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touchONCOLOGY – Leading the conversation in advanced breast cancer

On demand webinar: recorded in June 2018

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Disclosures

	Applicability	Company
(1) Advisory role	yes	Celgene, Daiichi-Sankyo, Hexal/Sandoz, Lilly, Novartis, Pfizer, Roche
(2) Stock ownership/profit	n/a	
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Webinar overview

1

Focus on the management of HR+/HER2- advanced breast cancer

- Where are we now?
- ASCO 2018: efficacy – trial data
- ASCO 2018: safety and quality of life – trial data
- ASCO 2018: real-world experience and optimizing patient management

2

Focus on other therapies for advanced breast cancer

- ASCO 2018: other breaking data
- ASCO 2018: clinical trials in progress

Please submit your questions throughout the presentation

ASCO, American Society of Clinical Oncology; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

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Part 1.
Where are we now?

Addressing the challenges for managing
HR+/HER2- advanced breast cancer

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

Therapeutic strategies in metastatic breast cancer

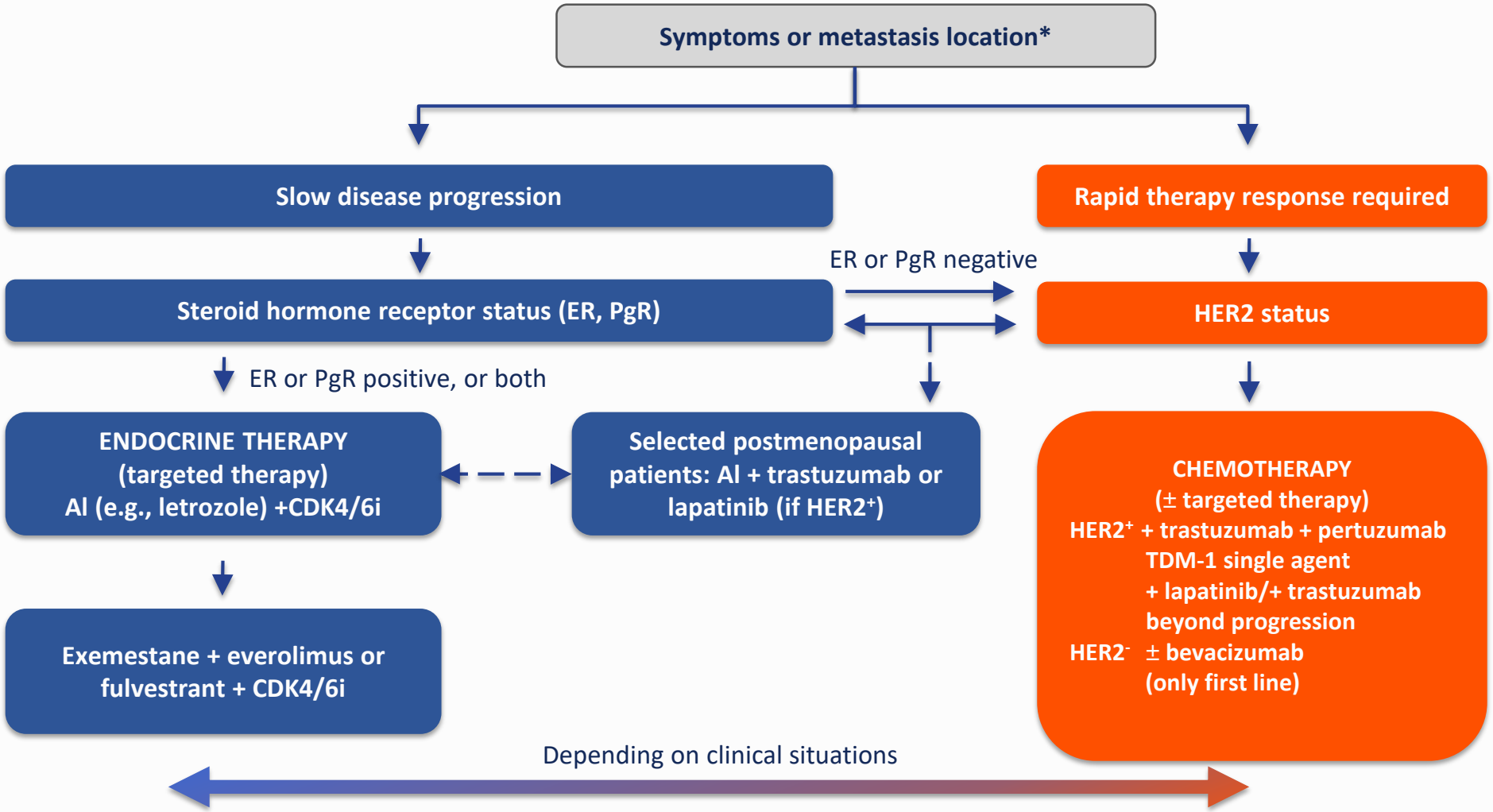

Figure reproduced from Harbeck & Gnant, 2017

Previous treatments of patient's preferences are key elements in deciding the individual therapeutic steps. Treatment decisions can thus differ for an individual patient. In patients with HR-positive HER2-negative tumours, endocrine therapy should be the first option unless there is life-threatening disease. Chemotherapy is always an additional therapy option depending on the course of the disease. So far, only one line of palbociclib therapy is evidence-based. Only applicable if ER or PgR positive, or both. AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PgR, progesterone receptor; TDM-1, trastuzumab emtansine. *If bone metastases: + bisphoshonates or denosumab. Always combine with ovarian suppression or ablation in premenopausal patients.

Harbeck N, Gnant M. Breast cancer. *Lancet* 2017;389(10074):1134-50.

