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SABCS Congress webinar

HR+/HER2- Advanced breast cancer: what are the latest developments in CDK4/6 inhibition?

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Learning objectives

- Describe the role of CDK4/6 inhibitors in the context of the current and evolving treatment landscape for patients with HR+/HER2- advanced breast cancer
- Evaluate the importance of selecting the optimal treatment based on the individual patient, and the challenges around subsequent sequencing of therapy
- Summarize the importance of managing the safety profiles of CDK4/6 inhibitor therapy, and recognize the significance of the multidisciplinary team in optimizing patient outcomes and maintaining on-treatment benefits

CDK, cyclin-dependent kinase; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

Webinar overview

HR+/HER2- advanced breast cancer

- Summary of the key trials for CDK4/6 inhibitors
- SABCS 2019 – Efficacy and safety – Extended and subgroup analyses
- SABCS 2019 – Biomarkers and resistance – What does the research show?
- SABCS 2019 – Real-world and practical insights for CDK4/6 inhibitors

CDK, cyclin-dependent kinase; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

Summary of the key trials for CDK4/6 inhibitors

Focus on CDK4/6 inhibitors for HR+/HER2- advanced breast cancer

CDK, cyclin-dependent kinase; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

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Clinical trials demonstrate the PFS benefit of CDK4/6 inhibitors, especially when combined with ET

In key clinical trials, **CDK4/6 inhibitors demonstrated significant improvements in PFS** vs. placebo for the treatment of HR+/HER2- ABC

Palbociclib	PALOMA-2 + LET (1st line) (N=666) PFS=27.6 vs. placebo 14.5[1,2] PALOMA-3 + FUL (2nd line) (N=521) PFS=11.2 vs. placebo 4.6[3,4]
Ribociclib	MONALEESA-2 + LET (1st line) (N=668), PFS = 25.3 vs. placebo 16.0[5,6] MONALEESA-3 + FUL (2nd line) (n=345), PFS = 14.6 vs. placebo 9.1[7] MONALEESA-7 + TAM/NSAI + gos (1st line) (N=672), PFS=23.8 vs. placebo 13.0[8]
Abemaciclib	MONARCH-2 + FUL (2nd line) (N=669) PFS = 16.4 vs. placebo 9.3[9] MONARCH-3 + LET/ANA (1st line) (N=493) PFS=28.2 vs. placebo 14.8[10,11]

±10 months PFS benefit in 1st line treatment

~5.5 to 7.5 months PFS benefit in 2nd line treatment

ABC, advanced breast cancer; ANA, anastrozole; CDK, cyclin-dependent kinase; ET, endocrine therapy; FUL, fulvestrant; gos, goserelin; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; PFS, progression-free survival, TAM, tamoxifen.

1. Finn RS, et al. *N Engl J Med* 2016;375:1925–1936; 2. Rugo H, et al. Poster presented at SABCS 2017. Abst; P5-21-03; 3. Turner N, et al. *N Engl J Med* 2015;373:209–219; 4. Turner NC, et al. Poster presented at SABCS 2016. Abst; P4-22-06; 5. Hortobagyi G, et al. *N Engl J Med* 2016;375:1738–1748; 6. Hortobagyi G, et al. *Ann Oncol* 2018;29:1541–1547; 7. Slamon DJ, et al. *J Clin Oncol* 2018;36:2465–2472; 8. Tripathy D, et al. *Lancet Oncol* 2018;19:904–915; 9. Sledge GW, et al. *J Clin Oncol* 2017;35:2875–2884; 10. Goetz M, et al. *J Clin Oncol* 2017;35:3638–3646; 11. Johnston S, et al. *NPJ Breast Cancer* 2019;5:5.

2019 data demonstrate that CDK4/6 inhibitors improve overall survival in HR+/HER2- ABC

MONALEESA-7

- Ribociclib plus endocrine therapy **significantly improved OS** vs. ET alone, in premenopausal ABC (HR=0.71; P=0.00973) with a **~29% relative reduction in risk of death**[1]

Presented at ASCO American Society of Clinical Oncology **2019**

MONALEESA-3

- The **median OS was not reached for ribociclib/fulvestrant** but was 40.0 months for placebo/fulvestrant, a **28% risk reduction**[2]
- In the early-relapse/second-line setting, the combination led to a **median survival benefit of 7.7 months**, a **27% risk reduction**[2]

MONARCH-2

- Abemaciclib plus fulvestrant led to a **median 9.4-month OS benefit** in patients who experienced disease progression with prior ET, a **24% reduction in risk**[3]

Presented at ESMO **2019**

5th ESO–ESMO International Consensus Guidelines for ABC will state[4]

'Adding a CDK4/6 inhibitor to ET is now the standard of care…'

ABC, advanced breast cancer; ESMO, European Society for Medical Oncology; ESO, European School of Oncology; ET, endocrine therapy; HER2- human epidermal receptor 2-negative; HR, hazard ratio; HR+ hormone receptor-positive; OS, overall survival.

