



**EPICS**

# **BREAST CANCER IN 2021 AND BEYOND**

April 28 and May 3, 2021

# REPORT CONTENTS

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Meeting Agenda	
Strategic Recommendations	
Global Perspectives	

# MEETING SNAPSHOT



**DATE:** April 28 and May 3, 2021



**PANEL:** Key experts in breast cancer  
8 from US



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



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



**INSIGHTS REPORT** including postmeeting  
analyses and actionable recommendations

**EPICS**

**VIRTUAL CLOSED-DOOR  
ROUNDTABLE**



# FACULTY

EPICS

**Mark Pegram, MD**  
Stanford University School of Medicine

**Hope S. Rugo, MD, FASCO**  
University of California San Francisco

**Priyanka Sharma, MD**  
University of Kansas Medical Center

**Joyce O'Shaughnessy, MD**  
CHAIR:  
Baylor University Medical Center  
Texas Oncology, US Oncology

**Bill Gradishar, MD**  
Northwestern University

**Sara Tolaney, MD, MPH**  
Dana-Farber Cancer Institute

**Monica N. Fornier, MD**  
Memorial Sloan Kettering Cancer Center

**Peter Kaufman, MD**  
University of Vermont Cancer Center

# MEETING AGENDA – APRIL 28, 2021

EPICS

Time	Topic	Speaker/Moderator
10.00 AM – 10.10 AM (10 min)	Welcome and Introductions	Joyce O’Shaughnessy, MD
10.10 AM – 10.30 AM (20 min)	Evolving Paradigms in HER2+ MBC	Bill Gradishar, MD
10.30 AM – 11.20 AM (50 min)	Key Questions and Topics for Discussion	
11.20 AM – 11.25 AM (5 min)	Summary and 3 Key Takeaways	
11.25 AM – 11.45 PM (20 min)	Individualizing Therapy for HER2+ Early Breast Cancer	Mark Pegram, MD
11.45 PM – 12.25 PM (40 min)	Key Questions and Topics for Discussion	
12.25 PM – 12.30 PM (5 min)	Summary and 3 Key Takeaways	
12.30 PM – 12.40 PM (10 min)	BREAK	
12.40 PM – 1.00 PM (20 min)	Current and Investigational Approaches in Metastatic Triple-Negative Breast Cancer	Priyanka Sharma, MD
1.00 PM – 1.45 PM (45 min)	Key Questions and Topics for Discussion	
1.45 PM – 1.50 PM (5 min)	Summary and 3 Key Takeaways	
1.50 PM – 2.00 PM (10 min)	Wrap-up and Overview of Day 2	Joyce O’Shaughnessy, MD



# MEETING AGENDA – MAY 3, 2021 (1/2)

EPICS

Time	Topic	Speaker/Moderator
9.00 AM – 9.05 AM (5 min)	Introduction and Review of Agenda	Joyce O’Shaughnessy, MD
9.05 AM – 9.25 AM (20 min)	Standard and Emerging Strategies for High-Risk Early Stage Triple-Negative Breast Cancer	Hope Rugo, MD, FASCO
9.25 AM – 9.50 AM (25 min)	Key Questions and Topics for Discussion	All
9.50 AM – 9.55 AM (5 min)	Summary and 3 Key Takeaways	
9.55 AM – 10.15 AM (20 min)	Novel Targets in Breast Cancer	Sara Tolaney, MD, MPH
10.15 AM – 10.40 AM (25 min)	Key Questions and Topics for Discussion	All
10.40 AM – 10.45 AM (5 min)	Summary and 3 Key Takeaways	
10.45 AM – 11.05 AM (20 min)	Evolving Treatments and New Developments in HR+ Metastatic Breast Cancer	Peter Kaufman, MD
11.05 AM – 11.40 AM (35 min)	Key Questions and Topics for Discussion	All
11.40 AM – 11.45 AM (5 min)	Summary and 3 Key Takeaways	
11.45 AM – 12.00 PM (15 min)	Break	



# MEETING AGENDA – MAY 3, 2021 (2/2)

Time	Topic	Speaker/Moderator
12.00 PM – 12.20 PM (20 min)	Evolving Paradigms in HR+ Early Breast Cancer	Joyce O’Shaughnessy, MD
12.20 PM – 12.50 PM (30 min)	Key Questions and Topics for Discussion	All
12.50 PM – 12.55 PM (5 min)	Summary and 3 Key Takeaways	
12.55 PM – 1.00 PM (5 min)	Conclusions and Wrap-up	Joyce O’Shaughnessy, MD

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# Evolving Paradigms in HER2+ mBC





# EVOLVING PARADIGMS IN HER2+ mBC (1/2)

PRESENTED BY BILL GRADISHAR, MD

## EVOLUTION OF OPTIONS FOR HER2+ BREAST CANCER

> Four new agents were added to the

### Timeline of FDA Approvals for HER2+ Breast Cancer

Year	2007	2008	2009	2010	2011	2012	2013
Agents		1	2	3	4	5	6





# EVOLVING PARADIGMS IN HER2+ mBC (2/2)

PRESENTED BY BILL GRADISHAR, MD

## RECENT ADVANCES

> The reported objective response rate (ORR) of 61% for

## RESEARCH AND FUTURE DIRECTIONS

> A number of additional HER2-targeted ADCs, including SYD985,



EPICS

Key Insights: HER2+ mBC



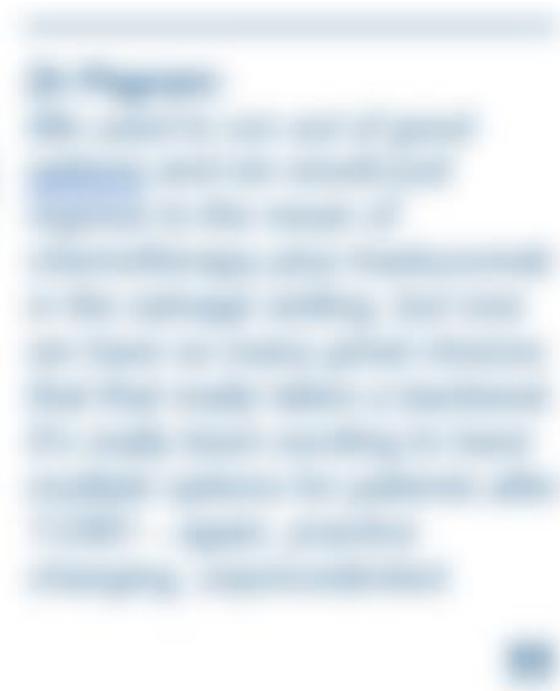
# EXPERT PERSPECTIVES ON CHANGES TO THE ALGORITHM FOR HER2+ mBC

## 4 NEW APPROVALS SINCE 2019 HAVE CHANGED PRACTICE PATTERNS

The treatment algorithm for HER2+ mBC continues to evolve, and results from



“



# EXPERTS DISCUSSED NEW AGENTS FOR HER2+ mBC

## TRASTUZUMAB DERUXTECAN

Trastuzumab deruxtecan is perceived to be a very active drug, and is the preferred option for patients with high disease burden, or in