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HR+/HER2- advanced breast cancer

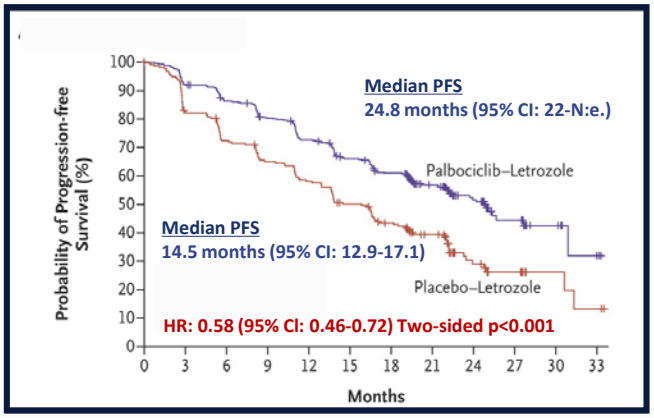
Three selective CDK inhibitor therapies are approved

Region	Date	Indication	Approval study
Palbociclib			
FDA	Feb15	2L + letrozole	**PALOMA-2**
EU	Aug15	In combination with endocrine therapy	
FDA	Feb16	2L in combination with fulvestrant after endocrine therapy	**PALOMA-3**
EU	Nov16	2L in combination with aromatase inhibitor after endocrine therapy	
EU	Nov16	After endocrine therapy progression	
FDA	Mar17	1L in combination with aromatase inhibitor	
Ribociclib			
FDA	Mar17	1L in combination with aromatase inhibitor*	**MONALEESA-2**
EU	Aug17	1L in combination with aromatase inhibitor*	**MONALEESA-2**
Abemaciclib			
FDA	Sep17	2L In combination with fulvestrant after endocrine therapy	**MONARCH-2**
FDA	Sep17	Monotherapy in ABC after disease progression with endocrine therapy and chemotherapy	**MONARCH-1**
FDA	Feb18	1L in combination with aromatase inhibitor	**MONARCH-3**

* EU approval for locally advanced and metastatic; FDA approval for ABC.
ABC, advanced breast cancer; 1L, first-line; 2L, second-line; CDK, cyclin-dependent kinase; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

First line Phase III CDK 4/6 inhibitors: PFS

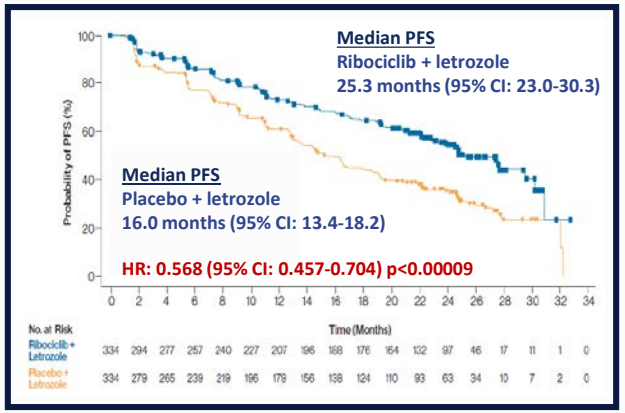
PALOMA-2[1]



Finn RS et al. N Engl J Med 2016

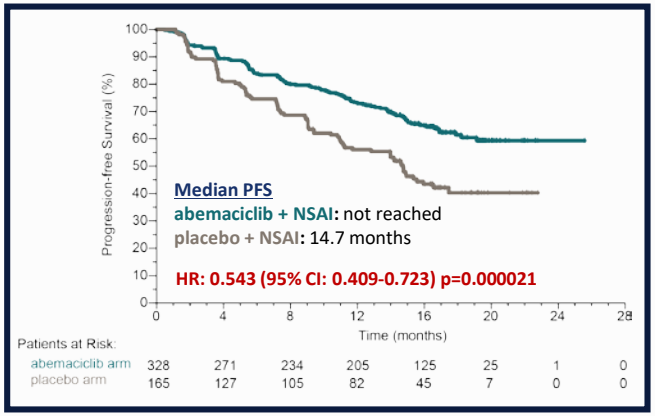
Monaleesa 2[3]

(updated results)



Hortobagyi G, et al. Ann Oncol 2018

Monarch-3[2]



Goetz M et al. J Clin Oncol 2017

95% CI, 95% confidence interval; CDK, cyclin-dependent kinase; HR, hazard ratio; N:e, not evaluable; NSAI, non-steroidal aromatase inhibitor; PFS, progression-free survival.

1. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. *N Engl J Med* 2016;375(20):1925-36. 2. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as Initial Therapy for Advanced Breast Cancer. *J Clin Oncol* 2017;35(32):3638-46. 3. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol* 2018 Apr 27. doi: 10.1093/annonc/mdy155. [Epub ahead of print]

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Challenges of current management

DISEASE

- Heterogeneity of disease and new mutations[1]
- Development of treatment resistance[1]

TREATMENT

- Endocrine therapy or chemotherapy[1]
- Sequence of treatment – inclusion of biologic agents[1]
- Lack of multidisciplinary treatment or specialized ABC nurses[2]
- Ongoing reassessment of genetic mutational status (ABC)[1]

ECONOMIC & CLINICAL

- Lack of clear and applicable management guidelines or high-level evidence for treatment options[2]
- Increasing, negative impact on healthcare budgets[3]

ABC, advanced breast cancer.

1. Hart CD, Migliaccio I, Malorni L, et al. Challenges in the management of advanced, ER-positive, HER2-negative breast cancer. *Nat Rev Clin Oncol* 2015;12:541-52; 2. McCutcheon S, Cardoso F Challenges in optimizing care in advanced breast cancer patients: Results of an international survey linked to the ABC1 consensus conference. *Breast* 2015;24:623-9; 3. Debald M, Kuhn W, Golubnitschaja O. Challenges in breast cancer management and prevention. *EPMA J* 2014;5(Suppl 1):A41.

Where are we with resistance?

Genetic landscape of resistance to CDK4/6 inhibition in circulating tumor DNA (ctDNA) analysis of the PALOMA-3 trial of palbociclib and fulvestrant versus placebo and fulvestrant
Turner NC, O'Leary B, Cutts R, et al.

