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EPICS

EPICS Global Perspectives: Current and Future Management of Breast Cancer

September 23 and 27, 2021

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Meeting Snapshot

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TWO-DAY VIRTUAL CLOSED-DOOR ROUNDTABLE

DATE:
September 23 and 27, 2021

DISEASE STATE AND DATA PRESENTATIONS by key experts

INSIGHTS REPORT including postmeeting analyses and actionable recommendations

PANEL: Key experts in breast cancer
> 4 from US
> 5 from Europe

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

Panel Consisting of 4 US and 5 European Breast Cancer Experts

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Mark Pegram, MD
Stanford University School of Medicine

William Gradishar, MD
Northwestern University Feinberg 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

Joseph Gligorov, MD, PhD
Sorbonne University

Pierfranco Conte, MD
University of Padua

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

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Meeting Agenda – September 23, 2021

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Time (CEST)	Topic	Speaker/Moderator
18.30 – 18.35	Welcome and Introductions	Nadia Harbeck, MD, PhD
18.35 – 18.50	Current and New Treatments in HER2+ Early Breast Cancer (BC)	Joseph Gligorov, MD, PhD
18.50 – 19.35	Discussion and Key Takeaways	
19.35 – 19.50	Current and New Treatments in HER2+ Metastatic Breast Cancer (mBC)	Javier Cortes, MD, PhD
19.50 – 20.35	Discussion and Key Takeaways	
20.35 – 20.45	Break	
20.45 – 21.00	Current and Emerging Approaches in HR+, HER2– Early BC	Guy Jerusalem, MD, PhD
21.00 – 21.30	Discussion and Key Takeaways	
21.30 – 21.45	Conclusions and Closing	Nadia Harbeck, MD, PhD

Meeting Agenda – September 27, 2021

EPICS

Time (CEST)	Topic	Speaker/Moderator
18.30 – 18.35	Welcome and Introductions	Joyce A. O'Shaughnessy, MD
18.35 – 18.50	Current and Emerging Approaches in HR+, HER2– mBC	Pierfranco Conte, MD
18.50 – 19.35	Discussion and Key Takeaways	
19.35 – 19.45	Novel Targets in Breast Cancer	Hope Rugo, MD, FASCO
19.45 – 20.15	Discussion and Key Takeaways	
20.15 – 20.35	Current and Emerging Approaches in Triple-Negative Breast Cancer (TNBC)	William Gradishar, MD
20.35 – 21.20	Discussion and Key Takeaways	
21.20 – 21.30	Conclusions and Closing	Joyce A. O'Shaughnessy, MD

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Current and New Treatments in HER2+ Early BC

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

Presented by Joseph Gligorov, MD, PhD

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Optimizing anti-HER2 treatment in neoadjuvant setting

> Trastuzumab-containing dual anti-HER2 therapy is superior to

Optimizing anti-HER2 treatment in adjuvant setting

> The KATHERINE trial established 1 year of adjuvant T-DM1 as

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

Presented by Joseph Gligorov, MD, PhD

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Current (neo)adjuvant approaches

Ongoing trials of interest

> The CompassHER2 trial is comparing adjuvant T-DM1 ±

The Role of (Neo)Adjuvant Therapy for HER2+ Breast Cancer Is Evolving

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Increased use of neoadjuvant therapy

Dual anti-HER2 blockade (trastuzumab-pertuzumab) plus chemotherapy has become the standard clinical

The Role of (Neo)Adjuvant Therapy for HER2+ Breast Cancer Is Evolving

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Adjuvant treatment is guided by achievement or not of pCR

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Unmet Needs and Future Perspectives in Early HER2+ Disease

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(Neo)adjuvant treatment approaches become more individualized

There is evidence to support the hypothesis that a group of selected HER2+ patients may not need

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Current and New Treatments in HER2+ Metastatic BC

