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touchONCOLOGY – Leading the conversation in advanced breast cancer

On demand webinar: recorded in April 2018

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Supported by an unrestricted independent educational grant from Eli Lilly

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Disclosures

	Applicability	Company
(1) Advisory role	Yes	AstraZeneca, Bayer, Celgene, Daichii-Sankyo, Ipsen, Lilly, Novartis, Pfizer, Puma Biotechnology, Roche
(2) Stock ownership/profit	None	
(3) Patent royalties/licensing fees	None	
(4) Lecture fees	Yes	AstraZeneca, Eisai, Genomic Health, Novartis, Pfizer, Pierre Fabre, Roche
(5) Manuscript fees	None	
(6) Scholarship fund	None	
(7) Other remuneration	None	

Webinar overview

1

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

- Where are we now?
- Breaking data from AACR 2018
- Optimizing patient management

2

Focus on other pipeline therapies for advanced breast cancer

- Breaking data from AACR 2018

Please submit your questions throughout the presentation

AACR, American Association for Cancer Research; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

Where are we now?

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

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

Current criteria used to support first-line treatment choices in HR+/HER2- advanced breast cancer

	In favour of chemotherapy	Uncertain	In favour of endocrine therapy
Disease-free interval	<1 year	1–2 years	>2 years
Visceral metastases	Massive burden (visceral crisis)	Moderate burden	Minimal burden or absence
Symptoms	Heavy	Moderate	Minimal or absence

HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.
Adapted from the clinical experience and practice of Professor Di Leo.

Breaking data from AACR 2018

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

AACR, American Association for Cancer Research; CDK, cyclin-dependent kinase; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.

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PALOMA-3 and palbociclib

Palbociclib + fulvestrant significantly increased PFS vs. fulvestrant alone

- Phase III, double-blind study in 521 patients with HR+/HER2- advanced breast cancer, who relapsed or progressed with prior endocrine therapy
- Patients received either palbociclib + fulvestrant or placebo + fulvestrant
- Primary endpoint of median PFS was 9.2 vs. 3.8 months for palbociclib vs. placebo, respectively
  - HR for disease progression or death, 0.42; 95% CI, 0.32–0.56; p<0.001