1. Hurvitz SA, et al. Abstract LBA 1008 Presented at the ASCO Annual Meeting 2019. 2. Slamon DJ, et al. *Ann. Oncol.* 2019; 30 (suppl_5): v851-v934; 3. Sledge GW, et al. *Ann. Oncol.* 2019; 30 (suppl_5): v851-v934; 4. Cardoso F. Personal communication. December 2019.

Safety profiles of CDK4/6 inhibitors in advanced breast cancer

Grade 3–4 neutropenia and leucopenia are commonly reported for CDK4/6 inhibitors in patients with HR+/HER2- ABC

	Ribociclib MONALEESA-2[1]	Palbociclib PALOMA-2[2]	Abemaciclib MONARCH-3[3]
Adverse events Any Grade	Neutropenia (77%) Leucopenia (33%) Nausea (53%)	Neutropenia (82%) Leucopenia (40%) Nausea (37%)	Neutropenia (44%) Diarrhoea (82%) Nausea (41%)
Adverse events Grade 3–4	Neutropenia (62%) Leucopenia (21%)	Neutropenia (69%) Leucopenia (25%)	Neutropenia (24%) Leucopenia (8.6%)

CDK, cyclin-dependent kinase.

1. Hortobagyi G, et al. *Ann Oncol* 2018;29:1541–1547; 2. Rugo H, et al. Poster presented at SABCS 2017. Abst; P5-21-03; 3. Johnston S, et al. *NPJ Breast Cancer* 2019;5:5.

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SABCS 2019
Efficacy and safety – Extended and subgroup analyses

Focus on CDK4/6 inhibitors for HR+/HER2- advanced breast cancer

CDK, cyclin-dependent kinase; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

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Safety and efficacy of abemaciclib plus ET in elderly patients with HR+/HER2- ABC: An age-specific subgroup analysis of MONARCH-2 and -3 trials

Goetz MP, et al.

To report exploratory subgroup analyses of MONARCH-2 and -3 to provide age-specific outcomes

MONARCH-2
Women with ET resistant HR+/HER2- ABC received ABE/PBO + FUL

MONARCH-3
Women with HR+/HER2- ABC received a ABE/PBO + NSAI as initial therapy

Age-specific subgroup analyses of most common TEAEs

Pooled safety data available for 1152 pts

59.7% pts <65yrs

28.7% pts 65–74yrs

11.5% pts ≥75yrs

ABE + ET (n=768) and PBO + ET (n=384)

Results (%) ABE treated pts	<65yrs	65–74yrs	≥75yrs
Grade 2/3 diarrhoea	39.5	45.2	55.4
PBO treated pts	*6.8*	*4.5*	*16*
Grade 3/4 neutropenia	25.8	27.4	18.1
Fatigue (any grade)	34.8	48.4	51.8

Clinically relevant diarrhoea was more common in the elderly

Grade 3/4 neutropenia did not differ as a function of age in either treatment group

Fatigue was more common in elderly ABE-treated groups but did not differ between PBO age groups

- The most frequent TEAE was diarrhoea and the most common Grade ≥3 TEAE was neutropenia
- For efficacy, a consistent PFS benefit was observed with ABE + ET vs. PBO +ET across all subgroups in the studies

ABE + ET demonstrates a tolerable safety profile and consistent efficacy benefit across all age subgroups examined, supporting the use of this combination in elderly patient populations

ABC, advanced breast cancer; ABE, abemaciclib; AE, adverse event; ET, endocrine therapy; FUL, fulvestrant; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; NSAI, nonsteroidal aromatase inhibitor; PBO, placebo; PFS, progression-free survival; pts, patients; TEAE, treatment emergent adverse event.

Goetz MP, et al. Poster P1-19-10. Presented at SABCS 2019, San Antonio.

Long-term pooled safety analysis of palbociclib in combination with endocrine therapy for HR+/HER2- ABC: An updated analysis

Finn RS, et al.

