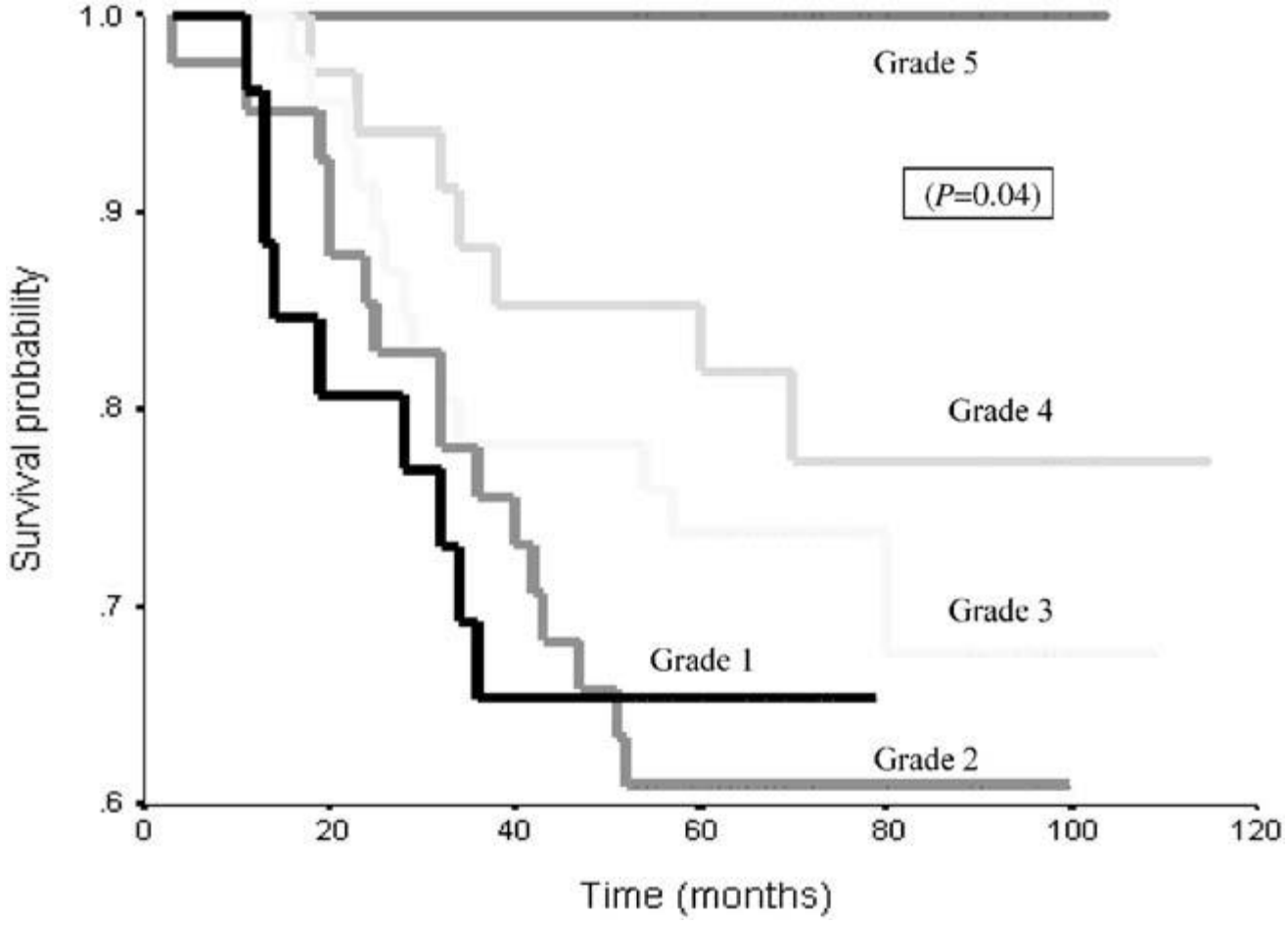




When the diagnostic biopsy is done
the surgeon leaves metal clips behind so
that the tumour bed can be found and excised
even if the tumour has been eradicated completely

