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ESMO 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

Webinar overview

HR+/HER2- advanced breast cancer

- The clinical efficacy and safety of CDK4/6 inhibitors
- ESMO Congress 2019 – What are the latest data for CDK4/6 inhibitors?
- ESMO Congress 2019 – Can patient or disease characteristics predict responsiveness to CDK4/6 inhibitors?
- ESMO Congress 2019 – The expanding armamentarium of therapies for advanced breast cancer

CDK, cyclin-dependent kinase.

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The clinical efficacy and safety of 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 benefit of CDK4/6 inhibitors, especially when combined with endocrine therapy

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

Palbociclib	PALOMA-2 **+ letrozole** (N=666) **PFS = 27.6** vs. placebo 14.5, HR 0.56 (CI 0.46–0.69) PALOMA-3 **+ fulvestrant (second-line)** (N=521) **PFS = 11.2** vs. placebo 4.6, HR 0.50 (CI 0.40–0.62)
Ribociclib	MONALEESA-2 **+ letrozole (**N=668), **PFS = 25.3** vs. placebo 16.0, HR 0.57 (CI 0.46–0.70) MONALEESA-3 **+ fulvestrant (2nd-line)** (n=343), **PFS = 14.6** vs. placebo 9.1, HR 0.57 (CI 0.43–0.74) MONALEESA-7 + **tamoxifen/NSAI + gos** (N=672), **PFS = 23.8** vs. placebo 13, HR 0.55 (CI 0.44–0.69)
Abemaciclib	MONARCH-2 **+ fulvestrant (second-line) (N=669) PFS=16.4** vs. placebo 9.3, HR 0.55 (CI 0.45–0.68) MONARCH-3 **+ letrozole/anastrozole (N=493) PFS=28.8** vs. placebo 14.8, HR 0.54 (CI 0.42–0.70)

More ongoing Phase II and III clinical studies are testing CDK4/6 inhibitors either as monotherapy or in combination with other targeted therapies in HR+/HER2- advanced breast cancer

CDK, cyclin-dependent kinase; CI, confidence interval; gos, goserelin; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; NSAI, nonsteroidal aromatase inhibitor; PFS, progression-free survival.

Finn, *N Engl J Med* 2016; Rugo H, SABCS 2017; Hortobagyi G, *N Engl J Med* 2016 & *Ann Oncol* 2018; Goezt M, *J Clin Oncol* 2017 & AACR 2018; Tripathy D. *Lancet Oncol.* 2018;19:904–915; Turner N, *N Engl J Med* 2015, updated SABCS 2016; Cristofanilli M, *Lancet Oncol* 2016; Sledge, *J Clin Oncol* 2017; Slamon DJ, ASCO 2018 & *J Clin Oncol.* 2018.

Safety profiles of CDK4/6 inhibitors in advanced breast cancer

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

	Ribociclib MONALEESA-2[1]	Palbociclib PALOMA-2[2]	Abemaciclib MONARCH-3[3]
Adverse events Any Grade	Neutropenia (74%), Leucopenia (33%), Nausea (52%)	Neutropenia (80%), Leucopenia (39%), Nausea (35%)	Neutropenia (41%), Diarrhoea (81%), Nausea (39%)
Adverse events Grade 3–4	Neutropenia (59%) Leucopenia (21%)	Neutropenia (66%) Leucopenia (25%)	Neutropenia (21%) Leucopenia (7.6%)

CDK, cyclin-dependent kinase.

1. Hortobagyi GN, et al. *New Engl J Med.* Med 2016;**375**:1738–1748; 2. Finn RS, et al. *N Engl J Med.* 2016;**375**:1925–1936; 3. Goetz MP, et al. *J Clin Oncol.* 2017;**35**:3638–3646.

ESMO CONGRESS 2019 – What are the latest data 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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The first report of an overall survival benefit with a CDK4/6 inhibitor + endocrine therapy was presented at ASCO 2019

OS data from the MONALEESA-7 trial showed that ribociclib plus endocrine therapy demonstrated a clinically and statistically significant longer OS than endocrine therapy alone in premenopausal patients with HR+/HER2- ABC*

Ribociclib	MONALEESA-7 +either tamoxifen or an NSAI plus goserelin, (N=672), **OS = NR vs. placebo 40.9, HR, 0.712** (95% CI, 0.54–0.95) p = 0.00973

~29% relative reduction in risk of death

***Pre-specified interim analysis:** Data cut-off Nov 30, 2018
The median follow up was 34.6 months.
In the treatment and placebo arms respectively: the number on treatment at data cut-off (N=173) was 116 and 57 patients; OS was evaluated after 192 deaths (83 and 109).

