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EPICS

BREAST CANCER IN 2021 AND BEYOND

April 28 and May 3, 2021

REPORT CONTENTS

EPICS

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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

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VIRTUAL CLOSED-DOOR ROUNDTABLE

FACULTY

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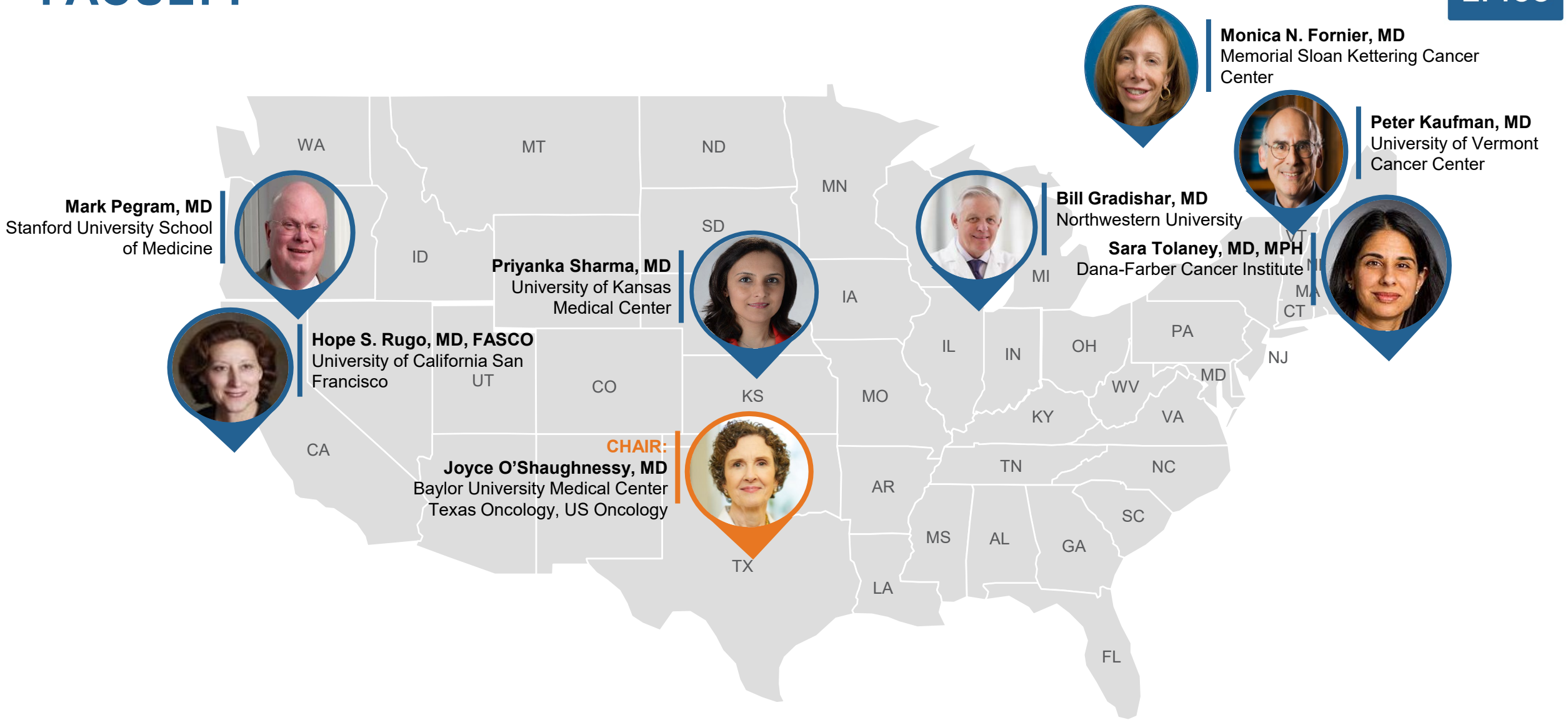

Monica N. Fornier, MD
Memorial Sloan Kettering Cancer Center

Peter Kaufman, MD
University of Vermont Cancer Center

Bill Gradishar, MD
Northwestern University

Sara Tolaney, MD, MPH
Dana-Farber Cancer Institute

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

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

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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)

