

2019
CARCINOMA MAMMARIO

I TRAGUARDI RAGGIUNTI E LE NUOVE SFIDE.

ROMA 4 - 5 OTTOBRE
STARHOTELS METROPOLIS



“Ormonoterapia e associazione con CDK 4/6 inhibitors: quali novità?”

Prof. Marina E Cazzaniga

UOC Centro di Ricerca Fase 1

ASST Monza & Milano Bicocca School of Medicine and Surgery

Contents

- 1. Are all the CDK 4/6 created equal?**
 - ✓ .. And provide same results?
- 2. Survival data of randomized clinical trials: the end of the story?**
 - ✓ .. Or the begin of new questions?
- 3. The unanswered questions and the unmet clinical needs**

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Are all the CDK 4/6 created equal ?

(..and are the treated populations similar?)

ENDOCRINE RESISTANT

< 12 months from adj 22.3%

ENDOCRINE SENSITIVE

De novo 37%

> 12 months from adj 40%

ENDOCRINE RESISTANT

< 12 & 12-24 months 5.6%

ENDOCRINE SENSITIVE

De novo 34.1%

> 12 months from adj 60.5%

ENDOCRINE RESISTANT

DFI (from diagnosis) </= 12 months 7%

ENDOCRINE SENSITIVE

De novo 40%

DFI (from diagnosis) > 12 months 53%

ENDOCRINE SENSITIVE

No adj 34%

TFI > 36 months 62%

TFI < 36 months 28%

PALOMA-2

MONALEESA-2

MONALEESA-7

MONARCH-3

PFS (HR)

0.58

Visceral

0.63[^]

Non-visceral

0.50

Bone-only

--

0.56

0.57^{^^}

--

0.69

ORR

42.1%

40.7%

CBR

84.9%

79.6%

0.43

MAINLY ENDOCRINE SENSITIVE

MONALEESA-2

MONARCH-3

MONALEESA-7

ENDOCRINE SENSITIVE + RESISTANT

PALOMA-2

Finn, 2016; Hortobagyi, 2016; Goetz 2017; Tripathy 2018

[^]Not defined

^{^^}Liver or lung

[^]Liver or lung

^{^^}Liver or lung

CDK 4/6 inhibitors in a prospective view

ENDOCRINE SENSITIVITY

PRIMARY ENDOCRINE RESISTANCE
(relapse during adj or < 12/24 mos
relapse < 6mos 1L)

SECONDARY ENDOCRINE RESISTANCE
(relapse > 24 mos
relapse > 6mos 1L)

PALOMA-2

77%

22%

Median PFS 27.6 mos

MONARCH-3

100%

Median PFS 28.2 mos

MONALEESA-2

94.5%

5.6%

Median PFS 25.3 mos

MONALEESA-7

93%

7%

Median PFS 23.8 mos

Contents

1. Are all the CDK 4/6 created equal?
2. **Survival data of randomized clinical trials: the end of the story?**
3. The unanswered questions and the unmet clinical needs

OS: still remains an important aim?

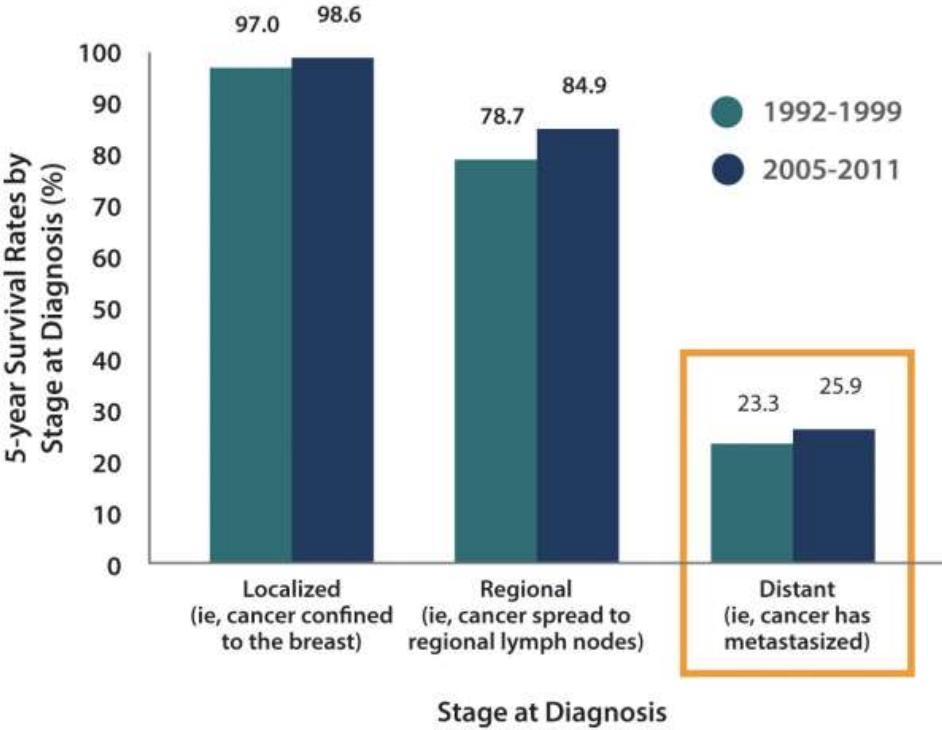
ABC Global Charter 10 goals for the next 10 years