Why is pCR important?
Miller-Payne Criteria – "correlation" with survival

Ogston, Miller, Payne *et al*. The Breast, 2003 Vol 12, Issue 5, pp320-327



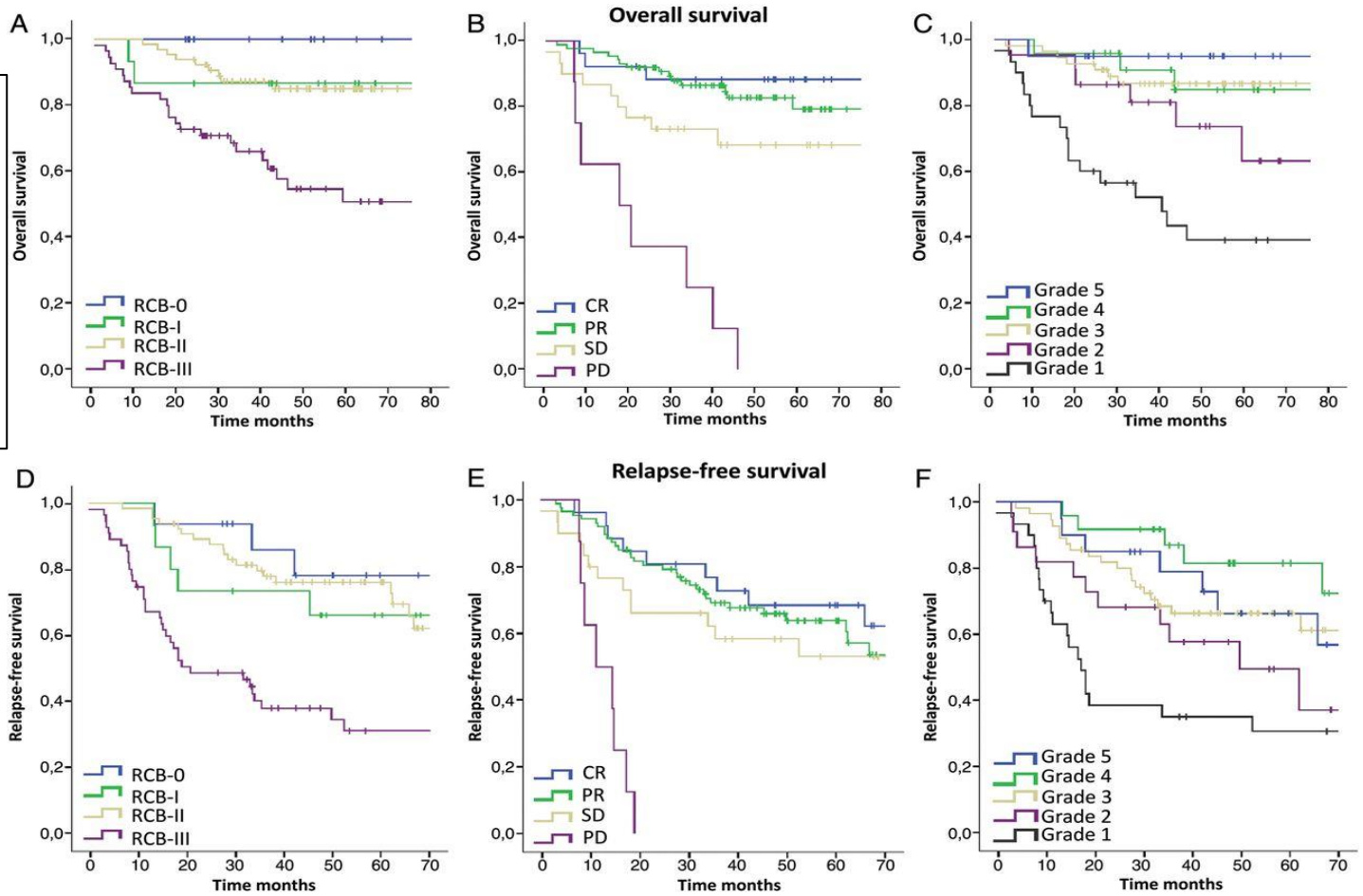
pCR and longer term outcomes using different definitions

Top Figures: Overall Survival; Lower Figures: Relapse-Free Survival

KEY:
A/D Residual Ca Burden (Symmans)

B/E RECIST

C/F Miller-Payne



Romero A et al. Ann Oncol 2013;24:655-661; See Also Symmans F, JCO, 25, 28, Oct 1 2007, pp4414-4422 and SABCS, 2013

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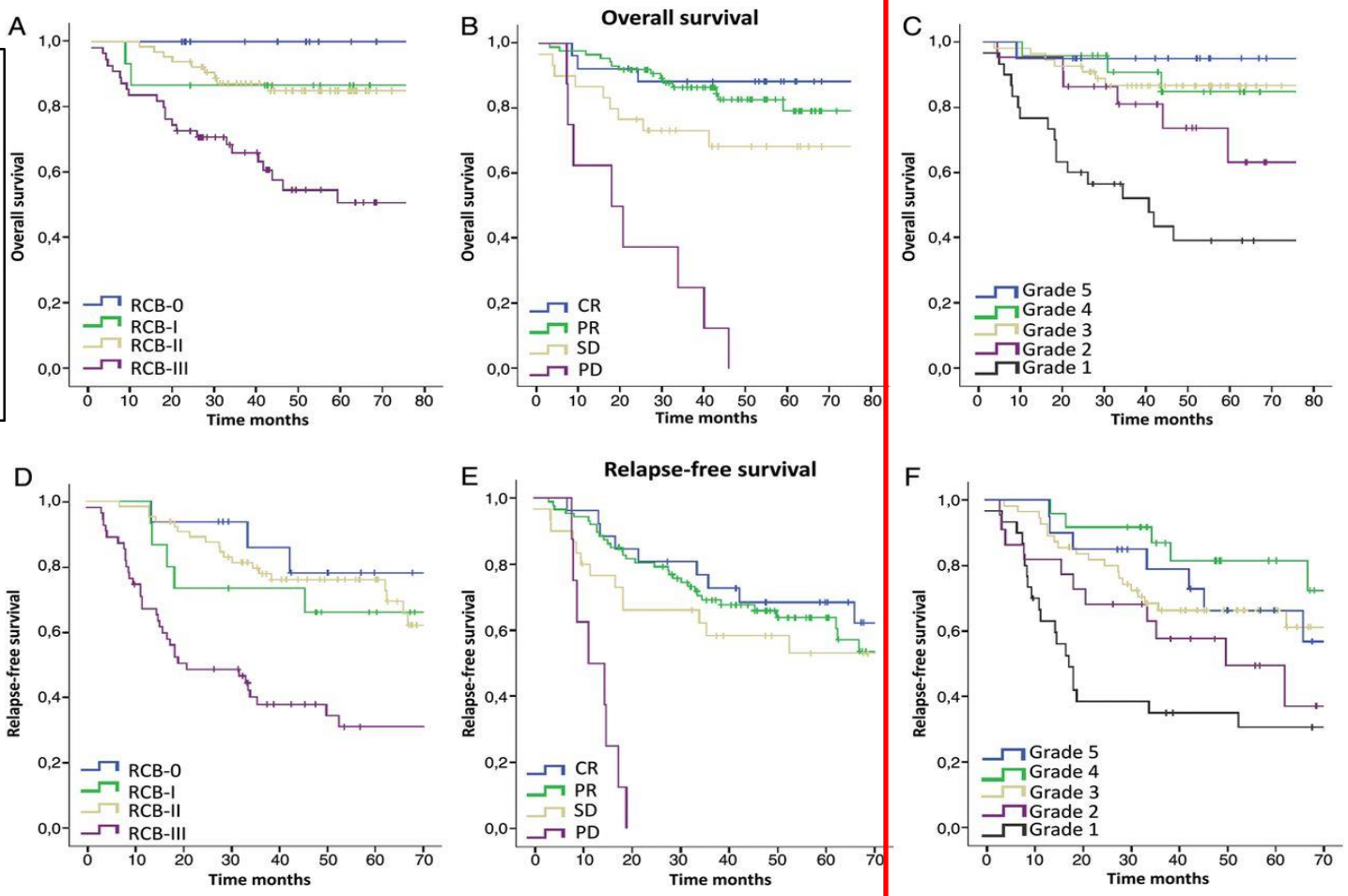