A longitudinal analysis of the PALOMA-3 population to assess driver mutation targeted sequencing and mechanism of resistance to CDK4/6 inhibitors

- **New driver mutations emerged for both PIK3CA and ESR1, especially mutation ESR1 Y537S; there were no differences in frequency between palbociclib and placebo groups**
- **Time on treatment was major factor for evolution of mutational resistance (p=0.0066), with driver mutations uncommon in patients progressing early on palbociclib + fulvestrant**
- **At end of treatment, only 4.8% of patients receiving palbociclib + fulvestrant developed an RB1 mutation; no mutations were reported in patients receiving fulvestrant alone (p=0.041)**

- Breast cancer driver mutation landscapes are largely similar after treatment with palbociclib + fulvestrant and with fulvestrant alone, with acquired PIK3CA and ESR1 Y537S mutations that likely contribute to fulvestrant resistance
- No mutations in CDK4/6 were reported, suggesting that gatekeeper mutation are uncommon
- There is a potential parallel evolution of resistance to fulvestrant and CDK4/6 inhibitors

CDK, cyclin-dependent kinase; ESR1, oestrogen receptor 1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Part 2.
ASCO 2018 – Efficacy

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

ASCO, American Society of Clinical Oncology; CDK, cyclin-dependent kinase; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

What's new with palbociclib at ASCO?

Treatment effect of palbociclib (PAL) plus endocrine therapy (ET) by prognostic and intrinsic subtype: A joint analysis of PALOMA-2 and PALOMA-3
Finn RS, Cristofanilli M, Ettl J, et al.

STEPP analyses of patients receiving adjuvant therapy to evaluate the effect of an initial TFI in PALOMA-2 or a DFI in PALOMA-3 on PFS outcomes

- **TFI did not have an impact on PFS with palbociclib in the overall population or in patients with visceral or nonvisceral metastases who received adjuvant therapy**
- **PALOMA-2: patients with luminal disease benefited from palbociclib + letrozole vs letrozole alone, regardless of subtype**
- **PALOMA-3: PFS with palbociclib was not affected by DFI in patients receiving adjuvant therapy; palbociclib + fulvestrant improved PFS vs fulvestrant, regardless of luminal subtype**

- Palbociclib plus ET improved PFS vs ET plus placebo in patients who received adjuvant therapy and developed disease recurrence
- Luminal A or luminal B subtypes benefited from palbociclib + ET vs ET + placebo
- These data support palbociclib + ET as a standard of care for HR+/HER2- ABC, regardless of baseline TFI/DFI or molecular subtype at time of diagnosis or disease recurrence

ABC, advanced breast cancer; ASCO, American Society of Clinical Oncology; DFI, disease-free interval; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; PFS, progression-free survival; STEPP, Subpopulation Treatment Effect Pattern Plot; TFI, treatment-free interval.

What's new with ribociclib at ASCO?

Ribociclib (RIB) + fulvestrant (FUL) in postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC): Results from MONALEESA-3
Slamon DJ, Neven P, Chia SKL, et al.

A randomized, double-blind, Phase III study of ribociclib + fulvestrant in HR+/HER2- ABC ET-naïve or -experienced (≤1 prior ET) patients, vs placebo + fulvestrant

- **PFS was significantly improved with ribociclib + fulvestrant vs placebo + fulvestrant (20.5 months vs 12.8 months, respectively; HR: 0.593; 95% CI: 0.480–0.732; p=0.00000041)**
  - **ORR was 41% vs 29% (p=0.003), respectively; CBR was 69% vs 60% (p=0.015), respectively**
- **PFS benefits of ribociclib were consistent between ET-naïve and -experienced patients**
- **Most common AEs were neutropenia (70% vs 2%), nausea (45% vs 28%), and fatigue (31% vs 33%) in the ribociclib vs placebo group, respectively**

- Patients receiving ribociclib had a significant and meaningful improvement in PFS vs placebo, with significant reduction in risk of disease progression
- Prolonged PFS was also observed with second-line ribociclib
- Ribociclib + fulvestrant may be a new first- or second-line treatment option for postmenopausal women with HR+/HER2- ABC

95% CI, 95% confidence interval; ABC, advanced breast cancer; AE, adverse event; ASCO, American Society of Clinical Oncology; CBR, clinical benefit rate; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; ORR, objective response rate; PFS, progression-free survival.

What's new with ribociclib at ASCO?

Ribociclib (RIB) + tamoxifen (TAM) or a non-steroidal aromatase inhibitor (NSAI) in premenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC) who received prior chemotherapy (CT): MONALEESA-7 subgroup analysis
Hurvitz SA, Wheatley-Price P, Tripathy D, et al.

Subgroup analyses of the Phase III MONALEESA-7 trial of pre- and perimenopausal women with HR+/HER2- ABC receiving no prior ET and ≤1 chemotherapy

- **PFS was prolonged with ribociclib vs placebo in patients with and without prior chemotherapy for ABC**
  - **16.6 vs 9.0 months (HR: 0.547; 95% CI: 0.314–0.954) and 24.7 vs 14.5 months (HR: 0.566; 95% CI: 0.443–0.724), respectively**
- **The most common all-grade, all-causality AEs were neutropenia, leukopenia and hot flash**

- Ribociclib + tamoxifen/NSAI + goserelin prolonged PFS in premenopausal women with HR+/HER2- ABC, regardless of prior chemotherapy for ABC
- Ribociclib combination therapy was associated with a manageable safety profile in premenopausal patients
- Ribociclib-based combinations may be considered for use as first-line therapy in premenopausal women with HR+/HER2- ABC

95% CI, 95% confidence interval; ABC, advanced breast cancer; AE, adverse event; ASCO, American Society of Clinical Oncology; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; NSAI, non-steroidal aromatase inhibitor; PFS, progression-free survival.

What's new with abemaciclib at ASCO?

Abemaciclib for pre/perimenopausal women with HR+, HER2- advanced breast cancer
Neven P, Rugo HS, Tolaney SM, et al.