COMPREHENSIVE NEEDS ASSESSMENT

DEFINES MOST URGENT AND ACTIONABLE GOALS

Done with (almost) all different stakeholders involved in ABC

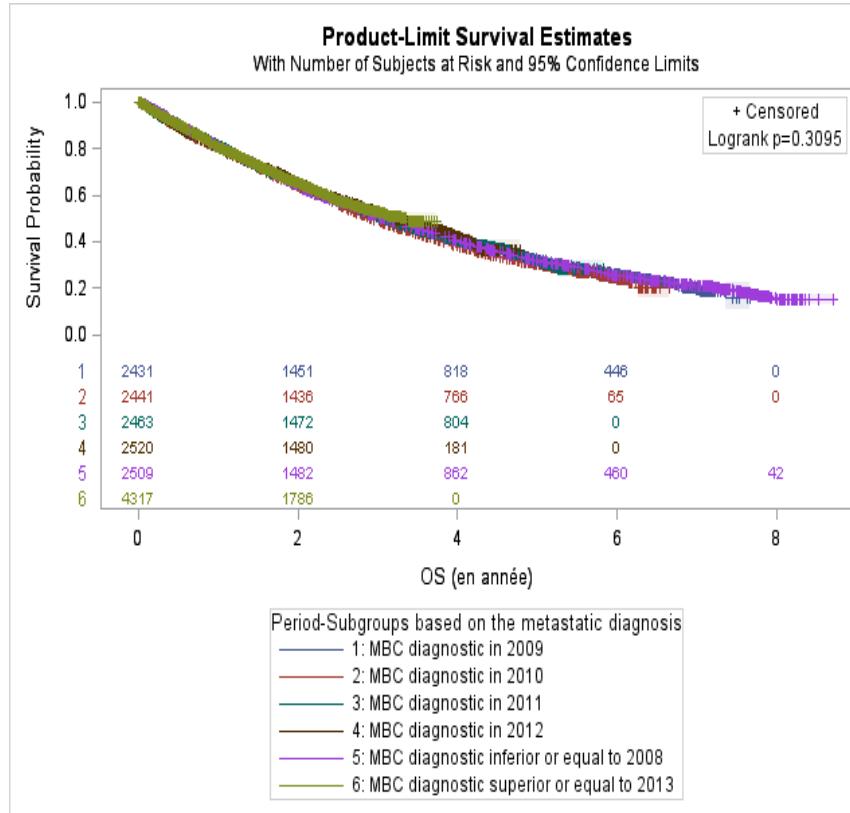


- 1 HELP PATIENTS WITH ABC LIVE LONGER BY DOUBLING ABC MEDIAN OVERALL SURVIVAL BY 2025
- 2 ENHANCE OUR UNDERSTANDING ABOUT ABC BY INCREASING THE COLLECTION OF HIGH QUALITY DATA
- 3 IMPROVE THE QUALITY OF LIFE (QOL) OF PATIENTS WITH ABC
- 4 ENSURE THAT ALL PATIENTS WITH ABC RECEIVE THE BEST POSSIBLE TREATMENT AND CARE BY INCREASING AVAILABILITY OF ACCESS TO CARE FROM A MULTIDISCIPLINARY TEAM
- 5 IMPROVE COMMUNICATION BETWEEN HEALTHCARE PROFESSIONALS (HCP) AND PATIENTS WITH ABC THROUGH THE PROVISION OF COMMUNICATION SKILLS TRAINING FOR HCPs
- 6 MEET THE INFORMATIONAL NEEDS OF PATIENTS WITH ABC BY USING EASY TO UNDERSTAND, ACCURATE AND UP-TO-DATE INFORMATION MATERIALS AND RESOURCES
- 7 ENSURE THAT PATIENTS WITH ABC ARE MADE AWARE OF AND ARE REFERRED TO NON-CLINICAL SUPPORT SERVICES
- 8 COUNTERACT THE STIGMA AND ISOLATION ASSOCIATED WITH LIVING WITH ABC BY INCREASING PUBLIC UNDERSTANDING OF THE CONDITION
- 9 ENSURE THAT PATIENTS WITH ABC HAVE ACCESS TO TREATMENT REGARDLESS OF THEIR ABILITY TO PAY
- 10 HELP PATIENTS WITH ABC CONTINUE TO WORK BY IMPLEMENTING LEGISLATION THAT PROTECTS THEIR RIGHTS TO WORK AND ENSURE FLEXIBLE AND ACCOMMODATING WORKPLACE ENVIRONMENTS

Evolution of OS over time

Observed Overall Survival From Diagnosis of Metastatic Disease All Patients

National cohort of 19.898
MBC pts diagnosed between
01/2008 and 12/2016 and
treated in 18 Comprehensive
Cancer centers



Median FU for the whole cohort is 4.05 yrs [95 CI: 3.98-4.12]

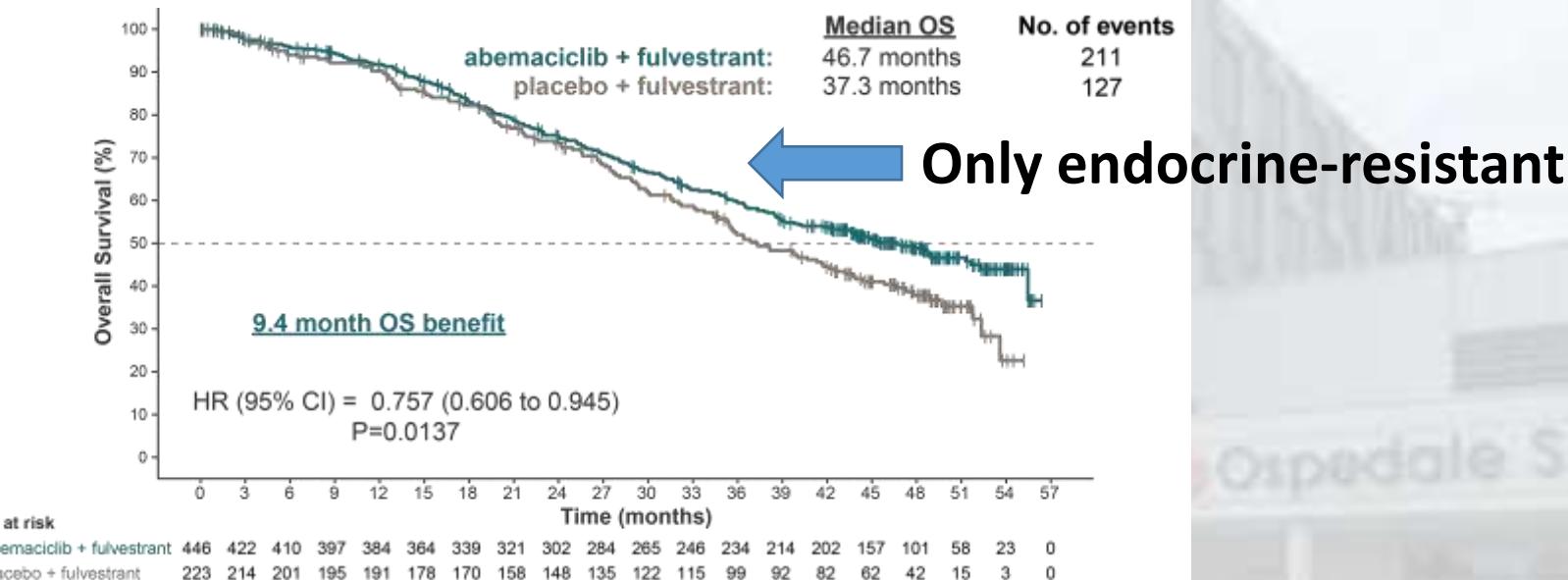
Period	2008	2009	2010	2011	2012	2013
Median OS	3.12	2.94	3.09	3.23	3.09	3.29
(95% CI)(yrs)	[2.92-3.31]	[2.78-3.09]	[2.94-3.24]	[3.02-3.48]	[2.89-3.25]	[3.09-ND]

Overall Survival data – the end of the story?

