LA MALATTIA METASTATICA ENDOCRINO SENSIBILE: OLTRE LA PRIMA LINEA CON INBITORI DELLE CICLINE

Una scelta clinica

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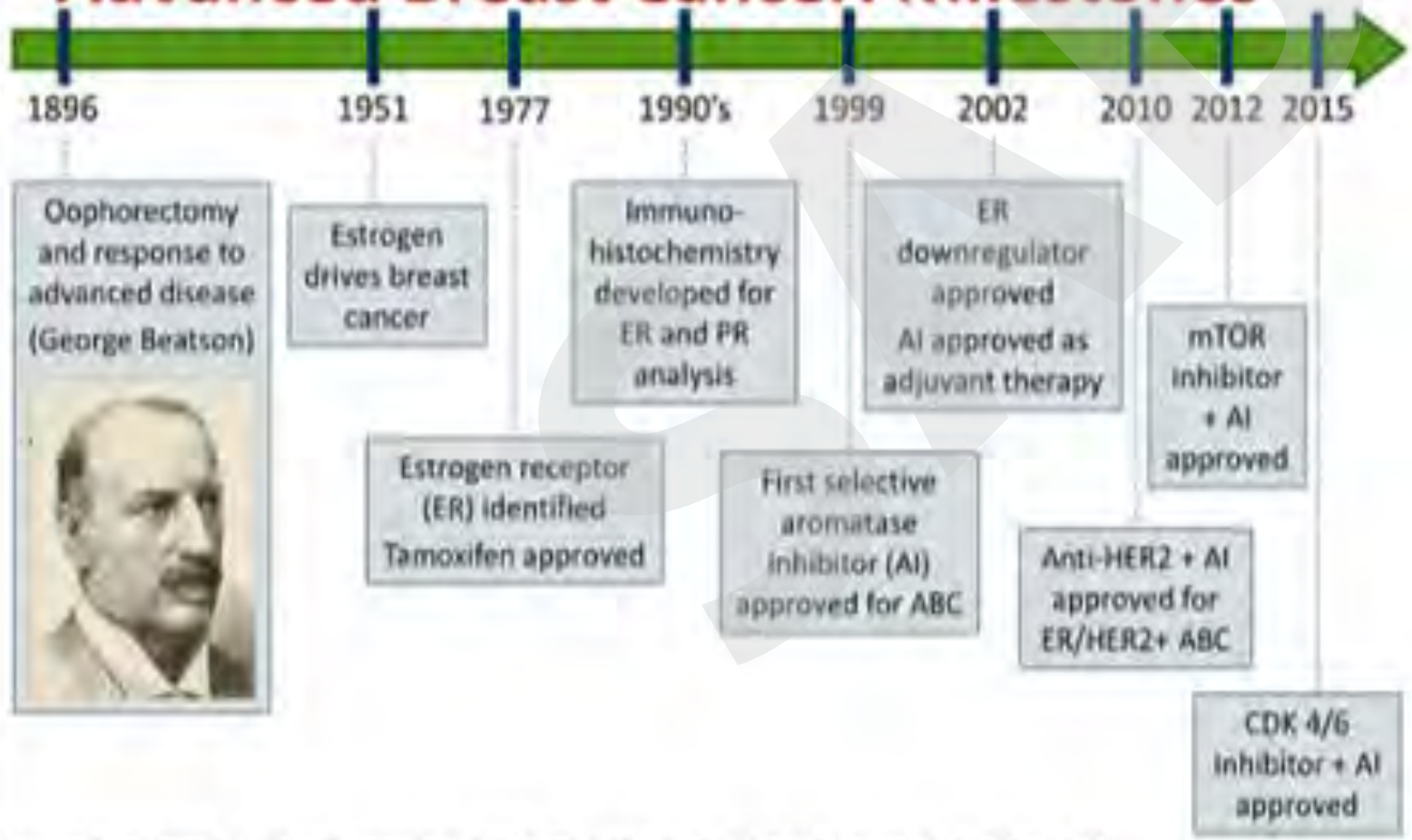
Hormonal Therapy for Advanced Breast Cancer: Milestones



Love RR, Philips J. *J Natl Cancer Inst*. 2002;94:1433-1434; Allred DC, et al. *Mod Pathol*. 1998;11:155-168; Bross PF, et al. *Oncologist*. 2002;7:477-480; Cohen MH, et al. *Oncologist*. 2001;6:4-11.