This pooled, post-hoc analysis examined the safety profile of PAL + ET in the PALOMA trials using data from more recent data cut off dates with longer drug exposure

Updated data cut-off
PALOMA-1 Dec 21, 2017
PALOMA-2 May 31, 2017
PALOMA-3 Apr 13, 2018

Total no of person-years of exposure: 1950 (528 ET, 1422 PAL + ET)

% pts treated for:	ET arm (n = 471)	PAL + ET (n = 872)
≥24 months	20.2	36
≥36 months	10.2	22.4

Serious AEs: 22.8% in PAL + ET arm vs. 15.5% in ET arm

Selected cumulative grade 3/4 event rates through 5 years	ET (%)	PAL + ET (%)
Neutropenia	0.8	68.3
Leukopenia	0.2	29.9
Infections	2.8	6.4
Anaemia	2.1	5.3
Fatigue	1.3	2.9
↑Alanine aminotransferase	0.2	2.2
↑Aspartate aminotransferase	1.3	2.9
Diarrhoea	1.1	1.0
Nausea	1.3	0.6
Vomiting	1.1	0.7
QTc prolongation	0.2	0.3

As expected, neutropenia and infections (any grade) were more frequent with PAL + ET vs. the ET arm

This 5-year, long-term safety analysis of PAL + ET showed a consistent profile with no new safety signals, and no cumulative/delayed toxicities

ABC, advanced breast cancer; AE, adverse event; ET, endocrine therapy; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; PAL, palbociclib; pts, patients.

Finn RS, et al. Poster/Scientific abstract P1-19-16. Presented at SABCS 2019, San Antonio.

Results from the PEARL study: A Phase III trial of palbociclib in combination with endocrine therapy vs. capecitabine in HR+/HER2- MBC patients whose disease progressed on aromatase inhibitors

Martín M, et al.

To demonstrate: 1) the superiority of PAL + FUL vs. CAPE in PFS; and 2) the superiority of PAL + ET (EXE or FUL) vs. CAPE in PFS in patients with ESR1 wt tumours, measured in ctDNA, at study entry

Post menopausal women with HR+/HER2-ABC whose disease had progressed on AIs (N=601 pts)

% of pts with:	Cohort 1 (n=296) EXE + PAL vs. CAPE	Cohort 2 (n=305) FUL + PAL vs. CAPE
ESR1 mutations	26.4	28.2
Visceral disease	66.6	65.3
Prior sensitivity to ET	71.3	79.0
1 prior CT for ABC	30.1	26.9
No prior ET for ABC	20.6	26.9

Results	Cohort 2 FUL + PAL vs. CAPE	ESR1 wt (Cohort 1 + Cohort 2) EXE + PAL vs. CAPE
Median PFS (m)	7.5 vs. 10, p=0.537	8 vs. 10.6, p=0.526
ORR (%)	27 vs. 33	28 vs. 37
Median PFS (m) Luminal pts	7.5 vs. 10, p=0.684	9.3 vs. 11, p=0.913
Median PFS (m) Non-luminal pts	4.4 vs. 14.8, p=0.116	2.7 vs. 13.7, p=0.013

- Most frequent grade 3–4 toxicities with EXE+PAL, FUL+PAL and CAPE, respectively were neutropenia (57.3%, 55.7% and 5.5%), febrile neutropenia (1.3%, 0.7% and 1.4%), hand/foot syndrome (0%, 0% and 23.5%) and diarrhoea (1.3%, 1.3% and 7.6%)

The PEARL study did not show a statistically superiority in PFS for PAL + ET vs. CAPE in ABC patients progressing to AIs. Treatment with PAL + ET was generally better tolerated than CAPE

ABC, advanced breast cancer; AI, aromatase inhibitor; CAPE, capecitabine; CT, chemotherapy; ctDNA, circulating tumour DNA; ESR1, estrogen receptor alpha gene; ET, endocrine therapy; EXE, exemestane; FUL, fulvestrant; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; m, months; MBC, metastatic breast cancer; ORR, objective response rate; PAL, palbociclib; PFS, progression-free survival; pts, patients; wt, wild-type.

Martín M, et al. GS2-07. Slide presentation and abstract. Presented at SABCS 2019, San Antonio.

What do these findings mean in practice?

- **In an age-specific subgroup analysis, CDK4/6 inhibitors had similar efficacy in elderly patients vs. other age subgroups, but some increased toxicity, namely diarrhoea**
  - Patient education, supportive measures and dose adaptations are crucial
- **Long-term safety of CDK4/6 inhibitors seems good**
  - Would be important to know if any specific infections occur after long-term exposure to neutropenia/leucopenia
- **The PEARL study has several limitations that limit its interpretation**
  - Median PFS in the CDK4/6 inhibitor arm was lower than in PALOMA trials; no OS nor QoL data
  - The main question is: What would be the outcomes of this comparison in the first-line setting?

CDK, cyclin-dependent kinase; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; OS, overall survival; PFS, progression-free survival; QoL, quality of life.

SABCS 2019
Biomarkers and resistance – What does the research show?

