Emerging Treatments for HER2+ and Mutant Breast Cancer

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## Emerging Treatments for HER2+ BC

### Novel anti-HER2 antibodies (Abs)
- Margetuximab
- MCLA-128
- ZW25

### New antibody drug conjugates (ADCs)
- SYD985
- MM-302
- ZW33
- DS-8201
- PF 06804103

### Potent tyrosine kinase inhibitors (TKIs)
- Neratinib
- Tucatinib
- Poziotinib

### Appealing combinations
- Immune therapy
- CDK4/6 inhibitors
- PI3K inhibitors
- Other

### Brain metastasis
- Neratinib

### HER2-mutant breast cancer
- Neratinib

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BC, breast cancer
Novel Anti-HER2 Abs: Margetuximab

Mechanism of Action

Anti-HER2 antibody that binds with elevated affinity to both the lower and higher affinity forms of CD16A (an Fcγ receptor important for antibody dependent cell-mediated cytotoxicity [ADCC]).

Available Results*

- Median PFS 24.1 weeks
- +30% Partial Response
- +20% Progressive Disease

Outstanding Ongoing Trials

Sophia trial: CP-MGAH22-04
- Prior pertuzumab, trastuzumab, T-DM1
- Second- through third-line

- Phase I: Median 4 lines of therapy
- Toxicty: Lymphopenia, infusion related reactions

Primary endpoints: PFS + OS
Secondary endpoints: RR, CB, QoL, and safety

CT of the investigator’s choice: Capecitabine, eribulin, gemcitabine, or vinorelbine

CB, clinical benefit; CT, chemotherapy; NK, natural killer; OS, overall survival; PFS, progression-free survival; QoL, quality of life; R, randomized; RR, relative risk

# Novel Anti-HER2 Abs: Other

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Trial Results</th>
<th>Trials Ongoing</th>
</tr>
</thead>
</table>
| **MCLA-128**  
Merus | ADCC-enhanced bispecific Ab, binds to HER2 and to HER3 | 11 HER2+ heavily pretreated MBC: CBR 64% (CR+PR+SD 12 w)* | Phase II  
MCLA-128-CL02 |
| **ZW25**  
Zymeworks Inc. | Bispecific Ab, two non-overlapping epitopes of HER2 | Ongoing | Phase I  
NCT02892123 |

CBR, clinical benefit rate; CR, complete response; MBC, metastatic breast cancer; PR, partial response; SD, stable disease; w, weeks

**New ADCs: SYD985**

**Mechanism of Action**
- Fully synthetic duocarmycin analogue

**Available Results**
- Phase I, part II: ≈90% patients ≥4 lines of therapy
- Toxicity: Conjunctivitis, keratitis

**Outstanding Ongoing Trials**
**Tulip trial: SYD985.002**
- Primary endpoint: PFS (centrally assessed)
- Secondary endpoints: OS, ORR, investigator assessed PFS, QoL, and safety

*ORR, overall response rate
## Novel Anti-HER2 Abs: Other

<table>
<thead>
<tr>
<th>Payload</th>
<th>Trial Results</th>
<th>Trials Ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MM-302 Merrimack</strong></td>
<td><strong>HERMIONE:</strong> Felt not to show benefit over control per DMC and confirmed via futility analysis¹</td>
<td>-</td>
</tr>
<tr>
<td>Liposomal doxorubicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DS-8201 Daiichi-Sankyo</strong></td>
<td><strong>Prior T-DM1:</strong> ORR was 45.7%, DCR was 100% / Prior T-DM1 plus pertuzumab: ORR was 46.7%, DCR was 100%²</td>
<td>Phase II: DESTINY-Breast01</td>
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<tr>
<td>Topoisomerase I inhibitor (DXd)</td>
<td></td>
<td></td>
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<tr>
<td><strong>PF-06804103 Pfizer</strong></td>
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<td>Phase I: C0541001</td>
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<tr>
<td>Auristatin analogue (Aur0101)</td>
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<td></td>
</tr>
<tr>
<td><strong>ZW33 Zymeworks</strong></td>
<td></td>
<td>Preclinical data</td>
</tr>
<tr>
<td>Potent cytotoxin (¿?)</td>
<td></td>
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</tbody>
</table>