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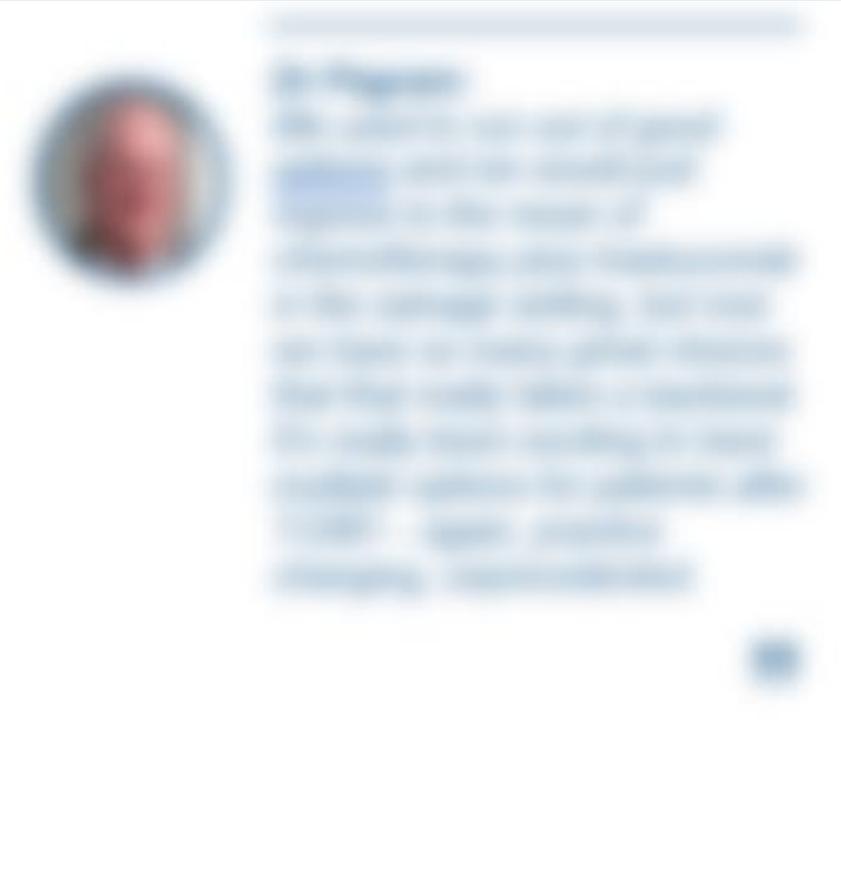
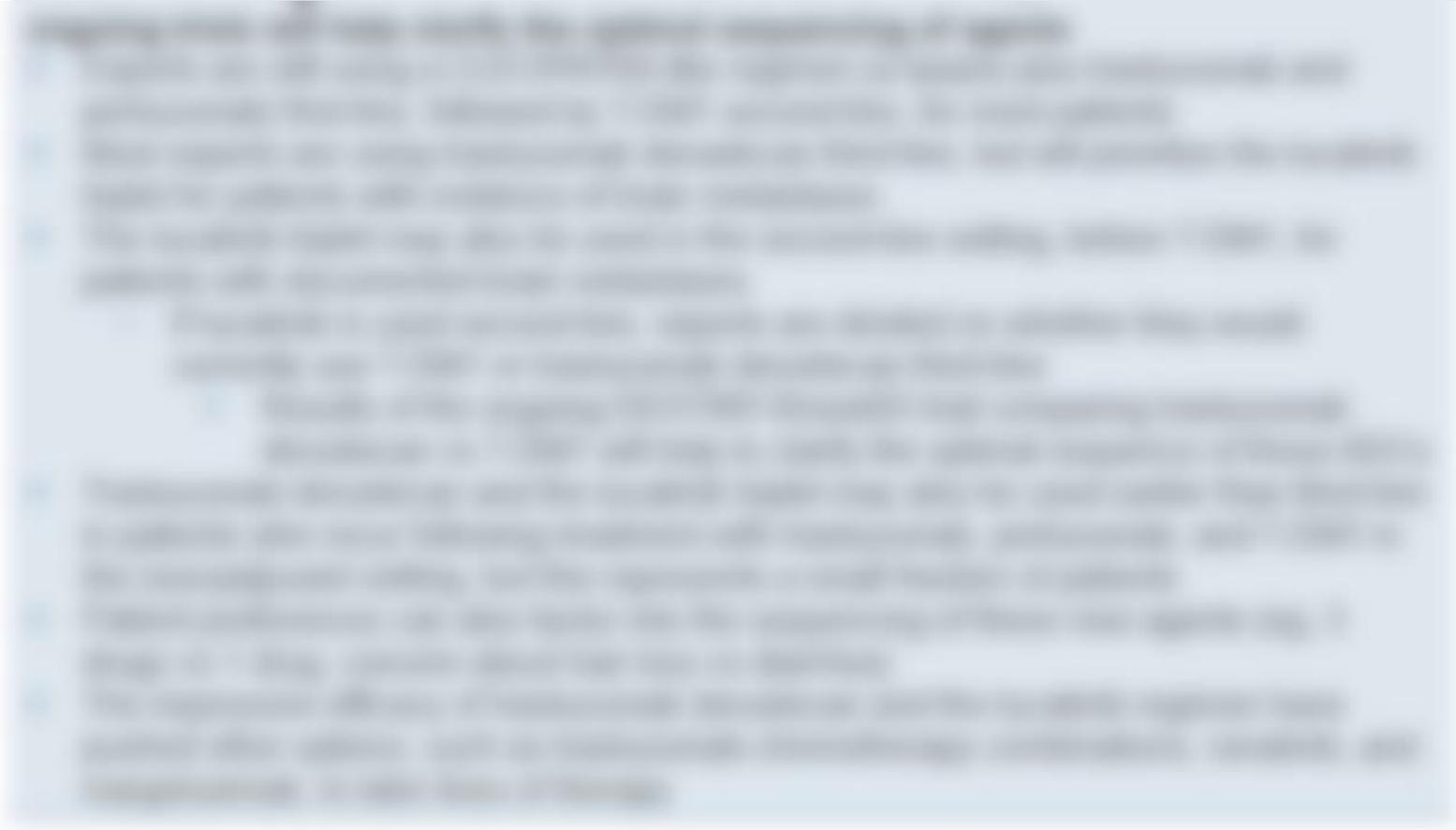
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# EXPERTS PROVIDED INSIGHTS INTO THE MANAGEMENT OF PATIENTS WITH HER2+ BRAIN METASTASES (1/2)

## TUCATINIB

> The HER2CLIMB regimen of tucatinib, trastuzumab, and capecitabine is considered a game-changer for patients with HER2+ CNS



# EXPERTS PROVIDED INSIGHTS INTO THE MANAGEMENT OF PATIENTS WITH HER2+ BRAIN METASTASES (2/2)

## IMAGING AND DETECTION OF CNS METASTASES

**Dr. [Name]**, [Title], [Institution]

Brain metastases are a common complication of systemic cancer, with a prevalence of approximately 30-40% in patients with advanced disease. The detection of brain metastases is crucial for determining the appropriate management strategy. The most common imaging modality for the detection of brain metastases is contrast-enhanced MRI. MRI is highly sensitive for the detection of brain metastases, particularly for enhancing lesions. However, MRI is not always able to detect non-enhancing lesions, such as those seen in low-grade gliomas or some types of metastases. In addition, MRI is not always able to distinguish between enhancing lesions and areas of blood-brain barrier breakdown. Therefore, a combination of imaging modalities, including MRI and PET, may be necessary for the accurate detection and characterization of brain metastases. PET imaging, particularly with radiotracers such as <sup>18</sup>F-FDG, can provide additional information about the metabolic activity of brain lesions, which can be helpful in distinguishing between enhancing lesions and areas of blood-brain barrier breakdown. In addition, PET imaging can be used to detect non-enhancing lesions that are not visible on MRI. Therefore, a combination of MRI and PET imaging may be necessary for the accurate detection and characterization of brain metastases.

**Dr. [Name]**, [Title], [Institution]

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**Dr. [Name]**, [Title], [Institution]

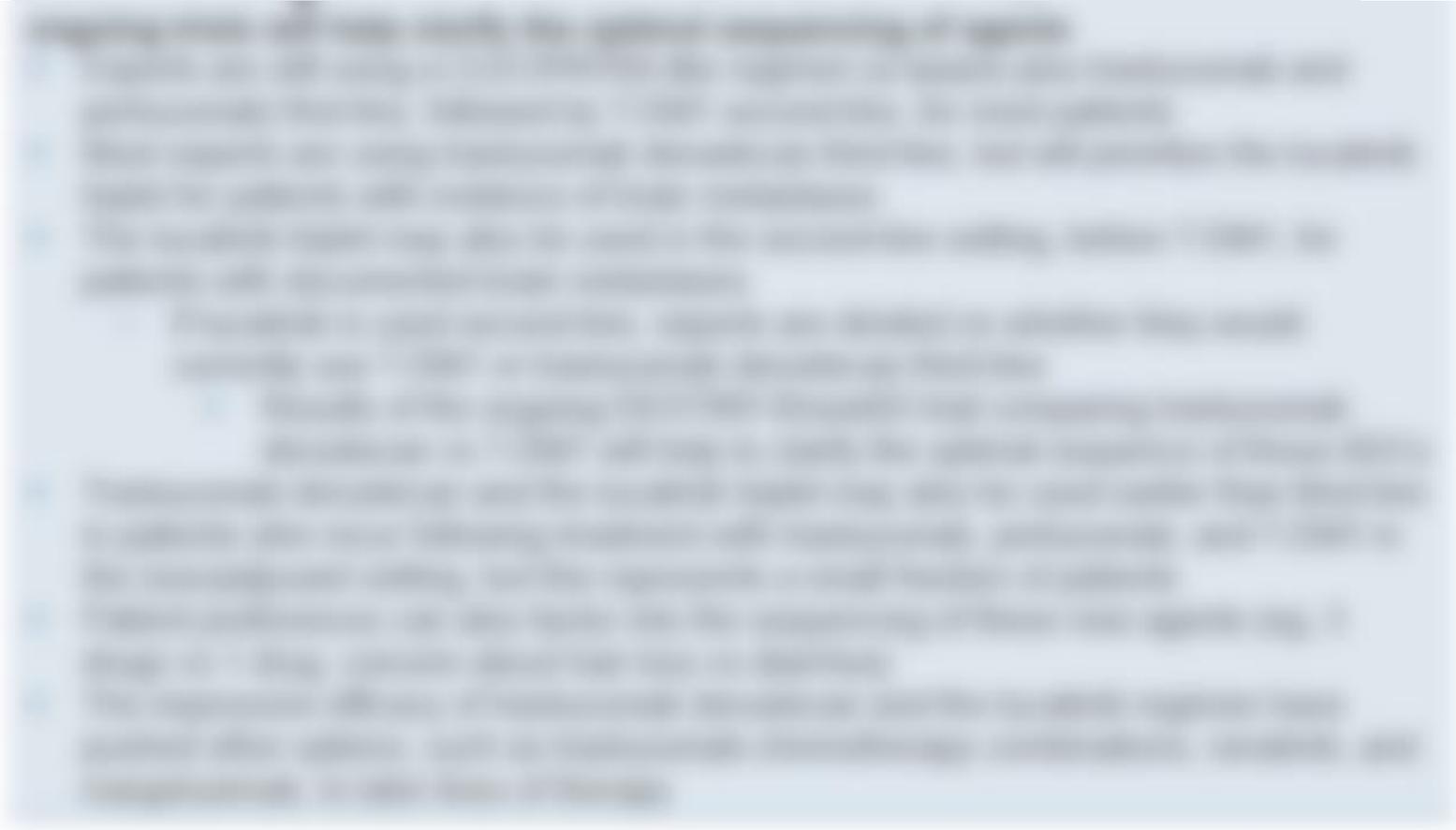
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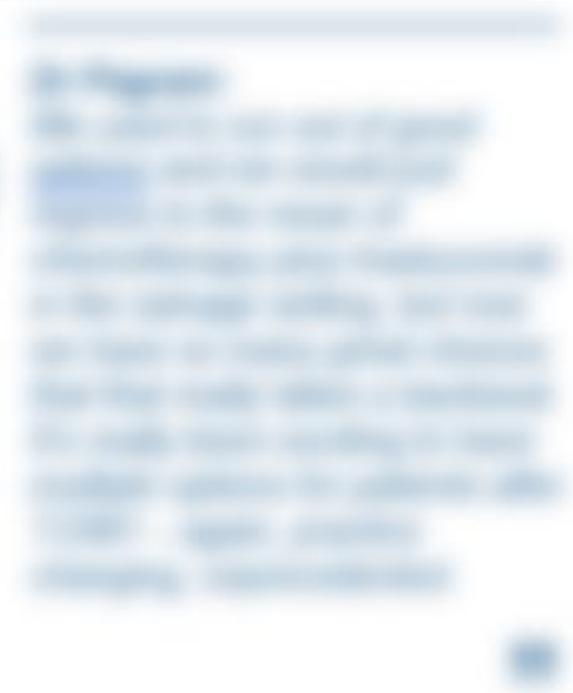
# EXPERTS SPECULATED ABOUT FUTURE DIRECTIONS IN RESEARCH FOR HER2+ mBC