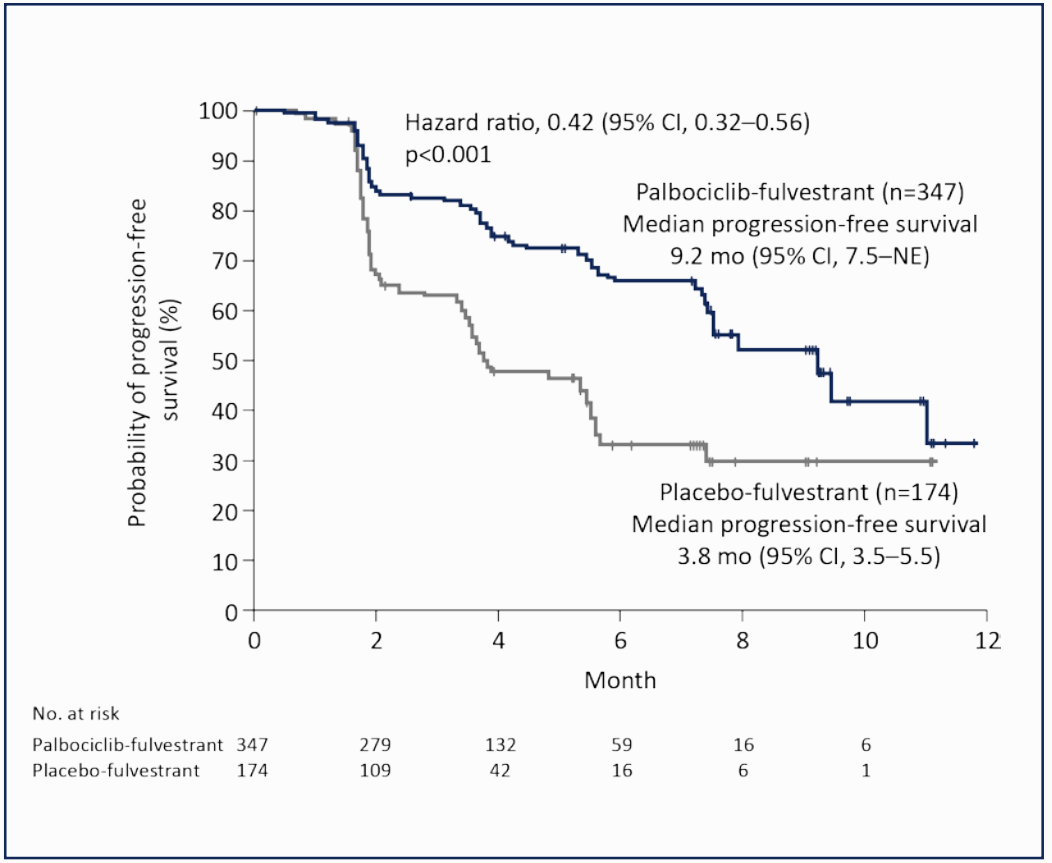

Figure reproduced from Turner et al., 2015

HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; mo., months; NE, not estimable; PFS, progression-free survival as assessed by the investigators in the intention-to-treat population (primary analysis). Premenopausal or perimenopausal women also received goserelin.

Turner N, Ro J, André F, et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. *N Engl J Med*. 2015;373(3):209-219.

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What's new with palbociclib at AACR?

CT039 - Cyclin E1 (CCNE1) expression associates with benefit from palbociclib in metastatic breast cancer in the PALOMA-3 trial

Turner N, Liu Y, Zhu Z, et al.

Subanalysis of PALOMA-3 to assess impact of CCNE1 expression on resistance to palbociclib + fulvestrant

- **Benefit from palbociclib + fulvestrant was greater in patients with low vs. high tumour CCNE1 expression**
  - Median PFS of 14.1 and 7.6 months, respectively; interaction p=0.0024
- **Levels of CDK4, CDK6, cyclin D1 and RB were not associated with increased benefit**
- **In exploratory analysis, high E2F activation was associated with relative resistance to palbociclib**

- Low expression of CCNE1 was predictive of benefit; high expression of CCNE1 was associated with relative resistance to palbociclib
- The CCNE1 association was stronger in metastatic tissue than primary tissue
- CCNE1 and CDK2 are the key bypass kinases of CDK4/6

AACR, American Association for Cancer Research; CCNE1, cyclin E1; CDK, cyclin-dependent kinase; E2F, transcription factor; PFS, progression-free survival; RB, retinoblastoma protein.

MONALEESA-2 and ribociclib

Ribociclib + letrozole significantly increased PFS vs. letrozole alone

- Phase III, double-blind study in 668 postmenopausal women with HR+/HER2- breast cancer, without prior treatment for advanced disease
- Patients received either ribociclib + letrozole or placebo + letrozole
- Primary endpoint of median PFS was not reached for palbociclib vs. 14.7 months for placebo
  - HR for disease progression or death, 0.56; 95% CI, 0.43–0.72; p<0.0001