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

Presented by Javier Cortes, MD, PhD

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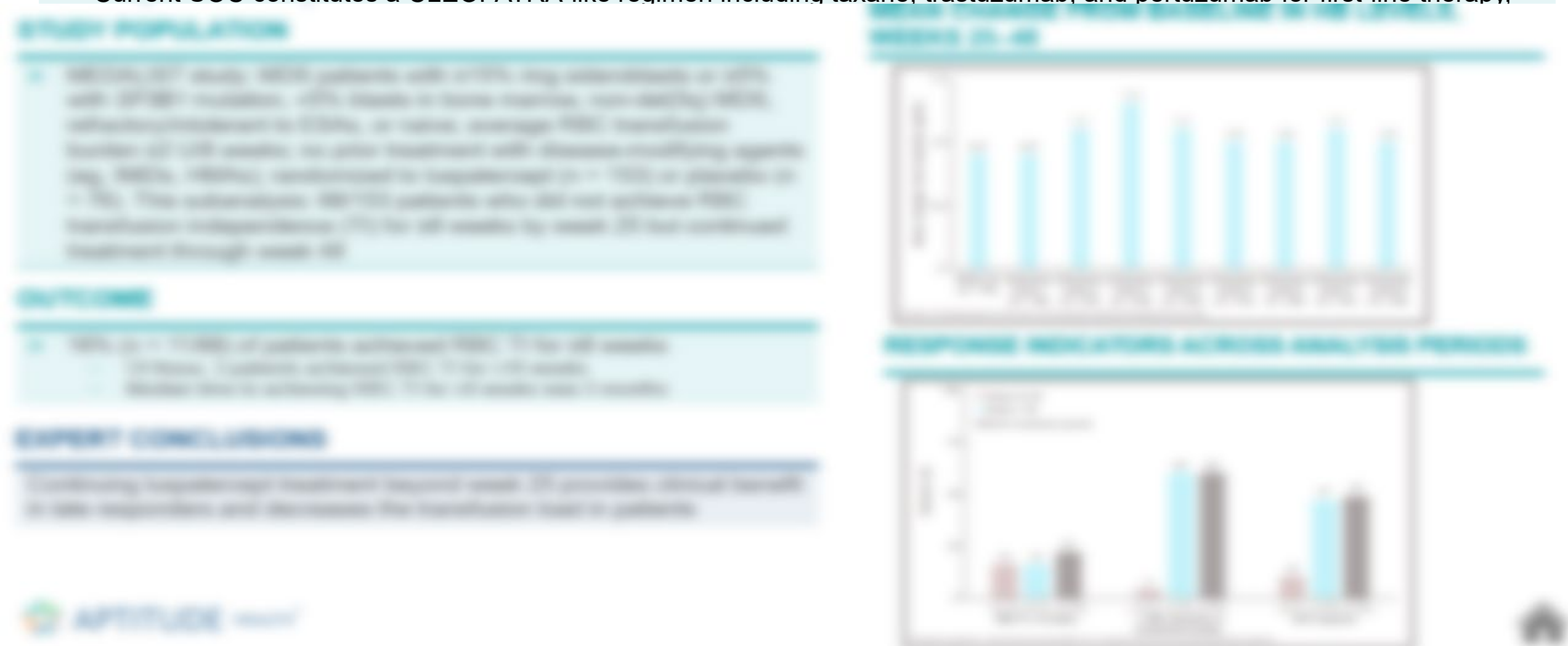
Current treatment landscape

> Current SOC constitutes a CLEOPATRA-like regimen including taxane, trastuzumab, and pertuzumab for first-line therapy,



Current and New Treatments in HER2+ mBC (2/2)

Presented by Javier Cortes, MD, PhD

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Recent advances and their impact on the treatment algorithm

> The DESTINY-Breast03 trial (NCT03529110) showed

STUDY POPULATION

OUTCOME

EXPERT CONCLUSIONS

Evolving Standards of Care in HER2+ mBC

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Current treatment landscape (pre-ESMO 2021)

Current standard sequencing approaches include a CLEOPATRA-like regimen (taxane-trastuzumab-

Evolving Standards of Care in HER2+ mBC

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Outcomes from DESTINY-Breast03 (DB03) are challenging current sequencing practices

Experts are clearly impressed by the DB03 results presented at ESMO

randomized phase 2 study – (ICML) Zhang #28

- Experts believe the resolution of molecular phenotypes is possible in real time, and these vulnerabilities can potentially be targeted