A Phase III study of abemaciclib + fulvestrant in pre/peri- (with GnRH agonist) and post-menopausal women progressing on (neo)adjuvant ET or first-line ET for ABC

- **Median PFS was not reached for abemaciclib + fulvestrant vs 10.5 months for placebo + fulvestrant (HR: 0.446; 95% CI: 0.264–0.754; p=0.002)**
- **In patients with measurable disease (69.3%), ORR was significantly higher with abemaciclib vs fulvestrant alone (60.8% [3.9% CR] vs 28.6% [0% CR]; p=0.006)**
- **Most frequent AEs in the abemaciclib vs placebo group included diarrhoea (87.3% vs 23.8%), neutropenia (59.2% vs 7.1%) and leukopenia (43.7% vs 4.8%)**
  - **39.4% of abemaciclib patients received a dose reduction**

- Abemaciclib delayed the time to initiation of subsequent chemotherapy, irrespective of menopausal status
- Diarrhoea associated with abemaciclib was predictable (occurring early), manageable and reversible
  - No additional safety signals were observed with the inclusion of a GnRH agonist

95% CI, 95% confidence interval; ABC, advanced breast cancer; AE, adverse event; ASCO, American Society of Clinical Oncology; CR, complete response; ET, endocrine therapy; GnRH, gonadotropin-releasing hormone; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; ORR, objective response rate; PFS, progression-free survival.

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Summary

- Joint analysis of PALOMA-2 and PALOMA-3 suggests that palbociclib has PFS benefits in patients with disease recurrence after adjuvant therapy[1]
  - Palbociclib + ET is a standard of care option for HR+/HER2- ABC, regardless of baseline treatment- or disease-free interval, or molecular subtype
- Ribociclib + fulvestrant may provide first- and second-line treatment options for postmenopausal women with HR+/HER2- ABC[2]
- In premenopausal patients from MONALEESA-7, ribociclib combination therapy prolonged PFS and had a manageable safety profile, regardless of prior chemotherapy for ABC[3]
  - Ribociclib-based combinations may be considered for use as first-line therapy in premenopausal women with HR+/HER2- ABC
- Abemaciclib + fulvestrant delayed the time to initiation of subsequent chemotherapy, irrespective of menopausal status[4]

ABC, advanced breast cancer; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; PFS, progression-free survival.

1. Finn RS, Cristofanilli M, Ettl J, et al. 1023 - Treatment effect of palbociclib (PAL) plus endocrine therapy (ET) by prognostic and intrinsic subtype: A joint analysis of PALOMA-2 and PALOMA-3. Presented at ASCO 2018; 2. Slamon DJ, Neven P, Chia SKL, et al. 1000 – Ribociclib (RIB) + fulvestrant (FUL) in postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC): Results from MONALEESA-3. Oral presentation at ASCO 2018. 3. Hurvitz SA, Wheatley-Price P, Tripathy D, et al. 1047 - Ribociclib (RIB) + tamoxifen (TAM) or a non-steroidal aromatase inhibitor (NSAI) in premenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC) who received prior chemotherapy (CT): MONALEESA-7 subgroup analysis. Presented at ASCO 2018. 4. Neven P, Rugo HS, Tolaney SM, et al. 1002 – Abemaciclib for pre/perimenopausal women with HR+, HER2- advanced breast cancer. Oral presentation at ASCO 2018.

Part 3.
ASCO 2018 –
Safety and quality of life

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

ASCO, American Society of Clinical Oncology; CDK, cyclin-dependent kinase; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

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Safety outcomes with CDK4/6 inhibitors

Neutropenia and diarrhoea are the most common adverse events

Study	Most common AEs	Most common Grade 3/4 AEs	Additional
PALOMA-2[1] Palbociclib	**Neutropenia (79.5%)** Leukopenia (39.0%) Fatigue (37.4%)	**Neutropenia (66.4%)** Leukopenia (24.8%) Fatigue (1.8%)	Febrile neutropenia (1.8%)
PALOMA-3[2] Palbociclib	**Neutropenia (78.8%)** Leukopenia (45.5%) Fatigue (38.0%)	**Neutropenia (62.0%)** Leukopenia (25.2%) Anaemia (2.6%)	Febrile neutropenia (0.6%)
MONALEESA-2[3] Ribociclib	**Neutropenia (74.3%)** Nausea (51.5%) Infections (50.3%)	**Neutropenia (59.3%)** Leukopenia (21.0%) Increase ALT (9.3%)	Increase in QTcF interval (2.7%)
MONARCH-2[4] Abemaciclib	**Diarrhoea (86.4%)** Neutropenia (46.0%) Nausea (45.1%) Fatigue (39.9%)	**Neutropenia (26.5%)** Diarrhoea (13.4%) Leukopenia (8.8%) Anaemia (7.2%)	Thromboembolic events (2.0%)
MONARCH-3[5] Abemaciclib	**Diarrhoea (81.3%)** Neutropenia (41.3%) Fatigue (40.1%) Nausea (38.5%)	**Neutropenia (21.1%)** Diarrhoea (9.5%) Leukopenia (7.6%) Anaemia (5.8%)	Thromboembolic events (4.9%)

AE, adverse event; CDK, cyclin-dependent kinase.

1. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. *N Engl J Med*.2016;375:1925-36; 2. Turner N, Ro J, André F, et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. *N Engl J Med* 2015;373:209-19; 3. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med* 2016;375:1738-48; 4. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2– Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. *J Clin Oncol* 2017;35:2875-84; 5. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as Initial Therapy for Advanced Breast Cancer. *J Clin Oncol* 2017;35:3638-46.

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ASCO – clinical safety outcomes

Hematologic adverse events following palbociclib (PAL) dose reduction in patients (pts) with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2-) advanced breast cancer (ABC): pooled analysis from randomized phase 2 and 3 studies
Verma S, Im SA, Ro J, et al.