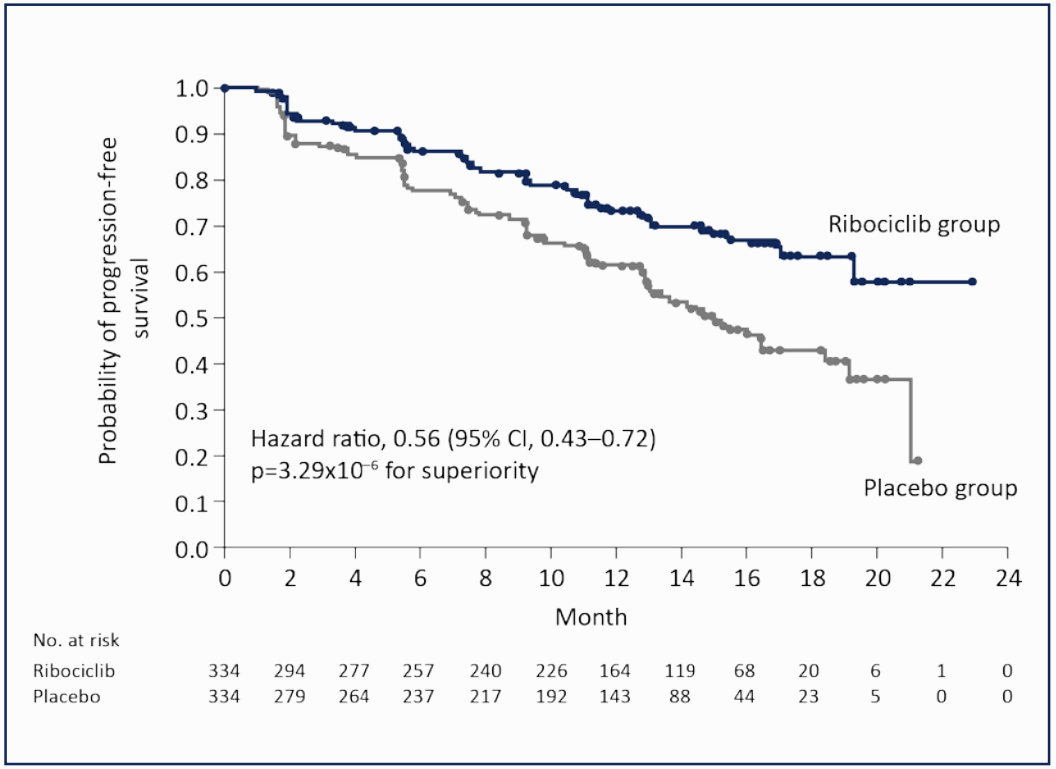

Figure reproduced from Hortobagyi et al., 2016

PFS was not reached for palbociclib (19.3 months to not reached) vs. 14.7 months for placebo (13.0 to 16.5 months)

HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; PFS, progression-free survival as assessed by the investigators in the intention-to-treat population (primary analysis).

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(18):1738-1748.

What's new with ribociclib at AACR?

CT107 / 28 - Ribociclib in combination with everolimus and exemestane in men and postmenopausal women with HR+/HER2- advanced breast cancer after progression on a CDK4/6 inhibitor: Efficacy and safety results from phase II of the TRINITI-1 study
Moulder S, Karuturi M, Yardley D, et al.

Efficacy and safety results from TRINITI-1 in patients with HR+/HER2- ABC with disease progression following ≤3 lines of therapy; including a CDK4/6 inhibitor

- **At week 24, 39.5% of patients (n=17) had clinical benefit with continuous ribociclib + EVE + EXE***
  - ORR was 7.0% (n=3); median PFS was 8.8 months (95% CI, 1.9 months-not evaluable)
- **Common AEs (≥25%) included neutropenia (68.2%), stomatitis (45.5%), fatigue (38.6%), nausea (34.1%), thrombocytopenia (34.1%), diarrhoea (29.5%), and anaemia (25.0%)**
- **Neutropenia was the most common Grade 3 AE (52.3%)**

- First trial suggesting the benefit and tolerability of continuous ribociclib, EVE, and EXE after progression on a CDK4/6 inhibitor
- No new safety signals were observed vs. previous trials of ribociclib, EVE, or EXE

*Ribociclib 300 mg/day + EVE 2.5 mg/day + EXE 25 mg/day
AACR, American Association for Cancer Research; ABC, advanced breast cancer; AEs, adverse events; CDK, cyclin-dependent kinase; EVE, everolimus; EXE, exemestane; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; PFS, progression-free survival.

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MONARCH-2 and abemaciclib

Abemaciclib + fulvestrant significantly increased PFS vs. fulvestrant alone

- Phase III, double-blind study in 669 women of any menopausal status with HR+/HER2- advanced breast cancer, who had progressed on endocrine therapy
- Patients received either abemaciclib + fulvestrant or placebo + fulvestrant
- Primary endpoint of median PFS was 16.4 vs. 9.3 months for abemaciclib vs. placebo, respectively
  - HR for disease progression or death, 0.55;
    95% CI, 0.45–0.68; p<0.001