Promising tolerability and efficacy results from dose-escalation in an ongoing phase 1b/II study of mosunetuzumab with polatuzumab vedotin for relapsed/refractory B-cell NHL – (EHA) Ghosh #6223

- The regimen is seen as effective, exciting, safe, and broadly applicable to many patients

Mosunetuzumab (Roche) monotherapy for elderly/unfit patients with first-line DLBCL continues to show promising safety and efficacy with durable complete responses – (EHA) Chavanel #EP1303

- This approach is seen as a great solution for a patient population in whom giving immunochemotherapy is difficult. It is viewed as effective and safe

FIRST-MIND: a phase Ib, open-label, randomized study to assess safety of telisotuzumab or telisotuzumab + tenalisib/zandelisib in addition to R-CHOP in patients with newly diagnosed DLBCL – (EHA) Benada #EP1306

- Experts believe the combination of telisotuzumab + tenalisib/zandelisib with R-CHOP is safe. However, they would like to see phase III data to confirm its activity in this setting

Long-term analyses from L-MIND, a phase II study of telisotuzumab plus tenalisib/zandelisib (tenz) in patients with R/R DLBCL – (ICML) Duell #28

- The L-MIND regimen is seen as useful in the specific patient population with refractory disease. It was noted to be effective, very safe, and well tolerated. Some of the responses seen were clearly very durable

Evolving Standards of Care in HER2+ mBC

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Remaining questions after DESTINY-Breast03

Data are missing on how to best treat patients who did not receive prior T-DM1 and have unstable brain metastasis

randomized phase 2 study – (ICML) Zhang #28

- Experts believe the resolution of molecular phenotypes is possible in real time, and these vulnerabilities can potentially be targeted

Promising tolerability and efficacy results from dose-escalation in an ongoing phase 1b/2 study of monomethasomab with pyrelotuzomab vedotin for relapsed/refractory B-cell NHL – (ENA) Ghosh #6222

- The regimen is seen as effective, exciting, safe, and broadly applicable to many patients

Monomethasomab (monom) monotherapy for elderly/unfit patients with first-line DLBCL continues to show promising safety and efficacy with durable complete responses – (ENA) Chuanwei #EP1001

- This approach is seen as a great solution for a patient population in whom giving immunochemotherapy is difficult. It is viewed as effective and safe

FIRST-MIND: a phase 1b, open-label, randomized study to assess safety of telfochlamab or telfochlamab + lenalidomide in addition to R-CHOP in patients with newly diagnosed DLBCL – (ENA) Renata #EP1006

- Experts believe the combination of telfochlamab + lenalidomide with R-CHOP is safe. However, they would like to see phase III data to confirm its activity in this setting

Long-term analyses from L-MIND, a phase II study of telfochlamab plus lenalidomide (len) in patients with R/R DLBCL – (ICML) Duell #28

- The L-MIND regimen is seen as useful in the specific patient population with refractory disease. It was noted to be effective, very safe, and well tolerated. Some of the responses seen were clearly very durable

we have any guidance yet. It is going to depend, to a large degree, on clinical presentation of the patient, particularly in respect of CNS disease.

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Unmet Needs and Future Perspectives in Metastatic HER2+ Disease

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Shift in the pattern of mBC

Experts recognize a shift in the pattern of mBC

randomized phase 2 study – (ICML) Zhang #28

- Experts believe the resolution of molecular phenotypes is possible in real time, and these vulnerabilities can potentially be targeted

Promising tolerability and efficacy results from dose-escalation in an ongoing phase I/II study of mosunetuzumab with polatuzumab vedotin for relapsed/refractory B-cell NHL – (EHA) Ghosh #6222

- The regimen is seen as effective, exciting, safe, and broadly applicable to many patients

Mosunetuzumab (mosun) monotherapy for elderly/unfit patients with first-line DLBCL continues to show promising safety and efficacy with durable complete responses – (EHA) Chavanel #6P1543

- This approach is seen as a great solution for a patient population in whom giving immunochemotherapy is difficult. It is viewed as effective and safe

FIRST-MIND: a phase Ib, open-label, randomized study to assess safety of tafasitamab or tafasitamab + lenalidomide in addition to R-CHOP in patients with newly diagnosed DLBCL – (EHA) Benada #EP1506