Focus on CDK4/6 inhibitors for HR+/HER2- advanced breast cancer

CDK, cyclin-dependent kinase; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

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A key challenge is the identification of predictive biomarkers for better patient selection in clinical practice

Potential clinical and molecular biomarkers for CDK4/6 treatment response have been investigated but so far **no clear biomarkers have been identified that can be applied in clinical practice**[1,2]

Clinical

- Visceral vs. non-visceral disease
- Disease-free interval
- Luminal-A-like vs. luminal-B-like disease

Molecular

- **Increased Rb expression and signature**
- ***ESR1* mutational status**
- Others including:
  - Cyclin D1 amplification, loss of p16 expression
  - Low Ki67 levels
  - TP53, PIK3CA
  - Hormone-receptor expression

Further biomarker analysis studies are indispensable to better select patients who derive the greatest benefit from CDK4/6 inhibitors[2]

CDK, cyclin-dependent kinase; ERS1, estrogen receptor alpha gene; PIK3CA; phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. Preusser M, et al. ESMO Open2019;3:e000368. 2. Ribnikar D, Volovat SR, Cardoso F. *The Breast* 2019;43:8e17.

Efficacy of abemaciclib based on genomic alterations detected in baseline circulating tumour DNA from the MONARCH-3 study of abemaciclib plus nonsteroidal aromatase inhibitor

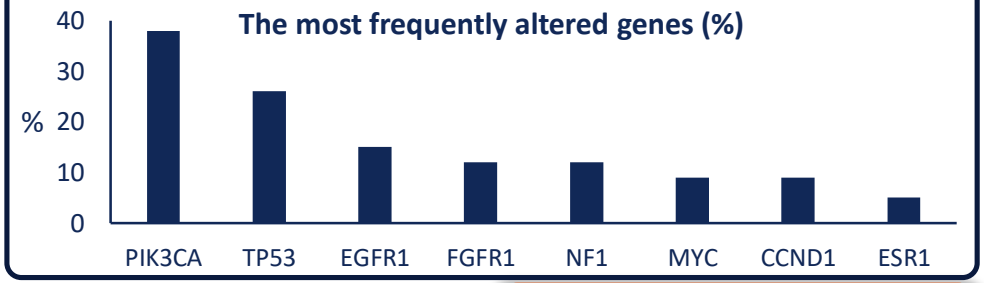
Goetz MP, et al.

An exploratory subgroup analysis to study clinical outcomes by genomic alterations detected in baseline ctDNA from patients treated with ABE + NSAI vs. PBO + NSAI in the Phase III MONARCH-3 study

MONARCH-3
Women with HR+/HER2- ABC (N=493) received ABE/PBO + NSAI as initial therapy

Biomarker analysis set: baseline ctDNA including Single Nucleotide Variant (SNV), indels, amplifications, and fusions
(N=295, ABE, n=201; PBO, n=94)
Clinical outcomes: PFS and ORR

83% of pts harboured ≥1 detectable genomic alterations



Overall, patients treated with PBO + NSAI with ctDNA genomic alterations:

- Had a shorter median PFS vs. patients without genomic alterations (14.9m vs. 19.2m)
- Genomic alterations in EGFR, FGFR1 and CCND1 were associated with median PFS <12m

Consistent with the ITT population, the addition of ABE to NSAI benefitted these genomic subgroups, regardless of ctDNA gene alterations

The presence of detectable ctDNA genomic alterations was associated with shorter PFS with placebo plus NSAI. Consistently, ABE added to NSAI improved outcomes for genomically identified subgroups. These findings are hypothesis-generating and warrant further investigation

ABC, advanced breast cancer; ABE, abemaciclib; ctDNA, circulating tumour DNA; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; ITT, intent-to-treat; m, months; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; PBO, placebo; PD, progressive disease; PFS, progression free survival; pts, patients; SNV, single nucleotide variant.

Goetz MP, et al. Abstract. Session PD2-06. Presented at SABCS 2019, San Antonio.

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BioitaLEE – biomarker analysis on liquid biopsies of patients treated with ribociclib and letrozole as first-line therapy for ABC

De Laurentiis M, et al.