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Common Definitions of pCR

	Breast pCR	Total pCR	GBG pCR
Meaning	Elimination of invasive disease from the breast	Elimination of invasive disease from breast ***and*** axillary nodes negative at surgery	Elimination of invasive disease ***and ductal carcinoma in situ*** from breast ***and*** axillary nodes negative at surgery
TNM	ypTO/is	ypTO/is NO	ypT0/NO
Used by:	Miller-Payne NSABP prior to 2008 [Bear, 2006] Michelangelo [NOAH, ECTO]	NSABP after 2008 [Rastogi, 2008] I-Spy [Esserman, 2013] FDA [Cortazar, 2014], CHMP	German Breast Group [von Minckwitz, 2012]

Each definition has been shown independently to be associated with favourable Event Free / Disease Free Survival and Overall Survival

Limitations of pCR

Although there is a consistent association between pCR and favourable clinical outcomes, pCR has not been shown formally to be a surrogate for outcomes

Cortazar et al attribute this to heterogeneity and to insufficient evidence in the specific sub-groups

[*The Lancet*, *Volume 384, Issue 9938*, *12–18 July 2014*, *Pages 164-172*]

Furthermore, the percentage increase in pCR that will be associated with a meaningful increase in outcomes is not known

Efficacious Agents in Breast Cancer:

pCR increases and long-term outcomes

	NEOADJUVANT	ADJUVANT
	bpCR Improvement	HR for DFS Improvement
Docetaxel	12.4 – 15.4% [1,2]	0.74 [4]
Anthracycline	14.0% [1]	0.69 [5]
Trastuzumab	17.6% [3]	0.48–0.67 [4]

[1] NSABP B-27; [2] Aberdeen; [3] NOAH; [4] Data from USPI; [5] NEAT.

Breast Cancer: genetic sub-types and corresponding phenotypes

Luminal A | Luminal B | HER2 | Basal | Normal

No specific targets
Chemotherapy sensitive

Estrogen Receptor +'ve
Hormonal therapy
Less chemotherapy sensitive
(*outcomes in relation to pCR are particularly difficult*)

HER2 amplification
Trastuzumab +/- hormonal therapy
Chemotherapy sensitive

Turner & Jones, BMJ, vol 337, 19 July, 2008, p165 (BMJ.com)
Rouzier R, Perou CM, *et al*, Clin Ca Res, 2005, Aug 15; 11: 5678-85

History of neoadjuvant registrations

www.ema.europa.eu and www.fda.gov

NOTE: First use of neoadjuvant therapy was in 1924 (Geoffrey Keynes used radiotherapy to shrink tumours prior to surgery)

Both EU and FDA Guidelines make provision for “conditional approval” or “accelerated approval” respectively – to enable promising new medications to be made available to patients with life-threatening diseases pending data from full Phase III studies.