## INVESTIGATIONAL APPROACHES

There is still room to improve outcomes for patients with HER2+ mBC,



“



# EXPERTS NOTED THAT THE TYPICAL FIRST-LINE PATIENT WITH HER2+ mBC HAS CHANGED

“

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# Individualizing Therapy for HER2+ Early Breast Cancer





# THERAPY FOR HER2+ EARLY BREAST CANCER (1/3)

PRESENTED BY MARK PEGRAM, MD

## LANDSCAPE OF EARLY STAGE HER2+ BREAST CANCER

> There is still a need for improved therapies for early stage HER2+ breast cancer

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# THERAPY FOR HER2+ EARLY BREAST CANCER (2/3)

PRESENTED BY MARK PEGRAM, MD

## RECENT ADVANCES IN (NEO)ADJUVANT THERAPY

**1. Systemic Therapy**

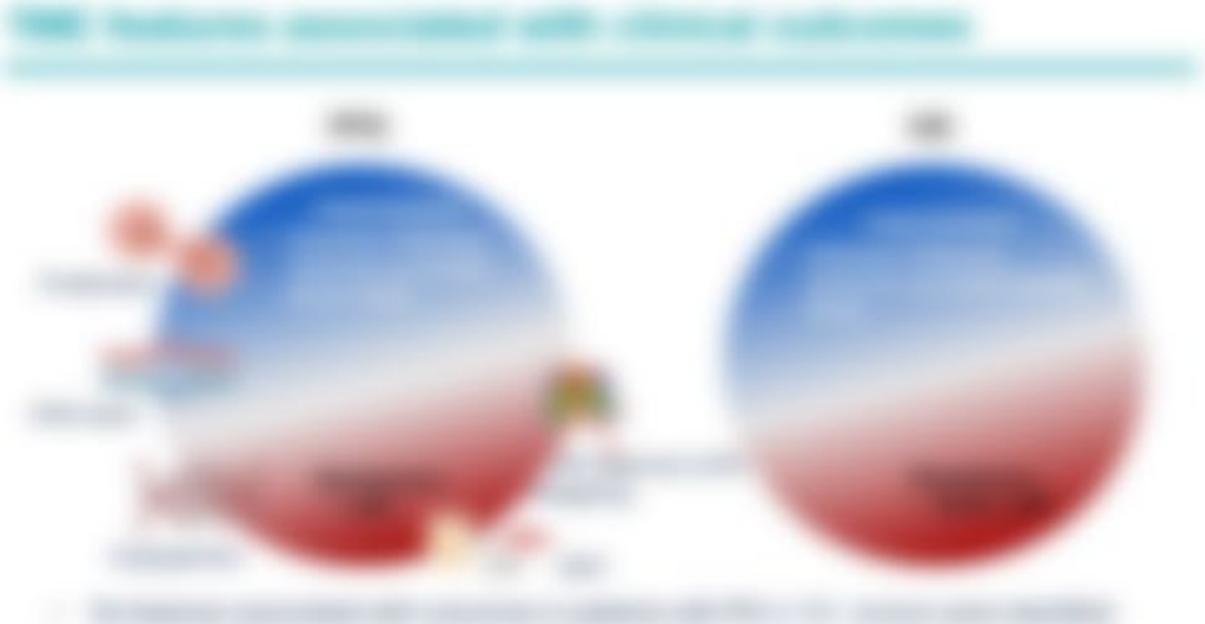
Standard of care for HER2+ early breast cancer includes a combination of chemotherapy and anti-HER2 therapy. Recent advances include the use of CDK4/6 inhibitors in the preoperative setting, which have been shown to improve pathologic complete response (pCR) rates and potentially reduce the need for mastectomy.

**2. Targeted Therapy**

Next-generation HER2 inhibitors, such as trastuzumab deruxtecan (TDM-10), have shown improved efficacy and a more favorable toxicity profile compared to traditional HER2 therapy. These agents are being evaluated in clinical trials for use in the neoadjuvant setting.

**3. Immunotherapy**

Immune checkpoint inhibitors, such as pembrolizumab, are being evaluated in clinical trials for use in the neoadjuvant setting for HER2+ breast cancer. Preliminary results suggest that the combination of immunotherapy with chemotherapy and anti-HER2 therapy may lead to improved pCR rates.





# THERAPY FOR HER2+ EARLY BREAST CANCER (3/3)

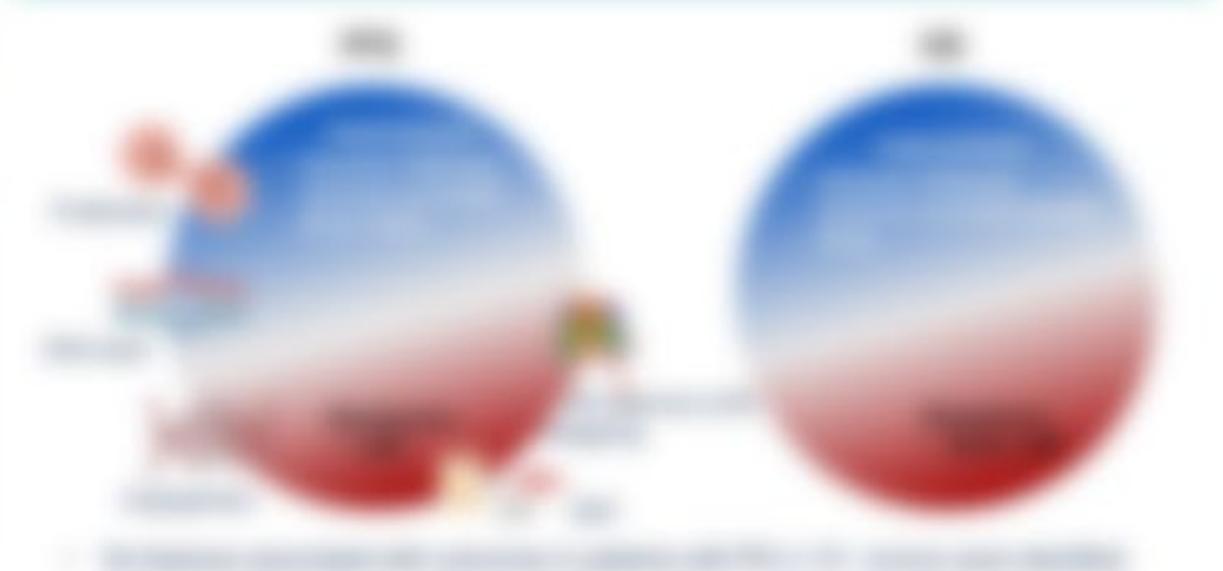
PRESENTED BY MARK PEGRAM, MD

HER2+ breast cancer is a type of breast cancer that is characterized by the presence of high levels of the protein HER2 on the surface of the cancer cells. This protein helps the cancer cells grow and spread. HER2+ breast cancer is more aggressive than other types of breast cancer and is often found in younger women.

The standard of care for HER2+ breast cancer is a combination of chemotherapy, endocrine therapy, and anti-HER2 therapy. Anti-HER2 therapy is a type of targeted therapy that blocks the action of the HER2 protein, which helps to slow down the growth of the cancer cells. The most commonly used anti-HER2 therapy is trastuzumab (Herceptin). Other anti-HER2 therapies include pertuzumab (Perjeta) and ado-trastuzumab emtansine (Kadcyla).

HER2+ breast cancer is often treated with a combination of chemotherapy, endocrine therapy, and anti-HER2 therapy. The most commonly used anti-HER2 therapy is trastuzumab (Herceptin). Other anti-HER2 therapies include pertuzumab (Perjeta) and ado-trastuzumab emtansine (Kadcyla). The combination of trastuzumab and pertuzumab has been shown to improve outcomes in HER2+ breast cancer. The combination of trastuzumab and ado-trastuzumab emtansine has been shown to improve outcomes in HER2+ breast cancer.