Barcelona
2019 ESMO congress

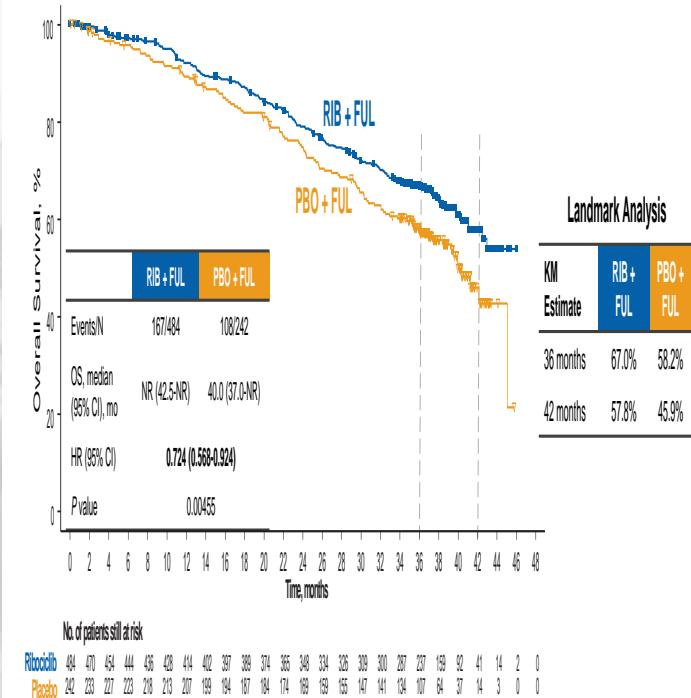
OVERALL SURVIVAL

Monarch-2



Overall Survival MONALEESA-3

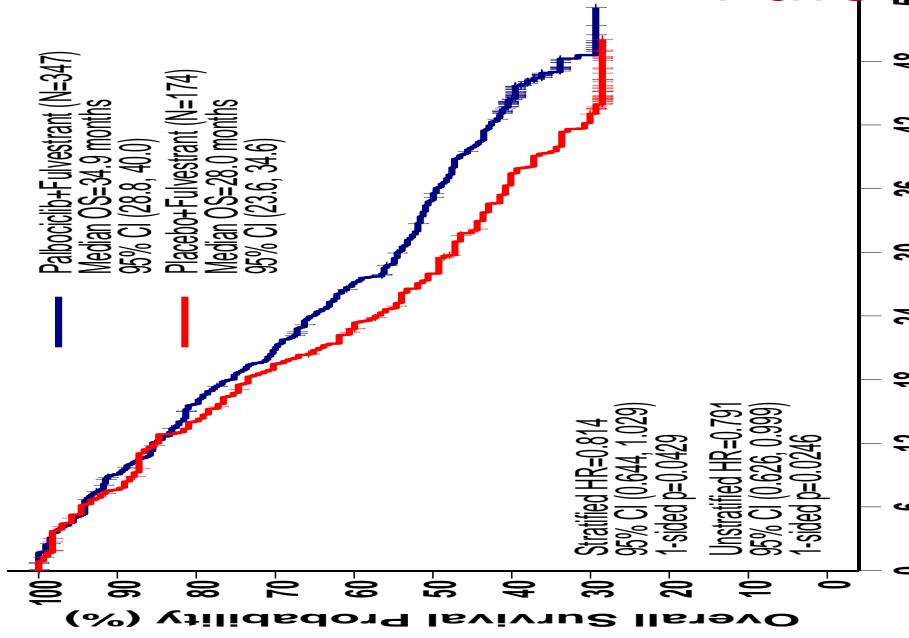
The relative reduction in risk of death with RIB was 28%



- The P value of 0.00455 crossed the prespecified boundary to claim superior efficacy ($P < 0.01129$)

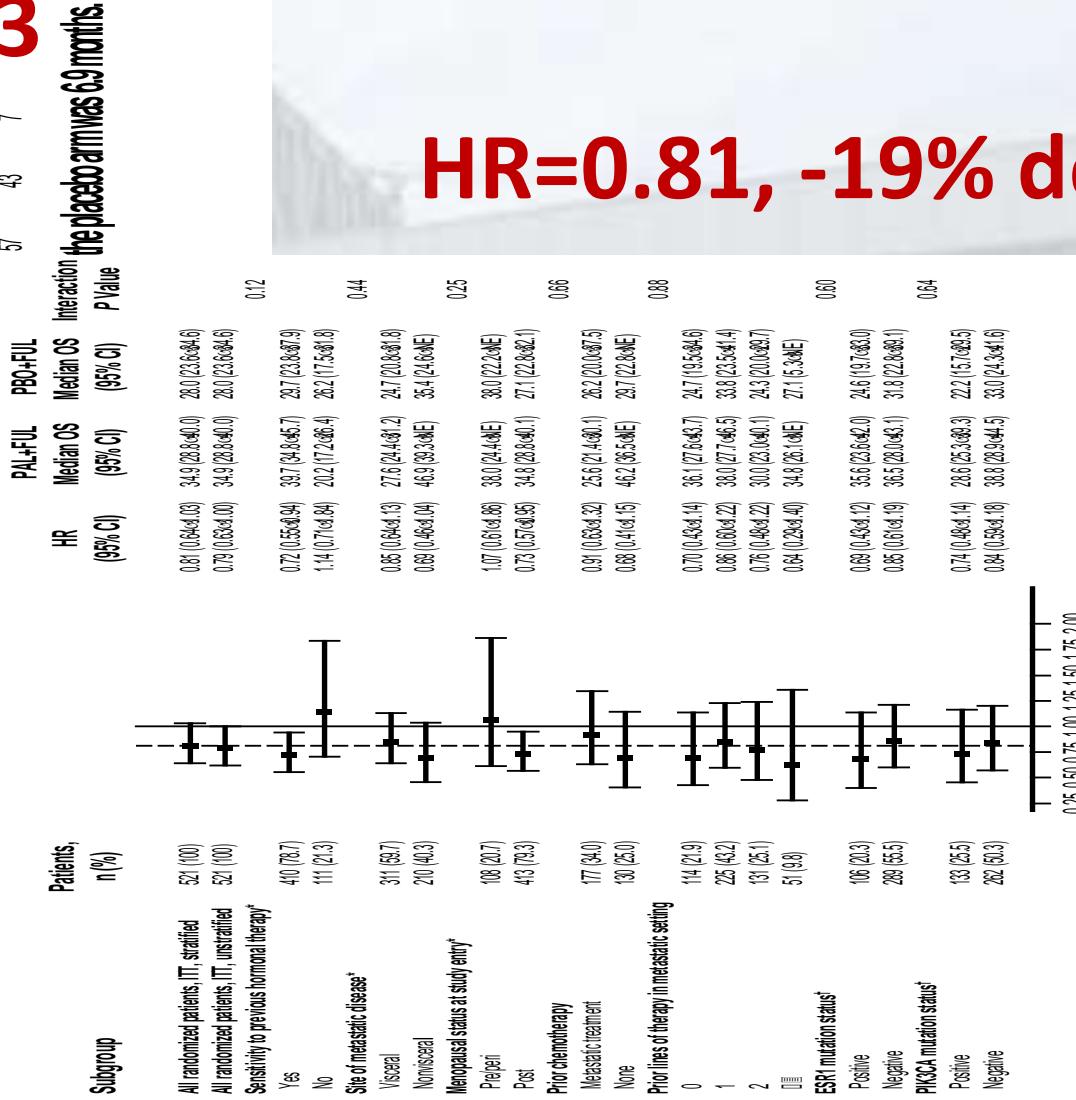
OS data: the end of the story?