In the EU, conditional approval is available only for the first registration of a new product

Letrozole (aromatase inhibitor) – registered in the EU for neoadjuvant use in the EU in 2012, added to the previous registrations as adjuvant therapy and for metastatic disease

Trastuzumab – registered in the EU for use in combination with chemotherapy for early breast cancer: adjuvant use: 2006; neoadjuvant 2012

Editorial, New England Journal of Medicine 6th June, 2012

Dr R Pazdur

(Director of the Office of Hematology and Oncology Products at FDA)

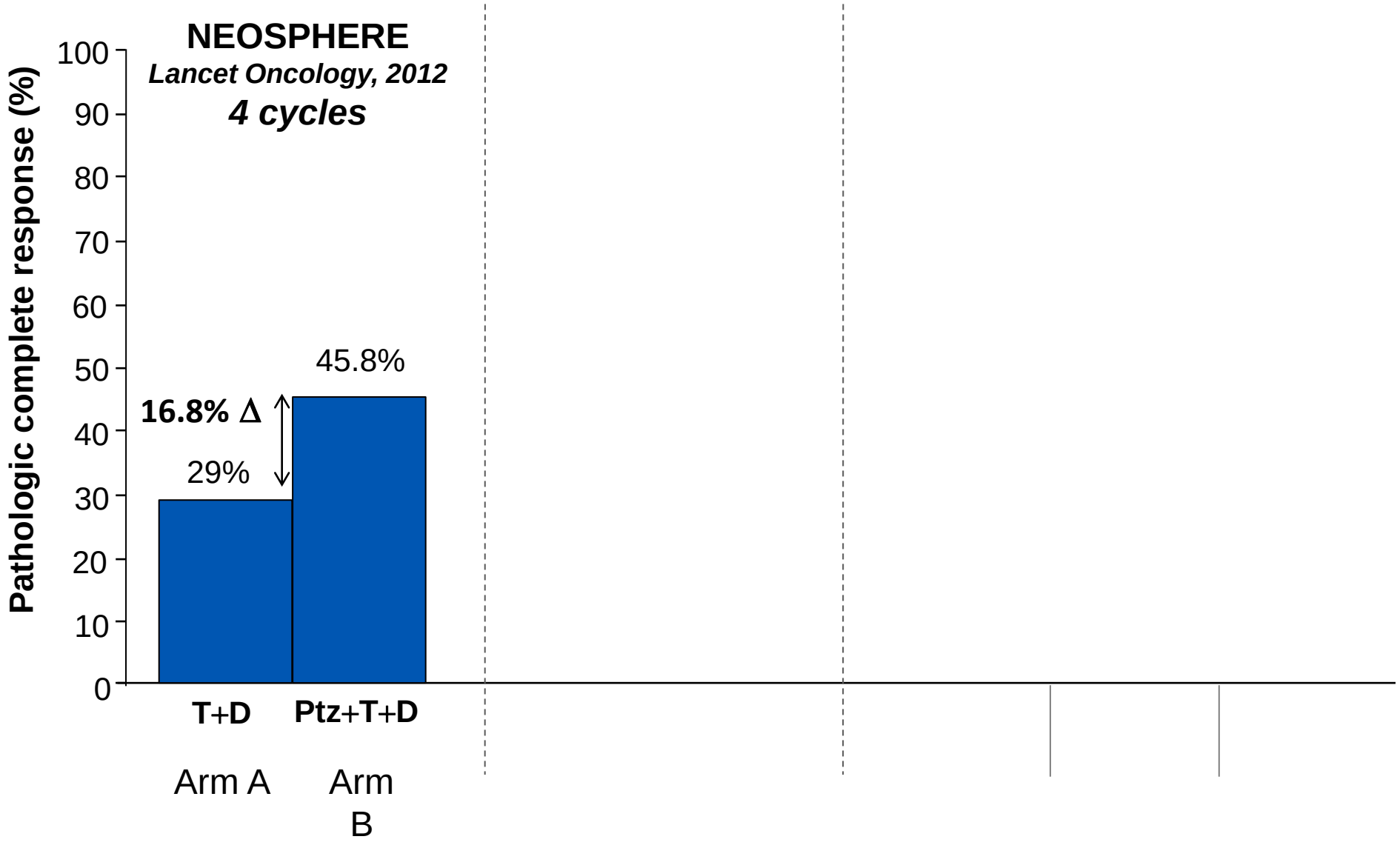
For a new therapy for which there is a convincing demonstration of effect on pathological Complete Response with a confirmatory study running there is potentially a path to accelerated approval

(ie a conditional licence as neoadjuvant therapy with conversion to full approval based on the data from the adjuvant / confirmatory study)

Note: the decision will be based on a body of evidence (not on a single study)

CASE STUDY: pertuzumab (NOTE: registered for metastatic HER2 positive breast cancer and confirmatory study (APHINITY / BIG 4-11) is fully enrolled)

pCR Rates in HER2 positive Early Breast Cancer:



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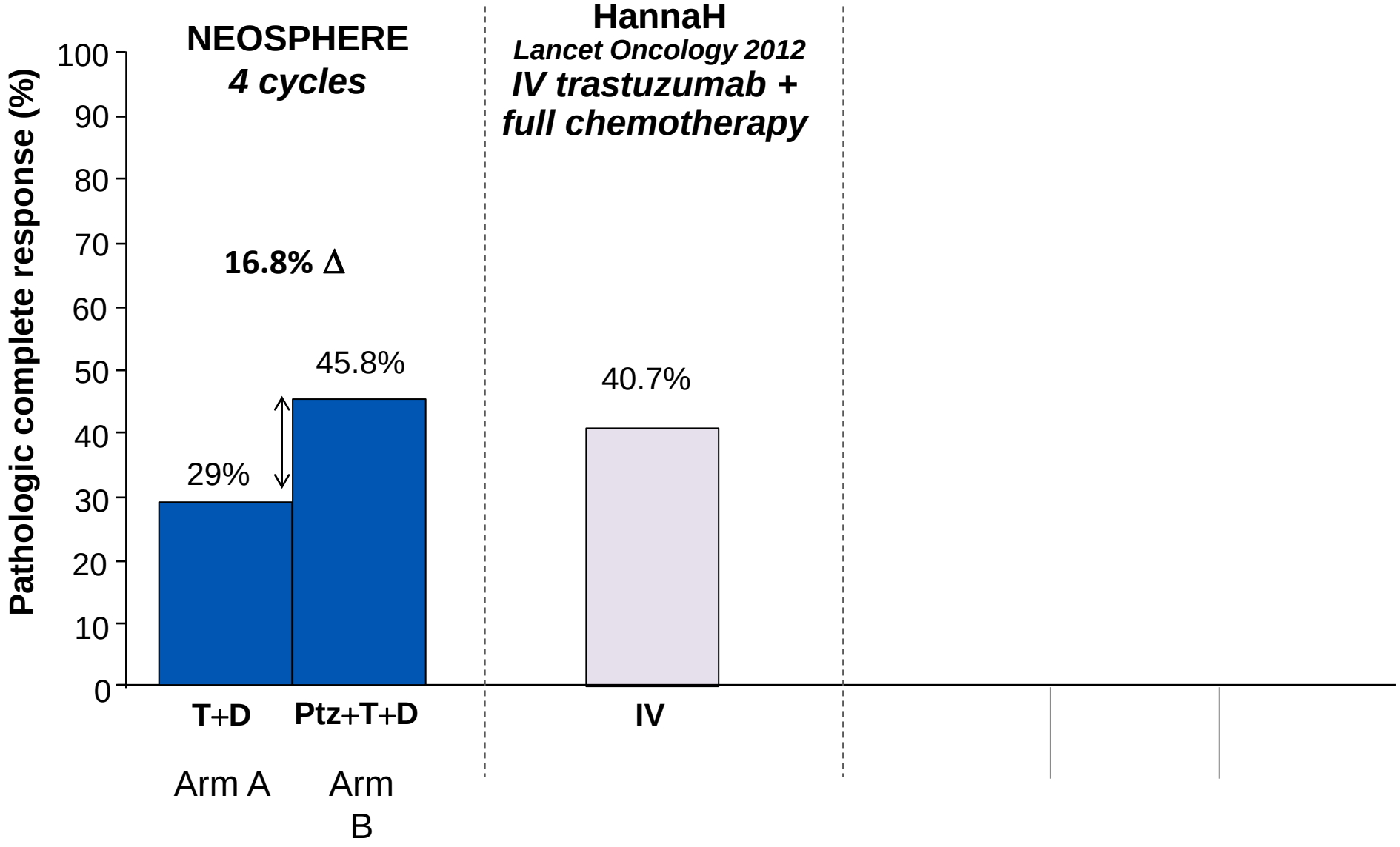
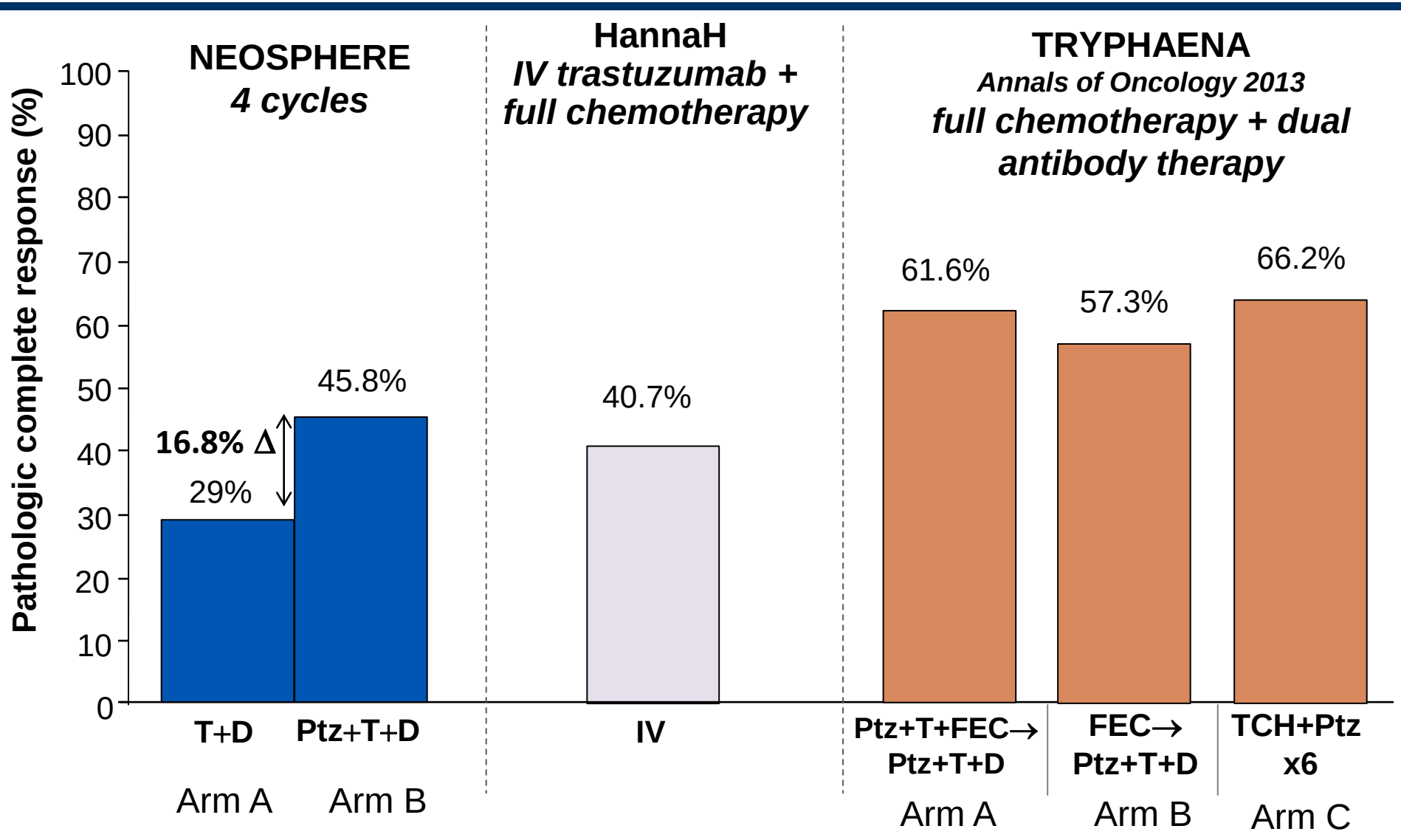