## HER2+ breast cancer treatment with anti-HER2 therapy



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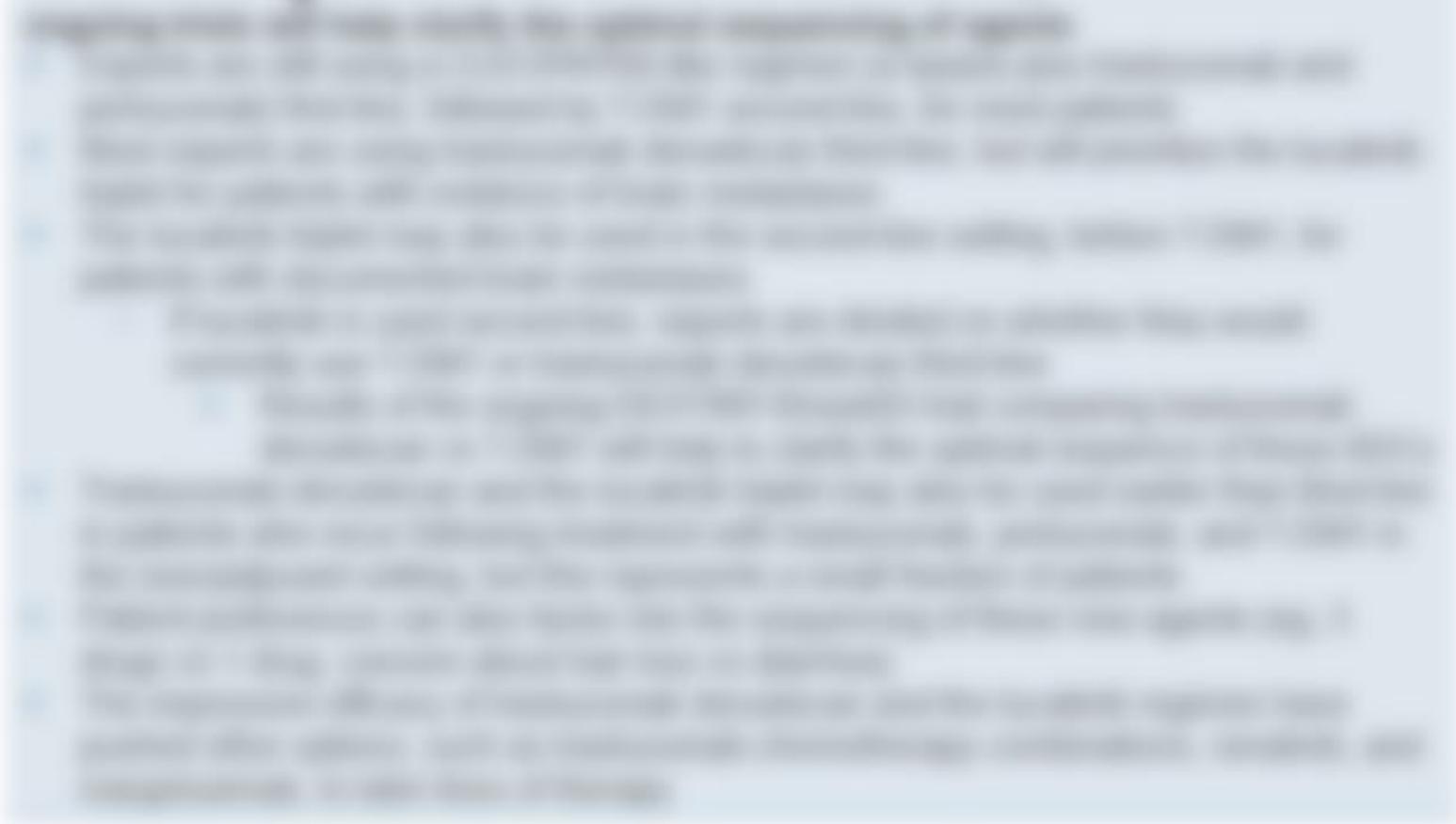
# Key Insights: Early Stage HER2+ Breast Cancer



# EXPERT PERSPECTIVES ON THE EVOLVING ROLE OF (NEO)ADJUVANT THERAPY FOR HER2+ BREAST CANCER

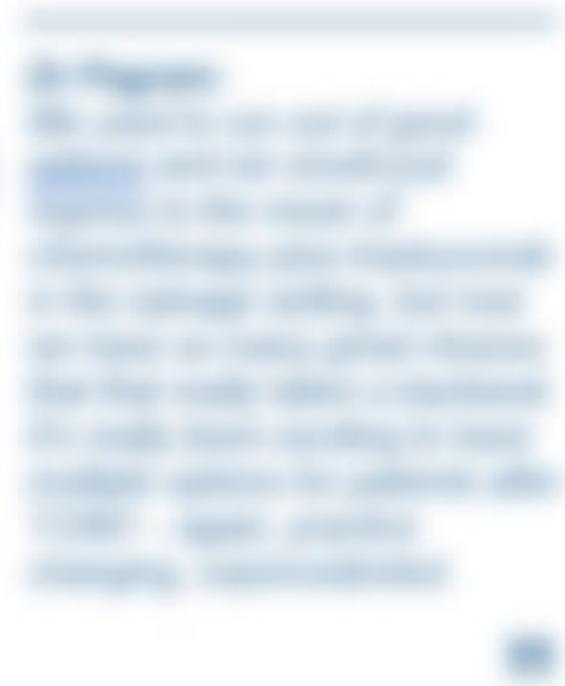
## INCREASED USE OF NEOADJUVANT THERAPY

Neoadjuvant therapy is the preferred approach for most patients



## MANAGEMENT OF SMALL NODE-NEGATIVE TUMORS

While surgery first followed by adjuvant therapy is being used



# EXPERTS DISCUSSED THE IMPACT OF RECENT TRIALS ON THE MANAGEMENT OF PATIENTS WITH RESIDUAL DISEASE

## CURRENT OPTIONS FOR RESIDUAL DISEASE



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# EXPERTS SPECULATED ON THE FUTURE FOR HER2+ EARLY STAGE BREAST CANCER

## FUTURE DIRECTIONS

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# EXPERTS DISCUSSED THE IMPACT OF THE COVID-19 PANDEMIC ON THEIR PRACTICES

## INCREASED USE OF TELEMEDICINE



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# Current and Investigational Approaches in Metastatic Triple-Negative Breast Cancer





# METASTATIC TRIPLE-NEGATIVE BREAST CANCER (1/4)

PRESENTED BY PRIYANKA SHARMA, MD

## IMMUNE CHECKPOINT INHIBITORS

Two randomized trials have now shown benefit for the addition of an immune checkpoint inhibitor to first-line chemotherapy for

*[Blurred text area]*





# METASTATIC TRIPLE-NEGATIVE BREAST CANCER (2/4)

PRESENTED BY PRIYANKA SHARMA, MD

## PARP INHIBITORS

The OlympiAD and EMBRACA trials showed a significant PFS advantage for

*[Blurred text area]*





# METASTATIC TRIPLE-NEGATIVE BREAST CANCER (3/4)

PRESENTED BY PRIYANKA SHARMA, MD

## ANTIBODY-DRUG CONJUGATES

## PI3K/AKT INHIBITORS

The Trop-2–directed ADC sacituzumab govitecan received full

> Although phase II results with the AKT inhibitor ipatasertib plus

[Blurred text area]





# METASTATIC TRIPLE-NEGATIVE BREAST CANCER (4/4)

PRESENTED BY PRIYANKA SHARMA, MD

## OTHER INVESTIGATIONAL APPROACHES

## TNBC SUBTYPES

Oral taxanes

Many gene expression signatures and other ways of molecularly



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# Key Insights: Metastatic Triple-Negative Breast Cancer



# EXPERTS COMMENTED ON CURRENT STANDARDS OF BIOMARKER TESTING AND UNMET NEEDS

## BIOMARKER TESTING

Testing for PD-L1 and *BRCA1/2* mutation status is considered

## REFINEMENT OF PATIENT SELECTION

Biology-based subtyping and further refinement of biomarkers

*[Blurred text area containing expert commentary]*



# EXPERTS PROVIDED INSIGHTS ON THE CURRENT USE OF IMMUNE CHECKPOINT INHIBITORS

## IMMUNE CHECKPOINT INHIBITORS

Chemotherapy with an immune checkpoint inhibitor is considered

“

*[Blurred text area containing expert insights on the current use of immune checkpoint inhibitors]*



# EXPERTS COMMENTED ON CURRENT AND FUTURE USES OF PARP INHIBITORS

## PARP INHIBITORS

## BEYOND gBRCA1/2

For patients with *BRCA1/2*-mutated, PD-L1- mTNBC, PARP

There is substantial interest in the continued investigation of

*[Blurred text area]*



## SACITUZUMAB GOVITECAN

Sacituzumab govitecan is viewed as a powerful, non-cross-

## FUTURE DIRECTIONS WITH ADCs

Experts also expressed interest in investigating sacituzumab,



# EXPERTS SPECULATED ON OTHER INVESTIGATIONAL AGENTS AND FUTURE DIRECTIONS IN TNBC

## CDK INHIBITORS

Emerging data with the CDK4/6 inhibitor trilaciclib are considered

## PI3K/AKT INHIBITORS

Despite the negative results from the IPATunitv130 trial, there is

*[Blurred text area containing additional information and references related to the CDK and PI3K/AKT inhibitor trials.]*



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**Standard and Emerging  
Strategies for High-Risk  
Early Stage Triple-Negative  
Breast Cancer**





# HIGH-RISK EARLY STAGE TNBC (1/4)

PRESENTED BY HOPE RUGO, MD, FASCO

## NEOADJUVANT PLATINUM TRIALS

Overall, preoperative trials of platinum agents for early stage

Overall, preoperative trials of platinum agents for early stage TNBC have shown promising results. The use of platinum agents in combination with chemotherapy and endocrine therapy has been shown to improve outcomes in early stage TNBC. The use of platinum agents in combination with chemotherapy and endocrine therapy has been shown to improve outcomes in early stage TNBC.