Pooled analysis of the PALOMA-1, -2 and -3 studies in post- and pre-/peri-menopausal women to evaluate the frequency of haematological AEs before and after dose reductions

- **35.5% of palbociclib patients with HR+/HER2- ABC required an initial dose reduction (93.6% due to AEs)**
- **Almost 90% of patients requiring a second dose reduction (12% of pooled population) from 100 to 75 mg had neutropenia (all grades)**
- **PFS associated with palbociclib combination therapies was similar among patients with or without dose reductions**

- Decreases in the frequency and severity of haematological AEs were observed after palbociclib dose reductions
- Palbociclib dose reductions did not impact PFS benefits
- Regular monitoring and algorithm-based dose reductions are recommended for the management of haematological AEs associated with palbociclib

ABC, advanced breast cancer; AE, adverse event; ASCO, American Society of Clinical Oncology; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; PFS, progression-free survival.

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ASCO – quality of life

Maintenance of health-related quality of life in elderly patients treated with ribociclib + letrozole in MONALEESA-2

Burris HA, Tolaney SM, Hart LL, et al.

To explore efficacy, safety, and HRQoL outcomes in HR+/HER2– ABC women ≥65 years treated with first-line ribociclib + letrozole in the MONALEESA-2 study

- **In elderly patients, ribociclib + letrozole showed continued PFS benefit vs placebo + letrozole (HR: 0.682; 95% CI: 0.485–0.960; p=0.028)**
- **There were no differences between regimens in EORTC QLQ-C30 global health status/HRQoL score according to treatment, time or treatment-time interaction**
- **A clinically meaningful improvement (>5 points) in EORTC QLQ-C30 pain score was observed with ribociclib during the first year; mild improvement was reported in the placebo group**

- In elderly patients, ribociclib + letrozole improved PFS, provided a manageable safety profile and showed similar HRQoL vs placebo + letrozole
- Efficacy and safety outcomes are consistent with reports in younger patients (<65 years)
- Ribociclib was associated with clinically meaningful improvements in HRQoL pain score from the start of Cycle 3 through to Cycle 11

95% CI, 95% confidence interval; ABC, advanced breast cancer; AE, adverse event; ASCO, American Society of Clinical Oncology; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; HRQoL, health-related quality of life; PFS, progression-free survival.

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ASCO – quality of life

Health-related quality of life (HRQoL) in MONARCH 2: Abemaciclib plus fulvestrant in women with HR+, HER2- advanced breast cancer (ABC) who progressed on endocrine therapy

Kaufman PA, Toi M, Neven P, et al.

To compare changes in QoL, functioning and symptoms in women with HR+/HER2-ABC in the Phase III MONARCH 2 study of fulvestrant + abemaciclib or placebo

- **Four EORTC QLQ-C30 symptom scores statistically significantly favoured placebo + fulvestrant**
  - **Appetite loss, nausea/vomiting, diarrhoea and systemic therapy AEs were significantly increased with abemaciclib + fulvestrant**
  - **Diarrhoea score was the only item considered clinically significant**
- **Higher EORTC symptom burden of nausea/vomiting, appetite loss, diarrhoea and systemic therapy were more likely in early treatment visits**

- Abemaciclib + fulvestrant did not show statistically or clinically meaningful differences in patient-reported global health or functioning vs placebo + fulvestrant
- Diarrhoea was the only item associated with a significant and clinically meaningful difference between treatment arms, suggesting abemaciclib-associated diarrhoea is predictable, manageable and reversible
- The higher symptom burden was generally reported during early visits

ABC, advanced breast cancer; AE, adverse event; ASCO, American Society of Clinical Oncology; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

Summary

- Pooled analysis of the PALOMA-1, -2 and -3 studies shows that palbociclib dose reductions do not impact PFS benefits[1]
  - Regular monitoring is recommended for the management of palbociclib-associated haematological AEs
- In elderly HR+/HER2- ABC patients, ribociclib + letrozole demonstrated efficacy and safety outcomes consistent with younger patients (<65 years)[2]
  - Ribociclib was associated with clinical improvements in HRQoL pain score
- Patient-reported global health or functioning is not significantly affected by abemaciclib + fulvestrant vs placebo + fulvestrant[3]
- Abemaciclib-associated diarrhoea is predictable and manageable, and generally more frequent at the start of therapy[3]

ABC, advanced breast cancer; AE, adverse event; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; PFS, progression-free survival.

1. Verma S, Im SA, Ro J, et al. 1060 - Hematologic adverse events following palbociclib (PAL) dose reduction in patients (pts) with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC): pooled analysis from randomized phase 2 and 3 studies. Presented at ASCO 2018; 2. Burris HA, Tolaney SM, Hart LL, et al. 1041 - Maintenance of health-related quality of life in elderly patients treated with ribociclib + letrozole in MONALEESA-2. Presented at ASCO 2018; 3. Kaufman PA, Toi M, Neven P, et al. 1049 - Health-related quality of life (HRQoL) in MONARCH 2: Abemaciclib plus fulvestrant in women with HR+, HER2- advanced breast cancer (ABC) who progressed on endocrine therapy. Presented at ASCO 2018.

Part 4.
ASCO 2018 – Real-world experience and optimizing patient management

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

ASCO, American Society of Clinical Oncology; CDK, cyclin-dependent kinase; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

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ASCO – real-world outcomes

RIBECCA: A Phase IIIb, multi-center, open label study for women with estrogen receptor positive locally advanced or metastatic breast cancer treated with ribociclib (LEE011) in combination with letrozole—Results of the first interim analysis

Fasching PA, Nusch A, Heinrich B, et al.

RIBECCA is an ongoing Phase IIIb, open-label study of ribociclib in combination with letrozole in male or premenopausal female patients with HR+/HER2- ABC pretreated with 1 CT line and/or ≤2 ET lines

- **The primary objective is to assess the clinical benefit rate after 6 months**
- **In patients with ≥8 weeks follow up (n=338), the most frequent AEs included neutropenia (54.1%), nausea (36.7%), fatigue (33.4%), alopecia (29.0%) and leukopenia (26.0%)**

- The first interim analysis suggests the data are similar to the Phase III MONALEESA-2 and MONALEESA-7 studies
- No new safety signals were observed
- Patient body-mass index correlates with the incidence of neutropenia

ABC, advanced breast cancer; AE, adverse event; ASCO, American Society of Clinical Oncology; CT, chemotherapy; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

ASCO – real-world outcomes

Ribociclib (RIBO) + letrozole (LET) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) with no prior endocrine therapy (ET) for ABC: Preliminary results from the phase 3b CompLEEment-1 trial
DeLaurentiis M, Neven P, Jerusalem GHM, et al.