pCR Rates in HER2 positive Early Breast Cancer:

Highest pCR rates following full chemotherapy with dual antibody therapy



FDA: final guidance, Oct 2014

Guidance for Industry

Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2014
Clinical/Medical

Some points from the FDA guidelines

Definition of pathological Complete Response: Total pCR or GBG pCR

Randomised, controlled neoadjuvant study; superiority design (standard therapy versus standard therapy plus new agent adde-on preferred)

Pathologists ***should*** be blinded to treatment assignment – note to pathologist describing the study, and primary tumour site, size, etc. so that the pathologist does not need to consult the hospital records in order to conduct the evaluation

NOTE: On page 16, Section E, 1st paragraph, pathologists should receive training at a small number of centralized geographic locations

Management of the axilla should be standardised within the protocol (but this is a very complex issue and the data are still emerging)

Confirmatory study: can be incorporated in one study (pCR and EFS) or separate confirmatory study

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 March 2014
EMA/CHMP/151853/2014
Committee for Medicinal Products for Human Use (CHMP)

The role of the pathological Complete Response as an endpoint in neoadjuvant breast cancer studies

Condition - specific guidance, Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man

Agreed by ONCWP	25 November 2013
Adopted by CHMP for release for consultation	20 March 2014
Start of public consultation	28 April 2014
End of consultation (deadline for comments)	31 July 2014

Comments should be provided using this template. The completed comments form should be sent to ONCWPsecretariat@ema.europa.eu

Keywords	Breast cancer, pCR, neoadjuvant treatment, surrogate endpoint

Background	Concept paper on the need to revise Condition – Specific guidance, Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man

European Medicines Agency anti-cancer guideline on pCR March 2014 (Draft Guideline, emphasis added)

«...approval based on pCR may be acceptable for patients with aggressive (high-risk) early stage breast cancer.....

as add-on to an established (neo) adjuvant regimen,

If
there is a well-characterised mechanism of action
and provided the results show major increase in pCR
with only minor changes in toxicity.

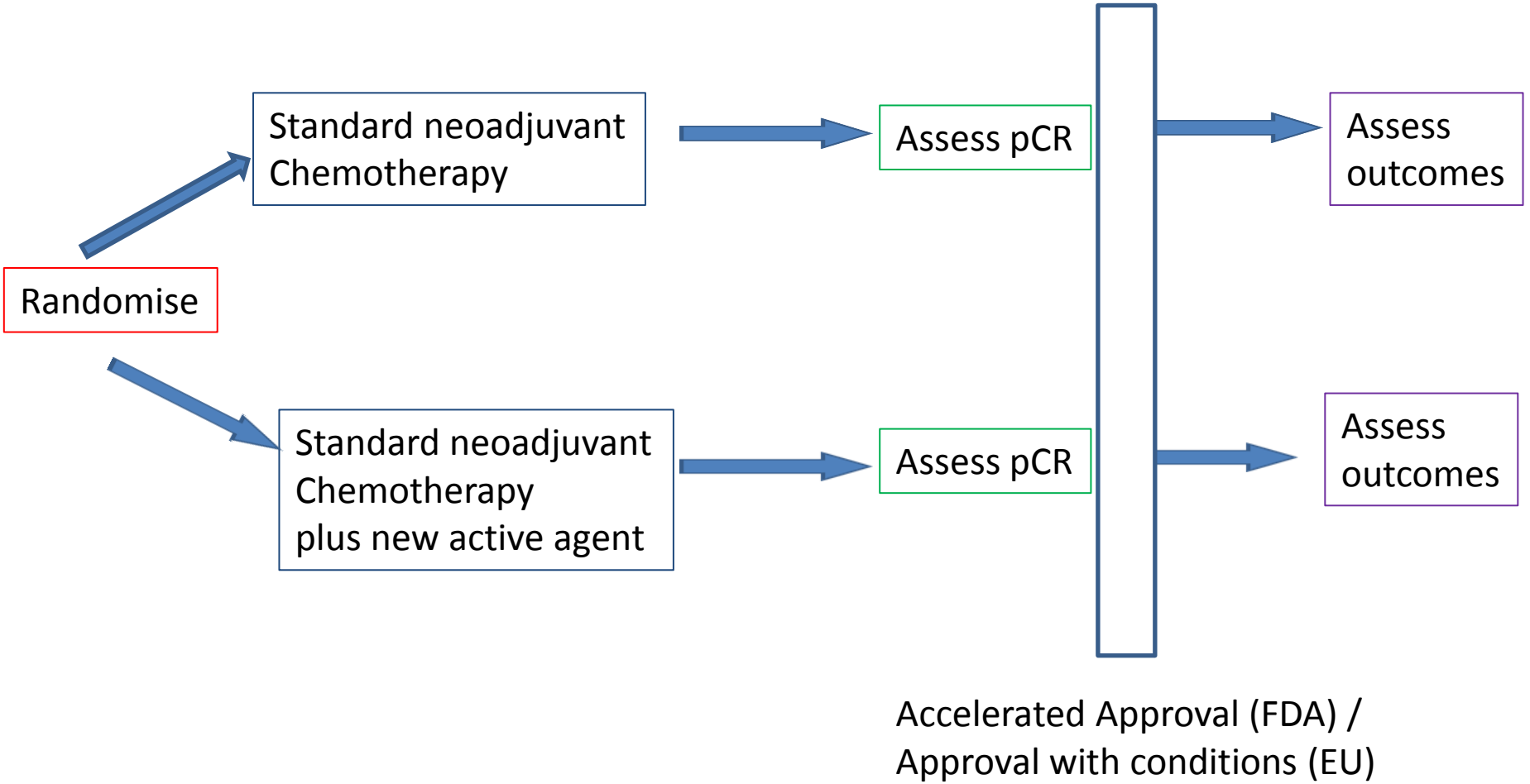
Such results may lead to an approval with agreed conditions for confirmatory study data in terms of DFS/OS...»