To study ctDNA alterations, their evolution during treatment and association with clinical outcome in patients receiving RIB + LET as first-line therapy for ABC

February to December 2018

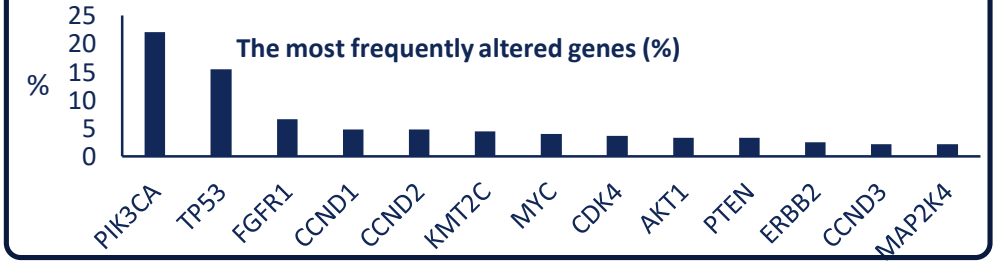
- 287 post-menopausal pts HR+/HER2-ABC receiving 1st line RIB+LET, 47 Italian Centers
- Biomarker Analysis Set (BAS) = 271 pts
- First imaging evaluation data = 225 pts
- Baseline analyses: CNV and Single Nucleotide Variant

Disease states at study entry:

- 60% (162) recurrent and 40% (109) *de-novo*
- 43% (117) visceral and 24% (64) with bone-only

At first imaging, CBR=90% and PD=10%

51% of pts had ≥1 CNV alteration or a hotspot mutation
28% of pts had >1 alteration (CNV or hotspots)



For pts with PD vs. CBR
↑ MYC gain, TP53 mutations & alterations in the HER family genes and CDK4/6 pathways

For visceral vs. bone-only disease
↑ Copy number gain of FGFRs

For recurrent vs. *de novo* disease
↑ KTM2C and ERnf pathway mutations

MYC gain, TP53 mutations, alterations in genes of the HER family and CDK4/6 pathway were more likely detected in patients with early PD suggesting these as potential markers of intrinsic resistance to 1st line treatment with RIB + LET

ABC, advanced breast cancer; BAS, biomarker analysis set; CBR, clinical benefit rate; CNV, copy number variation; ctDNA, circulating tumour DNA; ERnf, estrogen receptor nuclear function; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; LET, letrozole; PD, progressive disease; pts, patients; RIB, ribociclib; SNV, single nucleotide variant. De Laurentiis M, et al. Poster/abstract P5-01-07. Presented at SABCS 2019, San Antonio.

Clinical and biological efficacy of first line AI and palbociclib in HR+/HER2- ABC with detectable circulating ESR1 mutation prior to treatment initiation

Bidard F, et al.

An exploratory analysis to evaluate the biological and clinical outcome of patients who tested positive for *ESR1*mut at baseline

The PADA-1 Phase III trial

HR+/HER2- ABC pts (N=1017) with no prior therapy and no overt resistance to AI received AI +PAL

At baseline

- n=33 *ESR1*mut+ pts
- n=984 *ESR1*mut– pts

Kinetic evaluation of *ESR1*mut in the *ESR1*mut+ pts at inclusion (n=33)

- 1 pt died after 1 month on treatment
- 25/32 pts (78%), *ESR1*mut became undetectable (AF<0.1%) within first 5 months with a median time to ESR1mut 'clearance' in cfDNA of 34 days
- Among these 25 pts, with a median FU of 11.9 months: 14 pts (56%) had *ESR1*mut detected again in cfDNA during AI + palbociclib therapy; 2 pts (8%) experienced a disease progression with no *ESR1*mut detected; the remaining 9 pts (36%) are still both *ESR1*mut-free and disease progression-free at time of analysis

Prognostic impact of cfDNA *ESR1*mut status on PFS

- Median FU=12.4 months
- The *ESR1*mut+ pts had a shorter median PFS vs. *ESR1*mut- pts (**PFS=17.5m**, [95%CI,10.5–NR] and NR respectively, estimated HR=2.8 [95% CI, 1.6–5], p=0.002))

The quick 'clearance' of *ESR1*mut and the observed 17.5 month PFS suggest that AI + PAL retain clinical activity in *ESR1*mut+ ABC. However, in most patients, these mutations were eventually detected again and *ESR1*mut-positivity was associated with a significantly shorter PFS, suggesting that *ESR1*mut positivity at baseline could accelerate the onset of resistance to AI + PAL

ABC, advanced breast cancer; AI, aromatase inhibitor; cfDNA, circulating free DNA; FU, follow-up; HER2- human epidermal receptor 2-negative; HR, hazard ratio; HR+ hormone receptor-positive; mut, mutation; NR, not reached; PAL, palbociclib; PFS, progression-free survival; pts, patients.

Bidard F, et al. Poster P5-11-22. Presented at SABCS 2019, San Antonio.

What do these findings mean in practice?

- **At the present time, no biomarker exists to identify patients who do not derive benefit from CDK4/6 inhibitors, nor those who are more likely to benefit**
- **ESR1 mutations seems to have prognostic value as well as predictive value regarding resistance to AIs**
  - However, more data are needed before they can be used in clinical practice

AI, aromatase inhibitor; CDK, cyclin-dependent kinase.