A Phase IIIb, single-arm, open-label study to assess the safety and efficacy of ribociclib + letrozole in male and female HR+/HER2- ABC patients without prior ET

- **At the time of analysis, 95.0% of patients reported an AE**
- **The most common AEs were neutropenia, nausea, fatigue and diarrhoea**
- **The most common Grade 3/4 events included neutropenia, leukopenia, increased ALT levels and increased AST levels**

- CompLEEment-1 assessed the safety and tolerability of first-line ribociclib + letrozole in a larger and broader HR+/HER2- ABC population than previous trials
- Preliminary results are consistent with MONALEESA-2 and -7, and support the manageable safety profile of first-line ribociclib + letrozole
- Efficacy and further safety data are expected in 2019

ABC, advanced breast cancer; AE, adverse event; ALT, alanine aminotransferase; ASCO, American Society of Clinical Oncology; AST, aspartate aminotransferase; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

ASCO – ongoing patient management

Impact of abemaciclib on the time to subsequent chemotherapy and the time to second disease progression across the MONARCH 2 and 3 studies

Tolaney SM, Di Leo A, Llombart Cussac A, et al.

To assess the impact of abemaciclib on post-progression therapies following the MONARCH-2 and -3 studies

- **Time to subsequent CT was significantly increased in patients previously receiving abemaciclib + ET vs placebo + ET ($p<0.01$ and $p<0.001$ for the MONARCH-2 and -3 studies, respectively)**
- **Abemaciclib + ET was associated with a statistically significant increase in time to second disease progression or death vs placebo + ET ($p<0.05$ for the MONARCH-2 and -3 studies)**

- Combining abemaciclib with fulvestrant or an NSAI delayed the need to initiate a subsequent CT
- An efficacy benefit of combining abemaciclib with fulvestrant or an NSAI was observed in the subsequent line of therapy (after the initial disease progression)

ASCO, American Society of Clinical Oncology; CT, chemotherapy; ET, endocrine therapy; NSAI, non-steroidal aromatase inhibitor.

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Summary

- First interim analysis from the ongoing Phase IIIb RIBECCA study of ribociclib + letrozole suggests outcome data are similar to the Phase III MONALEESA-2 and MONALEESA-7 studies, with no additional safety signals[1]
- CompLEEment-1 assessed the safety and tolerability of first-line ribociclib + letrozole in a wide HR+/HER2- ABC population[2]
  - Preliminary results are consistent with MONALEESA-2 and -7
  - Efficacy and additional safety data are expected in 2019
- Abemaciclib + ET may significantly delay the need to initiate a subsequent chemotherapy[3]
- An efficacy benefit of abemaciclib + ET was observed in time to second disease progression or death, compared with placebo + ET[3]

ABC, advanced breast cancer; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

1. Fasching PA, Nusch A, Heinrich B, et al. 1051 - RIBECCA: A phase IIIb, multi-center, open label study for women with estrogen receptor positive locally advanced or metastatic breast cancer treated with ribociclib (LEE011) in combination with letrozole—Results of the first interim analysis. Presented at ASCO 2018; 2. DeLaurentiis M, Neven P, Jerusalem GHM, et al. 1056 - Ribociclib (RIBO) + letrozole (LET) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC) with no prior endocrine therapy (ET) for ABC: Preliminary results from the phase 3b CompLEEment-1 trial. Presented at ASCO 2018; 3. Tolaney SM, Di Leo A, Llombart Cussac A, et al. 1048 - Impact of abemaciclib on the time to subsequent chemotherapy and the time to second disease progression across the MONARCH 2 and 3 studies. Presented at ASCO 2018.

Part 5.
Other breaking data from ASCO 2018

Focus on other systemic therapies for advanced breast cancer

ASCO, American Society of Clinical Oncology.

A focus on other systemic therapies (1)

Taxane and taxane-refractory

Activity of tesetaxel, an oral taxane, given as a single-agent in patients (Pts) with HER2-, hormone receptor + (HR+) locally advanced or metastatic breast cancer (MBC) in a phase 2 study
Seidman AD, Schwartzberg LS, Gudena VK, et al.

- In patients with HER2-, HR+ ABC, single-agent tesetaxel showed a confirmed response rate of 45%, irrespective of previous exposure to taxanes
- Q3W oral dosing with low-grade neuropathy and alopecia may provide QoL advantages for ABC patients
- The Phase III registration study of tesetaxel (CONTESSA) is ongoing in patients with HER2-, HR+ ABC

Phase III multicentre, randomized study of utidelone plus capecitabine versus capecitabine alone for heavily pretreated, anthracycline- and taxane-refractory metastatic breast cancer
Binghe Xu, Zhang P, Sun T, et al.

- Utidelone + capecitabine significantly improved PFS (8.44 months vs 4.14 months [HR: 0.47; 95% CI: 0.37–0.59; p<0.0001), ORR and OS vs capecitabine alone in heavily pretreated patients with ABC
- The 2-year survival rate was 42% vs 32% for utidelone + capecitabine vs capecitabine alone: a significant increase of 10.7% (p=0.0389)
- Utidelone plus capecitabine increased OS without significant increases in myelosuppression or other AEs vs capecitabine alone

95% CI, 95% confidence interval; ABC, advanced breast cancer; AE, adverse event; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; Q3W, every 2 weeks.

A focus on other systemic therapies (2)

SANDPIPER and BOLERO-6

Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) v FULV in patients (pts) with estrogen receptor (ER)-positive, PIK3CA-mutant (MUT), locally advanced or metastatic breast cancer (MBC): Primary analysis from SANDPIPER
Baselga J, Dent SF, Cortés J, et al.

