Individualizing Systemic Therapy for Early Stage HER2-positive Breast Cancer

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Outline

• Introduction
• Trastuzumab/pertuzumab for early stage disease
• Trastuzumab-emtansine for residual disease post-neoadjuvant therapy
• Neratinib after standard anti-HER2 therapy
• De-escalation strategies
Introduction

- 15-20% of breast cancers are HER2-positive
- Targeting the HER2 receptor has led to improved patient outcomes
- Numerous targeted agents have been developed, varying degrees of effectiveness

PERTUZUMAB IN EARLY STAGE DISEASE

Neoadjuvant studies result in accelerated approval of pertuzumab

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Gianni et al. Lancet Oncol 2012
Schneeweiss et al. Ann Oncol 2013
Adjuvant Pertuzumab: APHINITY

APHINITY Main Results

Pertuzumab in Node Positive
When should we consider pertuzumab?

- Most benefit seen in LN+ disease → appropriate as part of (neo)adjuvant for patients with LN+ disease
- Consider when treating with a neoadjuvant approach

TDM1 FOR RESIDUAL DISEASE

KATHERINE study Design

* on baseline (pre-neoadjuvant) biopsy

von Minckwitz et al. NEJM 2018
In pts receiving pertuzumab, 3 year iDFS 80.9% (T) vs 91.4% (TDM1); unstratified HR=0.498 (95% CI 0.249–0.995)
- CNS site of 1st metastasis in 4.3% in T, 5.9% in TDM1

**Adverse events**

- Increased fatigue, nausea, LFTs, epistaxis
- Decreased plt

*2 cases of hepatic nodular regenerative hyperplasia*
Should all pts with iRD get TDM1?

- Mostly, unless contraindication; discussion of potential additional toxicity and benefits

- NCCN now states:
  > If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone.\(^1\)\(^2\) if ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.\(^1\)

**NERATINIB AFTER STANDARD ANTI-HER2 THERAPY**

When to consider a neoadjuvant approach?

**Indications**
- Inoperable disease
- Inflammatory breast cancer
- Poorly differentiated breast cancer
- Patient desire, but not a candidate for breast-conserving surgery at presentation

**Considerations**
- Early stage disease
- Stage II and III chemotherapy-sensitive subtypes (HER2-positive, TNBC)
- HER2-positive disease

**Relative contraindications**
- Chemoresistant subtypes (intrinsic lobular, luminal A)
- Stage I breast cancer

Determine sensitivity to trastuzumab-based chemotherapy; may risk stratify need for TDM1 for residual disease

\textsuperscript{1} Santa-Maria et al, Oncology 2015

**NERATINIB AFTER STANDARD ANTI-HER2 THERAPY**
Neratinb in early stage HER2-positive breast cancer

- Given for 1 year
- Pertuzumab not used
- Benefit mostly in ER-positive
- 40% grade 3 diarrhea

Role of neratinib after standard anti-HER2 therapy?

- Very few situations where may be considered
- High risk patients who cannot tolerate TDM1, ER+
- Consider toxicities, ppx anti-diarrheals
- Future research needed to see if a subset of pts has a major benefit, strategies in metastatic setting (ie CNS metastasis)

DE-ESCALATION STRATEGIES
Adjuvant TH for node-negative HER2-positive breast cancer

- **Treatment:**
  - Paclitaxel 80mg/m² weekly x12
  - Trastuzumab 4mg/kg loading, 2mg/kg weekly x12 (total)
    - Then continue weekly or change to 6mg/kg q3 weeks to complete 1 year

- **Eligibility:**
  - HER2 3+ or FISH ratio ≥2.0
  - Up to 3 cm in the greatest dimension
  - Initially only node-negative disease, but N1mic allowed (1.5%)  
  - Adequate organ function, LVEF >50%

De-escalation: Small HER2 (<3cm, N0)

ASCO update in 2017: 7-yr DFS was 93.3%

Future Directions in De-escalation Strategies

- **ATTEMPT study (TDM1 vs TH) for stage 1 HER2+**
- **Chemotherapy free approaches with biomarker selection (HER2-enriched, PET changes)**
  - HP x12 weeks in stage II/III ER+, pCR=34% → decreases in PET after 2 weeks associated with higher chance of pCR
A Multi-Disciplinary Approach

THANK YOU