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Global Perspectives in Current and Future Management of Breast Cancer

September 19 and 21, 2022

Report Contents

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Meeting Snapshot

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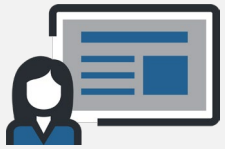
VIRTUAL CLOSED-DOOR ROUNDTABLE

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

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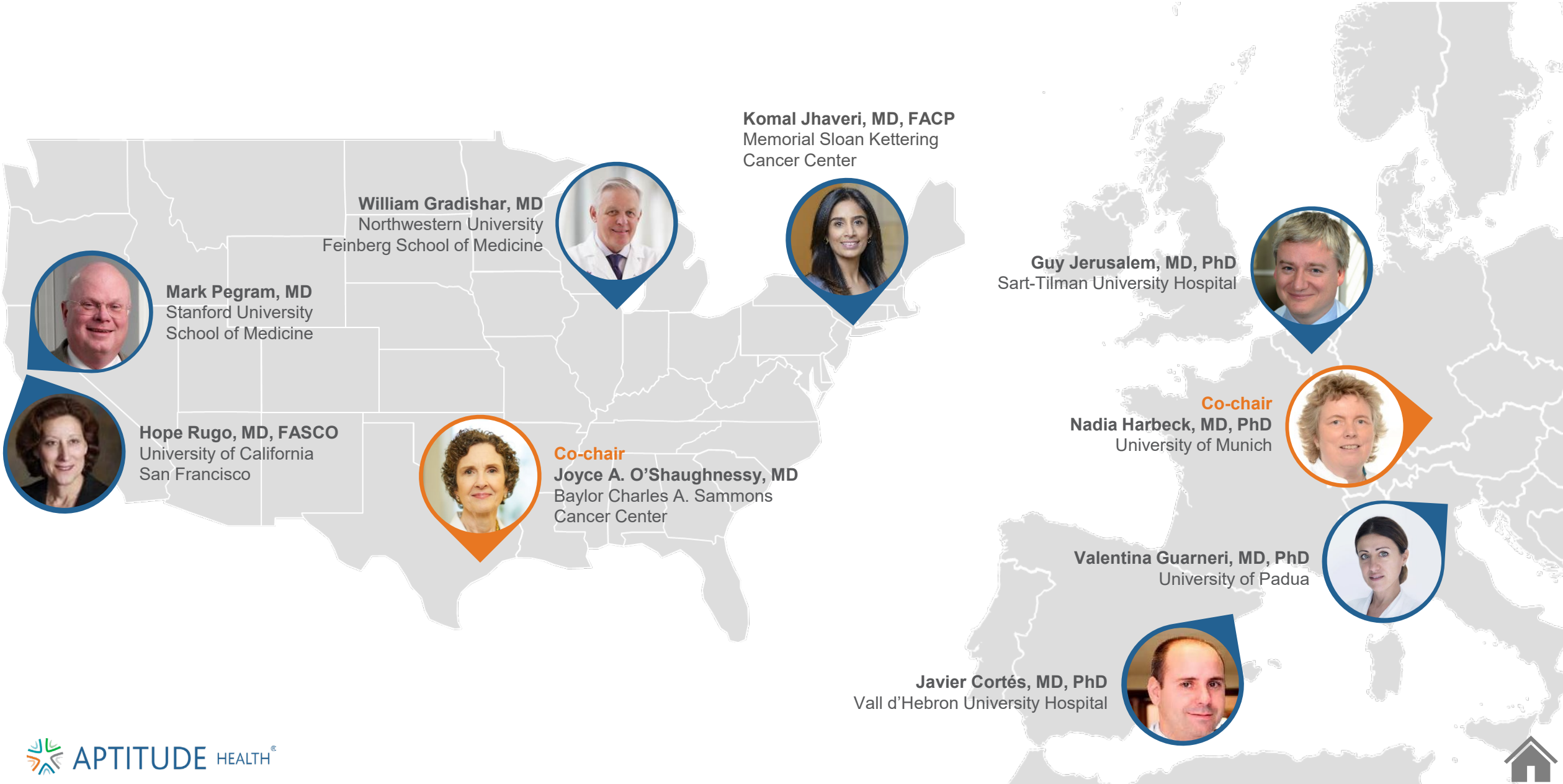