Pertuzumab received positive opinion for neoadjuvant therapy from CHMP June 2015 – ratification by EU Parliament within the statutory 67 days expected.

*Speaks of pCR as a "proposed surrogate" in the literature;" and of the "desirablity of a new surrogate", but does **not** say that surrogacy has been established.*

Confirmatory Study:
one study approach versus two-study approach

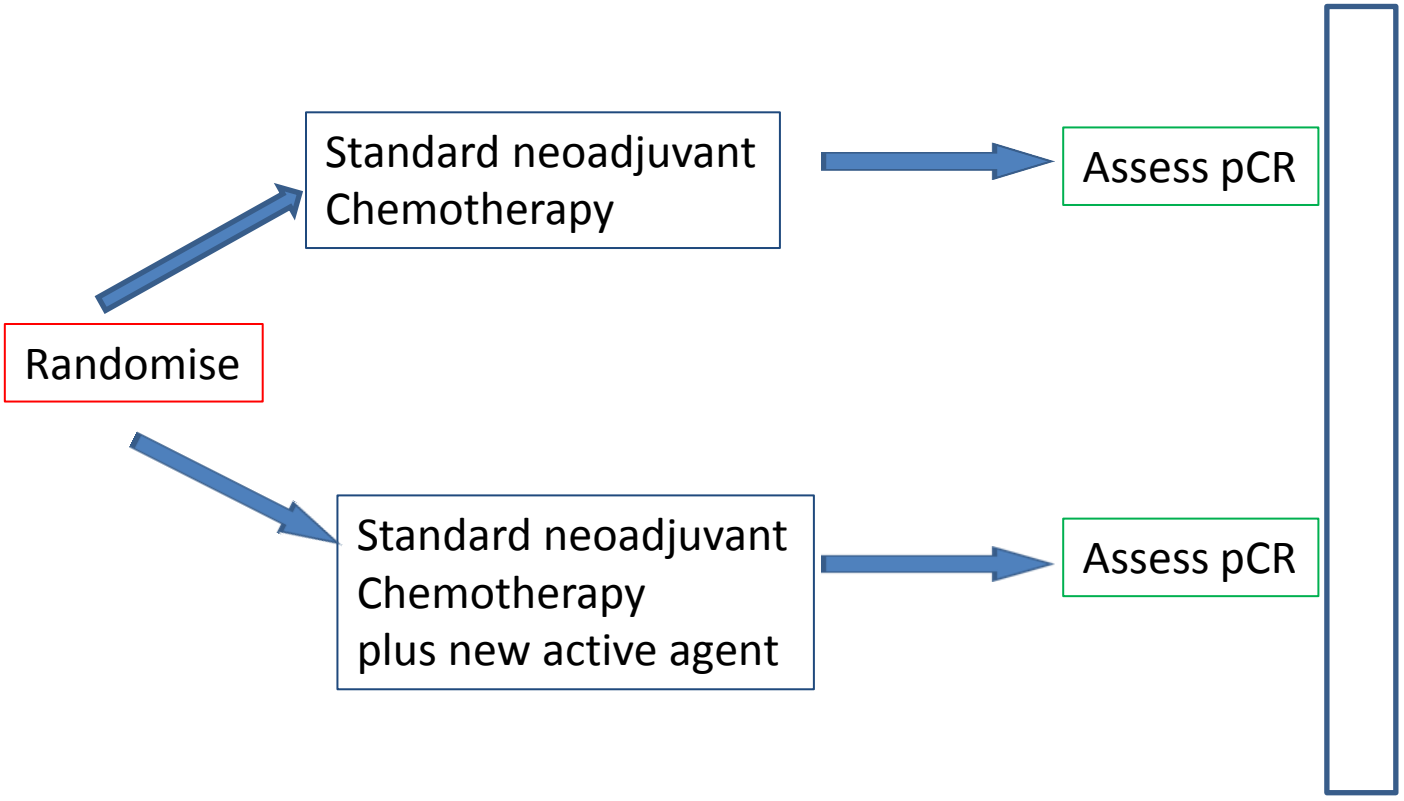
One study approach: assess pCR and outcomes in the same study