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# HIGH-RISK EARLY STAGE TNBC (2/4)

PRESENTED BY HOPE RUGO, MD, FASCO

## PARP INHIBITORS

A press release indicated that the OlympiAD trial investigating adjuvant olaparib in high-risk *gBRCA*-mutated HER2- breast cancer met

*[Blurred text from a press release, likely detailing the OlympiAD trial results and FDA approval.]*

### Timeline of FDA Approvals for HER2+ Breast Cancer

Year	2017	2018	2019	2020	2021	2022
2017						
2018						
2019						
2020						
2021						
2022						





# HIGH-RISK EARLY STAGE TNBC (3/4)

PRESENTED BY HOPE RUGO, MD, FASCO

## IMMUNE CHECKPOINT INHIBITORS

Both the KEYNOTE-522 and IMpassion031 trials have shown an

### Pembrolizumab for Triple-Negative Breast Cancer





# HIGH-RISK EARLY STAGE TNBC (4/4)

PRESENTED BY HOPE RUGO, MD, FASCO

## CAPECITABINE

> The CREATE-X trial demonstrated a PFS and an OS benefit for adjuvant

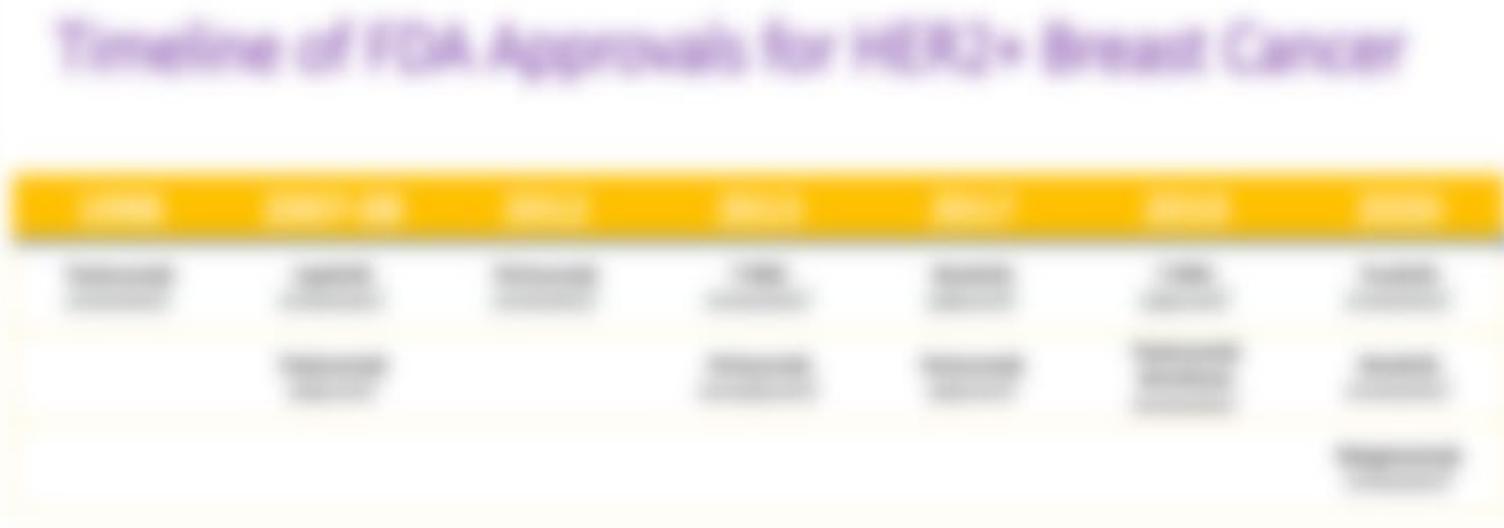
## OTHER STRATEGIES FOR RESIDUAL DISEASE

> The ECOG-ACRIN EA1131 trial compared adjuvant

• The CREATE-X trial (NCT01324065) compared adjuvant capecitabine (2000 mg bid) to placebo in patients with high-risk early-stage TNBC. The trial demonstrated a statistically significant improvement in PFS and OS for the capecitabine group.

• The ECOG-ACRIN EA1131 trial (NCT01324065) compared adjuvant capecitabine (2000 mg bid) to placebo in patients with high-risk early-stage TNBC. The trial demonstrated a statistically significant improvement in PFS and OS for the capecitabine group.

• The CREATE-X trial (NCT01324065) compared adjuvant capecitabine (2000 mg bid) to placebo in patients with high-risk early-stage TNBC. The trial demonstrated a statistically significant improvement in PFS and OS for the capecitabine group.



0 1 2 3 4 5  
Years since Randomization



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# Key Insights: High-Risk Early Stage Triple-Negative Breast Cancer



# EXPERTS COMMENTED ON THE ROLE OF PLATINUM AND FUTURE DIRECTIONS IN EARLY STAGE TNBC

## PLATINUM AGENTS

The benefit of platinum agents in the (neo)adjuvant setting for

*[Blurred content area]*

## MORE INDIVIDUALIZED THERAPY IN THE FUTURE

The future of treatment for early stage TNBC is personalization



# EXPERTS DISCUSSED THE ROLE OF NEOADJUVANT THERAPY AND TREATMENT FOR RESIDUAL DISEASE

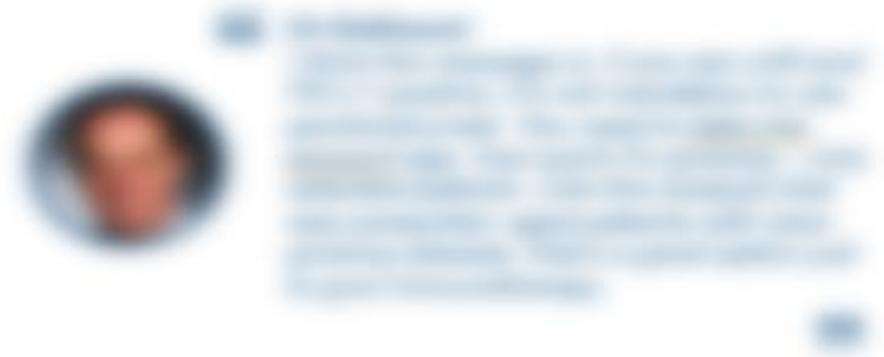
## CURRENT STANDARDS

Most experts favor using neoadjuvant therapy because it allows

*[Blurred content area under Current Standards]*

## FUTURE DIRECTIONS

There is substantial enthusiasm for evaluating sacituzumab



# EXPERTS SPECULATED ON THE POTENTIAL ROLE OF PARP INHIBITORS FOR EARLY STAGE DISEASE

## POTENTIAL IMPACT OF OlympiA TRIAL



**KEYNOTE 197: PARP INHIBITORS IN EARLY STAGE DISEASE**

The OlympiA trial is a phase III, randomized, controlled study evaluating the efficacy and safety of olaparib in combination with platinum-based chemotherapy versus platinum-based chemotherapy alone in patients with early-stage ovarian cancer. The trial is currently ongoing and is expected to complete enrollment in 2021. The results of the trial are expected to be presented at the ASCO 2021 meeting.

**PARP INHIBITORS IN EARLY STAGE DISEASE**

PARP inhibitors are a class of drugs that are used to treat certain types of cancer. They work by blocking the activity of the PARP enzyme, which is involved in DNA repair. PARP inhibitors are used in combination with chemotherapy to improve outcomes in patients with early-stage disease.



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Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173



# EXPERTS DISCUSSED THE IMPACT OF DATA WITH IMMUNE CHECKPOINT INHIBITORS FOR HIGH-RISK TNBC

## EMERGING NEOADJUVANT EVIDENCE

Preliminary data with immune checkpoint inhibitors in the

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## CURRENT PRACTICE

Most experts are not currently using immune checkpoint inhibitors



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# Novel Targets in Breast Cancer





# NOVEL TARGETS IN BREAST CANCER (1/2)

PRESENTED BY SARA TOLANEY, MD, MPH

## HER2-LOW BREAST CANCER

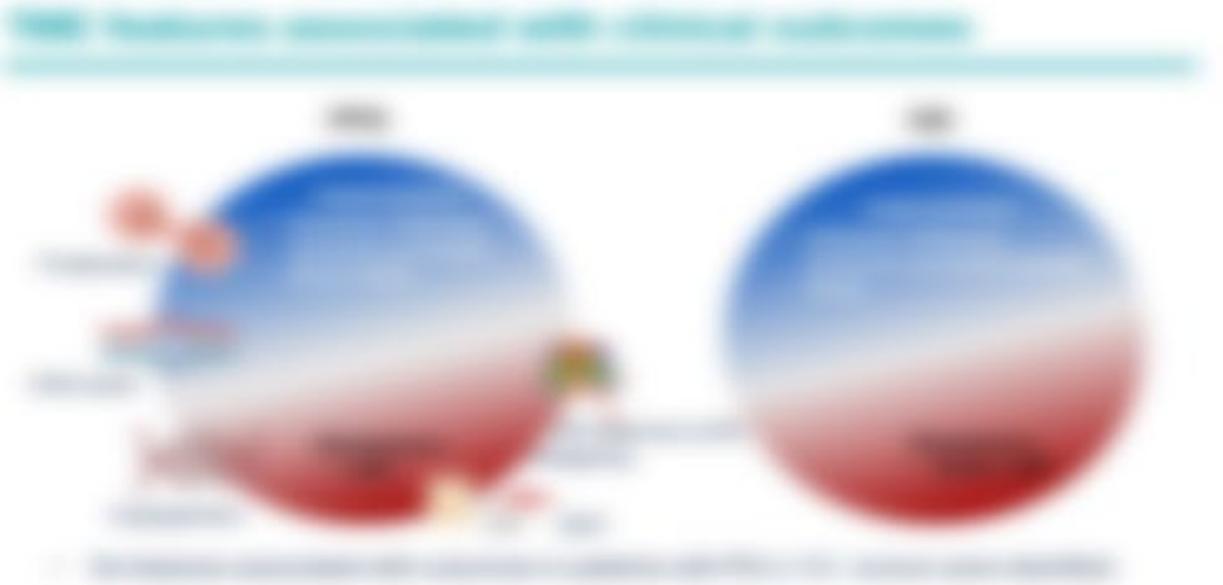
Approximately 60% of breast cancers are classified as HER2 low

**HER2-LOW BREAST CANCER**

HER2-low breast cancer is a subtype of breast cancer characterized by low levels of HER2 protein on the surface of cancer cells. This subtype is distinct from HER2-positive breast cancer, which has high levels of HER2 protein. HER2-low breast cancer is often associated with a better prognosis compared to HER2-positive breast cancer, but it may not respond as well to traditional HER2-targeted therapies like trastuzumab.

Diagnosis of HER2-low breast cancer typically involves immunohistochemistry (IHC) testing of the tumor tissue. IHC testing measures the amount of HER2 protein on the surface of cancer cells. HER2-low breast cancer is defined as having IHC scores of 1+ or 2+.

