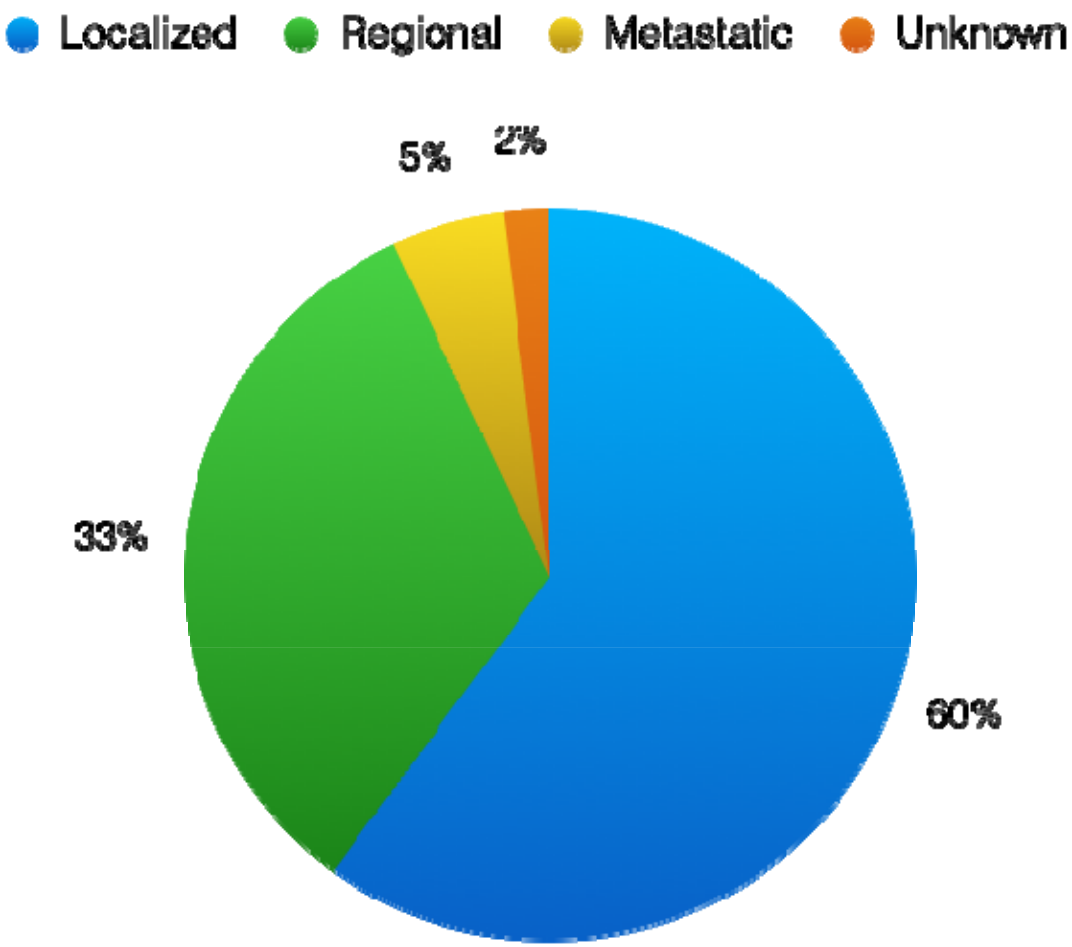
Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use of an Endpoint to Support Accelerated Approval

Tatiana Prowell, MD
Patricia Cortazar, MD
Office of Hematology Oncology Products (OHOP)
Division of Oncology Products 1 (DOP1)
Breast Oncology Group