Komal Jhaveri, MD, FACP
Memorial Sloan Kettering Cancer Center

William Gradishar, MD
Northwestern University Feinberg School of Medicine

Mark Pegram, MD
Stanford University School of Medicine

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

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Meeting Agenda: Day 1 – September 19, 2022

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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)	*BREAK*	
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)	*BREAK*	
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

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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

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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 (1/2)

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ER, PR, and HER2 remain the cornerstone of clinical decision-making

> Current clinical decision-making relies heavily on IHC analysis of 3 single biomarkers (ER, PR, and HER2) that provide prognostic information and predict response to specific therapies

[redacted]

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

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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

[redacted]

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Current and New Treatments in HER2+ Early BC

Current and New Treatments in HER2+ Early BC (1/2)

Presented by Valentina Guarneri, MD, PhD

EPICS

Evolving scenario of HER2+ early BC: Neoadjuvant therapies

> The APT trial (NCT00542451) evaluated adjuvant trastuzumab with an anthracycline-free, taxane-only chemotherapy backbone and

Current and New Treatments in HER2+ Early BC (2/2)

Presented by Valentina Guarneri, MD, PhD

EPICS

Adjuvant therapies

> The KATHERINE trial (NCT01772472) was the first to formally demonstrate the superiority of T-DM1 compared with trastuzumab alone in

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

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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)

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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

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Trial updates

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

Advances in HER2+ mBC (2/3)

Presented by Guy Jerusalem, MD, PhD

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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

Advances in HER2+ mBC (3/3)

Presented by Guy Jerusalem, MD, PhD

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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

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

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

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

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

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The future of treating HER2+ mBC

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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)

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Adjuvant ET is tailored on the basis of risk

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

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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

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Evolving treatment landscape

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

Presented by Komal Jhaveri, MD, FACP

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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

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

Presented by Komal Jhaveri, MD, FACP

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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

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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

Exciting Updates from TROPiCS-02

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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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*Sacituzumab govitecan is currently FDA approved for the treatment of adult patients with mTNBC who have received at least 2 prior therapies for metastatic disease. It is not yet approved in Europe.

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

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The future of oral SERDS

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

*Sacituzumab govitecan is currently FDA approved for the treatment of adult patients with mTNBC who have received at least 2 prior therapies for metastatic disease. It is not yet approved in Europe.

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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

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HER2-low BC requires further molecular and disease characterization

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

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

Presented by William Gradishar, MD

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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

The Concept of HER2 Status Is Evolving

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Improving HER2 testing reproducibility in HER2-low BC

> ***Dr Pegram:***

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

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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

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Advances in Early and Metastatic TNBC

Advances in Early and Metastatic TNBC (1/3)

Presented by Javier Cortés, MD, PhD

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Metastatic TNBC: Role of immunotherapy

> Phase III trials, IMpassion130 (NCT02425891) and IMpassion131

Metastatic TNBC: Role of PARP inhibition

> Two phase III trials investigated PARP inhibitor

Advances in Early and Metastatic TNBC (2/3)

Presented by Javier Cortés, MD, PhD

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Metastatic TNBC: Small molecules and ADCs

> The START trial (NCT03383679) compared the AR

Metastatic TNBC: Current treatment algorithm

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Advances in Early and Metastatic TNBC (3/3)

Presented by Javier Cortés, MD, PhD

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Early TNBC

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

[redacted]

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Emerging Strategies in (Neo)Adjuvant 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,

Advances in Early and Metastatic TNBC

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Treatment algorithm mTNBC

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

[redacted]

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*T-DXd is currently FDA approved only for patients with unresectable or metastatic HER2+ BC who have received 2 or more prior anti–HER2-based regimens in the metastatic setting.

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Abbreviations

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- +, 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