ABC, advanced breast cancer; CDK, cyclin-dependent kinase; CI, confidence interval; ET, endocrine therapy; HER2- human epidermal receptor 2-negative; HR, hazard ratio; HR+ hormone receptor-positive; NE, not evaluable; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PBO, placebo; RIB, ribociclib.
Hurvitz SA, et al. Abstract LBA 1008. Presented at the ASCO Annual Meeting 2019.

Overall survival results of the Phase III MONALEESA-3 trial of postmenopausal patients with HR+/ABC treated with fulvestrant ± ribociclib

Slamon DJ, et al.

To report OS and 1L progression-free survival results from the Phase III MONALEESA-3 trial

Data cut-off: 3 Jun 2019

Postmenopausal patients with HR+/HER2− ABC, in 1L and 2L settings, were randomized 2:1 to:

	RIB + FUL	PBO + FUL
On treatment at data cut-off n (%)	121 (25%)	32 (13.2%)
OS evaluated after 275 deaths	167 (34.5%)	108 (44.6%)

Median follow-up was 39.4 months

Results	RIB + FUL	PBO + FUL	
Median OS, months (Per protocol)	Not reached	40.0	HR=0.724 95% CI, 0.568-0.924 p = 0.00455
OS in 1L subgroup	Not reached	45.1	HR=0.700 95% CI, 0.479-1.021
OS in early-relapse/2L subgroup	40.2	32.5	HR=0.730 95% CI, 0.530-1.004
Median PFS, months 1L subgroup	33.6	19.2	HR=0.546 95% CI, 0.415-0.718

The safety profile was consistent with previously published analyses

These data, combined with results from MONALEESA-7, confirm the benefit of ribociclib in the first- and second-line settings in pre- and postmenopausal patients with HR+/HER2- ABC

ABC, advanced breast cancer; CI, confidence interval; HER2- human epidermal receptor 2-negative; 1l, first line; FUL, fulvestrant; HR, hazard ratio; HR+, hormone receptor-positive; OS, overall survival; PBO, placebo; PFS, progression-free survival; RIB, ribociclib; 2L, second line.

Slamon DJ, et al. *Ann Oncol.* 2019;**30**(suppl_5):v851–v934.

MONARCH 2: Overall survival of abemaciclib plus fulvestrant in patients with HR+, HER2- advanced breast cancer

Sledge GW, et al.

To report OS results of the prespecified interim analysis

Pre/peri- and postmenopausal women with advanced ET resistant HR+/ HER2-ABC

N=669 patients were randomized 2:1:

ABE + FUL

PBO + FUL

Patients were stratified based on site of metastasis (visceral, bone-only, or other) and resistance to prior ET (primary vs secondary)

At the prespecified interim analysis, 338 deaths (77% of the planned 441 events) were observed in the ITT population

Median OS benefit of 9.4 months

Results	ABE + FUL	PBO + FUL	
Median OS, months (Per protocol)	46.7	37.3	**HR=0.757** 95% CI 0.606-0.945 P = 0.0137

OS benefit was consistent in all stratification factors
More pronounced effects were observed in subgroups of:

- Visceral disease (HR: 0.675)
- Primary resistance to prior ET (HR: 0.686)
- PFS2 (HR: 0.675; 95% CI: 0.558,0.816)
- Time to chemotherapy (HR: 0.622; 95% CI: 0.499, 0.775)

Safety data were consistent with known abemaciclib safety profile

TABE+FUL provided a significant and clinically meaningful median OS benefit to pre- or perimenopausal and postmenopausal patients with HR+/HER2- ABC with disease progression on ET, with no new safety signals observed

ABC, advanced breast cancer; ABE, abemaciclib; CI, confidence interval; ET, endocrine therapy; FULV, fulvestrant; HER2- human epidermal receptor 2-negative; HR, hazard ratio; HR+ hormone receptor-positive; ITT, intent to treat; OS, overall survival; PBO, placebo.

Sledge GW, et al. *Ann Oncol.* 2019;**30**(suppl_5):v851–v934.