First line efficacy of endocrine ± targeted agents

Phase III trial	PALOMA 2 (n=666)	MONALEESA 2 (n=668)	MONARCH 3	MONALEESA 7 (N=672)
Targeted agent	Palbociclib	Ribociclib	Abemaciclib	Ribociclib
Endocrine agent	Letrozole	Letrozole	Anastrozole / Letrozole	Tamoxifen/ Anastrozole + LHRH
PFS	**24.8 vs. 14.5** months	**25.3 vs. 16.0** months	**n.r. vs. 14.7** months	23.8 vs. 13.0 months
HR (PFS)	**0.58**	**0.57**	**0.54**	0.55
Most frequent G3/4 side effects	**neutropenia**, leukopenia, anemia, fatigue	**neutropenia**, vomiting, back pain, fatigue	**diarrhea**, neutropenia, leukopenia, anemia	Same as observed in MONALEESA 2

Finn et al, NEJM 2016; Hortobagyi et al, ASCO 2017; Di Leo et al, ESMO 2017

So where do we go from here?

- New endocrine therapies, alone or in combination
- New targeted therapy plus endocrine therapy
- New schedules
- New approaches to predicting resistance and response

Breast Cancer Research and Treatment
https://doi.org/10.1007/s10549-018-4783-1

REVIEW

Use of cyclin-dependent kinase (CDK) 4/6 inhibitors for hormone receptor-positive, human epidermal growth factor receptor 2-negative, metastatic breast cancer: a roundtable discussion by The Breast Cancer Therapy Expert Group (BCTEG)

CDK 4/6 treatment: what are the differentiators?

What are the differentiators, current or future, that drive your decision to treat using the various endocrine options available for the treatment of metastatic breast cancer?

The principal drivers identified from the discussion included whether the patient was **symptomatic or asymptomatic** from the metastatic standpoint, whether the metastases were primarily **visceral or nonvisceral**, **menopausal status**, and the disease-free interval.

Barriers to use of CDK 4/6 inhibitors

What significant clinical toxicities, financial barriers, and/or common community practice misunderstandings exist regarding the use of CDK 4/6 inhibitors?

Several barriers to the widespread use of CDK 4/6 inhibitors were identified by the group:

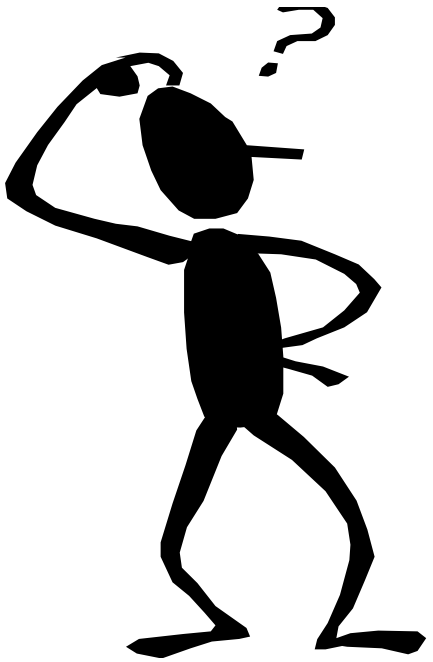
- concern over events such as fatigue, alopecia and diarrhea
- Monitoring for CBC and frequence
- Delays in institution of therapy due to the need for dose reductions
- Drug wastage was raised as an important issue in light of rising healthcare costs

Biomarkers for CDK 4/6 inhibitors

What biomarkers, if any, have been shown to predict benefit, or lack thereof, when using CDK4/6 inhibitors (e.g., ESR1, CND1 amplification, p16 loss, or RB1 expression)?