Outline

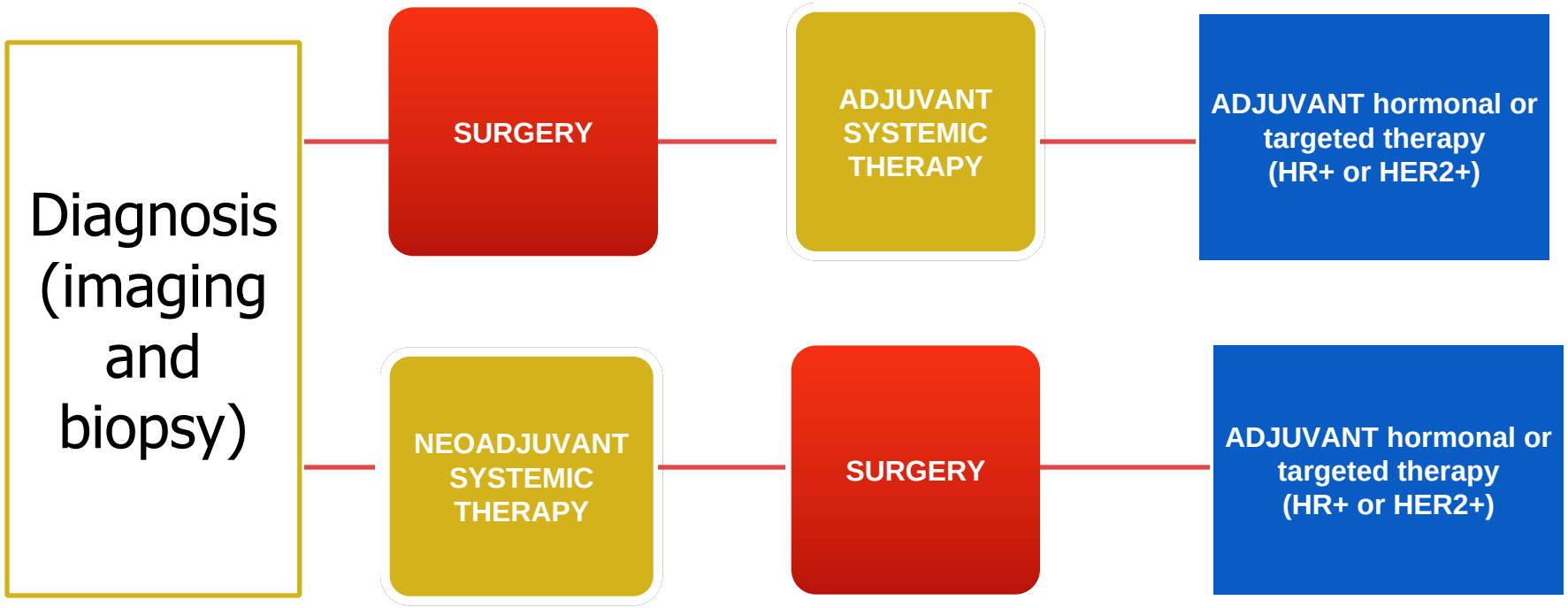
- Neoadjuvant trials background
- Why is FDA interested in neoadjuvant trials?
- Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC)
- Draft Guidance for Industry: Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

USA Breast Cancer Stage Distribution at Diagnosis



Based on Nov 2011 SEER Data

Sequence of Therapy for Early Breast Cancer



Rationale for Neoadjuvant Treatment

- In LABC and IBC: Tumor downstaging:
  - Inoperable → Operable
  - Mastectomy → Breast Conservation
- Reduce the likelihood of post-surgical metastatic disease
- *In vivo* tumor response assessment:
  - Identify unresponsive tumors and terminate ineffective therapy
  - Provide prognostic information
- Ideal scenario to study tumor biomarkers and intermediate endpoints

Sequence Therapy for Early Breast Cancer

NEOADJUVANT SYSTEMIC THERAPY

- Smaller sample size
- Primary endpoint: pCR (assessed months)
- Short drug exposure
- Needs prior safety information
- Needs safety information from longer exposure