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Updated overall survival and quality of life in premenopausal patients with ABC who received ribociclib or placebo plus goserelin and a NSAI in the MONALEESA-7 trial

Lu Yen-Shen

Updated OS and QoL data for patients who received an NSAI in the MONALEESA-7 trial

Data cut-off: 30 November 2018

Pre/perimenopausal patients with HR+/HER2-ABC

	N=248 RIB + GOS + NSAI or TAM	N=247 PBO + GOS + NSAI or TAM
On treatment at data cut-off , n	37.1%	18.6%

	RIB + ET	PBO + ET	
OS, months	Not reached	40.7	HR=0.699 (95% CI, 0.501–0.976) p=0.00973
Median TTDD in global QoL	34.2 months	23.3 months	HR=0.69 (95% CI, 0.52–0.91)

The TTDD of pain score was prolonged in the RIB vs. PBO arm, HR=0.641 (95%CI 0.430–0.955)

Updated analyses of AEs revealed no unexpected safety signals

Average QOL was maintained or improved in patients with HR+/HER2- ABC who received RIB in the NSAI cohort compared with those who received placebo

ABC, advanced breast cancer; AEs, adverse events; CI, confidence interval; ET, endocrine therapy; GOS, goserelin; HER2- human epidermal receptor 2-negative; HR, hazard ratio; HR+ hormone receptor-positive; NE, not evaluable; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PBO, placebo; QoL, quality of life; RIB, ribociclib; TTDD, Time to definitive (10%) deterioration.

Lu Y-S, et al. *Ann Oncol.* 2019;**30**(suppl_5):v104–v142.

MONARCHplus: A Phase 3 trial of abemaciclib plus NSAI or fulvestrant for women with HR+/HER2-ABC

Jiang Z, et al.

To evaluate the safety and efficacy of abemaciclib in combination with ET in predominantly Chinese postmenopausal women with HR+/HER2- ABC

Postmenopausal women with HR+, HER2- ABC, measurable disease or non-measurable bone only disease, ECOG PS ≤1

Cohort A
n=306
Randomized
ABE+NSAIs
or
PBO+NSAIs

Cohort B
n=157
Randomized
ABE+FULV
or
PBO+FULV

	Cohort A			Cohort B		
	ABE+NSAI (n=207)	**PBO+NSAI (n=99)**		**ABE+FULV n=104**	**PBO+FULV n=53**	
Median PFS (95%CI)	Not reached (22.32,–)	14.73 (11.21,18.87)	HR=0.499 (0.35,0.72) p=0.0001	11.47 (9.53,--)	5.59 (3.65,7.69)	HR=0.376 (0.240, 0.588) p<0.0001
ORR (95%CI)	56.0 (49.3 –62.8)	30.3 (21.3 –39.4)	p<0.0001	38.5 (29.1 –47.8)	7.5 (0.4 –14.7)	p<0.0001

The safety profile of abemaciclib in combination with NSAIs or FULV was tolerable in this patient population and no new safety signals were observed

Abemaciclib plus NSAI or FULV showed significant and clinically meaningful improvement in PFS and ORR in predominantly Chinese HR+/ HER2- advanced breast cancer patients. The efficacy benefit was consistent with global MONARCH 2 and 3 trials

ABC, advanced breast cancer; ABE, abemaciclib; CI, confidence interval; ET, endocrine therapy; FULV, fulvestrant; PBO, placebo; PFS, progression-free survival; HER2- human epidermal receptor 2-negative; HR, hazard ratio; HR+ hormone receptor-positive; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; PBO, placebo.

Jiang Z, et al. Poster LBA25. Presented at ESMO 2019, Barcelona.

What do these findings mean in practice?

- OS findings from MONALEESA-3 and MONARCH 2 were statistically significant and show that CDK4/6 inhibitors offer clear and meaningful clinical benefit for patients with HR+/HER2- advanced breast cancer
- Results confirm the PFS data reported previously, providing reassurance
- Sub-analysis of the MONALEESA-7 trial has shown that an NSAI can be used with the CDK4/6 inhibitor ribociclib without a change in benefit, and that this may maintain or possibly improve patient quality of life
- Findings from the MONARCHplus study extended this benefit into Chinese post-menopausal women with HR+/HER2- advanced breast cancer

CDK, cyclin-dependent kinase; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PFS, progression-free survival.