EPICS

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

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EVOLUTION OF OPTIONS FOR HER2+ BREAST CANCER

> Four new agents were added to the

EVOLVING PARADIGMS IN HER2+ mBC (2/2)

PRESENTED BY BILL GRADISHAR, MD

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RECENT ADVANCES

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

RESEARCH AND FUTURE DIRECTIONS

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

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Key Insights: HER2+ mBC

EXPERT PERSPECTIVES ON CHANGES TO THE ALGORITHM FOR HER2+ mBC

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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

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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

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

EPICS

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)

EPICS

IMAGING AND DETECTION OF CNS METASTASES

EXPERTS SPECULATED ABOUT FUTURE DIRECTIONS IN RESEARCH FOR HER2+ mBC

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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

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LANDSCAPE OF EARLY STAGE HER2+ BREAST CANCER

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

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

PRESENTED BY MARK PEGRAM, MD

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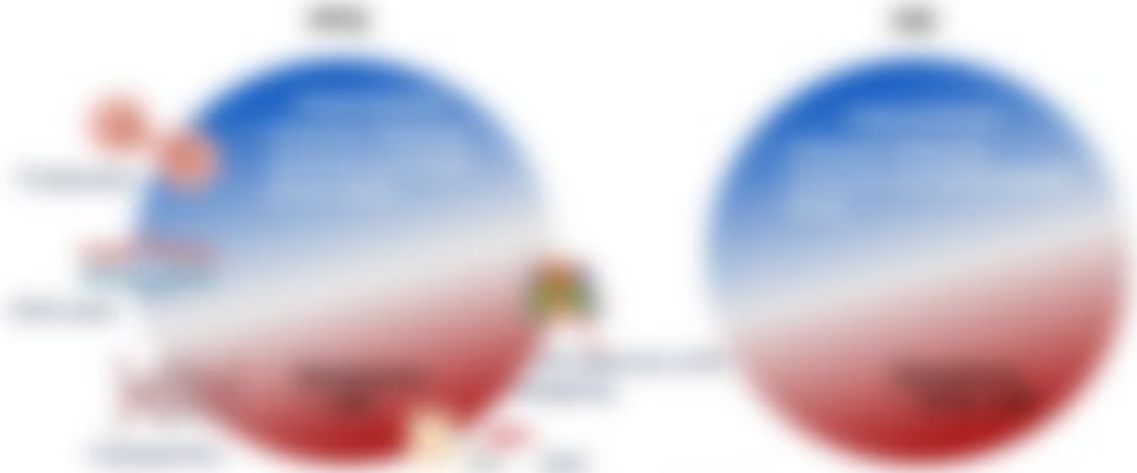
RECENT ADVANCES IN (NEO)ADJUVANT THERAPY



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

PRESENTED BY MARK PEGRAM, MD

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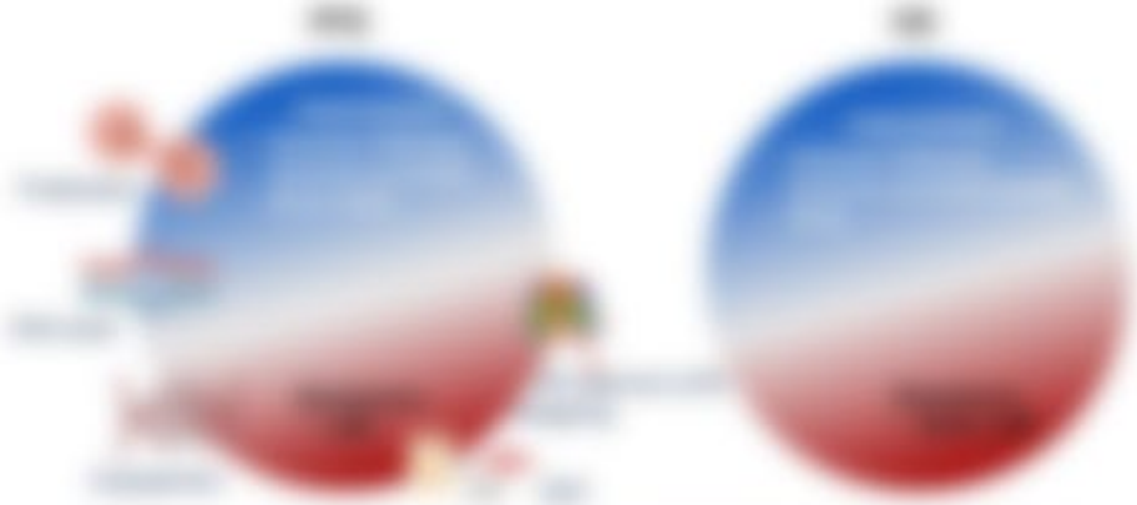

