















EPICS

Global Perspectives in Current and Future Management of Breast Cancer

September 19 and 21, 2022

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VIRTUAL CLOSED-DOOR ROUNDTABLE



DATES:
September 19 and
21, 2022



**DISEASE STATE AND
DATA PRESENTATIONS**
by key experts



INSIGHTS REPORT
including postmeeting
analyses and actionable
recommendations



PANEL: Key experts in
breast cancer

- > 5 from the US
- > 4 from the EU



**BREAST CANCER-
SPECIFIC DISCUSSIONS** on
therapeutic advances and
their application into clinical
decision-making

Panel Consisting of 5 US and 4 EU Breast Cancer Experts

EPICS

Mark Pegram, MD
Stanford University School of Medicine

William Gradishar, MD
Northwestern University Feinberg School of Medicine

Komal Jhaveri, MD, FACP
Memorial Sloan Kettering Cancer Center

Hope Rugo, MD, FASCO
University of California San Francisco

Co-chair
Joyce A. O'Shaughnessy, MD
Baylor Charles A. Sammons Cancer Center

Guy Jerusalem, MD, PhD
Sart-Tilman University Hospital

Co-chair
Nadia Harbeck, MD, PhD
University of Munich

Valentina Guarneri, MD, PhD
University of Padua

Javier Cortés, MD, PhD
Vall d'Hebron University Hospital



Meeting Agenda: Day 1 – September 19, 2022

EPICS

Time	Topic	Speaker/Moderator
12.00 – 12.05 PM/19.00 – 19.05 (5 min)	Welcome and Introductions	Nadia Harbeck, MD, PhD
12.05 – 12.15 PM/19.05 – 19.15 (10 min)	Current and Emerging Biomarkers and Testing Methodologies in BC	Mark Pegram, MD
12.15 – 12.30 PM/19.15 – 19.30 (15 min)	Discussion: Biomarkers	All Moderator: Nadia Harbeck, MD, PhD
12.30 – 12.35 PM/19.30 – 19.35 (5 min)	Key Takeaways: Biomarkers	Mark Pegram, MD
12.35 – 12.45 PM/19.35 – 19.45 (10 min)	Current and New Treatments in HER2+ Early BC	Valentina Guarneri, MD, PhD
12.45 – 1.10 PM/19.45 – 20.10 (25 min)	Discussion: HER2+ Early BC	All Moderator: Joyce A. O'Shaughnessy, MD
1.10 – 1.15 PM/20.10 – 20.15 (5 min)	Key Takeaways: HER2+ Early BC	Valentina Guarneri, MD, PhD
1.15 – 1.30 PM/20.15 – 20.30 (15 min)	Advances in HER2+ Metastatic Breast Cancer (mBC)	Guy Jerusalem, MD, PhD
1.30 – 2.05 PM/20.30 – 21.05 (35 min)	Discussion: HER2+ mBC	All Moderator: Nadia Harbeck, MD, PhD
2.05 – 2.10 PM/21.05 – 21.10 (5 min)	Key Takeaways: HER2+ mBC	Guy Jerusalem, MD, PhD
2.10 – 2.15 PM/21.10 – 21.15 (5 min)	<i>BREAK</i>	
2.15 – 2.25 PM/21.15 – 21.25 (10 min)	Current and Emerging Approaches in HR+, HER2– Early BC	Hope Rugo, MD, FASCO
2.25 – 2.50 PM/21.25 – 21.50 (25 min)	Discussion: HR+, HER2– Early BC	All Moderator: Joyce A. O'Shaughnessy, MD
2.50 – 2.55 PM/21.50 – 21.55 (5 min)	Key Takeaways: HR+, HER2– Early BC	Hope Rugo, MD, FASCO
2.55 – 3.00 PM/21.55 – 22.00 (5 min)	Conclusions and Closing	Nadia Harbeck, MD, PhD