- Experts believe the combination of tafasitamab + lenalidomide with R-CHOP is safe. However, they would like to see phase III data to confirm its activity in this setting

Long-term analyses from L-MIND, a phase II study of tafasitamab plus lenalidomide (len) in patients with R/R DLBCL – (ICML) Duell #28

- The L-MIND regimen is seen as useful in the specific patient population with refractory disease. It was noted to be effective, very safe, and well tolerated. Some of the responses seen were clearly very durable

Future perspectives

There is still room to improve outcomes for patients with

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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 Guy Jerusalem, MD, PhD

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Extended adjuvant therapy

> In women with HR+ breast cancer, treatment with tamoxifen and/or an AI for 5 years is effective in reducing the risk of

randomized phase 2 study – (ICML) Zhang #28

- Experts believe this resolution of molecular phenotypes is possible in real time, and these vulnerabilities can potentially be targeted

Promising tolerability and efficacy results from dose-escalation in an ongoing phase 1b/II study of mosunetuzumab with polatuzumab vedotin for relapsed/refractory B-cell NHL – (EHA) Olszert #6233

- The regimen is seen as effective, exciting, safe, and broadly applicable to many patients

Mosunetuzumab (Monovo) monotherapy for elderly/unfit patients with first-line DLBCL continues to show promising safety and efficacy with durable complete responses – (EHA) Chavanel #6P1343

- This approach is seen as a great solution for a patient population in whom giving immunochemotherapy is difficult. It is viewed as effective and safe

FIRST-MIND: a phase 1b, open-label, randomized study to assess safety of tafasitamab or tafasitamab + lenalidomide in addition to R-CHOP in patients with newly diagnosed DLBCL – (EHA) Bonada #6P1344

- Experts believe the combination of tafasitamab + lenalidomide with R-CHOP is safe. However, they would like to see phase III data to confirm its activity in this setting

Long-term analyses from L-MIND, a phase II study of tafasitamab plus lenalidomide (len) in patients with R/R DLBCL – (ICML) Duell #28

- The L-MIND regimen is seen as useful in the specific patient population with refractory disease. It was noted to be effective, very safe, and well tolerated. Some of the responses seen were clearly very durable

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

Presented by Guy Jerusalem, MD, PhD

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Adjuvant CDK4/6 inhibitor trials

> The monarchE trial evaluating 2 years of adjuvant abemaciclib in patients with high-risk, node-positive, HR+, HER2–

Current Role of Genomic Tools in Decision-Making When Considering Whether to Extend Adjuvant Endocrine Therapy Beyond 5 Years in HR+ Disease

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Tailoring adjuvant endocrine therapy on the basis of risk

There remains a high risk of BC recurrence, especially among node-positive patients

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Adjuvant CDK4/6 Inhibition Shows Potential in Early HR+, HER2– Breast Cancer, but More Data Are Needed

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Role of CDK4/6 inhibition

While the initial positive results from the monarchE trial are very encouraging, conflicting results from

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Current and Emerging Approaches in HR+, HER2– mBC

Current and Emerging Approaches in HR+, HER2– mBC (1/3)

Presented by Pierfranco Conte, MD

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Consolidated and new paradigms for endocrine therapy

> Endocrine therapy is the preferred option for most patients, and, in

Current and Emerging Approaches in HR+, HER2– mBC (2/3)

Presented by Pierfranco Conte, MD

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Role of PI3K inhibitors

> For patients with *PIK3CA*-mutated

The treatment algorithm for HR+, HER2– mBC is still evolving

Current and Emerging Approaches in HR+, HER2– mBC (3/3)

Presented by Pierfranco Conte, MD

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Investigational agents

> *ESR1* mutations are frequent after AI treatment (~50% of the patient

Evolving Role of CDK4/6 Inhibitors for HR+ mBC

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CDK4/6i have been practice-changing in the management of first-line HR+ mBC

CDK4/6i plus endocrine therapy (ET) are now SOC for the vast majority of patients with HR+ metastatic disease

randomized phase 2 study - (ASCO, Zhang #38)

- Experts believe the resolution of molecular phenotype is possible in real time, and these vulnerabilities can potentially be targeted