OVERALL SURVIVAL (OS)



Paloma-3

OVERALL SURVIVAL BY SUBGROUPS



HR=0.81, -19% deaths

PALOMA-3 STATISTICAL ANALYSIS

- **The PALOMA-3 study was adequately powered for the primary endpoint, PFS, but not for the secondary endpoint OS.**
- With a hierarchical testing strategy between PFS and OS, two interim OS analyses were conducted at 28 and 112 events after significant PFS outcomes were observed.
- Planned final OS analysis was performed at 310 events from 521 randomized patients with median follow-up of 44.8 months and approximately 60% data maturity.
- The prespecified significance threshold was 1-sided 0.0235, which was adjusted for the planned 2 interim analyses to preserve the family-wise error rate at the 1-sided 0.025 level.
- The RPSFT method was used as a sensitivity analysis to evaluate the impact of poststudy crossover to receive a CDK4/6 inhibitor in the PBO plus FU_L arm.

- **STOP ACCEPTING PFS BENEFIT ALONE AS THE MAIN GOAL**

- **OS MUST BE AT LEAST A CO-PRIMARY**

Cristofanilli et al, ESMO 2018

- **INVEST IN LESS BUT “BIGGER” (SUFFICIENTLY POWERED) TRIALS**

- **COLLECT POST-PROGRESSION DATA**

- **USE REAL WORLD DATA**

REVIEWS

The value of progression-free survival to patients with advanced-stage cancer

Journal of Clinical Oncology, Volume 37, Number 13, April 10, 2019
DOI: 10.1200/JCO.2018.80 1000 © 2019 by American Society of Clinical Oncology, Inc.
Abstract: Progression-free survival (PFS) has been considered as a surrogate marker for overall survival (OS). The advantage of PFS over OS is that it can be measured earlier than OS, which is often applied in intermediate and early diseases. The effect of PFS on prognosis has been well studied in breast cancer, especially in early-stage disease, and recently PFS has been used as a primary outcome in phase III trials. In contrast, the effect of PFS on prognosis has been less well studied in advanced-stage cancer. In this article, we review the role of PFS in advanced-stage cancer and its relationship with overall survival (OS). We highlight specific results in the following: (1) prognostic factors in advanced-stage cancer; (2) comparison of PFS and OS in advanced-stage cancer; (3) treatment effect on PFS and OS; (4) treatment effect on PFS and OS in different cancer types; (5) treatment effect on PFS and OS in different cancer stages; and (6) treatment effect on PFS and OS in different cancer sites. We conclude that PFS is a useful marker for advanced-stage cancer, but it is not sufficient to predict OS. In addition, PFS is not always a good marker for OS, especially in some cancers such as glioma, where PFS is longer than OS. Therefore, PFS and OS should be used together to predict survival in advanced-stage cancer.

**Phase III MONALEESA-7 Trial of Premenopausal
Patients With HR+/HER2- Advanced Breast
Cancer Treated With Endocrine Therapy
Ribociclib: Overall Survival Results**