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Key Insights: Early Stage HER2+ Breast Cancer

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

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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

EPICS

CURRENT OPTIONS FOR RESIDUAL DISEASE

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

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FUTURE DIRECTIONS

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

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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

EPICS

IMMUNE CHECKPOINT INHIBITORS

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

METASTATIC TRIPLE-NEGATIVE BREAST CANCER (2/4)

PRESENTED BY PRIYANKA SHARMA, MD

EPICS

PARP INHIBITORS

The OlympiAD and EMBRACA trials showed a significant PFS advantage for

METASTATIC TRIPLE-NEGATIVE BREAST CANCER (3/4)

PRESENTED BY PRIYANKA SHARMA, MD

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ANTIBODY-DRUG CONJUGATES

The Trop-2–directed ADC sacituzumab govitecan received full

PI3K/AKT INHIBITORS

> Although phase II results with the AKT inhibitor ipatasertib plus

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METASTATIC TRIPLE-NEGATIVE BREAST CANCER (4/4)

PRESENTED BY PRIYANKA SHARMA, MD

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OTHER INVESTIGATIONAL APPROACHES

Oral taxanes

TNBC SUBTYPES

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

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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

EXPERTS PROVIDED INSIGHTS ON THE CURRENT USE OF IMMUNE CHECKPOINT INHIBITORS

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IMMUNE CHECKPOINT INHIBITORS

Chemotherapy with an immune checkpoint inhibitor is considered

EXPERTS COMMENTED ON CURRENT AND FUTURE USES OF PARP INHIBITORS

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PARP INHIBITORS

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

BEYOND g*BRCA*1/2

There is substantial interest in the continued investigation of

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EXPERT PERSPECTIVES ON ANTIBODY-DRUG CONJUGATES

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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

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CDK INHIBITORS

Emerging data with the CDK4/6 inhibitor trilaciclib are considered

PI3K/AKT INHIBITORS

Despite the negative results from the IPATunity130 trial, there is

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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

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NEOADJUVANT PLATINUM TRIALS

Overall, preoperative trials of platinum agents for early stage

HIGH-RISK EARLY STAGE TNBC (2/4)

PRESENTED BY HOPE RUGO, MD, FASCO

EPICS

PARP INHIBITORS

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

- [illegible] 2019-2020, dramatically expanding options and improving outcomes for patients
- National Comprehensive Cancer Network (NCCN) guidelines recommend a CLEOPATRA-like regimen including a taxane, trastuzumab, and pertuzumab for first-line therapy, and T-DM1 for second-line therapy
  - Newer agents or regimens such as trastuzumab deruxtecan, tucatinib plus trastuzumab and capecitabine, neratinib plus capecitabine, and margetuximab, are recommended in the third line and beyond
  - Trastuzumab deruxtecan is preferred post T-DM1 for patients with visceral metastases
  - The tucatinib triplet is preferred post T-DM1 for patients with CNS metastases

Timeline of FDA Approvals for HER2+ Breast Cancer

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]
						[illegible]

HIGH-RISK EARLY STAGE TNBC (3/4)

PRESENTED BY HOPE RUGO, MD, FASCO

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IMMUNE CHECKPOINT INHIBITORS

Both the KEYNOTE-522 and IMpassion031 trials have shown an

Pembrolizumab for Triple-Negative Breast Cancer

Timeline of FDA Approvals for HER2+ Breast Cancer

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HIGH-RISK EARLY STAGE TNBC (4/4)

PRESENTED BY HOPE RUGO, MD, FASCO

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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

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

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PLATINUM AGENTS

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

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

EPICS

CURRENT STANDARDS

Most experts favor using neoadjuvant therapy because it allows

FUTURE DIRECTIONS

There is substantial enthusiasm for evaluating sacituzumab

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

EPICS

POTENTIAL IMPACT OF OlympiA TRIAL

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

Tutt A, et al. ASCO 2021. Abstract LBA1.