SABCS 2019
Real-world and practical insights for CDK4/6 inhibitors

CDK, cyclin-dependent kinase.

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Real-world evidence provides additional insights on how CDK4/6 inhibitors are used in clinical practice

Incorporating learnings from real-world data in addition to data gathered from clinical trials

Randomized Clinical Trials (RCTs)

- Considered the Gold Standard to provide evidence about the efficacy of new medications for approval
- Do not necessarily reflect real-world experience
- Patient population rigorously selected to meet inclusion and exclusion criteria
- Patients closely monitored during a defined clinical trial period

Real-World Data

- Healthcare data: electronic health records, insurance claims, patient registries
- Reflect treatment practices and outcomes in a real-world setting
- Offer additional evidence outside of the clinical trial setting regarding the benefits and risks of a treatment

Real-world evidence can provide insights into how drugs are used and how toxicity is managed in wider populations than in clinical trials e.g., older patients, different comorbidities, more diversity in terms of race and ethnicity and populations in different parts of the world

CDK, cyclin-dependent kinase.

Sherman RE, et al. N Engl J Med. 2016;375:2293–2297.

QT-interval prolongation during the treatment with ribociclib and endocrine agents in patients with HR+/HER2- metastatic breast cancer: A real-world experience

Kurbacher CM, et al.

To investigate the incidence and severity of QTc prolongation during ribociclib therapy

Premenopausal (n=7) and postmenopausal (n=23) women with HR+/HER2- ABC

- All premenopausal pts had ovarian suppression
- ET: LET (n=24), EXE (n=1) and FUL (n=5)

QTc was measured at start of ribociclib and thereafter every 2-4 wks for max. 262 days whilst on treatment
Mean QTc values were calculated at baseline and at 6 consecutive time points from baseline:
#1. 7–21 days, #2. 22–42 days, #3. 43–63 days, #4. 64–84 days, #5. 85–105 days, #6. 105–126 days

- QTc showed a slight but not significant increase during ribociclib treatment (p=0.309) with a maximum at #3
- Whenever observed, QTc prolongation was ≤110% from baseline in all but 4 pts. In the latter, QTc returned to normal values in all but 1 pt
- QTc exceeding 480ms were not observed at any time
- At baseline, 20 pts had a normal ECG whereas 10 pts had pre-existing ECG abnormalities other than long QT syndrome
- 5 pts with normal ECG at baseline developed ECG abnormalities during ribociclib treatment
- No pt experienced a significant deterioration of cardiac ejection fraction while being on treatment

Clinically meaningful QTc prolongations did not occur in this real-world population of ABC patients treated with RIB and endocrine agents

ABC, advanced breast cancer; ECG, electrocardiogram; ET, endocrine therapy; EXE, exemestane; FUL, fulvestrant; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; LET, letrozole; pts, patients.

Kurbacher CM, et al. Poster P5-14-22. Presented at SABCS 2019, San Antonio.

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Real-world benefit of CDK4/6 inhibitor and endocrine therapy combination in metastatic breast cancer and correlation with neutropenia

Jenneman D, et al.

To evaluate the real-world benefit of PAL + ET as the first-line treatment in HR+/ HER2- ABC and to correlate efficacy of the combination with neutropenia

A retrospective cohort study at Moffitt Cancer Center, USA, between January 1, 2015 and March 1, 2018

HR+/HER2- ABC pts (N=165) treated with palbociclib + letrazole

The predictive value of absolute neutrophil count (ANC) and neutrophil-to-lymphocyte ratio (NLR) for PFS were investigated

Results

Median PFS of the full cohort (N=165)	24.19 months 95% CI 18.93–NR
Median PFS of pts with bone metastasis only (n=54)	NR 95% CI 18.21–NR
Higher risk of disease progression in pts with higher ANCs	HR 1.15 95% CI 1.03–1.29, p=0.013
No significant association between the value of NLR and the risk of disease progression	HR 1.07 95% CI 0.97–1.18, p=0.203

The effectiveness of palbociclib + letrazole for HR+/HER2- ABC in the real-world setting was found to be similar to the results from the PALOMA-2 trial. In addition, patients with a higher ANC were found to have a higher risk for early disease progression

ABC, advanced breast cancer; ANC, absolute neutrophil counts; CDK, cyclin-dependent kinase; CI, confidence interval; ET, endocrine therapy; HER2- human epidermal receptor 2-negative; HR, hazard ratio; HR+ hormone receptor-positive; LET, letrozole; NLR, neutrophil-to-lymphocyte ratio; NR, not reached PAL, palbociclib; PFS, progression-free survival; pts, patients.