- Taselisib + fulvestrant significantly improved median PFS vs fulvestrant alone in PIK3CA-mutant tumours
  - 7.4 vs 5.4 months, respectively (HR: 0.7; 95% CI: 0.56–0.89; p=0.0037)
- Exploratory analysis of PFS suggests a treatment effect in patients without a detectable PIK3CA mutation cannot be completely ruled out
- Combination of taselisib + fulvestrant had an expected safety profile; the most common Grade ≥3 AEs were diarrhoea (12%), hyperglycaemia (10%), colitis (3%) and stomatitis (2%)

Everolimus (EVE) + exemestane (EXE) vs EVE alone or capecitabine (CAP) for estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC): BOLERO-6, an open-label phase 2 study
Jerusalem GHJ, Kovalenko E, Yardley DA, et al.

- A difference in PFS was observed for capecitabine vs everolimus + exemestane (9.6 vs 8.4 months; HR: 1.26; 90% CI: 0.96–1.66); potentially due to baseline characteristic imbalances favouring capecitabine
- Median OS was 23.1 months with everolimus + exemestane vs 29.3 months with everolimus alone (HR: 1.27; 90% CI: 0.95–1.70) and 25.6 months with capecitabine alone (HR: 1.33; 90% CI: 0.99–1.79)

90% CI, 90% confidence interval; 95% CI, 95% confidence interval; AE, adverse event; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

A focus on other systemic therapies (3)

Triple negative breast cancer

AZD5363 plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (PAKT): A randomised, double-blind, placebo-controlled, phase II trial
Schmid P, Abraham J, Chan S, et al.

- Median PFS was 5.9 months vs 4.2 months for AZD5363 + paclitaxel and placebo + paclitaxel, respectively (HR: 0.75; 95% CI: 0.52–1.08; p=0.06)
- In patients with PIK3CA/AKT1/PTEN-altered tumours, median PFS was 9.3 months vs 3.7 months, respectively (HR: 0.30; 95% CI: 0.11–0.79; p=0.01)
- Most common Grade ≥3 AEs for AZD5363 vs placebo included diarrhoea (12% vs 1%), infection (4% vs 1%), neutropenia (3% vs 3%), rash (4% vs 0%) and fatigue (4% vs 0%)

Overall survival (OS) update of the double-blind placebo (PBO)-controlled randomized phase 2 LOTUS trial of first-line ipatasertib (IPAT) + paclitaxel (PAC) for locally advanced/metastatic triple-negative breast cancer (mTNBC)
Dent R, Im S-A, Espie M, et al.

- Previously observed PFS improvements with ipatasertib were followed by a trend toward improved OS
  - ITT median OS was 23.1 vs 18.4 months for ipatasertib + paclitaxel and placebo + paclitaxel, respectively (HR: 0.62; 95% CI: 0.37–1.05)
- In patients with PIK3CA/AKT1/PTEN-altered tumours, PFS increased to 9.0 months vs 4.9 months with placebo (HR: 0.44; 95% CI: 0.20–0.99)

95% CI, 95% confidence interval; AE, adverse event; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival; PTEN, phosphatase and tensin homologue.

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ASCO 2018 – clinical trials in progress

CDK inhibitors

PADA-1: A randomized, open label, multicentric phase III trial to evaluate the safety and efficacy of palbociclib in combination with hormone therapy driven by circulating DNA *ESR1* mutation monitoring in ER-positive, HER2-negative metastatic breast cancer patients

Bidard FC, Sabatier R, Berger F, et al.

CDK inhibitor progression

BYLieve: A phase II study of alpelisib (ALP) with fulvestrant (FUL) or letrozole (LET) for treatment of *PIK3CA* mutant, hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (aBC) progressing on/after cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) therapy

Rugo HS, Bianchi GV, Chia SKL, et al.

Other systemic therapies

Contessa: A multinational, multicenter, randomized, phase 3 registration study of tesetaxel in patients (Pts) with HER2-, hormone receptor + (HR+) locally advanced or metastatic breast cancer (MBC)

O'Shaughnessy J, Piccart-Gebhart MJ, Schwartzberg LS, et al.

ER-positive, oestrogen-receptor positive; ESR1, oestrogen receptor 1; HER2-negative, human epidermal growth factor receptor 2 negative; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Summary

- Tesetaxel had a confirmed response rate of 45% in HR+/HER2- ABC[1]
  - Q3W oral dosing may provide QoL advantages for ABC patients
- Utidelone is the first microtubule inhibitor to demonstrate non-significant myelosuppression with a superior safety profile vs ixabepilone[2]
- Although SANDPIPER met its primary endpoint, the challenging tolerability of taselisib + fulvestrant may limit clinical benefit in this disease setting[3]
- In BOLERO-6, everolimus + exemestane provided a PFS benefit vs everolimus alone, supporting continued use in HR+/HER2- ABC patients progressing on NSAI therapy[4]
- For mTNBC, addition of AZD5363 to first-line paclitaxel therapy resulted in significantly longer PFS and OS; benefits were greater in patients with PIK3CA/AKT1/PTEN-altered tumours[5]
- An update to the LOTUS trial supports further evaluation of first-line ipatasertib + paclitaxel chemotherapy for PIK3CA/AKT1/PTEN-altered mTNBC or HR+/HER2- ABC in the ongoing IPATunity130 trial[6]
  - Final OS results from LOTUS are expected in 2019

ABC, advanced breast cancer; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; mTNBC, metastatic triple-negative breast cancer; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival; PTEN, Phosphatase and tensin homologue; QoL, quality of life; Q3W, every 3 weeks; TNBC, triple-negative breast cancer.