ADJUVANT SYSTEMIC THERAPY

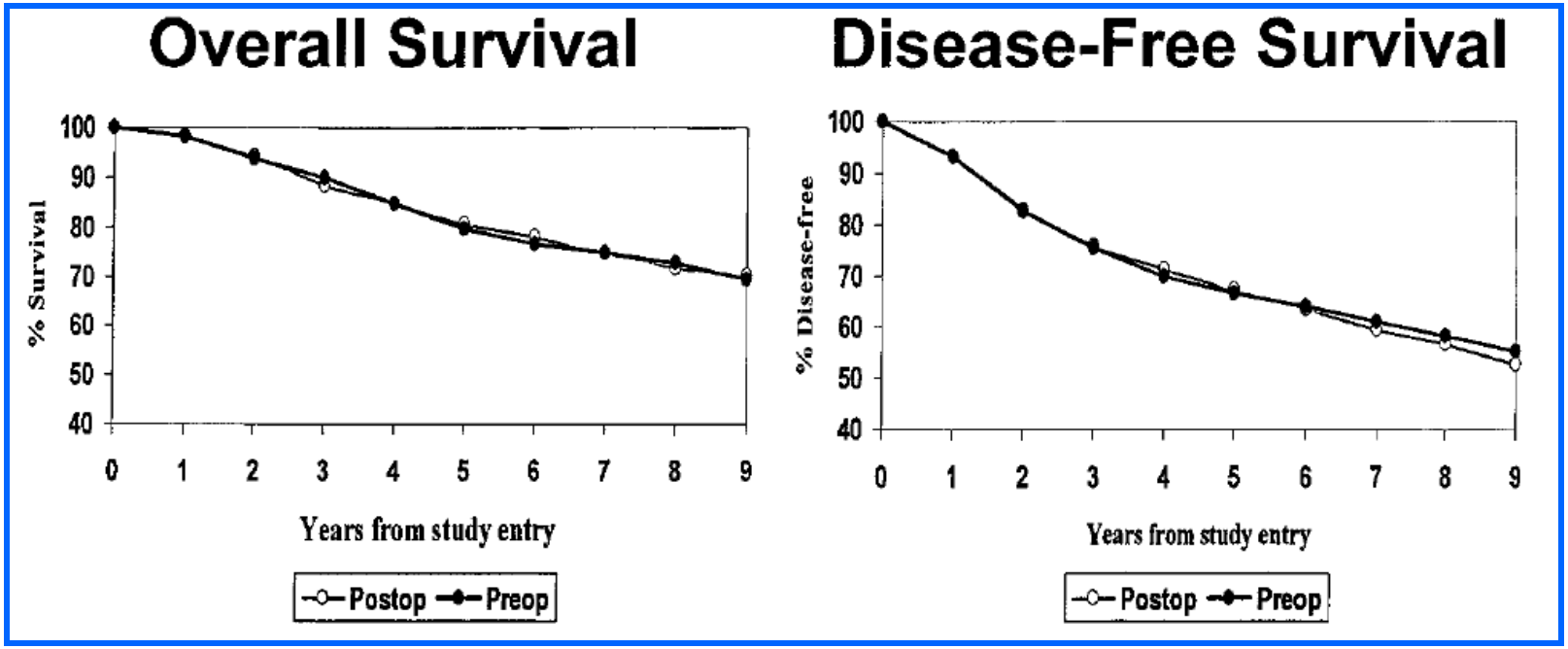
- Bigger sample size
- Primary endpoint: DFS, OS (assessed years)
- Best setting to assess long-term outcome (DFS, OS)
- Better safety assessment

FDA

Lessons Learned From Neoadjuvant Trials

No differences in DFS and OS between pre-op and post-op systemic therapy: AC x 4 cycles