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

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EMERGING NEOADJUVANT EVIDENCE

Preliminary data with immune checkpoint inhibitors in the

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

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HER2-LOW BREAST CANCER

Approximately 60% of breast cancers are classified as HER2 low

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NOVEL TARGETS IN BREAST CANCER (2/2)

PRESENTED BY SARA TOLANEY, MD, MPH

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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

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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

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

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EMERGING DATA WITH HER2-TARGETED ADCs

Preliminary data with the HER2-targeted ADCs trastuzumab

[illegible]

FUTURE DIRECTIONS WITH ADCs

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

[illegible]

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

EPICS

HER2-MUTATED BREAST CANCER

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

[redacted]

NEXT-GENERATION SEQUENCING

> Most experts now favor NGS mutational testing because it can

[redacted]

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

EPICS

HER3-TARGETED ADCs

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

[redacted]

[redacted]

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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

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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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HR+ METASTATIC BREAST CANCER (2/3)

PRESENTED BY PETER KAUFMAN, MD

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INVESTIGATIONAL AGENTS – AKT INHIBITORS

Although phase II results were encouraging, the phase III

[illegible]

[illegible]

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HR+ METASTATIC BREAST CANCER (3/3)

PRESENTED BY PETER KAUFMAN, MD

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INVESTIGATIONAL AGENTS – ORAL SERDs

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

[redacted]

[redacted]

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Key Insights: HR+ Metastatic Breast Cancer

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

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FIRST-LINE THERAPY

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

[illegible]

[illegible]

TOXICITY MANAGEMENT

> Diarrhea/cramping and cytopenias are seen more

[illegible]

[illegible]

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

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FITTING ORAL SERDs INTO THE ALGORITHM

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

[redacted]

[redacted]

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Evolving Paradigms in HR+ Early Breast Cancer

HR+ EARLY BREAST CANCER (1/3)

PRESENTED BY JOYCE O'SHAUGHNESSY, MD

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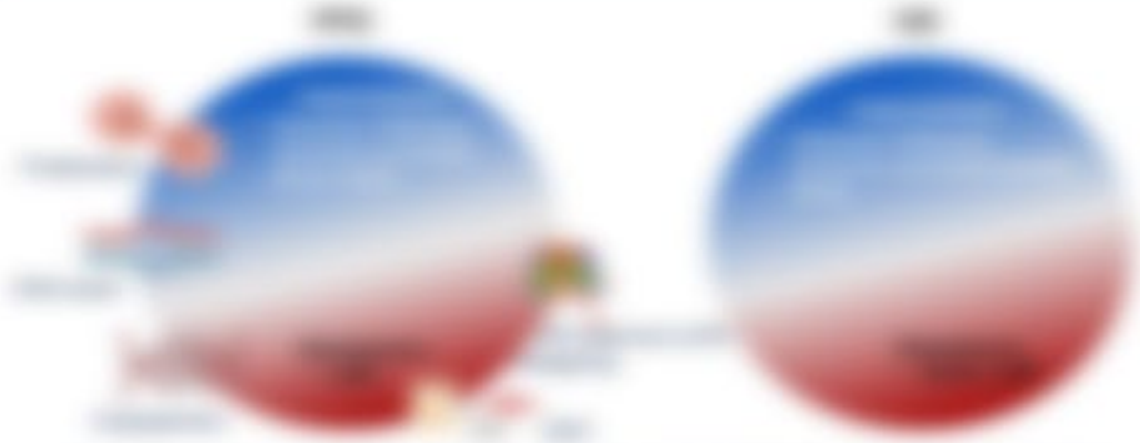
ADJUVANT CDK4/6 INHIBITOR TRIALS

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



HR+ EARLY BREAST CANCER (2/3)