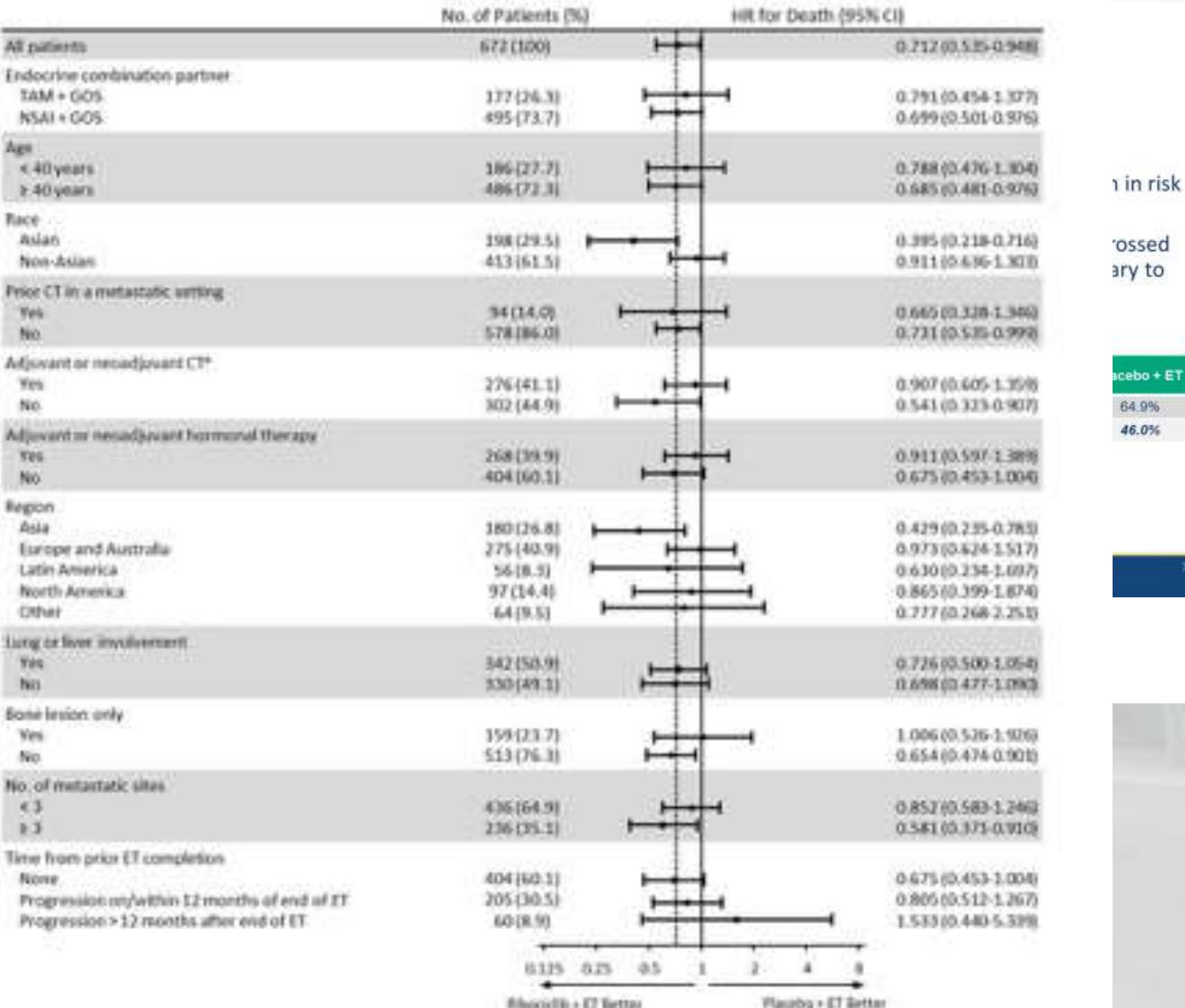
Sara Hurvitz,¹ Seock-Ah Im,² Yen-Shen Lu,³ Marco Colleoni,⁴ Fabio Franke,⁵ Aditya Harbeck,⁷ Louis Chow,⁶ Joohyuk Sohn,⁸ Keun Seok Lee,¹⁰ Saul Campos-Gomez,¹¹ Vazquez,¹² Kyung Hae Jung,¹³ Arunava Chakravarty,¹⁴ Gareth Hughes,¹⁵ Ioannis Rodriguez Lorenc,¹⁴ Tetiana Taran,¹⁴ Debu Tripathy¹⁶

¹MD Anderson Comprehensive Cancer Center, Houston, TX; ²Seoul National University Hospital, Seoul, South Korea; ³Institute of Medical Genetics, University Hospital Zurich, Zurich, Switzerland; ⁴Medical University of Innsbruck, Innsbruck, Austria; ⁵Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain; ⁶Universitaet Regensburg, Regensburg, Germany; ⁷Karlsruhe Institute of Technology, Karlsruhe, Germany; ⁸Yonsei University College of Medicine, Seoul, South Korea; ⁹Yonsei University Hospital, Seoul, South Korea; ¹⁰Yonsei University College of Medicine, Seoul, South Korea; ¹¹Yonsei University College of Medicine, Seoul, South Korea; ¹²Yonsei University College of Medicine, Seoul, South Korea; ¹³Yonsei University College of Medicine, Seoul, South Korea; ¹⁴Yonsei University College of Medicine, Seoul, South Korea; ¹⁵Yonsei University College of Medicine, Seoul, South Korea; ¹⁶Johns Hopkins University, Baltimore, MD, USA