Meeting Agenda: Day 2 – September 21, 2022

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Time	Topic	Speaker/Moderator
12.00 – 12.05 PM/19.00 – 19.05 (5 min)	Welcome and Introductions	Joyce A. O'Shaughnessy, MD
12.05 – 12.20 PM/19.05 – 19.20 (15 min)	Therapeutic Horizons in HR+, HER2– mBC	Komal Jhaveri, MD, FACP
12.20 – 12.55 PM/19.20 – 19.55 (35 min)	Discussion: HR+, HER2– mBC	All Moderator: Joyce A. O'Shaughnessy, MD
12.55 – 1.00 PM/19.55 – 20.00 (5 min)	Key Takeaways: HR+, HER2– mBC	Komal Jhaveri, MD, FACP
1.00 – 1.15 PM/20.00 – 20.15 (15 min)	Maximizing Potential Targeting of HER2 in HER2-Low mBC	William Gradishar, MD
1.15 – 1.50 PM/20.15 – 20.50 (35 min)	Discussion: HER2-Low mBC	All Moderator: Nadia Harbeck, MD, PhD
1.50 – 1.55 PM/20.50 – 20.55 (5 min)	Key Takeaways: HER2-Low mBC	William Gradishar, MD
1.55 – 2.00 PM/20.55 – 21.00 (5 min)	<i>BREAK</i>	
2.00 – 2.15 PM/21.00 – 21.15 (15 min)	Advances in Early and Metastatic Triple-Negative Breast Cancer (TNBC)	Javier Cortés, MD, PhD
2.15 – 2.55 PM/21.15 – 21.55 (40 min)	Discussion: TNBC	All Moderator: Joyce A. O'Shaughnessy, MD
2.55 – 3.00 PM/21.55 – 22.00 (5 min)	Key Takeaways: TNBC	Javier Cortés, MD, PhD
3.00 PM/22.00	Conclusions and Closing	Joyce A. O'Shaughnessy, MD



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Current and Emerging Biomarkers and Testing Methodologies in BC



Current and Emerging Biomarkers and Testing Methodologies in BC (1/2)

Presented by Mark Pegram, MD

The single-gene biomarker story in BC is evolving

> *ESR1* mutations are rare at the time of primary diagnosis but common in ER+ mBC. They are a common cause of acquired resistance to ER-



Current and Emerging Biomarkers and Testing Methodologies in BC (2/2)

Presented by Mark Pegram, MD

Patient-specific ctDNA analysis

> Although NGS can provide extensive mutational data, many

Life cycle of a tumor marker

> Drug resistance gene mutations are likely present from

Liquid Biopsy and Serial Assessments Are Anticipated to Shape the Future of Biomarkers in BC (2/2)

Dynamic biomarker sampling – the likely path forward in BC management

> Dynamic biomarker sampling to monitor treatment response provides distinct advantages over upfront biomarker testing only, and experts

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Current and New Treatments in HER2+ Early BC

Optimal Treatment of Early HER2+ BC Should Be Targeted to an Individual Patient's Risk of Recurrence (1/2)

Neoadjuvant therapy has become SOC for most women with early HER2+ BC

> Neoadjuvant therapy in HER2+ early BC offers the unique possibility of selecting adjuvant therapies according to pathologic response, thereby allowing more personalized treatment and more rational resource allocation. It is therefore the preferred treatment option for all

Optimal Treatment of Early HER2+ BC Should Be Targeted to an Individual Patient's Risk of Recurrence (2/2)

Risk-tailored adjuvant therapy is continuously evolving

- > In low-risk situations where patients have achieved a pCR, de-escalation of adjuvant therapy to chemotherapy plus trastuzumab for a total of 1 year is recommended for most patients. Exceptions include patients at higher risk of recurrence (eg, initially node positive, pathologic tumor size >2 cm) for

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Advances in HER2+ mBC



Advances in HER2+ mBC (1/3)

Presented by Guy Jerusalem, MD, PhD

Trial updates

> Abemaciclib-trastuzumab ± fulvestrant resulted in a numeric improvement in median OS in the monarchHER trial update (NCT02675231).