DCR, disease control rate; DMC, data monitoring committee

Potent TKIs: Neratinib

Mechanism of Action

• Neratinib is an oral TKI that irreversibly inhibits HER1, HER2, and HER4
Neratinib Breast Cancer Studies

- **17 July 2017: FDA approved Neratinib** for the extended adjuvant treatment based on the ExteNET pivotal study
- **EMA:** Marketing authorization application submitted

### Neoadjuvant
- **NSABP FB-7**
  - Neratinib + standard neoadjuvant therapy ± trastuzumab HER2+ LABC
- **I-SPY2**
  - Neratinib ± standard neoadjuvant therapy high-risk LABC

### HER2-Mutated
- **SUMMIT (PUMA-NER-5201)**
  - Neratinib ± fulvestrant tumors with HER2 mutations
- **MutHer (NCT01670877)**
  - Neratinib
- **plasmaMATCH (ISRCTN16945804)**
  - Neratinib plus fulvestrant if ER+

### Metastatic
- **NALA (PUMA-NER-1301)**
  - Neratinib + capecitabine vs lapatinib + capecitabine HER2+ ≥3rd line
  - NEFERT-T (3144A2-3005-WW)
  - Neratinib + pacitaxel vs trastuzumab + paclitaxel in HER2+ locally advanced
  - 3003 (3144A2-3003-WW)
  - Neratinib vs lapatinib + capecitabine HER2+ locally advanced
  - TBCRC 022
  - Neratinib ± capecitabine HER2+ CNS metastases
- **201 (3144A2-201-WW)**
  - Neratinib pretreated HER2+
- **10-005**
  - Neratinib + temsirolimus HER2+
- **202 (3144A2-202-WW)**
  - Neratinib + trastuzumab HER2+
- **203 (3144A2-203-WW)**
  - Neratinib + paclitaxel HER2+
- **2206 (3144A2-2206-WW)**
  - Neratinib + capecitabine HER2+
- **2204 (3144A2-2204-WW)**
  - Neratinib + vinorelbine HER2+
- **2205 (3144A2-2205-WW)**
  - Neratinib + temsirolimus solid tumors
- **102 (3144A2-102-US)**
  - Neratinib HER2+ solid tumors
- **NSABP FB-8**
  - Neratinib + trastuzumab + paclitaxel HER2+

**Extended Adjuvant**
- **ExteNET (3144A2-3004-WW)**
  - Neratinib vs placebo after HER2 targeted therapy for HER2+ early BC
- **CONTROL (PUMA-NER-6201)**
  - Incidence and severity of diarrhea in HER2+ BC patients treated with neratinib + loperamide
  - Neratinib Expanded Access Program
  - Neratinib observational safety after HER2-targeted therapy for HER2+ early BC

**EMA, European Medicines Agency; ER, estrogen receptor; FDA, US Food and Drug Administration; LABC, locally advanced breast cancer**
**Mechanism of Action**

- Orally bioavailable, potent HER2 selective TKI
- HER2 IC50 8 nM > EGFR IC50 > 10,000 nM: Decreased potential for EGFR-related toxicities

**Available Results**

- Phase Ib of Tucatinib + capcitabine + trastuzumab in HER2+ MBC, including patients with BM
- Progression after trastuzumab, taxane, and T-DM1. Pertuzumab or lapatinib permitted. Three to six previous lines

**Outstanding Ongoing Trials**

**HER2CLIMB trial**

- Primary endpoint: PFS assessed by central review
- Key secondary endpoints: PFS in patients with BM, OS

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BM, brain metastases; MBC, metastatic breast cancer; TKI, tyrosine kinase inhibitor

Potent TKIs: Poziotinib (NOV120101)

**Mechanism of Action**

- Orally available, irreversible pan-HER inhibitor

**Available Results**

- Median PFS: 4.04 months (95% CI 2.96-4.40)

Appealing Combinations: Immune Therapy

- Preclinical data suggested that the immune system influences prognosis and response to chemotherapy
- FinHer adjuvant study: Suggested that stromal tumor-infiltrating lymphocytes (STILs) are predictive of benefit to adjuvant trastuzumab, nine weeks$^1$
  