MONALEESA-7

Overall Survival Subgroup Analysis

- Consistent OS benefit seen within subgroups

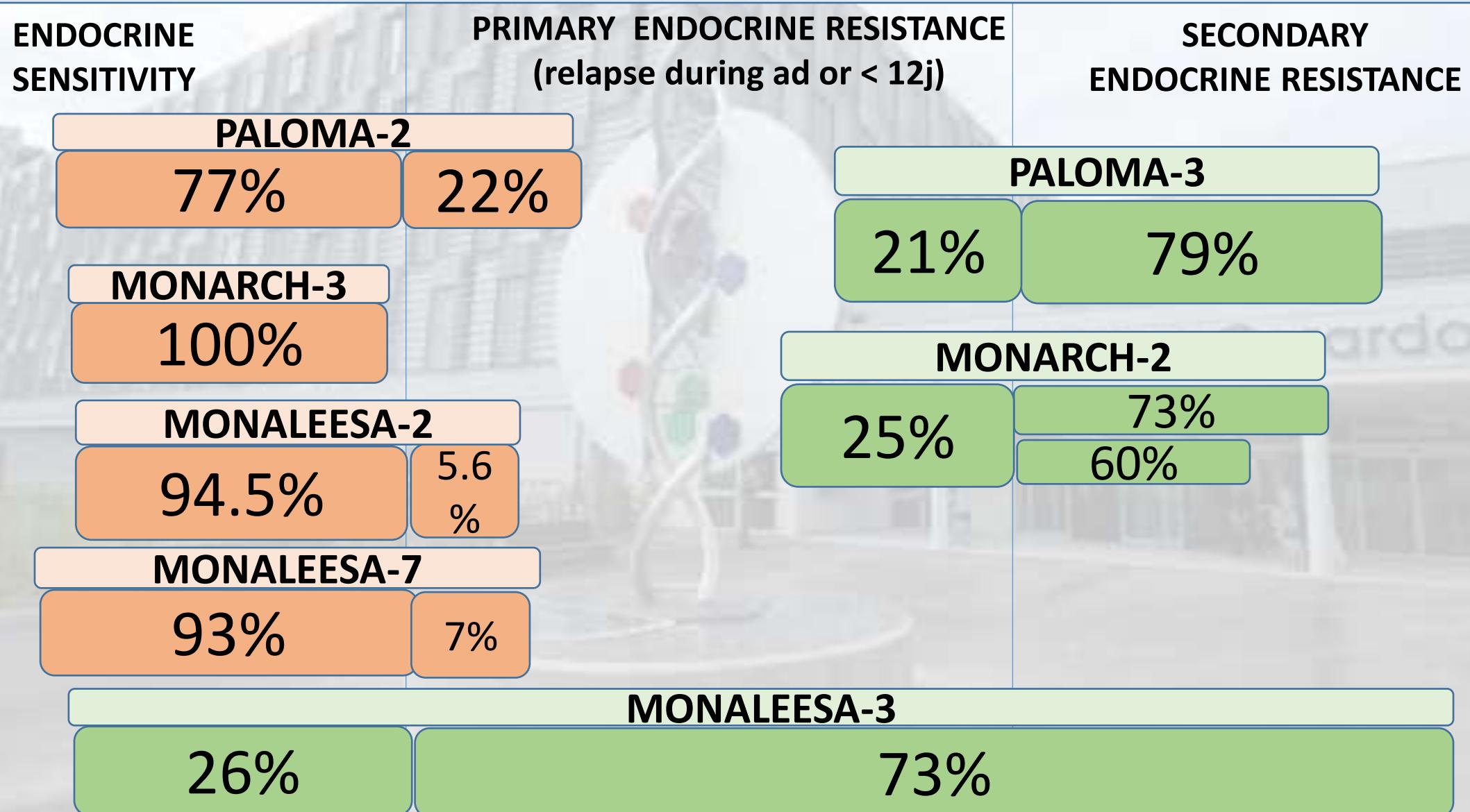


PRESENTED AT: 2019 ASCO ANNUAL MEETING

#ASCO19
July 20-24, 2019, Chicago, IL, USA

PRESENTED BY:

CDK 4/6 inhibitors in a prospective view



PALOMA-3 STATISTICAL ANALYSIS

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- COLLECT POST-PROGRESSION DATA

- USE REAL WORLD DATA

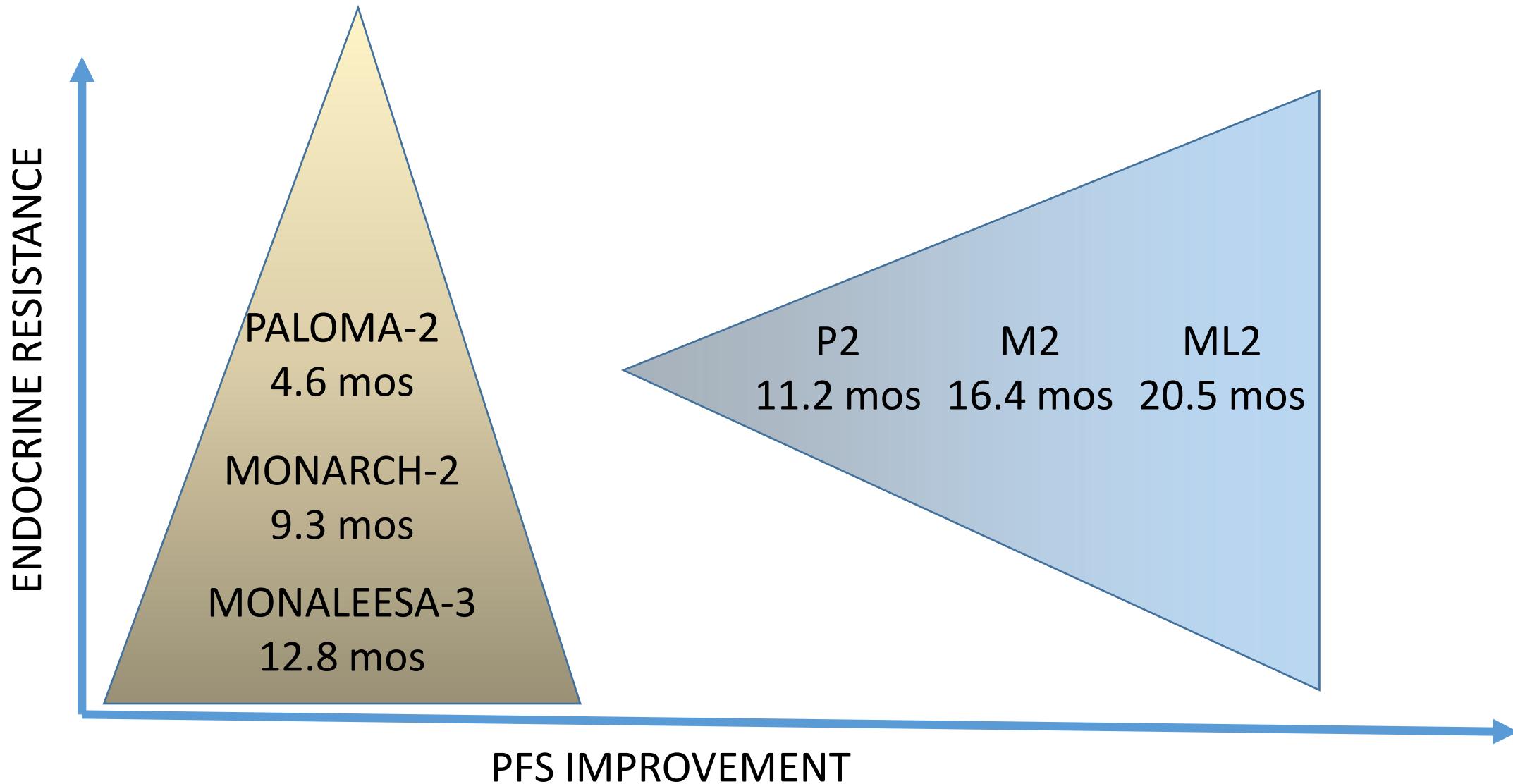
Cristofanilli et al, ESMO 2018

REVIEWS

The value of progression-free survival to patients with advanced-stage cancer

Journal of Clinical Oncology, Volume 37, Number 10, March 1, 2019
DOI: 10.1200/JCO.2018.77.10_suppl
© 2019 by the American Society of Clinical Oncology
Abstract: Progression-free survival (PFS) has been considered as a measure of outcome in cancer trials, although it is often not the primary outcome. This article highlights the importance of PFS in cancer trials, particularly in advanced-stage cancer, and discusses the effect of PFS on therapeutic decisions. It is also noted that PFS is often used as an intermediate endpoint in trials with fewer patients recruited than those required for the primary endpoint. In such trials, PFS is often used as a surrogate endpoint for overall survival (OS). The use of PFS as a primary endpoint can lead to misleading results, as well as unnecessary costs associated with drug development. An argument for using PFS as a primary endpoint in cancer trials is made. The authors argue that PFS is a useful endpoint in cancer trials, particularly in advanced-stage cancer, and that PFS is an important endpoint in cancer trials. The authors argue that PFS is a useful endpoint in cancer trials, particularly in advanced-stage cancer, and that PFS is an important endpoint in cancer trials.

How can we read these data?