Promising tolerability and efficacy results from dose-escalation in an ongoing phase I/II study of revumenibenemab with proteasomal revoluto for relapsed/refractory B-cell NHL - (EHA, Ghosh #6222)

- The regimen is seen as effective, exciting, safe, and broadly applicable to many patients

Mosunetuzumab (Avosun) monotherapy for elderly/unfit patients with first-line DLBCL continues to show promising safety and efficacy with durable complete responses - (EHA, Chavanel #EP561)

- This approach is seen as a great solution for a patient population in whom giving immunochemotherapy is difficult. It is viewed as effective and safe

FIRST-MIND: a phase Ib, open-label, randomized study to assess safety of tafasitamab or tafasitamab + lenalidomide in addition to R-CHOP in patients with newly diagnosed DLBCL - (EHA, Briseda #EP599)

- Experts believe the combination of tafasitamab + lenalidomide with R-CHOP is safe. However, they would like to see phase III data to confirm its activity in this setting

Long-term analyses from L-MIND, a phase II study of tafasitamab plus lenalidomide (len) in patients with R/R DLBCL - (ASH, Duell #28

- The L-MIND regimen is seen as useful in the specific patient population with refractory disease. It was noted to be effective, very safe, and well tolerated. Some of the responses seen were clearly very durable

Factors Impacting Preference/Usage of CDK4/6 Inhibitors in the Metastatic Setting

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How to select between available CDK4/6 inhibitors?

“

Experts do not believe there is a clinically meaningful difference in efficacy between the 3 CDK4/6i,

randomized phase 2 study - (ICML) Zhang #28

- Experts believe the resolution of molecular phenotype is possible in real time, and these vulnerabilities can potentially be targeted

Promising tolerability and efficacy results from dose-escalation in an ongoing phase I/II study of mosunetuzumab with polatuzumab vedotin for relapsed/refractory B-cell NHL - (EHA) Sharon #6223

- The regimen is seen as effective, exciting, safe, and broadly applicable to many patients

Mosunetuzumab (mosun) monotherapy for elderly/unfit patients with first-line DLBCL continues to show promising safety and efficacy with durable complete responses - (EHA) Chavanel #EP593

- This approach is seen as a great solution for a patient population in whom giving immunochemotherapy is difficult. It is viewed as effective and safe

FIRST-MIND: a phase Ib, open-label, randomized study to assess safety of tafasitamab or tafasitamab + lenalidomide in addition to R-CHOP in patients with newly diagnosed DLBCL - (EHA) Belada #EP594

- Experts believe the combination of tafasitamab + lenalidomide with R-CHOP is safe. However, they would like to see phase III data to confirm its activity in this setting

Long-term analyses from L-MIND, a phase II study of tafasitamab plus lenalidomide (len) in patients with R/R DLBCL - (ICML) Duell #28

- The L-MIND regimen is seen as useful in the specific patient population with refractory disease. It was noted to be effective, very safe, and well tolerated. Some of the responses seen were clearly very durable

The Evolving Role of Oral SERDs in HR+ BC

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Fitting oral SERDs into the algorithm for HR+ BC

Experts like oral SERDs as a drug class, as they provide a convenient alternative to the oftentimes for

randomized phase 2 study - (ICML) Zhang #28

- Experts believe the resolution of molecular phenotype is possible in real time, and these vulnerabilities can potentially be targeted

Promising tolerability and efficacy results from dose-escalation in an ongoing phase I/II study of revumenibenemab with proteasomal inhibitor for relapsed/refractory B-cell NHL - (EHA) Shoeh #6223

- The regimen is seen as effective, exciting, safe, and broadly applicable to many patients

Mosunetuzumab (Monuvi) monotherapy for elderly/unfit patients with first-line DLBCL continues to show promising safety and efficacy with durable complete responses - (EHA) Chavanel #EP593

- This approach is seen as a great solution for a patient population in whom giving immunochemotherapy is difficult. It is viewed as effective and safe

FIRST-MIND: a phase Ib, open-label, randomized study to assess safety of telisotuzumab or telisotuzumab + tenalisib in addition to R-CHOP in patients with newly diagnosed DLBCL - (EHA) Sonata #EP599