Jenneman D, et al. P2-17-03 Presented at SABCS 2019, San Antonio.

Quality of life in patients with HR+/HER2- ABC treated with palbociclib in real-world practice settings

Rocque G, et al.

To evaluate QoL experiences of patients diagnosed with HR+/HER2- ABC treated with palbociclib in the routine course of care

A noninterventional, prospective, multicentre study in the US and Canada

Female and male pts diagnosed with HR+/HER2- ABC and treated with PAL as indicated by the attending physician routine care

QoL assessment using the EORTC QLQ-C30

At baseline, monthly for the first 3 months of treatment with PAL, and then every 3 months until the end of treatment or pt withdrawal or death

Interim analysis included 522 pts who completed ≥6 months of PAL treatment as of May 20, 2019

- 390 prescribed PAL as first-line treatment
- The remaining 132 pts initiated PAL in second- and later-lines
- Median age at enrolment = 64 years
- 98% female, and 83% white
- >50% pts (n = 285) received PAL + LET or ANA; of the remaining patients, 218 received PAL + FUL and 19 received PAL + EXE

- **Mean EORTC QLQ-C30 scores remained similar over the first 6 months of treatment**: 66.2 at baseline, 68.3 at 3 months, and 70.2 at 6 months
- In addition, the mean scores for each functional scale and symptom scale on the EORTC QLQ-C30 also remained stable over the first 6 months

Patients in this interim analysis experienced stable to modestly improved QoL from baseline to 6 months after starting palbociclib. Changes from baseline in EORTC QLQ-C30 scores generally were below the 10-point threshold regarded as clinically meaningful

ABC, advanced breast cancer; ANA, anastrozole; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30; ET, endocrine therapy; EXE, exemestane; FUL, fulvestrant; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; LET, letrozole; OS, overall survival; PAL, palbociclib; pts, patients; QoL, quality of life.

Rocque G, et al. PD10-03. Presented at SABCS 2019, San Antonio.

Overall survival for first-line palbociclib plus letrozole vs. letrozole alone for HR+/HER2- ABC patients in US real-world clinical practice

DeMichele A, et al.

To describe overall survival of ABC patients treated with PAL + LET vs. LET in a cohort of US routine clinical practices

A retrospective, observational analysis using the Flatiron Health Analytic database

Between February 2015 to February 2019 HR+/HER2- ABC adult women (N=1430) received first-line therapy (physicians' choice)

Cohort after 1:1 PSM	PAL + LET (n=464)	LET (n=464)
Median FU:	23.1m	24.4m

Evaluations were from the start of therapy to May 2019, death, or last visit, whichever came first

Results (after PSM)	PAL + LET	LET
Median age (years)	68	67
White (%)	69	69
De novo ABC (%)	42.5	41.4
Visceral disease (%)	35.8	38.6
Bone only disease (%)	41.4	40.5
Estimated OS rate (%) at 24m	80.1	63.9

This real-world analysis demonstrates significant OS benefit of first-line PAL + LET vs. LET alone in patients with HR+/HER2- ABC. Acknowledging the limitations of an EHR database analysis, these data support PAL + LET in improving long-term outcomes in the real-world setting

ABC, advanced breast cancer; EHRs, electronic health records; ET, endocrine therapy; FU, follow-up; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; LET, letrozole; m, months; OS, overall survival; PAL, palbociclib; PSM, propensity score matched..

DeMichele A, et al. Poster P1-19-02. Presented at SABCS 2019, San Antonio.

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What do these findings mean in practice?

- **Real-world evidence confirms:**
  - The efficacy of CDK4/6 inhibitors both in terms of PFS as well as OS
  - The good safety profile of these agents, highlighting that QTc prolongation with ribociclib may not be clinically significant
- **CDK4/6 inhibitors' use in the 1st line setting maintain, but do not significantly improve, QoL**
  - Better and more specific QoL tools are needed for advanced breast cancer

CDK, cyclin-dependent kinase; PFS, progression-free survival; QoL, quality of life; OS, overall survival.

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5th ESO-ESMO International Consensus Guidelines for ABC coming soon…

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 0: 1–24, 2018
doi:10.1093/annonc/mdy192