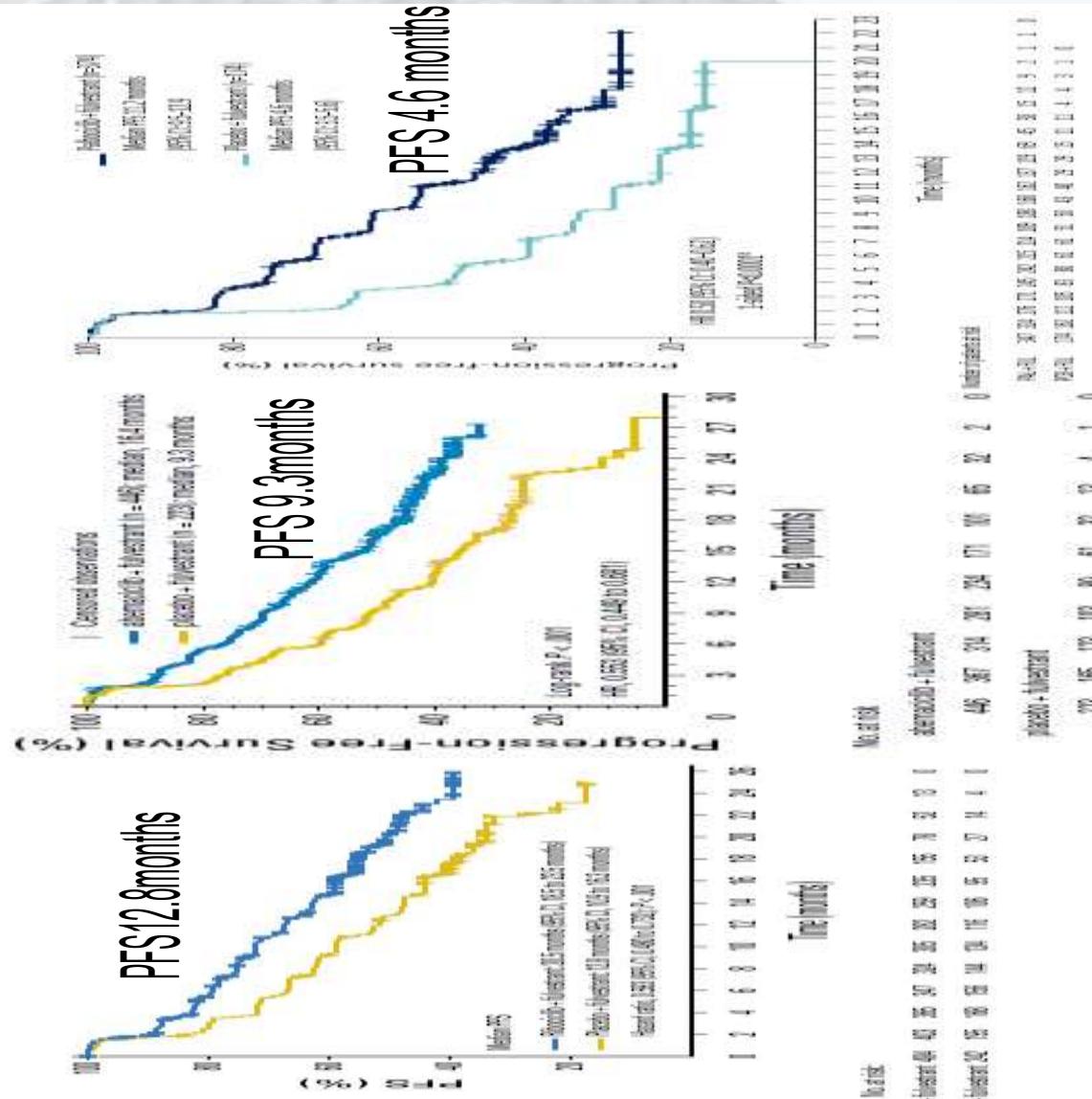
Control Arm Performance - Endocrine resistant