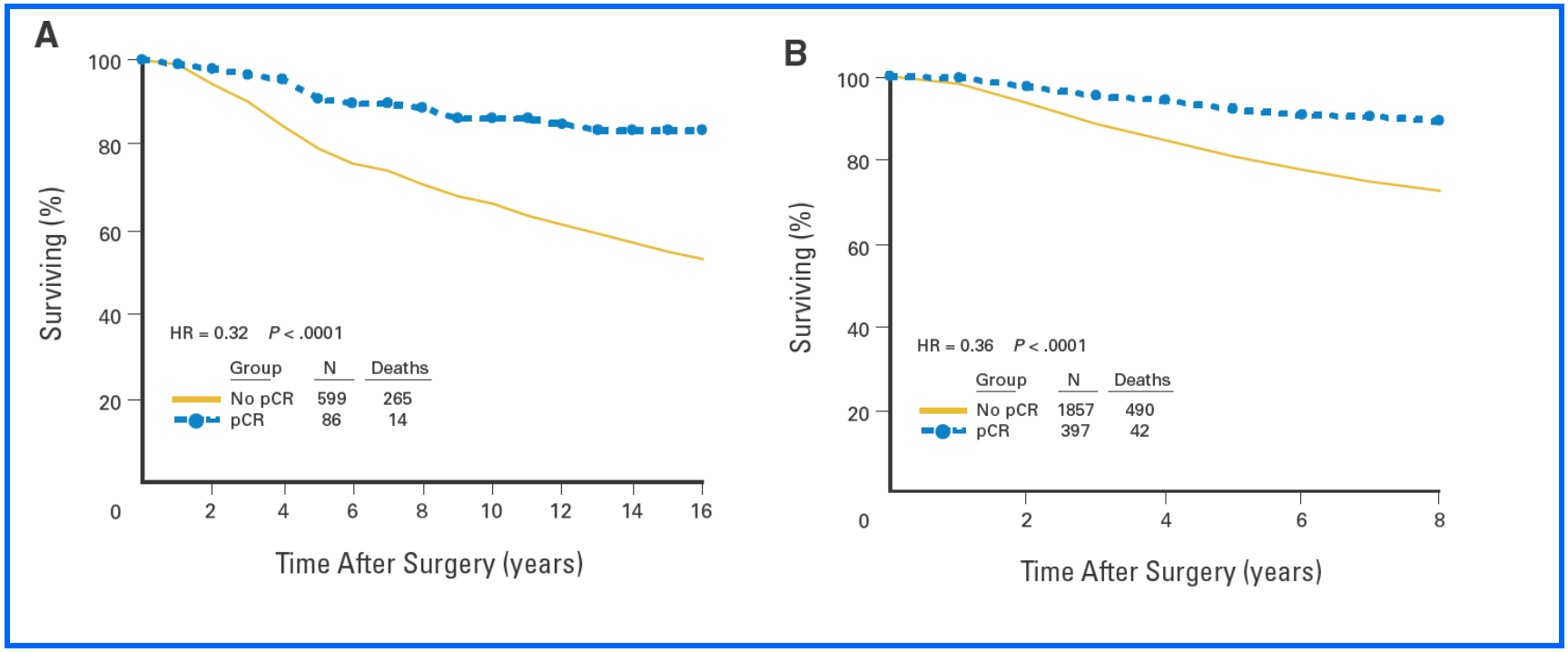
NSABP B-18: 9 yrs follow-up



Wolmark: JNCI Monographs 2001

Lessons Learned From Neoadjuvant Trials

Patients with pCR have a better long-term outcome.
NSABP B-18 and B-27



Rastogi: JCO 2008

Why is FDA interested in Neoadjuvant Trials?

- Neoadjuvant trials can improve drug development
- Recently being used to support drug approvals in advanced breast cancer

Considerations for Future Neoadjuvant Breast Cancer Approvals

- Is pCR the appropriate primary endpoint?
- What is the pCR association with long term outcomes (DFS and OS)?
- Can pCR predict efficacy in adjuvant and MBC settings?