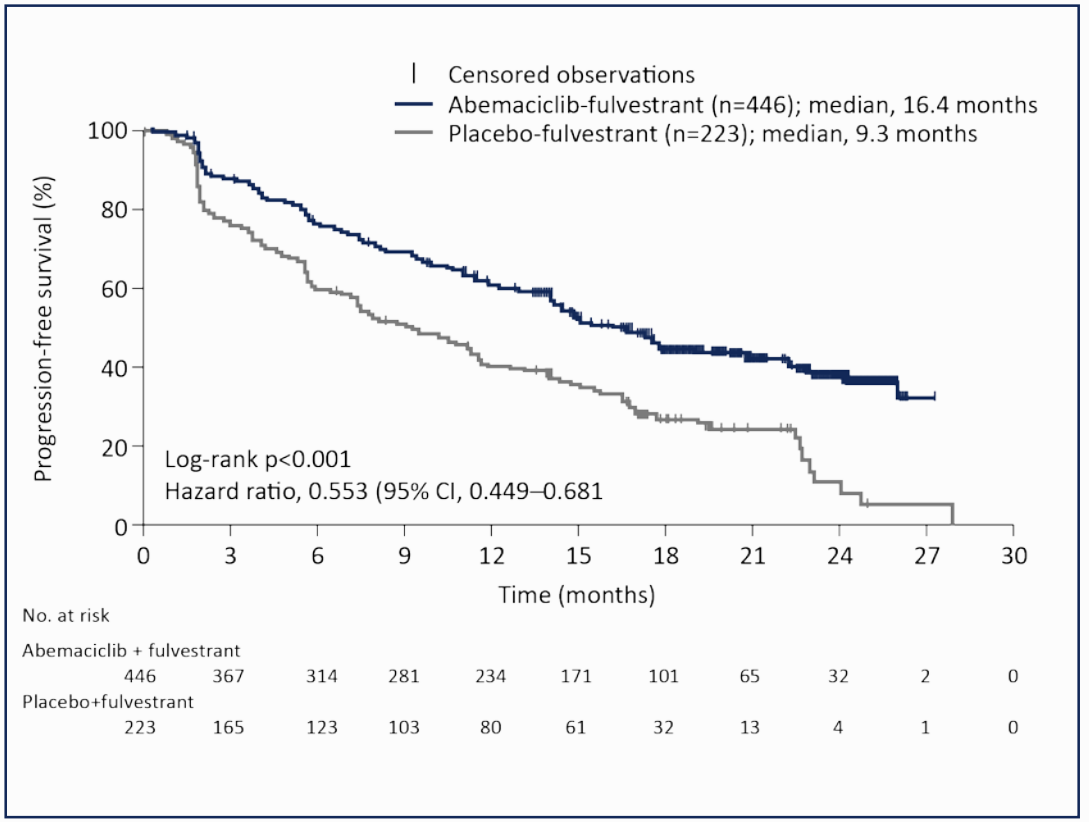

Figure reproduced from Sledge et al., 2017

HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; PFS, progression-free survival as assessed by the investigators in the intention-to-treat population (primary analysis).

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(25):2875-2884.

MONARCH-3 and abemaciclib

Abemaciclib + AI significantly increased PFS vs. AI alone

- Phase III, double-blind study in 493 postmenopausal women with HR+/HER2- advanced breast cancer, previously treated with endocrine therapy
- Patients received either abemaciclib + AI or placebo + AI
- Primary endpoint of median PFS was not reached for abemaciclib vs. 14.7 months for placebo
  - HR for disease progression or death, 0.54; 95% CI, 0.41–0.72; p<0.0001

Final MONARCH-3 PFS data were presented at AACR 2018

AI, aromatase inhibitor; HER2-, human epidermal growth factor receptor 2 negative; HR, Hazard ratio; HR+, hormone receptor positive; PFS, progression-free survival as assessed by the investigators in the intention-to-treat population (primary analysis).

Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as Initial Therapy for Advanced Breast Cancer. J Clin Oncol. 2017;35(32):3638-3646.

What's new with abemaciclib at AACR?

CT040 - MONARCH 3: Abemaciclib as initial therapy for patients with HR+/HER2- advanced breast cancer - Results from the pre-planned final PFS analysis
Goetz M, Martin M, Di Leo A, et al.

Final pre-planned efficacy results from MONARCH-3 of postmenopausal women with HR+/HER2- ABC who received no prior systemic therapy

- **Abemaciclib + AI significantly extended median PFS vs. placebo + AI**
  - 28.2 vs. 14.8 months, respectively; HR, 0.54; 95% CI, 0.418-0.698; p=0.000002
- **ORR was 61.0% with abemaciclib vs. 45.5% for placebo (p=0.003)**
  - CBR was 79.0% and 69.7%, respectively (p=0.037)
- **Median DoR with abemaciclib was 27.4 months vs. 17.5 months with placebo – OS was not mature at the time of analysis**
- **Safety profile was consistent with other abemaciclib studies**

- Responses generally occurred early, were maintained over time, and led to substantial tumour shrinkage
- AEs of diarrhoea did not affect median PFS in patients receiving abemaciclib

AACR, American Association for Cancer Research; ABC, advanced breast cancer; AI, aromatase inhibitor; CBR, clinical benefit rate; DoR, duration of response; HER2-, human epidermal growth factor receptor 2 negative; HR, Hazard ratio; HR+, hormone receptor positive; OS, overall survival; PFS, progression-free survival.