SPECIAL ARTICLE

4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†

F. Cardoso[1*], E. Senkus[2], A. Costa[3], E. Papadopoulos[4], M. Aapro[5], F. André[6], N. Harbeck[7], B. Aguilar Lopez[8], C. H. Barrios[9], J. Bergh[10], L. Biganzoli[11], C. B. Boers-Doets[12], M. J. Cardoso[13], L. A. Carey[14], J. Cortés[15], G. Curigliano[16], V. Diéras[17], N. S. El Saghir[18], A. Eniu[19], L. Fallowfield[20], P. A. Francis[21], K. Gelmon[22], S. R. D. Johnston[23], B. Kaufman[24], S. Koppikar[25], I. E. Krop[26], M. Mayer[27], G. Nakigudde[28], B. V. Offersen[29], S. Ohno[30], O. Pagani[31], S. Paluch-Shimon[32], F. Penault-Llorca[33], A. Prat[34], H. S. Rugo[35], G. W. Sledge[36], D. Spence[37], C. Thomssen[38], D. A. Vorobiof[39], B. Xu[40], L. Norton[41] & E. P. Winer[42]

The updated ABC 5 Guidelines will be published in early 2020

ABC, advanced breast cancer; ESMO, European Society of Medical Oncology; ESO, European School of Oncology.

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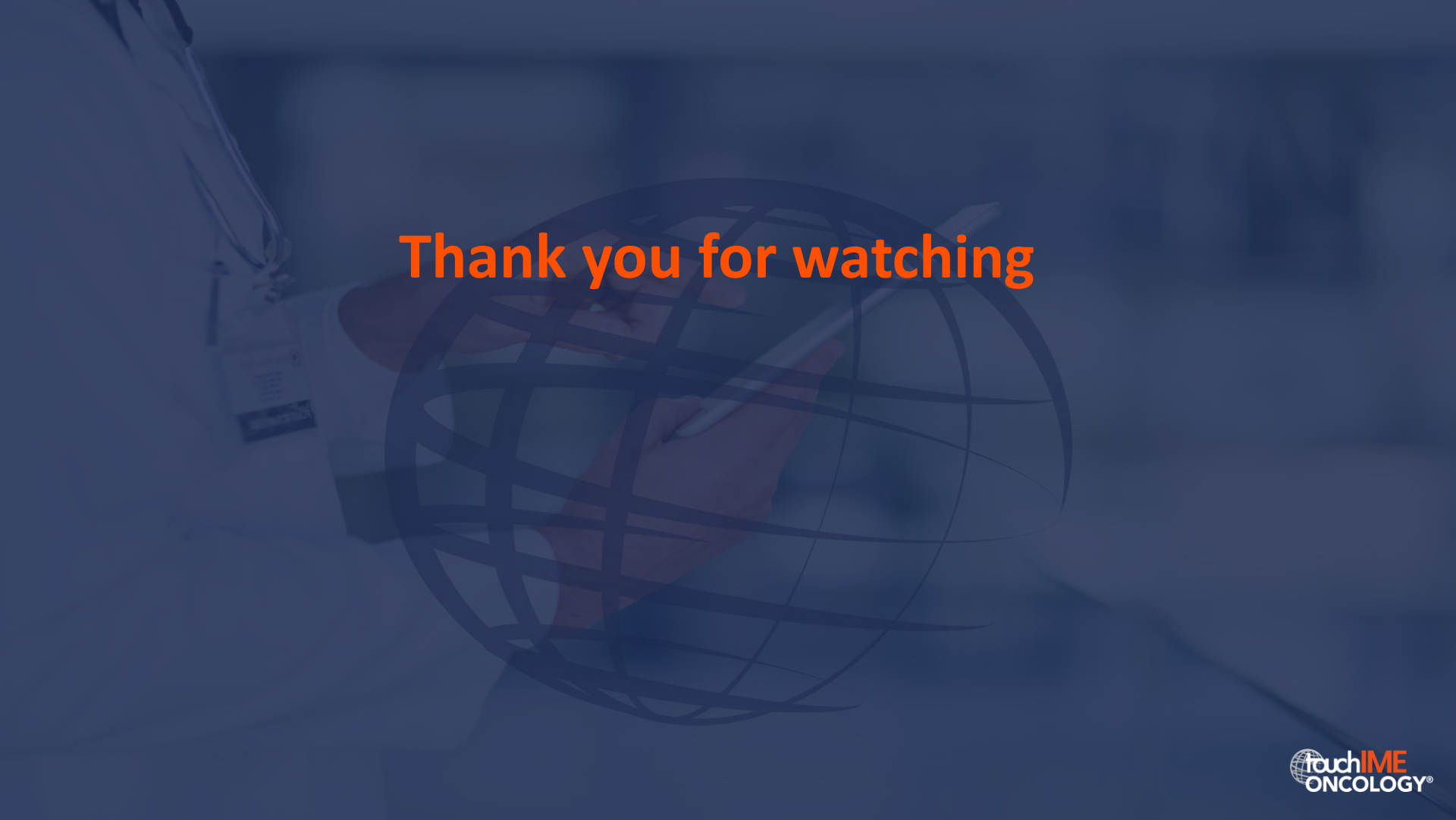
Thank you for watching