Issues with pCR

- Lack of uniform pCR definition
- Surgical management of axilla is evolving
- Trials included heterogeneous tumor subtypes
  - can attenuate pCR
  - pCR varies by molecular subtypes

pCR Definitions

- Absence of invasive cancer:
  - In the breast only
  - In the breast and axillary lymph nodes
- Absence of invasive and in situ cancer
  - In the breast only
  - In the breast and axillary lymph nodes

pCR differs according to molecular subtypes

Anthracycline / taxane-based neoadjuvant response

Courtesy Chuck Perou (Cheung et al SABCS 2011)

	Classification	pCR rate	# of patients	MVA* OR (95% C.I.)	p-value
	All Patients	123 (22%)	568		
PAM50	Luminal A	5 (3%)	163	1	-
	Luminal B	14 (16%)	87	6 (1.5-23)	0.011
	Normal-like	10 (18%)	56	7 (1.8-30)	0.006
	HER2-E	22 (33%)	66	11 (2.7-46)	0.001
	Basal-like	72 (37%)	196	16 (4.4-61)	<0.001
ER	ER+	36 (11%)	329	1	-
	ER-	87 (37%)	238	2 (0.9-3.1)	0.132
clinHER2	clinHER2-	97 (19%)	501	1	-
	clinHER2+	26 (39%)	67	2 (0.8-3.8)	0.141

*MVA model included grade, clinical T stage and nodal status measured at baseline

Collaborative Trials in Neoadjuvant Breast Cancer CTNeoBC

Project Collaborators:

FDA

US and EU Cooperative Groups (NSABP,

German Breast Study Group (GBG, AGO-B),

Italian Breast Group, EORTC?)

Charles Perou

NIH

Criteria for Trial Selection

- Neoadjuvant randomized controlled trials
- pCR clearly defined with all necessary data collected
- Long-term follow-up DFS and OS data collected

Analysis Objectives

- To evaluate the association between pCR and long-term outcome (DFS/OS) in > 12,000 patients with early breast cancer treated with neoadjuvant therapy
- Identify breast cancer subgroups in whom pCR is likely to predict clinical benefit

What is FDA doing to expedite the development of breakthrough therapies to treat high risk, early-stage breast cancer

- Opening path forward to neoadjuvant trials to support drug approval
  - CTNeoBC meta-analysis will help us better understand pCR correlation with long-term outcome
  - Draft Guidance on Neoadjuvant Trials
- Looking at other alternatives to accelerate drug development in breast cancer

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

Tatiana M. Prowell, M.D.
Breast Oncology Group,
Office of Hematology & Oncology Products

Goals of the Guidance

- Propose a uniform definition of pCR
- Briefly summarize current knowledge of relationship between pCR and outcome
- Identify patient populations in whom pCR is reasonably likely to predict clinical benefit
- Describe neoadjuvant trial designs for accelerated approval and conversion to regular approval

Accelerated Approval Regulations

- "FDA may grant marketing approval for a new drug [or biological] product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely…to predict clinical benefit..." (21 CFR 314.510 and 21 CFR 601.41)
- Require confirmation of clinical benefit (DFS or OS) and include provision for withdrawal of indication if fail to confirm clinical benefit

Proposed Definition of pCR

- ***Pathological complete response (pCR)*** is defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0 ypN0).

Rationale for pCR Definition

- Neither LCIS nor DCIS is believed to regress with chemotherapy.
- Persistence of LCIS or DCIS after chemotherapy is probably not of prognostic significance.
- Regional nodal involvement, either at presentation or after neoadjuvant therapy, is associated with decreased OS.
- Surgical mgmt of axilla is evolving: full ALND is performed less frequently and will likely not be required in future trials.

A Note on Local Therapy

- Primary endpoint includes pathologic status of the axilla
  - Approach to local therapy <u>must</u> be consistent across treatment arms to avoid confounding of endpoint.
- All patients should receive lumpectomy/radiotherapy or mastectomy +/- PMRT, according to current standards of care, regardless of response.

