Atlanta Breast Cancer CONFERENCE

September 27, 2025

Partners for Advancing Clinical Education

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Case 1

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Case 1 – Initial Presentation

69-year-old Female with history of DCIS (8 yrs ago) → Right lumpectomy + adjuvant RT + 5 yrs endocrine therapy

Screening mammogram: Possible architectural distortion, right breast

Diagnostic MMG/Ultrasound:

- **Lesion A:** 11 × 7 × 11 mm, irregular hypoechoic mass, R breast 10:00, 8 cm from nipple
- **Lesion B:** 14 × 9 × 13 mm, irregular taller-than-wide hypoechoic mass, R breast 10:00, 7 cm from nipple
- **Axilla:** No suspicious adenopathy

Biopsy Results:

	Lesion A (10:00, 8 cm)	Lesion B (10:00, 7 cm)
Histology	Invasive carcinoma, grade 3	Invasive carcinoma, grade 3
ER/PR	Negative	Negative
HER2	2+ (FISH negative)	2+ (FISH negative)
Ki-67	70%	60%

Genetics: Negative

Case 1 – Neoadjuvant Therapy

Clinical Question:

How would you select the neoadjuvant regimen for this patient?

- Treat as **two separate stage I TNBCs** with standard ddAC-T?
- Or **upstage** due to multifocality and initiate **KN-522 regimen?**

Case 1 – Neoadjuvant Therapy (What Was Done)

Initial regimen: ddAC-T

- **Response after AC assessed with ultrasound:**

Lesion	Baseline Size	Post-AC Size
A	11 × 7 × 11 mm	8 × 6 × 8 mm
B	14 × 9 × 13 mm	13 × 9 × 9 mm

Escalated to KEYNOTE-522 regimen:

- Carbo/paclitaxel + Pembrolizumab

Toxicities: Grade 2 neuropathy

Case 1 – Surgery & Pathology

Procedure: Right mastectomy + sentinel lymph node biopsy (5 nodes negative)

Pathology findings:

- Residual invasive carcinoma in 2nd lesion, grade III
- Largest focus: **8 × 5 mm**
- Residual disease in 2nd lesion, margins negative
- Focal lymphovascular invasion (LVI) present

Pathologic stage: pT1bN0M0

Case 1 – Adjuvant Therapy

Clinical Question:

What **adjuvant therapy plan** would you select based on these findings?

- Pembrolizumab alone (continue per KN-522 trial design)
- Capecitabine alone (per CREATE-X, esp. with residual disease)
- Combination pembrolizumab + capecitabine

Case 1 – Adjuvant Therapy

Planned/ongoing:

- Pembrolizumab (continuing per KN-522 protocol)
- Capecitabine added 2 months later
  - delayed start due to flap necrosis and re-operation

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Case 2

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Case 2 – Initial Presentation

60-year-old female presents with breast skin changes + itching

Diagnostic MMG:

- Diffuse skin thickening + trabecular thickening in right breast
- Nipple retraction, smaller right breast
- Concern for inflammatory breast cancer vs ILC

Ultrasound:

- Diffuse edema + skin thickening
- No discreate mass
- No suspicious axillary adenopathy

Case 2 – Biopsy & Staging

Skin punch biopsies:

- Invasive ductal carcinoma, Nottingham grade 2
- Dermal involvement, abuts epidermis
- **Biopsy A (3:00):** ER 70%, PR-, **HER2 3+**
- **Biopsy B (12:00):** ER 30%, PR-, **HER2 3+**

Genetics: Negative

PET:

- Breast + dermal + pectoralis involvement
- LN mets (bilateral axillary, mediastinal, hilar)
- Distant mets: liver, bone, suspicious lung + pleural effusion

Brain MRI:

- 2 enhancing lesions (R frontal, R midbrain)

Case 2 – First-Line Treatment

Clinical Question:

What is your preferred **first-line regimen** for **de novo HER2+ MBC with brain metastases**?

Site / Biopsy	Histology	ER	PR	HER2
Skin, R breast 3:00	IDC, grade 2	70%	Negative	3+
Skin, R breast 12:00	IDC, grade 2	30%	Negative	3+

Case 2 – First-Line Treatment (What Was Done)

Systemic therapy: THP (docetaxel + trastuzumab + pertuzumab)

- **SRS after 3 cycles** (for brain metastases)
- Completed 4 cycles → transitioned to **maintenance HP** (taxane stopped due to rash)

Endocrine therapy: AI (anastrozole) added during maintenance

Initial response: Stable systemic disease, CNS controlled post-SRS

Case 2 – 6 months later

- Hospitalized for shortness of breath
- **Findings:**
  - **TTE:** EF ~50%
  - **Imaging:** Pulmonary edema, bilateral pleural effusions
  - Managed with diuresis
- **Concern:** Cardiac toxicity and development of HFpEF

- Progression of Disease
- **Brain MRI:**
  - Multiple new/enlarging parenchymal lesions
  - Possible leptomeningeal disease
- **PET:**
  - No extracranial GDG-avid disease

Case 2- Second Line Treatment

In a patient with **HER2+ MBC and CNS progression after THP**, what would you choose as **second-line therapy**?

Site / Biopsy	Histology	ER	PR	HER2
Skin, R breast 3:00	IDC, grade 2	70%	Negative	3+
Skin, R breast 12:00	IDC, grade 2	30%	Negative	3+

For this patient (unique scenario):

- Requests to avoid further **IV therapy** and **trastuzumab exposure** (concern for CHF)

What systemic therapy would you recommend in this context?

Case 2 – Second-Line Treatment (What Was Done)

Underwent Whole Brain Radiation

Discussed therapies:

- Fam-trastuzumab deruxtecan (T-DXd) – declined (CHF/IV concerns)
- HER2CLIMB regimen (tucatinib + trastuzumab + capecitabine) – declined (trastuzumab retiral)

Attempted oral therapy:

- **Neratinib + Capecitabine** → self-discontinued after 1 cycle (severe GI toxicity)
- Initial MRI with treatment response to WBRT

Therapy after treatment break:

- Restarted **AI (anastrozole)** after 2-month gap
- Later added **Tucatinib 150 mg BID** (declined dose escalation)

Brain MRI after 2 months: CNS progression (new/enlarging lesions)

Patient decision:

- Declined fam-trastuzumab deruxtecan again
- **Tucatinib increased to 300 mg BID + AI**

Case 2 – Wrap Up

Questions for Panel

Are there any upcoming trials or regimens you are excited about in the HER2+ brain metastases space?

What do you want to see in future research or drug development for this population?