ESMO CONGRESS 2019 – Can patient or disease characteristics predict responsiveness to 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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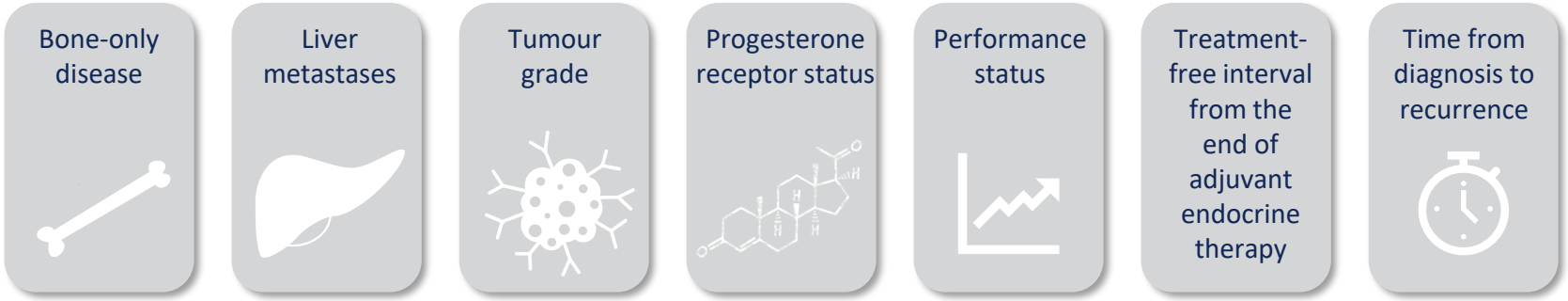
Analysis of patient subgroups may help inform the use of CDK4/6 inhibitors in the treatment paradigm

- In patients with HR+/HER2− ABC treated with abemaciclib in addition to endocrine therapy*, clinical factors with prognostic value included:



- A combined analysis of MONARCH 2 and 3 examined patient and disease characteristics to determine significant prognostic factors

MONARCH 2 and 3 enrolled women with HR+/HER2- ABC:

- In MONARCH 2, patients whose disease had progressed while receiving endocrine therapy received fulvestrant + abemaciclib/placebo
- In MONARCH 3, patients received a NSAI plus abemaciclib/placebo as initial therapy for advanced disease

ABC, advanced breast cancer; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; NSAI, nonsteroidal aromatase inhibitor.

Di Leo A, et al. *NPJ Breast Cancer* 2018;**4**:41.

Ribociclib + letrozole in patients with visceral metastases or bone-only metastases in HR+/HER2- ABC: Subgroup analysis from the CompLEEment-1 trial

De Laurentiis M, et al.

A subgroup analysis of patients with VM or BOM metastases from CompLEEment-1, an open-label, Phase IIIb trial evaluating RIB + LET as first-line therapy in an expanded population

Men and women (N=3,246) with HR+/HER2- ABC and no prior ET received RIB+LET and concomitant goserelin or leuprolide

Sub-group analysis:

- 1,983 (61.1%) with VM, of which 1,309 (66.0%) also had bone metastases
- 706 patients (21.7%) with BOM

In patients with VM:
The most common AEs were neutropenia (70.9%), nausea (35.2%), and fatigue (22.5%)
13.4% discontinued due to AEs

In patients with BOM
The most common AEs were neutropenia (72.8%), nausea (33.3%), and fatigue (21.5%)
12.5% discontinued due to AEs

Results:	With VM	With BOM
Median follow up	10.15 months	
Median duration of RIB exposure	8 months	8.8 months
Estimated 12 month EFP	**63.1%** 95% CI, 59.5–66.6	**82.8%** 95% CI, 78.6–86.3
ORR (patients with measurable disease)	**30.7%** 95% CI, 28.4–33.1	**20.6%** 95% CI, 14.8–27.3
Clinical benefit rate (patients with measurable disease)	**62.8%** 95% CI, 60.3–65.2	**69.1%** 95% CI,61.7–75.9

Patients with BOM were less likely to have an objective tumour response but more likely to be progression free at 12 months

This subgroup analysis supports the safety and efficacy of RIB + LET in patients with HR+/HER2- ABC with VM and BOM

ABC, advanced breast cancer; AE. adverse event; BOM, bone-only metastases; CDK, cyclin-dependent kinase; EFP, event-free probability; ET, endocrine therapy; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; LET, letrozole; NE, non evaluable; ORR, overall response rate; RIB, ribociclib; SAE, serious adverse event; TTP, time to progression; VM, visceral metastases.