1. Seidman AD, Schwartzberg LS, Gudena VK, et al. 1042 – Activity of tesetaxel, an oral taxane, given as a single-agent in patients (Pts) with HER2-, hormone receptor + (HR+) locally advanced or metastatic breast cancer (MBC) in a phase 2 study. Presented at ASCO 2018; 2. Binghe Xu, Zhang P, Sun T, et al. 1003 – Phase III multicentre, randomized study of utidelone plus capecitabine versus capecitabine alone for heavily pretreated, anthracycline- and taxane-refractory metastatic breast cancer. Oral presentation at ASCO 2018; 3. Baselga J, Dent SF, Cortés J, et al. LBA1006 – Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) v FULV in patients (pts) with estrogen receptor (ER)-positive, PIK3CA-mutant (MUT), locally advanced or metastatic breast cancer (MBC): Primary analysis from SANDPIPER. Oral presentation at ASCO 2018. 4. Jerusalem GHJ, Kovalenko E, Yardley DA, et al. 1005 – Everolimus (EVE) + exemestane (EXE) vs EVE alone or capecitabine (CAP) for estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC): BOLERO-6, an open-label phase 2 study. Oral presentation at ASCO 2018. 5. Schmid P, Abraham J, Chan S, et al. 1007 – AZD5363 plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (PAKT): A randomised, double-blind, placebo-controlled, phase II trial. Oral presentation at ASCO 2018. 6. Dent R, Im S-A, Espie M, et al. 1008 – Overall survival (OS) update of the double-blind placebo (PBO)-controlled randomized phase 2 LOTUS trial of first-line ipatasertib (IPAT) + paclitaxel (PAC) for locally advanced/metastatic triple-negative breast cancer (mTNBC). Oral presentation at ASCO 2018.

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Summary – breaking data from ASCO 2018

CDK4/6 inhibitors

- PALOMA-2 and -3 outcomes show that palbociclib + ET is a standard of care option for HR+/HER2- ABC, regardless of treatment- or disease-free interval[1]
  - Palbociclib dose reductions do not impact PFS benefits[2]
- MONALEESA-7 results suggest that ribociclib-based may be used first-line in premenopausal women with HR+/HER2- ABC, regardless of prior chemotherapy[3]
- Abemaciclib + ET may significantly delay the need to initiate a subsequent chemotherapy[4]
- An efficacy benefit of abemaciclib + ET was observed in time to second disease progression or death, compared with placebo + ET[4]

ABC, advanced breast cancer; CDK, cyclin-dependent kinase; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; PFS, progression-free survival.

1. Finn RS, Cristofanilli M, Ettl J, et al. 1023 - Treatment effect of palbociclib (PAL) plus endocrine therapy (ET) by prognostic and intrinsic subtype: A joint analysis of PALOMA-2 and PALOMA-3. Presented at ASCO 2018; 2. Verma S, Im SA, Ro J, et al. 1060 – Hematologic adverse events following palbociclib (PAL) dose reduction in patients (pts) with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC): pooled analysis from randomized phase 2 and 3 studies. Presented at ASCO 2018; 3. Hurvitz SA, Wheatley-Price P, Tripathy D, et al. 1047 – Ribociclib (RIB) + tamoxifen (TAM) or a non-steroidal aromatase inhibitor (NSAI) in premenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC) who received prior chemotherapy (CT): MONALEESA-7 subgroup analysis. Presented at ASCO 2018; 4. Tolaney SM, Di Leo A, Llombart Cussac A, et al. 1048 – Impact of abemaciclib on the time to subsequent chemotherapy and the time to second disease progression across the MONARCH 2 and 3 studies. Presented at ASCO 2018.

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Summary – breaking data from ASCO 2018

Other systemic therapies

- Tesetaxel oral dosing may provide efficacy and QoL benefits in HR+/HER2- ABC[1]
- Utidelone demonstrates non-significant myelosuppression[2]
- The challenging tolerability of taselisib + fulvestrant may limit clinical benefit in this disease setting[3]
- Everolimus + exemestane provides PFS benefits vs everolimus alone, supporting use in HR+/HER2- ABC patients progressing on NSAI therapy[4]
- For mTNBC, first-line AZD5363 + paclitaxel resulted in significantly improved clinical outcomes, especially in PIK3CA/AKT1/PTEN-altered tumours[5]
- First-line ipatasertib + paclitaxel will be further evaluated for PIK3CA/AKT1/PTEN-altered mTNBC or HR+/HER2- ABC in the ongoing IPATunity130 trial[6]

ABC, advanced breast cancer; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; mTNBC, metastatic triple-negative breast cancer; NSAI, non-steroidal aromatase inhibitor; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival; PTEN, Phosphatase and tensin homologue; QoL, quality of life.

1. Seidman AD, Schwartzberg LS, Gudena VK, et al. 1042 – Activity of tesetaxel, an oral taxane, given as a single-agent in patients (Pts) with HER2-, hormone receptor + (HR+) locally advanced or metastatic breast cancer (MBC) in a phase 2 study. Presented at ASCO 2018; 2. Binghe Xu, Zhang P, Sun T, et al. 1003 – Phase III multicentre, randomized study of utidelone plus capecitabine versus capecitabine alone for heavily pretreated, anthracycline- and taxane-refractory metastatic breast cancer. Oral presentation at ASCO 2018; 3. Baselga J, Dent SF, Cortés J, et al. LBA1006 – Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) v FULV in patients (pts) with estrogen receptor (ER)-positive, PIK3CA-mutant (MUT), locally advanced or metastatic breast cancer (MBC): Primary analysis from SANDPIPER. Oral presentation at ASCO 2018; 4. Jerusalem GHJ, Kovalenko E, Yardley DA, et al. 1005 – Everolimus (EVE) + exemestane (EXE) vs EVE alone or capecitabine (CAP) for estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC): BOLERO-6, an open-label phase 2 study. Oral presentation at ASCO 2018; 5. Schmid P, Abraham J, Chan S, et al. 1007 – AZD5363 plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (PAKT): A randomised, double-blind, placebo-controlled, phase II trial. Oral presentation at ASCO 2018; 6. Dent R, Im S-A, Espie M, et al. 1008 – Overall survival (OS) update of the double-blind placebo (PBO)-controlled randomized phase 2 LOTUS trial of first-line ipatasertib (IPAT) + paclitaxel (PAC) for locally advanced/metastatic triple-negative breast cancer (mTNBC). Oral presentation at ASCO 2018.

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