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What's new with abemaciclib at AACR?

CT099 / 20 - The benefit of abemaciclib in prognostic subgroups: An update to the pooled analysis of MONARCH 2 and 3

O'Shaughnessy J, Goetz M, Sledge G, et al.

Pooled analysis of pre-planned PFS data from MONARCH-2 and -3 to identify significant prognostic factors for worse outcome regardless of therapy received

- **Patients with prognostic factors for progression received the greatest benefit from abemaciclib + AI vs. endocrine therapy alone**
- **Bone-only disease, liver metastases, tumour grade, PgR status, and ECOG PS remained significantly prognostic, regardless of regimen**
- **Patients with a shorter TFI had a worse prognosis and received relatively greater benefit from abemaciclib + AI vs. those with a longer interval**

- Adding abemaciclib to endocrine therapy may provide relatively greater benefit for patients with poor prognostic factors
- Data may provide insight for developing personalized therapy for women with HR+/HER2- ABC
- In bone-only disease and/or TFI ≥3 years, endocrine therapy alone may be considered as a reasonable first-line therapy

AACR, American Association for Cancer Research; ABC, advanced breast cancer; AI, aromatase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; PgR, progesterone receptor; TFI, disease-free/treatment-free interval.

Optimizing patient management

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

CDK, cyclin-dependent kinase.

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Safety outcomes with CDK 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; 375:1925-1936; 2. Turner N, Ro J, André F, et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. *N Engl J Med*. 2015;373(3):209-219; 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(18):1738-1748; 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(25):2875-2884; 5. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as Initial Therapy for Advanced Breast Cancer. *J Clin Oncol*. 2017;35(32):3638-3646.

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Side-effect management in clinical practice

Implications for tailored monitoring of patients treated with CDK inhibitors

	Palbociclib	Ribociclib	Abemaciclib*
Haemogram q2w during the first 2-4 cycles → q4w	+	+	+
Liver biochemistry q4w	-	+	+
Creatinine q4w	-	-	+
ECG q2w during the first 2 cycles	-	+	-

*Pro-active strategy to manage diarrhoea.
CDK, cyclin-dependent kinase; ECG, electrocardiogram; q2w, every 2 weeks; q4w, every 4 weeks.
Adapted from the clinical experience and practice of Professor Di Leo.

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What do CDK inhibitors mean for patients?

Patient management and treatment sequencing

Robust evidence of prolonged PFS with upfront combination[1-5]

- Lack of cross-over in the first-line Phase III trials
- Activity of CDK4/6 inhibition in pre-treated patients

Subgroups where single-agent HT may still be an option[6]

- Bone-only disease
- Treatment-free interval ≥3 years

CDK, cyclin-dependent kinase, HT, hormone therapy; 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; 375:1925-1936; 2. Turner N, Ro J, André F, et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. *N Engl J Med*. 2015;373(3):209-219; 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(18):1738-1748; 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(25):2875-2884; 5. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as Initial Therapy for Advanced Breast Cancer. *J Clin Oncol*. 2017;35(32):3638-3646; 6. O'Shaughnessy J, Goetz M, Sledge G, et al. CT099 / 20 - The benefit of abemaciclib in prognostic subgroups: An update to the pooled analysis of MONARCH 2 and 3. Presented at AACR 2018.

Breaking data from AACR 2018

Focus on other pipeline therapies for advanced breast cancer

AACR, American Association for Cancer Research.

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A focus on other therapies (1)

CDK inhibitors and immunotherapy

CDK inhibitors

Session CTMS01 - New Treatment Approaches for Breast and Ovarian Cancer

CT037 - Phase I safety, pharmacokinetic and pharmacodynamic study of CYC065, a cyclin dependent kinase inhibitor, in patients with advanced cancers (NCT02552953)

Do K, Chau N, Wolanski A, et al.

- CYC065 is a selective inhibitor of CDK2 and CDK9
- Dose escalation study (n=26, mainly ovarian cancer)
- Grade 3/4 adverse events were mainly haematological
- Stable disease was the best response (11/20 patients; 6 with stable disease >6 months)

Immunotherapy for HR+/HER2-

Session PO.CT05 - Phase I/II, II, and III Trials in Progress

CT152 / 4 - A phase II study of pembrolizumab and eribulin in patients with HR-positive/HER2-negative metastatic breast cancer previously treated with anthracyclines and taxanes (KELLY study)

Pérez García J, Llombart A.