De Laurentiis M, et al. *Ann Oncol.* 2019;**30**(suppl_5):v104–v142.

Ribociclib + letrozole in patients with HR+/HER2- ABC and central nervous system metastases: Subgroup analysis from the phase 3b CompLEEment-1 trial

Cottu P, et al.

A subgroup analysis of patients with CNS metastases from CompLEEment-1, an open-label, Phase IIIb trial evaluating RIB + LET as first-line therapy in an expanded population

Men and women (N=3,246) with HR+/HER2- ABC and no prior ET received RIB+LET and concomitant goserelin or leuprolide

Sub-group analysis:

- : Patients with CNS metastases (n=50)

Results	
Median follow up	10.35 months
Median duration of RIB exposure	7.8 months
ORR	**41.2%** 95% CI, 24.6–59.3
Clinical benefit rate	**61.8%** 95% CI, 43.6–77.8
Median TTP	16 months 95% CI, 16.0-NE

- Treatment of 32 (64%) patients was ongoing by cut-off date

AEs were reported in 48 (96%) patients
- 46 patients had treatment-related AEs

Grade 3/4 AEs were reported in 34 (68%) patients
- 4 severe AEs

There was 1 treatment related fatal AE (sepsis)

The most common all-grade AEs were
- Neutropenia (52%), nausea (36%), and fatigue (26%)

The most common grade 3/4 AEs were
- Neutropenia (40%), neutrophil count↓(14%), leukopenia (6%), and ↑AST (6%) and ↑ALT (6%)

No neurological AEs were recorded

- 17 (34%) patients had ≥ 1 dose reduction of RIB, 12 due to AEs, and 18 (36%) patients permanently discontinued treatment, 5 due to AEs

This subgroup analysis demonstrated that the efficacy and safety of RIB+ LET in patients with HR+/HER2– ABC and CNS metastases was similar to that for the full CompLEEment-1 study population

ABC, advanced breast cancer; AE. adverse event; ALT: Alanine aminotransferase; AST: aspartate aminotransferase; CDK, cyclin-dependent kinase; CNS, central nervous system; ET, endocrine therapy; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; LET, letrozole; NE, non evaluable; ORR, overall response rate; RIB, ribociclib; SAE, serious adverse event; TTP, time to progression.

Cottu P, et al. *Ann Oncol.* 2019;**30**(suppl_5):v104–v142.

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Ribociclib + letrozole in male patients with HR+/HER2- ABC: Sub-group analysis from the CompLEEment-1 trial

Campone M, et al.

A sub-group analysis of male patients in CompLEEment-1, an open-label, Phase IIIb trial evaluating RIB + LET as first-line therapy in a patient population with broad inclusion/exclusion criteria to reflect real-world practice

Sub-group analysis:

- **Male patients (n=39)** with HR+/HER2- ABC and no prior ET received RIB+LET and concomitant goserelin or leuprolide

Results

Median follow up	12.3 months
Median duration of RIB exposure	8.0 months
ORR	**34.4%** 95% CI, 18.6–53.2
Clinical benefit rate	**68.8%** 95% CI, 50.0–83.9
Median TTP	Not reached, 95% CI, 9.8–NE

Any-grade AEs were reported in 38 patients

- 36 AEs were treatment-related

SAEs were reported in 4 patients

- 1 SAE was related to treatment
- No fatal treatment-related SAEs

Most common any-grade AEs (≥ 20%)

- Neutropenia (n=20)
- Hot flush (n=12)
- Diarrhoea (n=10)
- Fatigue (n=8)

- There were 31 patients with at least 1 dose adjustment of RIB
  - 5 reductions and 27 interruptions were due to AEs
- Fourteen patients permanently discontinued treatment
  - 7 due to progressive disease and 4 due to AEs

This subgroup analysis supports the safety and efficacy of RIB + LET in men with HR+/HER2- ABC

ABC, advanced breast cancer; AE. adverse event; CDK, cyclin-dependent kinase; ET, endocrine therapy; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; LET, letrozole; Ne, not evaluable; ORR, overall response rate; RIB, ribociclib; SAE, serious adverse event; TTP, time to progression.

Campone M, et al. *Ann. Oncol.* 2019; **30** (suppl_5): v104-v142.