PFS data of fulvestrant + CDK4/6 inhibitor Phase III trials in ET pretreated

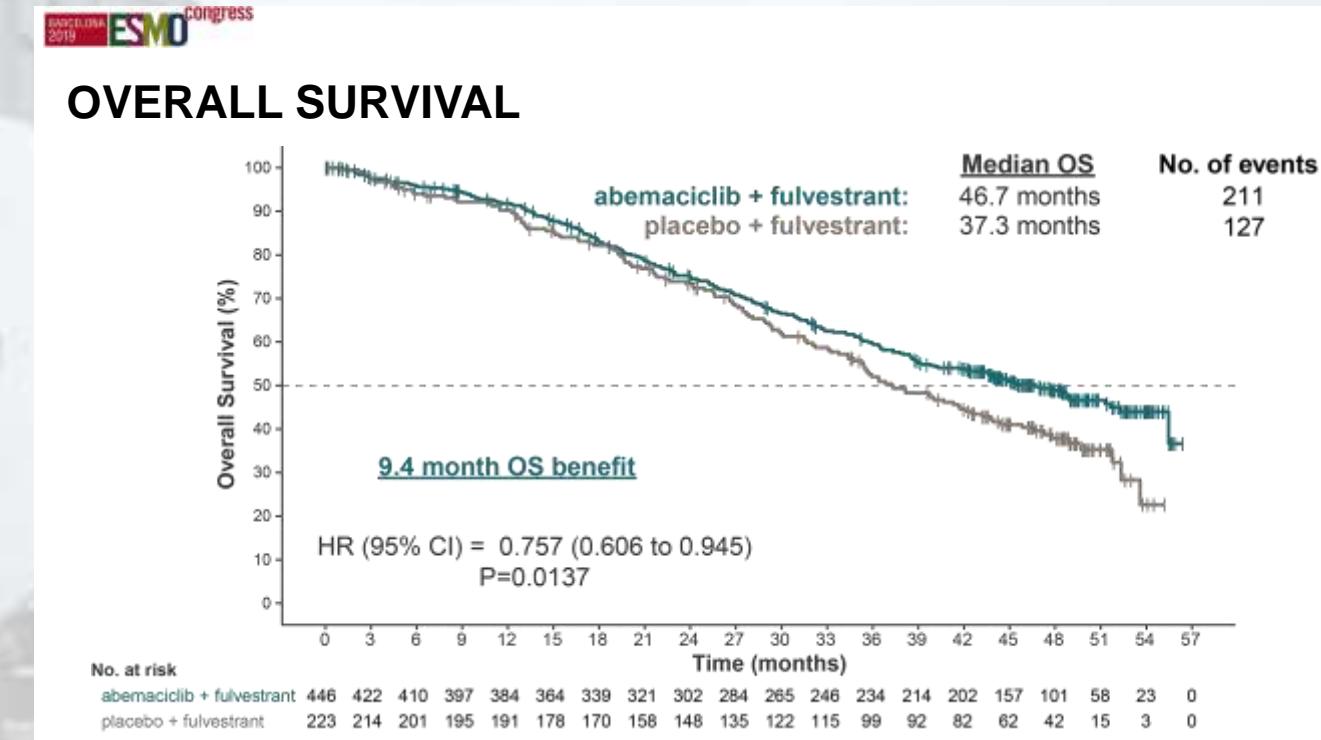
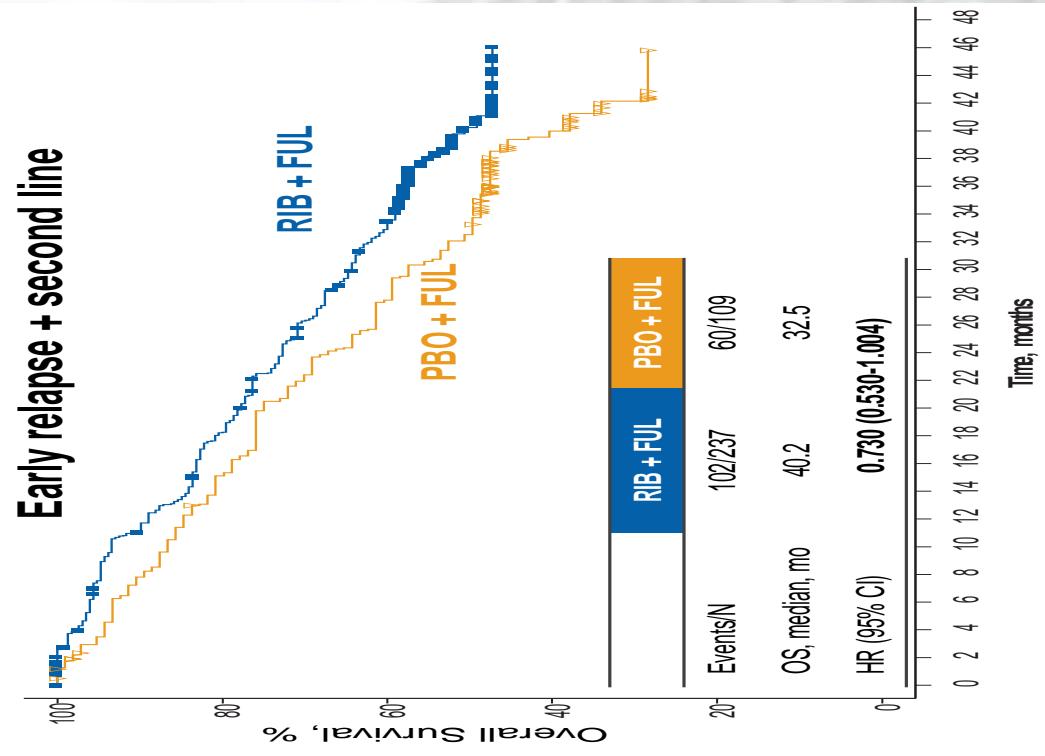
MONALEESA-3¹

MONARCH-2²

PALOMA-3³



LET'S TRY TO PUT DATA IN THE RIGHT PERSPECTIVE



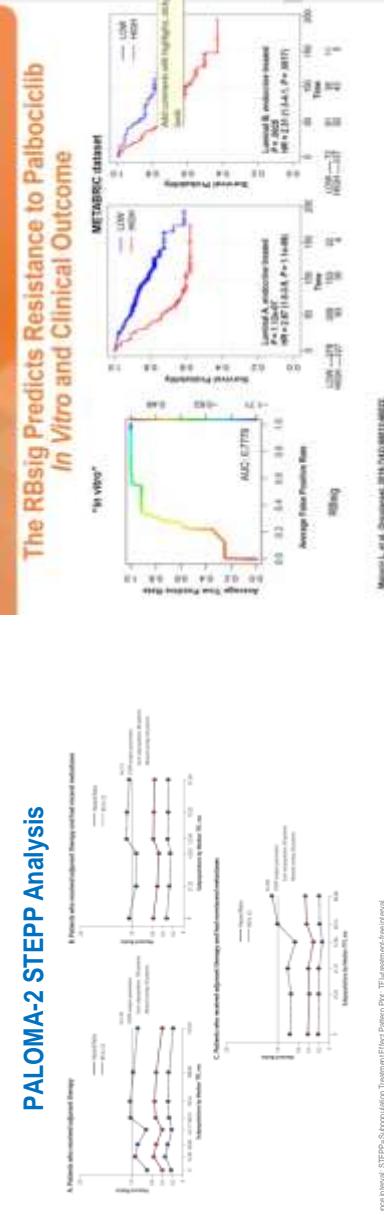
Alltogether these trials have established a very important thing:
finally, in 2019 OS of HR+ ABC patients has improved!

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Cardoso, ESMO 2018

Can we identify which patients benefit and/or which ones do not benefit from ET + CDK4/6i?



Is it better to use a CDK4/6i in 1st line or 2nd line (in previous ET exposed or ET-naïve patients)?

UNCONFIRMED PROBLEM: PROGRESSION AFTER CDK4/6i IS FASTER?

MORE POST-PROGRESSION DATA NEEDED

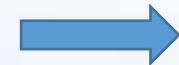
Will there be a role for “continuing beyond progression”?



HERMIONE-7 STUDY

An exploratory, Phase 2, single arm trial evaluating the activity and safety of Abemaciclib+ Aromatase Inhibitors (AIs) after 1st-line treatment with High-Dose Fulvestrant (HD-FUL) in Hormone-Receptor-Positive (HR+), Human-Epidermal-Growth-factor-negative (HER2-) advanced breast cancer patients

HD-FUL



ABEMA + AIs

**Approved September 12, 2019
Centres: 39**

HERMIONE-8 STUDY

Prospective evaluation of Ribociclib activity and safety in a real-world setting

**Approved September 06, 2018
Centres: 27**

Conclusions

1. Are all the CDK 4/6 created equal?

✓ PROBABLY YES, BUT DIFFERENT POPULATIONS ENROLLED MAKE THE PICTURE A BIT CONFUSING

2. Survival data of randomized clinical trials: the end of the story?

✓ NOT YET, MORE DATA ARE NEEDED, ESPECIALLY IN ENDOCRINE-SENSITIVE PTS

3. The unanswered questions and the unmet clinical needs

✓ LOTS OF TRIALS ONGOING, WE WILL WAIT FOR RESULTS