- Study design describing the KELLY trial – an open-label, non-randomized Phase IIA study
- Planned to examine the efficacy of pembrolizumab + eribulin in HR+/HER2- mBC
- Patients will have received prior therapy with an anthracycline and a taxane
- The primary objective is CBR; secondary outcomes comprise ORR, DoR, PFS, and OS
- A total of 44 patients are planned for accrual

CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DoR, duration of response; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

A focus on other therapies (2)

PARP inhibitors

PARP inhibitor for HER2- and gBRCAm
Session CTMS01 - New Treatment Approaches for Breast and Ovarian Cancer
CT038 - OlympiAD final overall survival: Olaparib versus chemotherapy treatment of physician's choice (TPC) in patients with HER2-negative metastatic breast cancer (mBC) and a germline BRCA mutation (gBRCAm)
Robson M, Im S-A, Senkus E.

- Median OS was 2.2 months longer for olaparib monotherapy vs. TPC in overall population
- The Phase III OlympiAD study was not powered to demonstrate differences in OS between vs. TPC
- Potential greater benefit in patients with no prior chemotherapy for mBC
  - Median OS: 22.6 for olaparib vs. 14.7 months for TPC; HR 0.51, 95% CI, 0.29-0.90, p=0.02

gBRCAm, germline BRCA mutation; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; mBC, metastatic breast cancer; OS, overall survival; PARP, poly ADP ribose polymerase; TPC, treatment of physician's choice.

Summary - new clinical study data from AACR 2018

- Low CCNE1 expression is predictive of clinical benefit in patients receiving palbociclib + fulvestrant[1]
- Abemaciclib + AI significantly extended median PFS vs. placebo + AI[2]
  - Safety profile consistent with other abemaciclib studies
- Combined prognostic factors analysis of MONARCH-2 and -3[3]
  - Patients with bone-only disease and/or TFI ≥3 years may potentially receive single-agent endocrine therapy in the first-line setting
- The TRINITI-1 study is the first trial to show the benefits of continuous ribociclib, EVE, and EXE following CDK4/6 progression[4]
- Selective inhibition of CDK2/9 is a potential treatment target[5]
- The PARP inhibitor olaparib showed a greater OS benefit in patients without prior chemotherapy[6]
- The KELLY study will examine efficacy of pembrolizumab + eribulin[7]

AACR, American Association for Cancer Research; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; EVE, everolimus; EXE, exemestane; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; mBC, metastatic breast cancer; OS, overall survival; PARP, poly ADP ribose polymerase; PFS, progression-free survival; TFI, disease-free/ treatment-free interval.

1. Turner NC, Liu Y, Zhu Z, et al. CT039 - Cyclin E1 (CCNE1) expression associates with benefit from palbociclib in metastatic breast cancer (MBC) in the PALOMA-3 trial. Presented at AACR 2018; 2. Goetz MP, Martin M, Di Leo A, et al. CT040 - MONARCH 3: Abemaciclib as initial therapy for patients with HR+/HER2- advanced breast cancer - Results from the pre-planned final PFS analysis. Presented at AACR 2018; 3. O'Shaughnessy J, Goetz MP, Sledge GW, et al. CT099 / 20 - The benefit of abemaciclib in prognostic subgroups: An update to the pooled analysis of MONARCH 2 and 3. Presented at AACR 2018; 4. Moulder S, Karuturi M, Yardley D, et al. CT107 / 28 - Ribociclib in combination with everolimus and exemestane in men and postmenopausal women with HR+/HER2- advanced breast cancer after progression on a CDK4/6 inhibitor: Efficacy and safety results from phase II of the TRINITI-1 study. Presented at AACR 2018; 5. Do KT, Chau N, Wolanski A, et al. CT037 - Phase I safety, pharmacokinetic and pharmacodynamic study of CYC065, a cyclin dependent kinase inhibitor, in patients with advanced cancers (NCT02552953). Presented at AACR 2018; 6. Robson ME, Im S-A, Senkus E. CT038 - OlympiAD final overall survival: Olaparib versus chemotherapy treatment of physician's choice (TPC) in patients with HER2-negative metastatic breast cancer (mBC) and a germline BRCA mutation (gBRCAm). Presented at AACR 2018; 7. Pérez García J, Llombart A. CT152 / 4 - A phase II study of pembrolizumab and eribulin in patients with HR-positive/HER2-negative metastatic breast cancer previously treated with anthracyclines and taxanes (KELLY study). Presented at AACR 2018.

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Question time

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