- **monarchHER** is a phase III, open-label, randomized study to assess safety and efficacy of abemaciclib ± trastuzumab ± fulvestrant in addition to endocrine therapy in patients with locally advanced HER2+ mBC. (NCT02675231)
- The approach is seen as effective, working well, and broadly applicable to many patients.
- **monarchHER2** is a phase III, open-label, randomized study to assess safety and efficacy of abemaciclib ± trastuzumab ± fulvestrant in addition to endocrine therapy in patients with locally advanced HER2+ mBC. (NCT02675231)
- The approach is seen as a great option for a patient population in which giving endocrine therapy is difficult. It is seen as effective and safe.
- **monarchHER3** is a phase III, open-label, randomized study to assess safety and efficacy of abemaciclib ± trastuzumab ± fulvestrant in addition to endocrine therapy in patients with locally advanced HER2+ mBC. (NCT02675231)
- Experts believe the combination of abemaciclib ± trastuzumab ± fulvestrant is safe. However, they would like to see phase II data to confirm its activity in this setting.
- **monarchHER4** is a phase III, open-label, randomized study to assess safety and efficacy of abemaciclib ± trastuzumab ± fulvestrant in addition to endocrine therapy in patients with locally advanced HER2+ mBC. (NCT02675231)
- The ± endocrine approach is seen as useful in the specific patient population with advanced disease. It was noted to be effective, very safe, and well-tolerated. Some of the responses were seen with fairly low doses.





Advances in HER2+ mBC (2/3)

Presented by Guy Jerusalem, MD, PhD

Pyrotinib: A novel pan-HER2 TKI

> The phase III pheNIX trial (NCT03952156) reported an impressive

Recent data in HER2+ BC with brain metastasis

> Bottosso et al (ESMO 2022 abstract 240P) reported that

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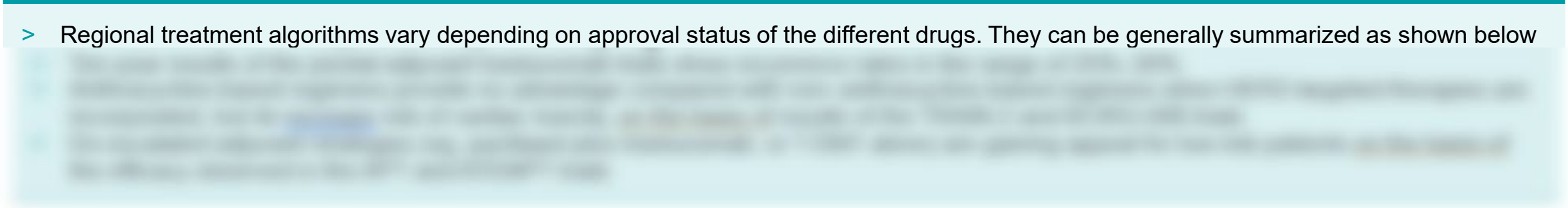


Advances in HER2+ mBC (3/3)

Presented by Guy Jerusalem, MD, PhD

A 2022 approach to therapy for HER2+ BC

> Regional treatment algorithms vary depending on approval status of the different drugs. They can be generally summarized as shown below



ADCs Are Expanding Treatment Options in HER2+ mBC (1/3)

HER2+ mBC: A Review of the Current Standard of Care

HER2+ mBC is a subtype of breast cancer characterized by overexpression of the HER2 receptor. The current standard of care for HER2+ mBC includes a combination of chemotherapy and anti-HER2 therapy. The most commonly used regimen is a combination of epirubicin, cyclophosphamide, and fluorouracil (ECF) with trastuzumab. Other regimens include docetaxel, cyclophosphamide, and epirubicin (DEC) with trastuzumab, and docetaxel, cyclophosphamide, and epirubicin (DEC) with trastuzumab and pertuzumab. The addition of anti-HER2 therapy to chemotherapy has been shown to significantly improve overall survival in HER2+ mBC.

ADCs: A New Class of Therapeutic Agents

Antibody-drug conjugates (ADCs) are a class of therapeutic agents that combine the specificity of an antibody with the cytotoxicity of a drug. ADCs are designed to target specific receptors on the surface of cancer cells, delivering the cytotoxic drug directly to the tumor. This targeted approach can improve the efficacy of the drug while minimizing toxicity to normal cells. ADCs are being developed for a variety of cancer types, including breast cancer. In HER2+ mBC, ADCs are being evaluated as potential alternatives to the current standard of care. ADCs are being developed for a variety of cancer types, including breast cancer. In HER2+ mBC, ADCs are being evaluated as potential alternatives to the current standard of care.