clinicians should not use biomarkers to make treatment decisions

- The group thought that markers of response early in the course of single-agent therapy are urgently needed



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REVIEW

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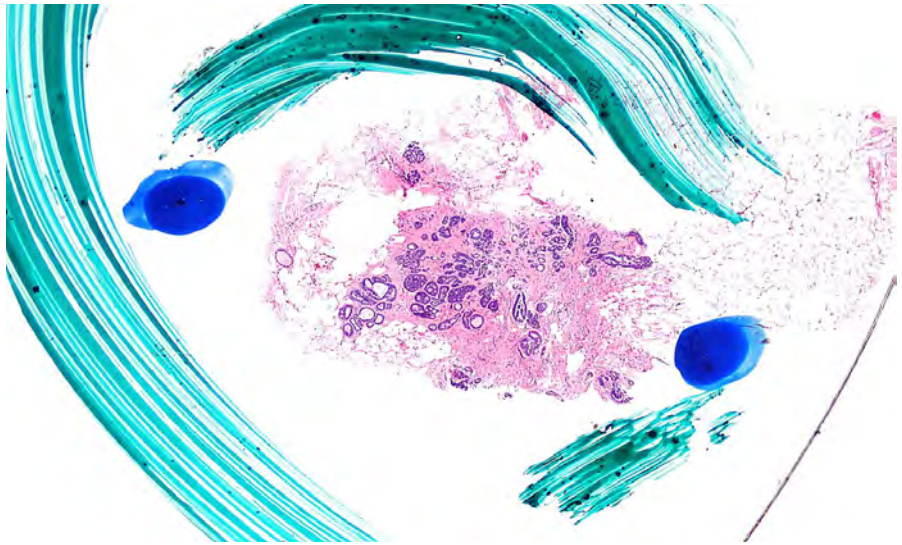
Sequencing Therapies for ER+/HER2– MBC

How would you approach patients that have progressed on a CDK 4/6 inhibitor?

The group was generally in agreement on the **upfront use of an AI with a CDK 4/6 inhibitor**, followed by (upon progression) **Fulvestrant or exemestane with mTOR inhibitor** (e.g. Everolimus).

Data on **switching between CDK 4/6 inhibitors** are not yet available, and while the label for Abemaciclib does not exclude patients who previously received a CDK4/6 inhibitor, the Monarch-1 study did not allow prior CDK4/6 inhibitors.



CDK 4/6 → PIK3CA → CHT → ET maintenance

CDK 4/6 → ? → CDK 4/6 beyond PD → PIK3CA → CHT

CDK 4/6 → CHT → ET+TT → ET/CHT

CHT → ? → CDK 4/6 → ET/CHT → ET + TT

Alpelisib (ALP) + Fulvestrant (FUL) for Advanced Breast Cancer (ABC): Phase 3 SOLAR-1 Trial Results

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Hiroji Iwata,[7] Pierfranco Conte,[8] Ingrid A. Mayer,[9] Bella Kaufman,[10] Toshinari Yamashita,[11] Yen-Shen Lu,[12]
Kenichi Inoue,[13] Masato Takahashi,[14] Zsuzsanna Pápai,[15] Anne-Sophie Longin,[16] David Mills,[17] Celine Wilke,[17] Michelle Miller,[18] Naveen Babbar,[18] Fabrice André[19]