- Experts believe the combination of telisotuzumab + tenalisib with R-CHOP is safe. However, they would like to see phase II data to confirm its activity in this setting

Long-term analyses from L-MIND, a phase II study of telisotuzumab plus tenalisib (tenz) in patients with R/R DLBCL - (ICML) Duell #28

- The L-MIND regimen is seen as useful in the specific patient population with refractory disease. It was noted to be effective, very safe, and well tolerated. Some of the responses seen were clearly very durable

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Current and Emerging Approaches in TNBC

Current and Emerging Approaches in TNBC (1/4)

Presented by William Gradishar, MD

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(Neo)adjuvant chemotherapy remains the mainstay in early TNBC

- Neoadjuvant chemotherapy in TNBC leads to higher pCR rates

Current and Emerging Approaches in TNBC (2/4)

Presented by William Gradishar, MD

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PARP inhibitors

> As single agents, the efficacy of 2 PARP inhibitors, olaparib and talazoparib, was shown in 2 independent phase III trials (OlympiAD and

Current and Emerging Approaches in TNBC (3/4)

Presented by William Gradishar, MD

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Immunotherapy

> Phase III clinical trials have shown that immune checkpoint inhibition is well tolerated in combination with chemotherapy, with PFS benefit in

Current and Emerging Approaches in TNBC (4/4)

Presented by William Gradishar, MD

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Antibody-drug conjugates

- The TROP2-directed ADC sacituzumab

Metastatic TNBC: Algorithm for treatment 2021

Standard of Care for Biomarker Testing in TNBC

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Biomarker testing

Testing for *BRCA* mutational status as well as PD-L1 positivity is now considered standard for patients with TNBC and is generally done in early stage disease

Dr Rugo:

Role of Chemotherapy and PARP Inhibitors in (Neo)Adjuvant TNBC

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(Neo)adjuvant chemotherapy remains the mainstay in early stage TNBC

Updates from BrighTNess are perceived as reassuring and helpful to clarify the long-standing debate whether to add platinum agents in the (neo)adjuvant setting

Immune Checkpoint Inhibitors Have Entered the (Neo)Adjuvant Setting in TNBC

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Impact of KEYNOTE-522

Recent EFS findings from the KEYNOTE-522 trial support the use of pembrolizumab with neoadjuvant platinum-based chemotherapy and as monotherapy in the adjuvant setting as a new treatment option for higher-risk patients

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Current Standards in mTNBC

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First-line therapy

PARP inhibitors and immune checkpoint inhibitors have significantly expanded the first-line

*IMpassion131 failed to meet its primary endpoint of PFS, while the mature OS analysis of IMpassion130 upheld the benefit of atezolizumab plus *nab*-paclitaxel.

Current Standards in mTNBC

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Relapsed/refractory setting

Sacituzumab govitecan is another valuable addition to the treatment armamentarium that experts

[redacted]

[redacted]

Future Perspectives in TNBC

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Optimal sequencing and combination strategies remain open questions

Despite substantial progress over the last years, TNBC remains an area of unmet need. Further research is required to determine optimal sequencing strategies and identify new actionable targets and/or novel combinations to improve efficacy

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Novel Targets in Breast Cancer

Novel Targets in Breast Cancer (1/2)

Presented by Hope Rugo, MD, FASCO

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Targeting HER2 in HER2-low BC

> The frequency of HER2-low disease is higher in HR+ BC than

Targeting HER2 in HER2 non-amplified BC

> Probody therapeutics, a new class of recombinant, proteolytically

Novel Targets in Breast Cancer (2/2)

Presented by Hope Rugo, MD, FASCO

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Novel anti-HER2 drugs and strategies

AKT inhibitors

> The phase II FAKTION trial reported a significant improvement in

Next-Generation ADCs Show Promising Potential for Treating HER2-Low Tumors

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Defining HER2-low breast cancer

The HER2-low phenotype is emerging as a potentially important

Emerging data with HER2-targeted ADCs

Due to the retention of all trastuzumab antitumor properties,

Other Novel Targets in Breast Cancer

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HER3 as a target

Experts find HER3 interesting as a novel target, but are unclear about its role in

"

Dr Harbeck:
With HER3, I think we also have a biomarker problem here. We don't know which biomarker

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