One study approach

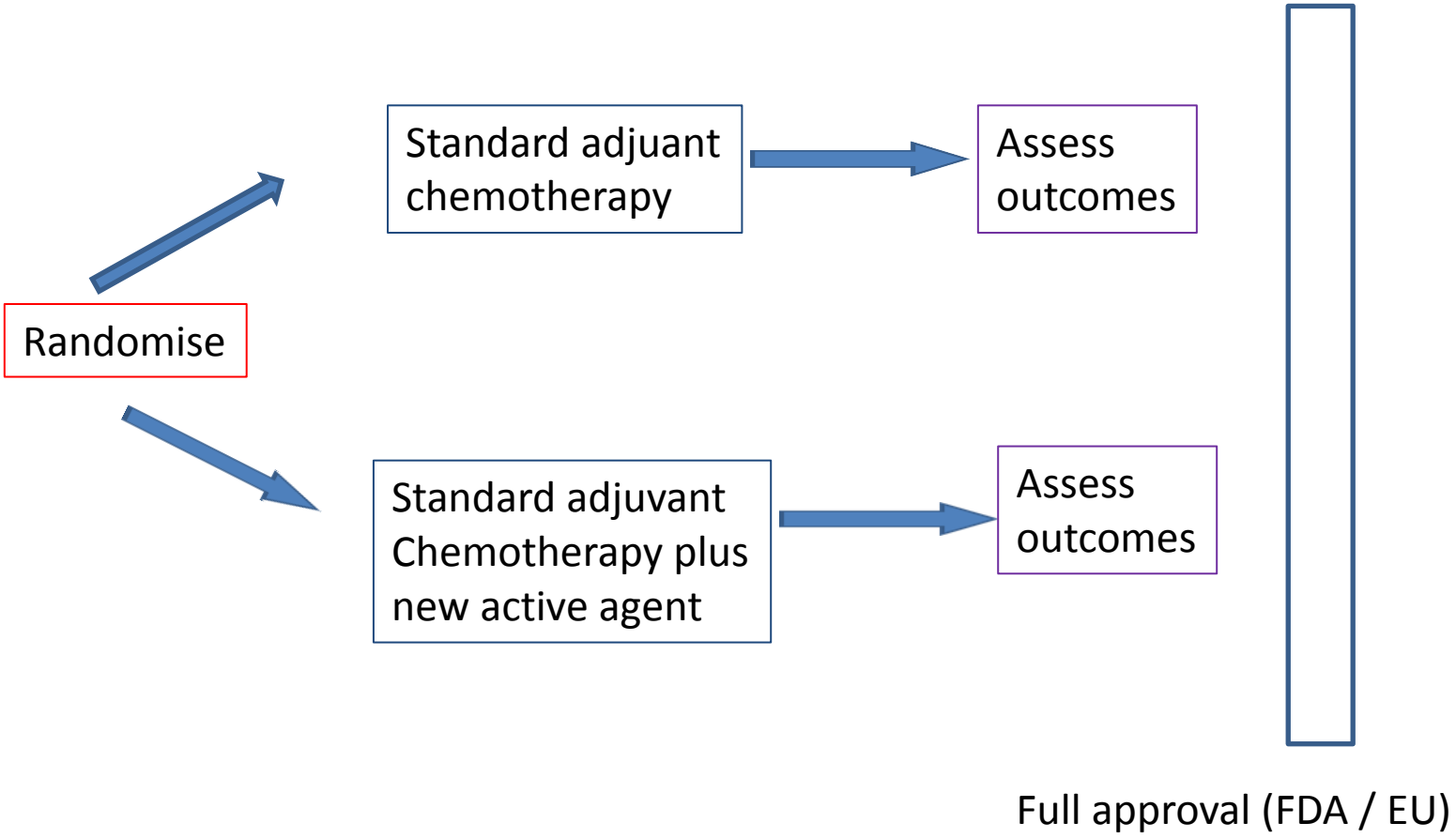
PRO's	Con's
Single study – will prove the effect of the new agent on pCR and on outcomes	Study will be large and time-consuming
	Still requires interaction and Phase II studies – time lost

Confirmatory Study:
Two-study approach 1) neoadjuvant



?Accelerated Approval (FDA) /
?Approval with conditions (EU)

Confirmatory Study:
Two-study approach 2) Adjuvant confirmatory study



Two study approach

PRO's	CON's
Neoadjuvant studies serve as interaction and Phase II studies – off-sets risk and saves time	Does not directly link pCR with new active agent to outcomes with new active agent
Confirmatory study is simple in design and execution	

Conclusions

For patients in whom pCR is achieved following neoadjuvant therapy, there is a consistent association with favourable long term outcomes

For a therapeutic with a well established profile (including good tolerability), and a substantial effect on pCR with a confirmatory study ongoing, there is potential for approval with conditions / accelerated approval

The confirmation (conditional approval -> approval) can be based on either one study or two studies

Overall, new active agents can potentially be made available to patients expeditiously