PRESENTED BY JOYCE O'SHAUGHNESSY, MD

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RISK ASSESSMENT AND CHEMOTHERAPY DE-ESCALATION

Results of the RxPONDER trial

Patients at Risk, n	Yrs Since Randomization									
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									
CT + ET	834	763	704	625	535	454	272	116	34	1
ET	831	760	699	602	529	429	245	99	31	2

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HR+ EARLY BREAST CANCER (3/3)

PRESENTED BY JOYCE O'SHAUGHNESSY, MD

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RISK ASSESSMENT AND EXTENDED ENDOCRINE THERAPY

> ASCO guidelines now recommend extended

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Key Insights: HR+ Early Breast Cancer

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

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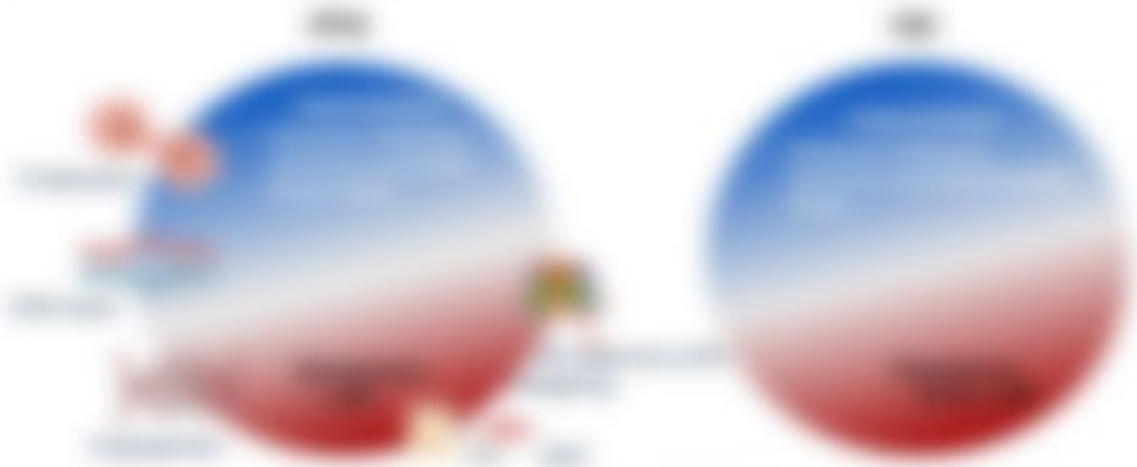
ADJUVANT CDK4/6 INHIBITION – DATA AND APPLICATION



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

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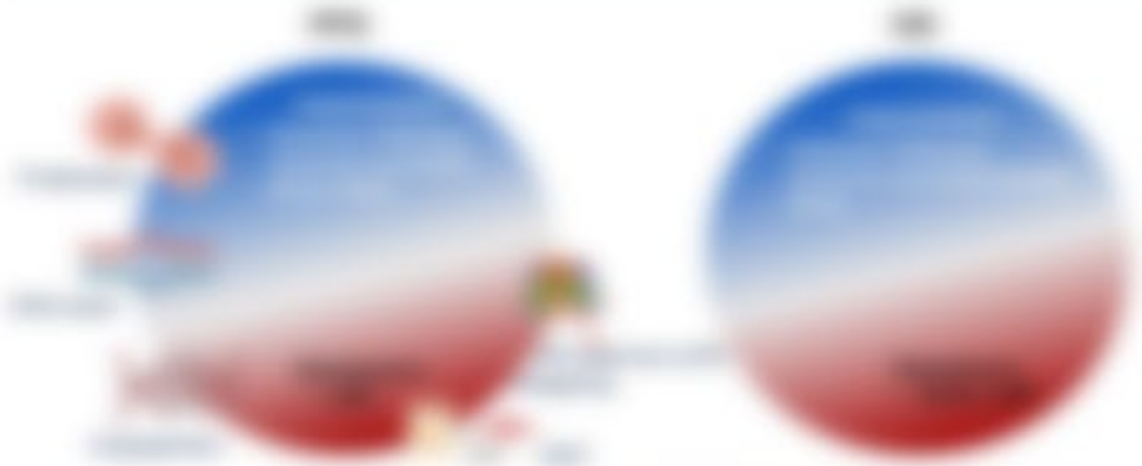
RxPONDER

ADAPT



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

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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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