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ADCs Are Expanding Treatment Options in HER2+ mBC (2/3)

Approval of T-DXd broadens treatment choices in second line and beyond for HER2+ mBC

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ADCs Are Expanding Treatment Options in HER2+ mBC (3/3)

The future of treating HER2+ mBC

Key Takeaway: ADCs are expanding treatment options in HER2+ mBC

Antibody-Drug Conjugates (ADCs) are a class of targeted cancer therapies that combine a monoclonal antibody with a cytotoxic drug. In HER2+ metastatic breast cancer (mBC), ADCs like trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) have shown promising results in clinical trials, offering improved efficacy and potentially reduced toxicity compared to traditional chemotherapy. The future of treating HER2+ mBC lies in the continued development and optimization of ADCs, including the exploration of novel antibody-drug linkages and payloads to further enhance their therapeutic potential.

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**Current and Emerging
Approaches in HR+, HER2–
Early BC**



Current and Emerging Approaches in HR+, HER2- Early BC (1/2)

Presented by Hope Rugo, MD, FASCO

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Current and Emerging Approaches in HR+, HER2- Early BC (2/2)

Presented by Hope Rugo, MD, FASCO

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Management of HR+, HER2- Early BC Is Shifting to an Individualized Approach (1/2)

Adjuvant ET is tailored on the basis of risk

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Management of HR+, HER2- Early BC Is Shifting to an Individualized Approach (2/2)

Adjuvant ET is tailored on the basis of risk – cont.

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Therapeutic Horizons in HR+, HER2– mBC



Therapeutic Horizons in HR+, HER2- mBC (1/3)

Presented by Komal Jhaveri, MD, FACP

Evolving treatment landscape

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Therapeutic Horizons in HR+, HER2– mBC (2/3)

Presented by Komal Jhaveri, MD, FACP

CDK4/6 inhibitors

> MONALEESA-2 (NCT01958021) reported that ribociclib with letrozole led to an OS of 64 months, with a statistically significant hazard ratio of 0.76

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Therapeutic Horizons in HR+, HER2– mBC (3/3)

Presented by Komal Jhaveri, MD, FACP

CDK4/6 inhibition beyond progression

> It remains unclear whether both ET and CDK4/6i need to be switched in ET-resistant patients (eg, those with an *ESR1* mutation)

CDK4/6 Inhibition Remains SOC in First-Line HR+, HER2- mBC



First line: Selecting between available CDK4/6i

> ET plus CDK4/6 inhibition remains first-line SOC for the

Second line: Treatment post-CDK4/6i progression is evolving

> Current second-line options are typically fulvestrant-based



Third line: Beyond ET, novel ADCs might replace single-agent chemotherapy

> Experts are excited about the OS results from the TROPiCS-02 trial (NCT03901339) and believe they will lead to a label extension of

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Oral SERDs: A More Prominent Role in the Adjuvant Than Metastatic Setting for HR+, HER2- BC?

The future of oral SERDS

> Experts like oral SERDs, as they could provide advantages over the SERD fulvestrant with regard to bioavailability, administration



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Maximizing Potential Targeting of HER2 in HER2– Low mBC



Maximizing Potential Targeting of HER2 in HER2-Low mBC (1/2)

Presented by William Gradishar, MD

HER2-low BC requires further molecular and disease characterization

> In BC, it is unclear whether HER2-low populations have different

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Maximizing Potential Targeting of HER2 in HER2-Low mBC (2/2)

Presented by William Gradishar, MD

ADCs for the treatment of HER2-low disease

> A phase Ib trial (NCT02564900) showed that T-DXd had promising preliminary antitumor activity in approximately one-third of patients with

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The Concept of HER2 Status Is Evolving

Improving HER2 testing reproducibility in HER2-low BC

“ Dr Pegram:

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ADCs Are the Future in HER2+ and HER2-Low BC

ADCs: Shaping the future management of BC

> Development of ADCs has been one of the most successful advances in BC over the last decade, and experts are very excited about their potential to improve outcomes for patients with HER2+ and HER2-low breast cancer. ADCs combine the cytotoxic power of chemotherapy with the precision of antibody therapy, targeting cancer cells more effectively and sparing healthy tissue. This targeted approach has led to significant improvements in response rates and overall survival for patients with HER2+ breast cancer, and is now being explored for HER2-low breast cancer. The development of ADCs represents a paradigm shift in breast cancer treatment, offering a more personalized and effective way to manage the disease.