  ![Diagram showing survival curves for LPBC and Non-LPBC phenotypes with and without trastuzumab.](image)

- N9831 adjuvant trial: STILs were prognostically associated with recurrence-free survival (RFS) in patients treated with chemotherapy alone, but not prognostically associated with RFS in patients treated with chemotherapy plus trastuzumab. High STILs were predictive of lack of trastuzumab benefit$^2$

LPBC, lymphocyte-predominant breast cancer

Appealing Combinations: Immune Therapy

- NeoALTTO: Presence of TILs at diagnosis is an independent, positive, prognostic marker in HER2-positive EBC treated with neoadjuvant anti-HER2 agents and chemotherapy for both pCR and EFS endpoints\(^1\)

- Neosphere: Trastuzumab and/or pertuzumab regimens modulated the amount of TILs and the expression of markers of immune activation (ICOS, 4-1BB) and inhibition (CTLA-4, PD-L1). Such modulation is linked to DEFS of patients with RD, and carries more prognostic information than either pre or post-treatment STILs. PD-L1 expression is dynamic and can be modulated by treatments\(^2\)

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CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DEFS, distant EFS; EFS, event-free survival; pCR, pathologic complete response; PD-L1, programmed death ligand-1; RD, residual disease; TIL, tumor-infiltrating lymphocyte.
Appealing Combinations: CDK4/6 Inhibitors

Patricia: SOLTI-1303

Stage I \( N_p = 15 \)
- Palbociclib + Trastuzumab
- Palbociclib + Trastuzumab

Stage II \( N_p = 31 \)
- Palbociclib + Trastuzumab
- Palbociclib + Trastuzumab + Letrozole
- Palbociclib + Trastuzumab + Letrozole

Randomization

Safety Run-in phase \( N_p = 12 \)
\( N_{total} = 15 + 31 = 46 \) arm

INTERIM ANALYSIS Stage I
Go on if >5/15 PFS6

FINAL ANALYSIS Stage II
Efficacy if >18/46 PFS6

Patina: AFT-38

Randomization

ARM A
- Palbociclib 125mg PO daily (D1 to D21 followed by 7 days off) + Anti-HER2 Therapy * (every 3 weeks) + Endocrine Therapy ** until disease progression***

- No prior treatment in the advanced setting beyond induction treatment
- Induction treatment: Anti-HER2 based chemotherapy given prior to study randomization
- Screening procedures (before during or after induction treatment):
  - Screening consent
  - Biopsy of metastatic disease strongly recommended (not mandatory)
- Baseline clinico-pathologic characteristics

ARM B
- Anti-HER2 Therapy * (every 3 weeks) + Endocrine Therapy ** until disease progression***

Clinical Follow-up
(for pts who discontinue treat prior to disease progression):
q12 weeks until tumor progression

Survival Follow-up
Every 6 months until 5 years from randomization

Appealing Combinations: CDK4/6 Inhibitors


Women with HR+, HER2+ advanced breast cancer with prior exposure to ≥2 HER2-directed therapies in the advanced setting

Arm A: abemaciclib 150 mg + fulvestrant + trastuzumab

Arm B: abemaciclib 150 mg + trastuzumab

Arm C: trastuzumab + physician’s choice single-agent chemotherapy

Primary endpoint: Progression-free survival
PI3K signaling is essential for the oncogenic function of HER2

**PI3KCA** mutations observed in ~23% of HER2+ breast cancers

PI3K pathway alterations have been implicated in resistance to anti-HER2 therapies *in vitro* and in retrospective studies

**BOLERO-3:** Vinorelbine + trastuzumab +/- everolimus, trastuzumab-resistant population
- PFS: 7.0 months vs 5.78 months, *P* = .0067

**BOLERO-1:** Paclitaxel + trastuzumab +/- everolimus
- PFS: 14.95 months vs 14.49 months, *P* = NS
- PFS HR-negative subpopulation: 20.27 months vs 13.08 months (not crossed the protocol-specified significance threshold)

Buparlisib trials also showed benefit

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Appealing Combinations: Neratinib + T-DM1

NSABP FB-10: Phase Ib/II dose-escalation study evaluating T-DM1+ neratinib in HER2+ MBC