HER2-low breast cancer is often associated with a better prognosis compared to HER2-positive breast cancer, but it may not respond as well to traditional HER2-targeted therapies like trastuzumab. However, there are emerging treatments specifically designed for HER2-low breast cancer, such as trastuzumab deruxtecan (TDM-10), which has shown promising results in clinical trials.





# NOVEL TARGETS IN BREAST CANCER (2/2)

PRESENTED BY SARA TOLANEY, MD, MPH

## HER2-MUTATED BREAST CANCER

*HER2* mutations are found in approximately 2%–3% of all breast cancers, but the frequency is approximately 10% in HR+ mBC

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# Key Insights: Novel Targets in Breast Cancer



# EXPERTS NOTED THE EMERGING IMPORTANCE OF THE HER2-LOW SUBTYPE OF BREAST CANCER

## DEFINING HER2-LOW BREAST CANCER

The HER2-low phenotype is emerging as a potentially important

## MORE INDIVIDUALIZED THERAPY IN THE FUTURE

The future of treatment for early stage TNBC is personalization



# EXPERTS PROVIDED INSIGHTS ON THE POTENTIAL ROLE OF ADCs IN TREATING HER2-LOW BREAST CANCER



## EMERGING DATA WITH HER2-TARGETED ADCs

### Preliminary data with the HER2-targeted ADCs trastuzumab

**Emerging Data with the HER2-targeted ADCs trastuzumab**

The addition of the HER2-targeted ADC trastuzumab to the standard of care (SOC) for HER2-low breast cancer is a promising development for the treatment of this cancer. Preliminary data from a phase II trial (NCT04101010) showed that the combination of trastuzumab and SOC significantly improved overall survival (OS) compared to SOC alone in patients with HER2-low breast cancer.

- Patients who received trastuzumab with SOC had a significantly higher OS compared to those who received SOC alone. The median OS was 24.1 months for the trastuzumab group versus 18.1 months for the SOC group.
- The addition of trastuzumab to SOC was well-tolerated, with no significant increase in adverse events compared to SOC alone.

## FUTURE DIRECTIONS WITH ADCs

### Ongoing trials of HER2-targeted ADCs will also need to analyze

**Ongoing trials of HER2-targeted ADCs will also need to analyze**

There are ongoing trials with the aim to "test out" the combination of trastuzumab and SOC in patients with HER2-low breast cancer. These trials will need to analyze the following:

- The addition of an antibody drug conjugate (ADC) may provide the necessary cytotoxicity and death signals to the cells of the HER2-low population, as shown in the NCT04101010 trial. The addition of trastuzumab to SOC is a promising approach to improve outcomes in HER2-low breast cancer.
- The use of trastuzumab as a HER2-targeted ADC may improve outcomes in patients with HER2-low breast cancer. However, it is important to evaluate the safety and efficacy of these ADCs in this population, especially for patients who are unable to tolerate SOC.



# EXPERTS COMMENTED ON THE EMERGENCE OF *HER2* MUTATIONS AS AN ACTIONABLE ALTERATION

## HER2-MUTATED BREAST CANCER

Although only 2%–3% of all breast cancers harbor *HER2*

**Key Takeaways**

- The addition of an antibody drug conjugate (ADC) to the treatment of breast cancer has demonstrated a significant benefit for the addition of trastuzumab emtansin (T-DM1) in high-negative breast cancer (HNBC).
- Patients who showed positive results with trastuzumab and pertuzumab combination in the progression-free survival (PFS) and overall survival (OS) populations, with high negative results in the OS population, were observed in patients with high negative results in the OS population.
- The PFS in negative PFS in combination did not benefit from the addition of trastuzumab to high-negative in any negative results.

## NEXT-GENERATION SEQUENCING

> Most experts now favor NGS mutational testing because it can

**Key Takeaways**

- There are clinical trials with the aim to "test up" the tumor, using NGS to increase understanding of actionability, especially from immunotherapy.
- The addition of an antibody drug conjugate (ADC) may provide the necessary immunogenic cell death required for the activity of ADC in the PFS in patients, as shown in the HNBC and OS populations. The addition of trastuzumab emtansin (T-DM1) to trastuzumab showed overall survival with a PFS in high-negative results.
- The use of routine immunotherapy (ICI) may increase immunogenicity, immunogenic immunotherapy efficiency, and increase OS in high negative results. Immunotherapy is combined with trastuzumab and trastuzumab emtansin (T-DM1) in patients, supporting the clinical use of effective testing in breast.

# EXPERTS DISCUSSED THE POTENTIAL OF HER3 AS A TARGET IN BREAST CANCER

## HER3-TARGETED ADCs

> More information is needed on the overlap between HER2 and HER3 expression in breast cancer cells

### Introduction

The addition of the third antibody component (ADC) to the HER2-targeted ADC trastuzumab (T-DM1) is a promising strategy for the enhanced effect of antibody-drug conjugates (ADCs) in triple-negative breast cancer (TNBC).

- Patients who showed positive results with trastuzumab and pertuzumab combination in the adjuvant setting with trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1) in the adjuvant setting, and higher overall survival (OS) compared with trastuzumab alone in patients with stage II breast cancer who received trastuzumab in the adjuvant setting.
- The T-DM1 + pertuzumab (T-DM1 + P) combination did not benefit from the addition of trastuzumab in the adjuvant setting in any molecular subtype.

### Combination of ADCs in HER2+ TNBC

There are clinical trials with the aim to "stack up" the ADCs using trastuzumab to increase trastuzumab's efficacy against TNBC.

- The addition of an antibody drug conjugate (ADC) may provide the necessary trastuzumab cell death required by the activity of ADC in the TNBC population, as shown in the T-DM1 + P trial. The addition of trastuzumab to T-DM1 is a promising strategy to increase overall survival in TNBC.
- The use of trastuzumab as a third antibody component may increase trastuzumab's efficacy against TNBC, but higher overall survival. Trastuzumab is considered to be a third antibody component in the ADC.

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# Evolving Treatments and New Developments in HR+ Metastatic Breast Cancer





# HR+ METASTATIC BREAST CANCER (1/3)

PRESENTED BY PETER KAUFMAN, MD



## CURRENT ALGORITHM FOR HR+ mBC

Endocrine therapy remains the mainstay of treatment for HR+ disease

Phase 3 Trial	PALOMA-2 (N=666)	MONALEESA-2 (N=668)	MONARCH-3 (N=493)	MONALEESA-7 (N=672)
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### Endocrine Therapy

The addition of the selective estrogen receptor modulator (SERM) to the aromatase inhibitor (AI) regimen has been shown to improve overall survival in the adjuvant setting for the endocrine therapy of breast cancer (HR+ mBC).

- Tamoxifen also showed improved overall survival with aromatase and endocrine therapy compared to the aromatase and endocrine therapy alone in the adjuvant setting. Higher endocrine therapy response rates were observed in patients with lower endocrine therapy response rates and higher estrogen receptor (ER) expression. ER expression was also higher in patients with lower endocrine therapy response rates.
- The ER $\alpha$  expression in ER $\alpha$  expression did not predict for the addition of endocrine therapy to endocrine therapy in any endocrine therapy.

### Endocrine Therapy in Metastatic (mBC)

There are clinical trials with the aim to "build up" the endocrine therapy regimen to increase endocrine therapy response rates in patients with endocrine therapy resistance.

- The addition of an endocrine therapy (ET) to the aromatase inhibitor (AI) regimen in the ER $\alpha$  population, as shown in the MONARCH-3 trial, showed improved overall survival with AI + ET vs AI alone.
- The use of selective estrogen receptor modulators (SERMs) may increase endocrine therapy response rates, endocrine therapy response rates, and overall survival in patients with endocrine therapy resistance. However, it is unclear if higher endocrine therapy response rates are associated with overall survival. Further research is needed to determine if endocrine therapy can be effective in building up a regimen.





# HR+ METASTATIC BREAST CANCER (2/3)

PRESENTED BY PETER KAUFMAN, MD

## INVESTIGATIONAL AGENTS – AKT INHIBITORS

Although phase II results were encouraging, the phase III

### Investigational Agents

The addition of the novel immunomodulator (NMI) to the standard of care (SOC) for metastatic breast cancer (MBC) is a promising approach to improve overall survival (OS) in hormone receptor positive (HR+) metastatic breast cancer (MBC).

- Phase II data showed promising results with immunotherapy and the addition of NMI to the SOC in the adjuvant and metastatic setting. Phase II results showed that the addition of NMI to the SOC significantly improved OS, progression-free survival (PFS), and quality of life (QoL) in patients with HR+ MBC. These results were observed in patients with both the hormone receptor positive (HR+) and hormone receptor negative (HR-) subgroups.
- The HR+ and HR- subgroups did not benefit from the addition of immunotherapy to the SOC in any metastatic setting.

### Investigational Agents in Metastatic Breast Cancer

There are clinical trials with the aim to "test out" the novel drug NMI to increase immunomodulation to address improved results from immunotherapy.

- The addition of an antibody drug conjugate (ADC) may provide the necessary immunogenic cell death (ICD) required for the activity of NMI in the HR+ population, as shown in the HR+ phase II trial. The addition of immunotherapy to the SOC in metastatic breast cancer requires both a HR+ and HR- population.
- The use of novel immunomodulators (NMI) may increase immunogenicity, immunogenic cell death (ICD), and increase CD8+ T cell tumor response. Immunotherapy is combined with NMI and immunotherapy to address immune response, suggesting that NMI can be effective in treating breast cancer.