HER2+ Breast Cancer

ADCs have revolutionized the treatment of HER2+ breast cancer. The combination of a cytotoxic drug with an antibody that targets the HER2 receptor has shown superior efficacy compared to traditional chemotherapy. This targeted approach has led to higher response rates and improved overall survival for patients with HER2+ breast cancer. The development of ADCs represents a significant advance in breast cancer treatment, offering a more personalized and effective way to manage the disease.

HER2-Low Breast Cancer

ADCs are also being explored for the treatment of HER2-low breast cancer. This subtype of breast cancer is characterized by lower levels of HER2 expression, but ADCs are designed to target these lower levels effectively. The development of ADCs for HER2-low breast cancer represents a significant advance in breast cancer treatment, offering a more personalized and effective way to manage the disease.

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Advances in Early and Metastatic TNBC



Advances in Early and Metastatic TNBC (1/3)

Presented by Javier Cortés, MD, PhD

Metastatic TNBC: Role of immunotherapy

Metastatic TNBC: Role of PARP inhibition

> Phase III trials, IMpassion130 (NCT02425891) and IMpassion131

> Two phase III trials investigated PARP inhibitor





Advances in Early and Metastatic TNBC (2/3)

Presented by Javier Cortés, MD, PhD

Metastatic TNBC: Small molecules and ADCs

Metastatic TNBC: Current treatment algorithm

> The START trial (NCT03383679) compared the AR

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Advances in Early and Metastatic TNBC (3/3)

Presented by Javier Cortés, MD, PhD

Early TNBC

> The role of platinum compounds now is quite well defined in early TNBC

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KEYNOTE-522 has been practice changing

> Experts opined that all patients with early-stage TNBC should ideally be tested for PD-L1 expression, the presence of *BRCA1/2* and *PALB2* mutations,

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Treatment algorithm mTNBC

> Biomarker testing for PD-L1 and germline *BRCA* mutation is standard for all patients with mTNBC

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Abbreviations

- > +, positive
- > -, negative
- > ADC, antibody-drug conjugate
- > AE, adverse event
- > AI, aromatase inhibitor
- > Akt, protein kinase B
- > AR, androgen receptor
- > ASCO, American Society of Clinical Oncology
- > BC, breast cancer
- > CDK4/6, cyclin-dependent kinase 4/6
- > CPS, Combined Positive Score
- > CT, computed tomography
- > ctDNA, circulating tumor DNA
- > DFI, disease-free interval
- > EFS, event-free survival
- > ER, estrogen receptor
- > ESMO, European Society for Medical Oncology
- > ET, endocrine therapy
- > FDA, US Food and Drug Administration
- > HER2, human epidermal growth factor receptor 2
- > HR, hormone receptor
- > i, inhibitor
- > IDFS, invasive disease-free survival
- > IHC, immunohistochemistry
- > ILD, interstitial lung disease
- > ISH, in situ hybridization
- > ITT, intention-to-treat
- > m, metastatic

- > mBC, metastatic breast cancer
- > MOA, mechanism of action
- > mTNBC, metastatic triple-negative breast cancer
- > mTOR, mechanistic target of rapamycin
- > NGS, next-generation sequencing
- > NTRK, neurotrophic tyrosine receptor kinase
- > ORR, objective response rate
- > OS, overall survival
- > PARP, poly(ADP-ribose) polymerase
- > pCR, pathologic complete response
- > PCR, polymerase chain reaction
- > PD-1, programmed cell death protein 1
- > PD-L1, programmed cell death protein 1 ligand 1
- > PFS, progression-free survival
- > PI3K, phosphoinositide 3-kinase
- > PR, progesterone receptor
- > PRO, patient-reported outcome
- > QOL, quality of life
- > RNAseq, RNA sequencing
- > RT-PCR, reverse transcription polymerase chain reaction
- > SERD, selective estrogen receptor downregulator
- > SOC, standard of care
- > T-DM1, trastuzumab emtansine
- > T-DXd, trastuzumab deruxtecan
- > TFI, treatment-free interval
- > TIL, tumor-infiltrating lymphocyte
- > TKI, tyrosine kinase inhibitor
- > TNBC, triple-negative breast cancer