HER2+ mBC
Prior anti-HER2 regimen for metastatic disease

Phase 1
Neratinib 120, 160, 200 or 240 mg/day + trastuzumab emtansine 3.6 mg/kg on day 1 q21d (n=25)

Phase 2
Neratinib 160mg/day + trastuzumab emtansine 3.6 mg/kg on day 1 q21d (n=50)

Loperamide 4 mg q 6 h initiated with first dose of neratinib

• Trastuzumab and pertuzumab as neoadjuvant, adjuvant, or in first-line metastatic disease

AE, adverse event

**Table 2** Novel Therapeutic Strategies Undergoing Evaluation for the Treatment of BCBM

<table>
<thead>
<tr>
<th>Target</th>
<th>Therapy</th>
<th>Combination Therapy</th>
<th>Phase of Trial</th>
<th>BCBM Subtype</th>
<th>NCI ClinicalTrials.gov Identifier</th>
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</thead>
<tbody>
<tr>
<td>HER2</td>
<td>Intrathecal trastuzumab</td>
<td>WBRT</td>
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<td>HER2-positive</td>
<td>NCT01373710, NCT0125207</td>
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<td>Neratinib</td>
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<td>Afatinib</td>
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<td>ARRY-380</td>
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<td>mTOR</td>
<td>Everolimus</td>
<td>Trastuzumab + vinorelbine</td>
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<td>VEGF</td>
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<td>All</td>
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<tr>
<td></td>
<td>Sorafenib</td>
<td>WBRT</td>
<td>I</td>
<td>All</td>
<td>NCT01480583</td>
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<tr>
<td>Other</td>
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<td>(see&lt;sup&gt;4&lt;/sup&gt;)</td>
<td>II</td>
<td>All</td>
<td>NCT01386580</td>
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<td>2B3-101</td>
<td>(see&lt;sup&gt;4&lt;/sup&gt;)</td>
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<td></td>
<td>DM-CHOC-PEN</td>
<td></td>
<td>II</td>
<td>All</td>
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</tbody>
</table>

BCBM, breast cancer brain metastases; mTOR, mammalian target of rapamycin; NCI, National Cancer Institutes; WBRT, whole-brain radiation therapy.


<sup>4</sup>Given in combination with trastuzumab in the subgroup of patients with HER2-positive disease.
Brain Metastasis

TBCRC 022: A phase II trial of neratinib for patients with HER2+ BC and brain metastasis

- Brain metastases ≥1 cm in longest dimension
- Progression in the CNS after one or more line of CNS-directed therapy, such as whole-brain radiotherapy, stereotactic radiosurgery, and/or surgical resection
- Patients received neratinib 240 mg orally once per day, and tumors were assessed every two cycles
- The primary endpoint was composite CNS ORR, requiring all of the following: ≥50% reduction in volumetric sum of target CNS lesions and no progression of nontarget lesions, new lesions, escalating corticosteroids, progressive neurologic signs/symptoms, or nonCNS progression

CNS, central nervous system; SRS, stereotactic radiosurgery
NALA trial: A study of neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2+ metastatic breast cancer who have received two or more prior HER2 directed regimens in the metastatic setting (NCT01808573)

Secondary CNS endpoint: Time to intervention for symptomatic metastatic CNS disease
**HER2-Mutant Breast Cancer**

- Somatic HER2 mutations are seen at relatively low frequencies across multiple tumor types
- Breast cancer: Mutations ≈ 2% to 4%, preferably in HR+*
- A subset of HER2 mutations result in constitutive kinase signaling, oncogenic transformation, and enhanced tumor growth in preclinical models

*HER2 mutations

Activation of downstream signal transduction pathways and tumor growth survival

HER2-Mutant Breast Cancer

SUMMIT: A global, multihistology, open-label, phase II ‘basket’ study

HER2-Mutant Breast Cancer

MutHER: Phase II trial of neratinib in HER2-mutated nonamplified metastatic breast cancer (NCT01670877)

- Prior number of metastatic regimens: 3 (range, 2-10)

Thank You!
INTEGRATING NEW TREATMENTS FOR HER2+ EARLY BREAST CANCER:
Time for a Risk-Adapted Approach