# HR+ METASTATIC BREAST CANCER (3/3)

PRESENTED BY PETER KAUFMAN, MD

## INVESTIGATIONAL AGENTS – ORAL SERDs

Several novel oral SERDs are now in late-phase clinical development; most have shown activity in *ESR1*-mutated and fulvestrant-

### Investigational Agents

- The addition of the novel investigational SERD, *ORX-006*, to the fulvestrant regimen may increase the anti-proliferative effect of fulvestrant in *ESR1*-mutated HR+ metastatic breast cancer (MBC).
- Phase 1b study showed promising results with *ORX-006* and fulvestrant combination in the progression-free survival (PFS) endpoint. Higher PFS, overall survival (OS), progression-free survival (PFS), response rate (RR), and higher overall survival (OS) were observed in patients with *ESR1* mutations compared to patients with wild-type *ESR1*.
- The *ESR1* wild-type patients did not benefit from the addition of *ORX-006* to fulvestrant in any endpoint.

### Investigational Agents in Fulvestrant (FULV)

- There are clinical trials with the aim to "block up" the estrogen receptor to increase fulvestrant's activity against breast cancer cells.
- The addition of an orally drug conjugate (ODC) may provide the necessary estrogenic cell death required by the activity of fulvestrant in *ESR1* wild-type patients, as shown in the *ORX-006* study.
- The addition of investigational SERD, *ORX-006*, to fulvestrant showed overall response rate in *ESR1* wild-type patients.
- The use of novel investigational SERDs may increase fulvestrant's anti-proliferative activity and increase overall survival in patients with *ESR1* wild-type metastatic breast cancer.
- Investigational SERDs with higher and sustained overall survival response, suggesting that *ORX-006* can be effective in blocking up a target.



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# Key Insights: HR+ Metastatic Breast Cancer



# EXPERTS COMMENTED ON THE EVOLVING ROLE OF CDK4/6 INHIBITORS FOR HR+ mBC

## FIRST-LINE THERAPY

The vast majority of patients with HR+ mBC are receiving a CDK4/6

**Key Takeaways**

- The addition of a CDK4/6 inhibitor to endocrine therapy (ET) in the first-line setting for HR+ mBC is supported by clinical trial data demonstrating improved overall survival (OS) compared to ET alone.
- The addition of a CDK4/6 inhibitor to ET is supported by clinical trial data demonstrating improved OS compared to ET alone.
- The addition of a CDK4/6 inhibitor to ET is supported by clinical trial data demonstrating improved OS compared to ET alone.

## TOXICITY MANAGEMENT

> Diarrhea/cramping and cytopenias are seen more

**Key Takeaways**

- There are clinical trials with the aim to "back up" the CDK4/6 inhibitor to increase its tolerability and reduce toxicity.
- The addition of a CDK4/6 inhibitor to ET is supported by clinical trial data demonstrating improved OS compared to ET alone.
- The use of a CDK4/6 inhibitor in the first-line setting for HR+ mBC is supported by clinical trial data demonstrating improved OS compared to ET alone.

# EXPERTS SPECULATED ON THE POTENTIAL ROLE OF ORAL SERDs FOR HR+ mBC

## FITTING ORAL SERDs INTO THE ALGORITHM

There is substantial enthusiasm for the development of oral SERDs, and this would

### Immunotherapy

The addition of the cancer immunomodulator (ICI) to the endocrine therapy regimen has demonstrated a 2.4 percentage point increase in overall survival compared with endocrine therapy in high-risk hormone-sensitive mBC.

- Patients who received endocrine therapy with immunotherapy and endocrine therapy alone in the progression-free survival analysis had a 1.9 percentage point increase in progression-free survival, a 1.4 percentage point increase in overall survival, and a 1.4 percentage point increase in time to next treatment. These benefits were observed in patients with both the hormone-sensitive and hormone-resistant subgroups.
- The ICI in combination with endocrine therapy did not result from the addition of immunotherapy to endocrine therapy in any individual subgroup.

### Combining Endocrine Therapy with Immunotherapy (ICI)

There are ongoing trials with the aim to “test out” the combination of endocrine therapy with immunotherapy to address questions currently being investigated.

- The addition of an antibody drug conjugate (ADC) may provide the necessary immunogenic cell death required for the activity of ICI in the HR+ population, as shown in the HR+ cohort. The addition of endocrine therapy to ICI is a promising strategy to address questions such as ICI in HR+ and HR-.
- The use of hormone-depleting endocrine therapy may increase immunogenicity, improve immunotherapy efficiency, and decrease HR+ endocrine therapy resistance. Knowledge is continuing to expand and evolving around these clinical questions, suggesting that ICI can be effective in fitting in a role.

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# Evolving Paradigms in HR+ Early Breast Cancer





# HR+ EARLY BREAST CANCER (1/3)

PRESENTED BY JOYCE O'SHAUGHNESSY, MD

## ADJUVANT CDK4/6 INHIBITOR TRIALS

The monarchE trial evaluating 2 years of adjuvant abemaciclib in patients with

**Background**

CDK4/6 inhibitors are a class of drugs that block the activity of cyclin-dependent kinases 4 and 6, which are involved in cell cycle regulation. Inhibiting these kinases can lead to cell cycle arrest and apoptosis of cancer cells.

**MonarchE Trial**

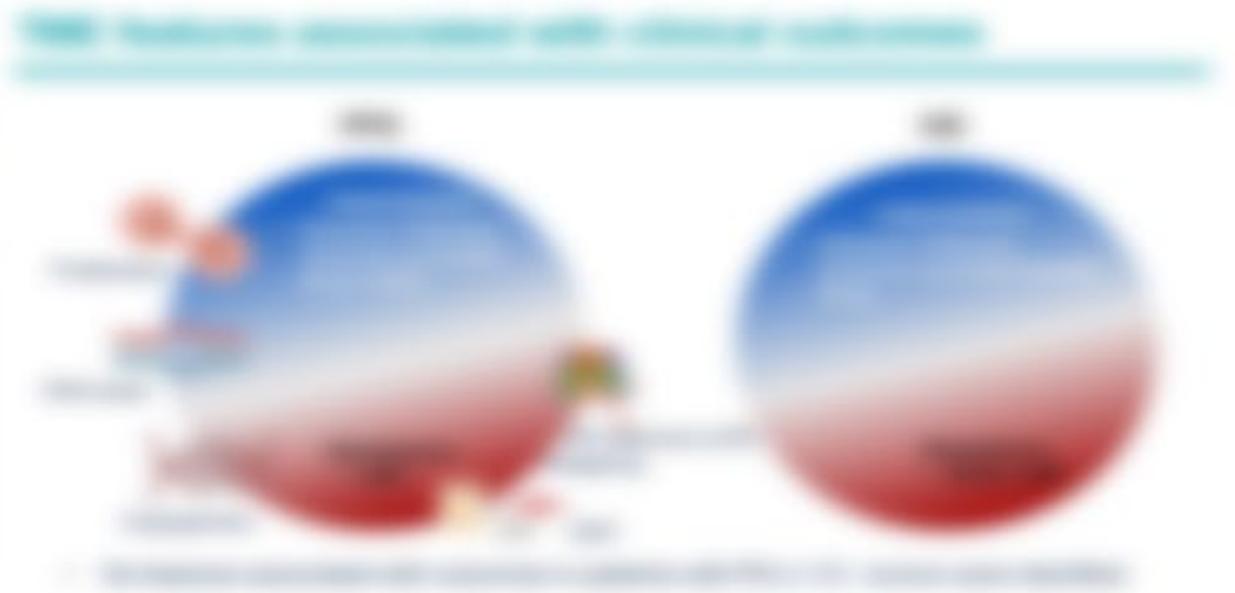
The MonarchE trial is a phase III, randomized, controlled trial evaluating the efficacy and safety of 2 years of adjuvant abemaciclib in patients with HR+ early breast cancer. The trial compares abemaciclib to placebo in addition to standard of care (tamoxifen and endocrine therapy).

**Primary Endpoints**

- Overall survival (OS)
- Recurrence-free interval (RFI)
- Time to distant recurrence (TDR)

**Secondary Endpoints**

- Local recurrence-free interval (LRFI)
- Time to local recurrence (TLR)
- Time to distant recurrence (TDR)
- Time to death (TTD)
- Time to death from breast cancer (TTD-BC)
- Time to death from non-breast cancer (TTD-NBC)
- Time to death from unknown cause (TTD-UC)
- Time to death from unknown cause (TTD-UC)
- Time to death from unknown cause (TTD-UC)





# HR+ EARLY BREAST CANCER (2/3)

PRESENTED BY JOYCE O'SHAUGHNESSY, MD

## RISK ASSESSMENT AND CHEMOTHERAPY DE-ESCALATION

### Results of the RxPONDER trial

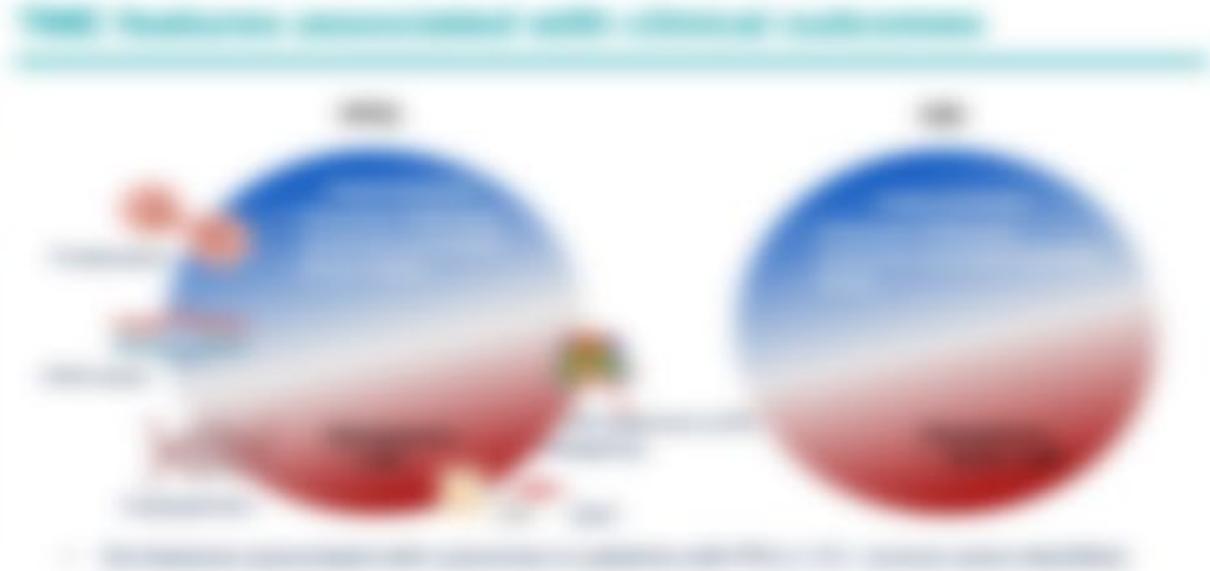
**TRIAL DESIGN**

Phase III, randomized, controlled trial comparing endocrine therapy (ET) alone versus endocrine therapy (ET) plus chemotherapy (CT) in patients with hormone receptor-positive (HR+), HER2-negative, early-stage breast cancer.