Appropriate Patient Populations for This Pathway

- Populations at high-risk of recurrence and death despite best, modern systemic therapy
  - May be defined conventionally (histology, receptor status, etc.) or via appropriately validated genomic measures
  - Focus on triple negative (ER-,PR-,HER2-) and HER2+ pts
    - Highest likelihood of pCR
    - Most compelling data to date that pCR predicts clinical outcome
    - Clear unmet need in triple-negative→ benefit/risk more appropriate
    - Low-risk hormone receptor-positive both less likely to attain pCR and more likely to have long-term survival with available therapy→pCR not likely to predict clinical benefit

Neoadjuvant Trials to Support Accelerated Approval

- Trials utilizing pCR as primary endpoint should be RCTs.
  - A high pCR rate in a single-arm trial may reflect tumor biology, efficacy of standard therapy “backbone,” efficacy of the investigational agent, or all of these.
- Add-on design preferred:
  - Standard therapy + investigational agent vs. standard therapy (+ placebo, if toxicity will not unblind)
- Pathologists interpreting pCR should unequivocally be blinded to treatment arm.
- Patients and investigators should be blinded unless toxicity of investigational agent precludes.

Neoadjuvant Trials to Support Accelerated Approval

- Postoperative systemic therapy should be avoided, especially allowing use of the investigational agent in the control arm.
  - Not clear that giving additional postop chemo for patients with residual disease improves outcome
  - If postop systemic therapy is required (e.g., completion of 1 yr of trastuzumab for HER2+ breast cancer), should be the same in both arms to avoid confounding DFS/OS.

A Single Trial May Support Both Accelerated and Regular Approval

- A single trial should be powered to detect a clinically and statistically significant improvement in DFS and/or OS.
- All patients should be accrued before efficacy analyses are conducted.
- Analysis of DFS/OS must use ITT population, NOT responders only.
- Interim analyses are acceptable for DFS/OS, but not pCR, due to concern for early termination.
- Analyses for futility may be appropriate.
- A clear, pre-specified plan to control type I error for both pCR and DFS/OS is required.
  - Should allocate a larger portion of alpha to DFS/OS and a smaller portion of alpha to pCR endpoint

Alternate Approaches

- Alternate approaches to a one or more large neoadjuvant efficacy/safety trial(s) may be acceptable for drugs with:
  - More extensive prior efficacy/safety data in breast cancer
  - Evidence of unprecedented efficacy in breast cancer
  - Ongoing randomized adjuvant trials
- All require early discussion with FDA

Potential Benefits of Using a Single Trial for Both Accelerated and Regular Approval

- A single large trial provides a larger body of safety data at the time of approval.
  - Especially important if neoadjuvant setting may be initial US approval
- Greater likelihood that the data needed for conversion to regular approval will be:
  - Collected in a timely fashion
  - Adequately powered to assess DFS/OS

Concerns with Using pCR to Support Accelerated Approval

- Delay between initial US approval and availability of data that confirm (or fail to confirm) clinical benefit
  - Some high-risk patients will be cured with existing systemic therapy (or local therapy alone) with long-term survival.
  - These patients may be exposed to added toxicity with no benefit or even diminished efficacy
  - Should ensure that patients are carefully selected and counseled to justify the risk/benefit of this approach

Safety Considerations at Time of Accelerated Approval

- Safety database for acute AEs expected to be comparable to that of adjuvant trials if trials powered for DFS/OS.
- Limitations:
  - Data on outcome of cumulative toxicities (e.g., neuropathy)
  - Data on rare or late toxicities (e.g. cardiomyopathy, secondary malignancy)
  - Underscores need to limit these trials to patients at high-risk of recurrence and death with existing therapy
- Postmarketing safety studies will likely be required.
  - What is needed will depend on prior experience with drug in breast cancer or other disease settings or with other drugs in the same class.

Other Issues to Consider

- This pathway creates two new potential disease settings:
  - Neoadjuvant
  - Post-neoadjuvant residual disease
- Extrapolation of neoadjuvant results to adjuvant setting
- Continued development of drugs for metastatic breast cancer

Summary

- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf
- NEJM Perspective online first in May 2012 and in print June 2012
- OHOP will make final determination on use of pCR as endpoint for accelerated approval in early-stage breast cancer based upon public commentary regarding the draft guidance and results of the CTneoBC meta-analysis.

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