MONARCH 3: Updated time to chemotherapy and disease progression following abemaciclib plus aromatase inhibitor in HR+/HER2- ABC

Martín M, et al.

Analysis to identify subgroups that may be clinically prognostic at 12 month follow-up of MONARCH 3, a randomized, double-blind, Phase III trial of abemaciclib plus an AI in patients with HR+/ HER2- ABC

Data cut-off: 31 October 2018

Methods: Kaplan-Meier analyses of intermediate efficacy parameters in the ITT and subgroups previously identified as significantly prognostic

Intermediate efficacy parameters

- TCT: time to subsequent chemotherapy
- CT: time from randomization to first chemotherapy
- PFS2: time to second disease progression
- PDT: time from randomization to discontinuation date of first post-discontinuation treatment

Time to subsequent chemotherapy

Prognostic subgroups		Abemaciclib + AI Events/N	Placebo + AI Events/N	HR (95% CI)
Bone only disease	Y	13/69	16/40	0.440 (0.211–0.914)
	N	80/259	66/125	0.495 (0.357–0.686)
Liver metastases	Y	21/47	21/31	0.572 (0.313–1.048)
	N	72/281	61/134	0.504 (0.358–0.709)

- **Updated PFS** was 28.2 months with abemaciclib (n=328) and 14.8 months with placebo (n=165) (HR=0.525; 95%CI 0.415–0.665; p<0.0001)
- **Addition of abemaciclib to AI deferred the initiation of CT** both in the ITT (HR=0.513, 95% CI 0.380–0.691, p<.0001) and in subgroups

The safety profile was consistent with previously disclosed results

ABC, advanced breast cancer; AI, aromatase inhibitor; CT, chemotherapy; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive; ITT, intent to treat; PFS, progression-free survival.

Martín M, et al. *Ann Oncol.* 2019;**30**(suppl_5):v104–v142.

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What do these findings mean in practice?

- Results from the large CompLEEment-1 study have shown that the benefit of the CDK4/6 inhibitor ribociclib is similar in patients with bone-only and visceral metastases
- Similarly, the results from the MONARCH 3 trial have shown that the CDK4/6 inhibitor abemaciclib extended the chemotherapy-free period for patients with bone-only or visceral metastases
- Study results have also shown that patients with CNS metastases derive similar benefit from ribociclib as the overall study population
- Findings from CompLEEment-1 have extended the benefit of ribociclib to men with HR+/HER2- advanced breast cancer

ESMO CONGRESS 2019 – The expanding armamentarium of therapies for advanced breast cancer

CDK4/6 inhibitors in breast cancer: Several questions remain

Are CDK4/6 inhibitors likely to be useful for other breast cancer subtypes?

HER2 positive breast cancers
TNBC

There is a strong preclinical rationale for testing CDK4/6 inhibitors in other breast cancer subtypes (especially HER2 positive disease)

Is there a rationale for novel CDK4/6 inhibitor combinations?

HER2 inhibitors
PI3K inhibitors
mTOR inhibitors
Immune checkpoint inhibitors

Crosstalk between the CDK4/6 and the PI3K–AKT–mTOR pathways provides a rationale for combining inhibitors to inhibit tumour growth

Is there a role for continuing CDK4/6 inhibition beyond progression?

Under investigation in clinical trials

CDK, cyclin-dependent kinase; HER2-, human epidermal growth factor receptor 2 negative; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide-3-kinase; TNBC, triple-negative breast cancer

Pernas S, et al. *Ther Adv Med Oncol.* 2018;**10**:1–15.

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An expanding armamentarium of therapies for advanced breast cancer

Data presented at ASCO Congress, June 2019

Continuous triplet therapy (continuous ribociclib, everolimus, exemestane) showed clinical benefit with a manageable tolerability profile in patients with endocrine therapy-refractory HR+/ HER2- advanced breast cancer post-disease progression during CDK4/6 inhibitor.
Tumour genomic profile might impact the clinical outcome with triplet therapy

CDK, cyclin-dependent kinase; HER2- human epidermal receptor 2-negative; HR+ hormone receptor-positive.
Rugo HS, et al. Abstract 1040 Presented at the ASCO Annual Meeting 2019; Bardia A, et al. *J Clin Oncol*. 2019:37:1016-1016.

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monarcHER: A randomized Phase 2 study of abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with HR+/HER2+ ABC Tolaney SM, et al.