**Primary Endpoints:** Overall survival (OS), distant recurrence-free survival (DRFS), and quality of life (QoL).

**Secondary Endpoints:** Local recurrence-free survival (LRFS), distant recurrence-free survival (DRFS), and quality of life (QoL).

**Results:** The trial demonstrated that for patients with low-risk disease, endocrine therapy alone was non-inferior to endocrine therapy plus chemotherapy. For patients with high-risk disease, the addition of chemotherapy significantly improved overall survival and distant recurrence-free survival.



**CONCLUSIONS**

The RxPONDER trial results support a risk-stratified approach to treatment. For patients with low-risk disease, endocrine therapy alone is a reasonable and potentially less toxic treatment option. For patients with high-risk disease, the addition of chemotherapy remains a standard of care to improve survival outcomes.

Patients at Risk, n	Yrs Since Randomization									
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10
CT + ET	1675	1514	1400	1268	1113	943	585	287	88	3
ET	1675	1567	1462	1308	1167	975	601	298	104	9

Patients at Risk, n	Yrs Since Randomization									
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10
CT + ET	834	763	704	625	535	454	272	116	34	1
ET	831	760	699	602	529	429	245	99	31	2





# HR+ EARLY BREAST CANCER (3/3)

PRESENTED BY JOYCE O'SHAUGHNESSY, MD

## RISK ASSESSMENT AND EXTENDED ENDOCRINE THERAPY

> ASCO guidelines now recommend extended

**Background**

Endocrine therapy is the mainstay of treatment for HR+ breast cancer. The use of extended endocrine therapy (EET) has been shown to improve overall survival in several clinical trials. The ASCO guidelines now recommend EET for HR+ breast cancer.

**Key Points**

- EET is defined as the continuation of endocrine therapy beyond the standard 5-year duration.
- The use of EET is supported by clinical trials showing improved overall survival.
- The ASCO guidelines now recommend EET for HR+ breast cancer.

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# Key Insights: HR+ Early Breast Cancer

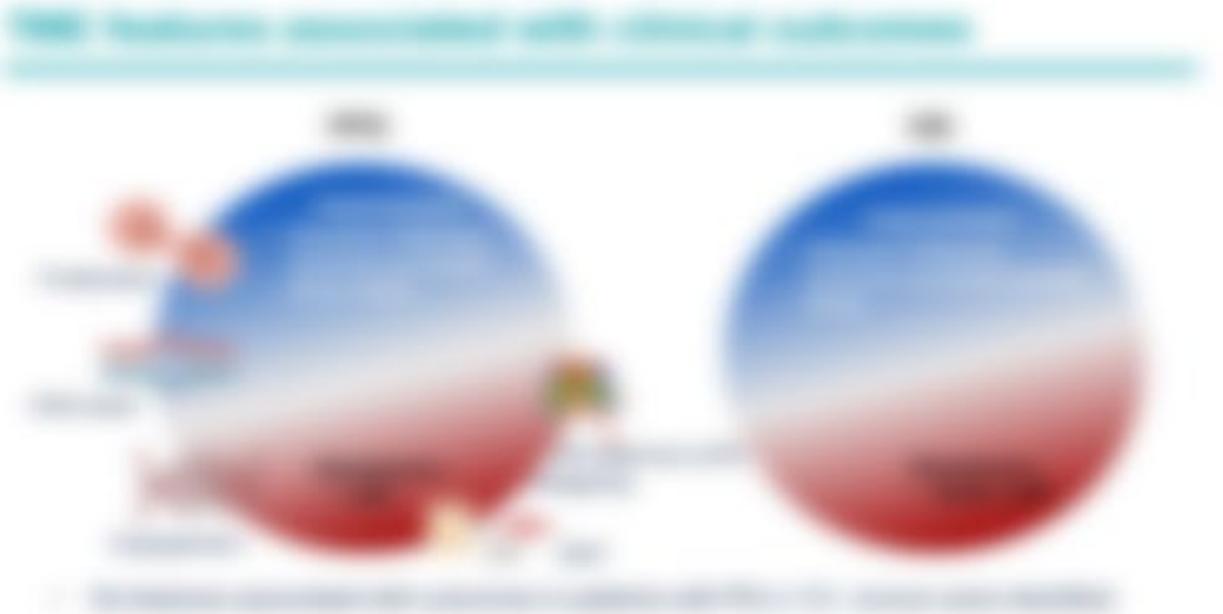


# EXPERTS PROVIDED INSIGHT INTO THE IMPACT OF THE ADJUVANT CDK4/6 TRIAL DATA

## ADJUVANT CDK4/6 INHIBITION – DATA AND APPLICATION

**Key findings from the clinical trial:**

- The combination of CDK4/6 inhibitor and endocrine therapy significantly improved progression-free survival (PFS) compared to endocrine therapy alone.
- The combination also showed a trend towards improved overall survival (OS) and a lower risk of distant recurrence.
- The most common side effects were neutropenia, thrombocytopenia, and fatigue, which were generally manageable with supportive care.



# EXPERTS DISCUSSED TAILORING ADJUVANT CHEMOTHERAPY ON THE BASIS OF RISK-STRATIFICATION

## RxPONDER

**Background**

Adjuvant chemotherapy is a standard of care for breast cancer patients. However, not all patients benefit from the same intensity of treatment. The RxPONDER trial is a phase III clinical trial that aims to determine if a lower intensity of chemotherapy (one cycle) is as effective as a higher intensity (four cycles) for patients with hormone receptor-positive, HER2-negative breast cancer. The trial is currently ongoing and results are expected in the near future.

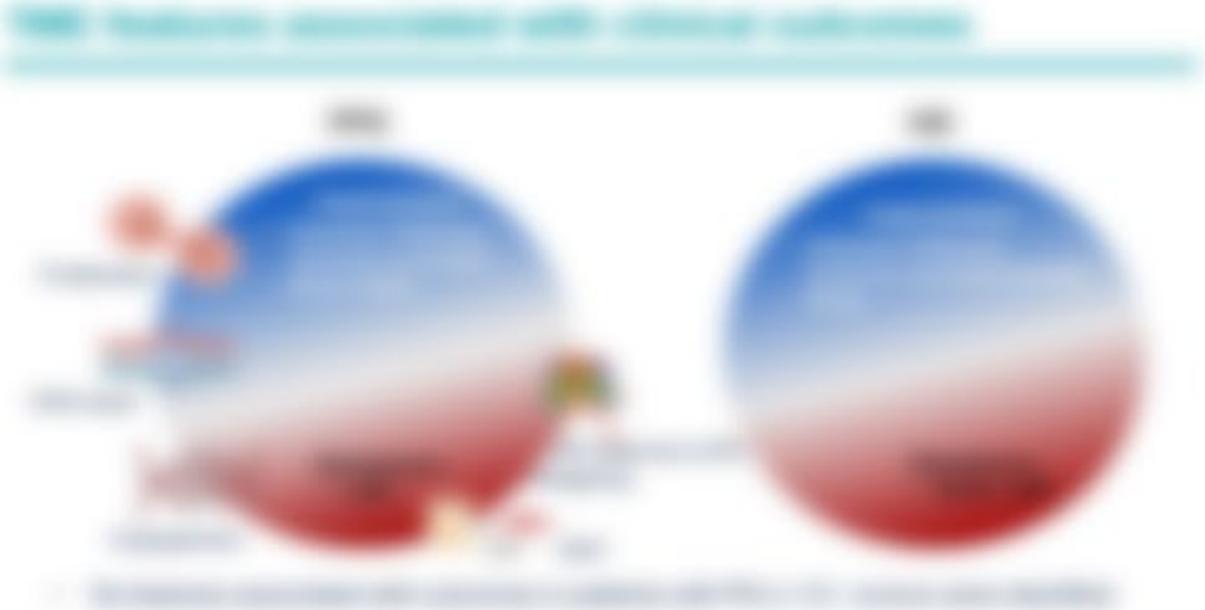
**Key Findings**

The trial is designed to compare two treatment groups: one receiving four cycles of chemotherapy and another receiving one cycle. The primary endpoint is overall survival. Secondary endpoints include quality of life, toxicity, and health economics. The trial is stratified by genomic subtypes, including Luminal A, Luminal B, and HER2-negative/HER2-enriched.

**Implications**

The results of the RxPONDER trial will have significant implications for the management of breast cancer. If the trial shows that one cycle of chemotherapy is as effective as four cycles for certain patient subgroups, this would represent a major advance in personalized medicine, allowing for more tailored and potentially less toxic treatment for individual patients.

## ADAPT



# EXPERTS COMMENTED ON UTILIZING GENOMIC TOOLS FOR DECISION-MAKING ABOUT EXTENDED ENDOCRINE THERAPY

## TAILORING ADJUVANT ENDOCRINE THERAPY ON THE BASIS OF RISK

The Breast Cancer Index is perceived to have the most robust data

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