To investigate efficacy and safety of abemaciclib with ET plus trastuzumab vs. trastuzumab plus standard-of-care chemotherapy in women with HR+/HER2+ ABC

HR+/HER2+ ABC, ≥2 prior HER targeted therapies, prior T-DM1 and taxane, CDK4/6/fulvestrant naïve, no untreated/symptomatic CNS metastases

Arm A (n=79)	Arm B (n=79)	Arm C (n=79)
Abemaciclib + trastuzumab + fulvestrant	Abemaciclib + trastuzumab	Trastuzumab + investigator's choice CT

Median duration of treatment (cycles) was 10, 8 and 7.5 for Arms A, B and C, respectively

There was a generally tolerable safety profile with no new safety signals identified

Results	Arm A	Arm B	Arm C	
Median PFS (months)	**8.32**	5.65	**5.69**	A vs. C HR 0.673
ORR, months (ITT population)	**32.9% (n=26)**	13.9% (n=11)	13.9% (n=11)	
ORR, months, (measurable disease)	**35.7% (n=25)**	16.2% (n=11)	15.9% (n=11)	

This is the first Phase II study of a CDK4/6 inhibitor with ET vs. standard of care CT together with HER directed treatment in HR+/HER2+ ABC to report positive results

ABC, advanced breast cancer; CDK, cyclin-dependent kinase; CT, chemotherapy; ET, endocrine therapy; HER2+ human epidermal receptor 2-positive; HR, hazard ratio; HR+ hormone receptor-positive; ORR, overall response rate; PFS, progression-free survival; T-DM1, ado-trastuzumab emtansine.

Tolaney SM, et al. *Ann Oncol.* 2019;**30**(suppl_5):v851–v934.

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Trilaciclib improves overall survival when given with gemcitabine/carboplatin in patients with mTNBC in a randomized phase 2 trial

O'Shaughnessy J, et al.

To report the safety and efficacy data for trilaciclib + GC in patients with mTNBC

Adult patients with evaluable confirmed locally recurrent or mTNBC who had ≤2 prior lines CT

Randomized 1:1:1, stratified by number of previous lines of CT and presence of liver metastases (21-day treatment cycles):

	Group 1 (n=34) GC on days 1 & 8	Group 2 (n=33) GC + trilaciclib on days 1 & 8	Group 3 (n=35) GC on days 2 & 9 + trilaciclib on days 1, 2, 8 & 9
Median FU months (IQR)	8.4 (3.8–13.6)	12.7 (5.5–17.4)	12.9 (6.7–16.8)

Results	Group 1	Group 2	Group 3	Group 3 vs. Group 1
During cycle 1, mean duration of severe neutropenia	1 day	2 days	1 day	One-sided adjusted p=0.70
OS, months (IQR)	12.6 (5.8–15.6)	20.1 (9.4–not reached)	17.8 (8.8–not reached)	Two-sided p=0.0023
Most common TEAEs	Anaemia 22 (73%), Neutropenia 21(70%) Thrombocytopenia 18 (60%)	Neutropenia 27 (82%) Thrombocytopenia 18 (55%) Anaemia 17 (52%)	Neutropenia 23 (66%) Thrombocytopenia 22 (63%) Nausea 17 (49%)	

No significant differences were observed in myelosuppression endpoints with trilaciclib + GC in patients with mTNBC, however, the regimen was generally well tolerated and OS results were encouraging

CT, chemotherapy; FU, follow up; GC, gemcitabine/carboplatin; IQR, interquartile range; mTNBC, metastatic triple negative breast cancer.

O'Shaughnessy J. LBA22. Presented at ESMO 2019, Barcelona. Tan AR, et al. *Lancet Oncol* 2019; September 28, 2019 http://dx.doi.org/10.1016/S1470-2045(19)30616-3.

What do these findings mean in practice?

- Interesting results, but not practice-changing at this stage
- Results from monarcHER show that the CDK4/6 inhibitor abemaciclib may be combined with trastuzumab for use in patients with HR+/HER2+ advanced breast cancer, potentially extending the benefit of CDK4/6 inhibitors to this population
- Findings from the Phase II study of the emerging CDK4/6 inhibitor trilaciclib suggest that it may offer survival benefit for patients with triple-negative advanced breast cancer in combination with gemcitabine and carboplatin, but we await further data

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