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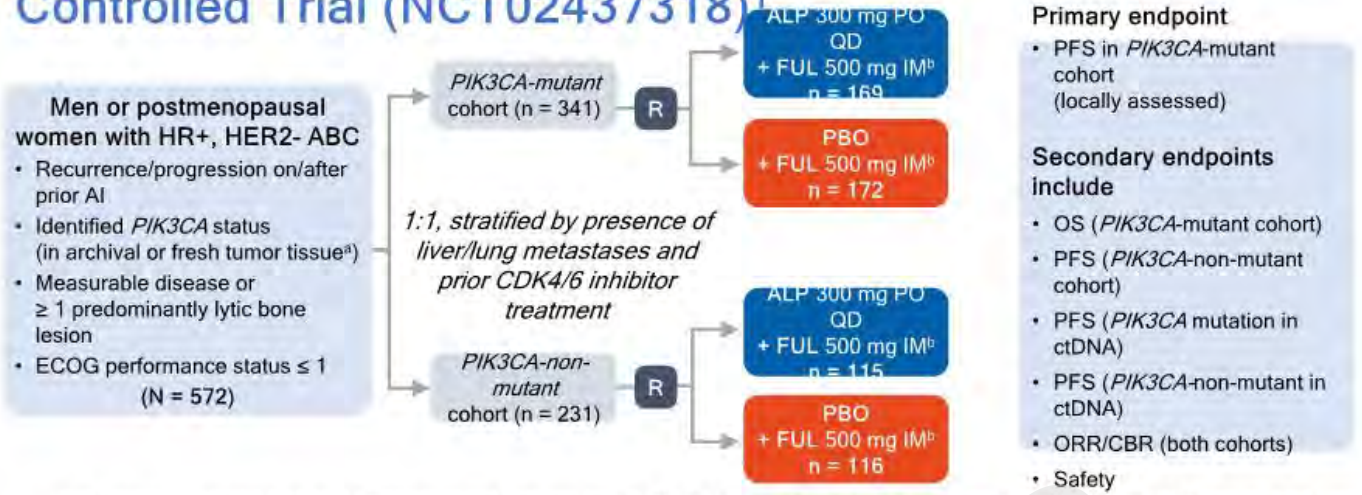
*Presenting author

San Antonio Breast Cancer Symposium®, December 4-8, 2018

SOLAR-1: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial (NCT02437318)[1]



Primary endpoint

- PFS in *PIK3CA*-mutant cohort (locally assessed)

Secondary endpoints include

- OS (*PIK3CA*-mutant cohort)
- PFS (*PIK3CA*-non-mutant cohort)
- PFS (*PIK3CA* mutation in ctDNA)
- PFS (*PIK3CA*-non-mutant in ctDNA)
- ORR/CBR (both cohorts)
- Safety

- The primary endpoint included all randomized patients in the *PIK3CA*-mutant cohort; PFS was analyzed in the *PIK3CA*-non-mutant cohort as a proof of concept
- Safety was analyzed for all patients who received ≥ 1 dose of study treatment, in both cohorts

ABC, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; HER2-, human epidermal growth factor receptor-2-negative; IM, intramuscular; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, oral; QD, once daily; R, randomization.

[a] More than 90% of patients had mutational status identified from archival tissue.

[b] Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.

1 Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

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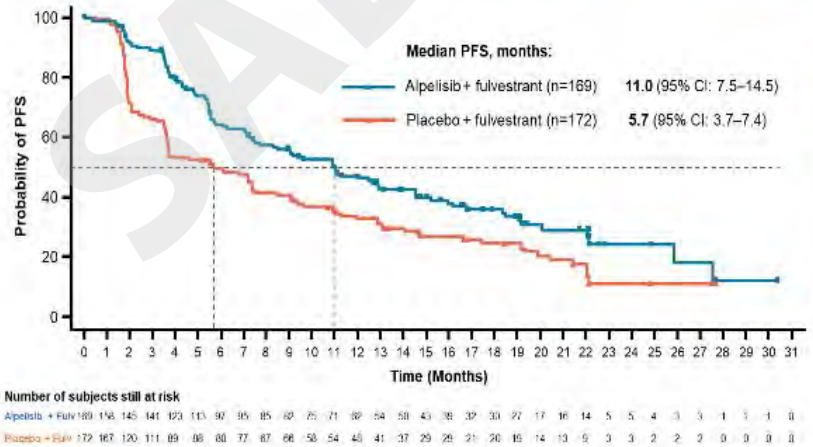
Primary Endpoint: Locally Assessed PFS in the *PIK3CA*-mutant Cohort[1,a]



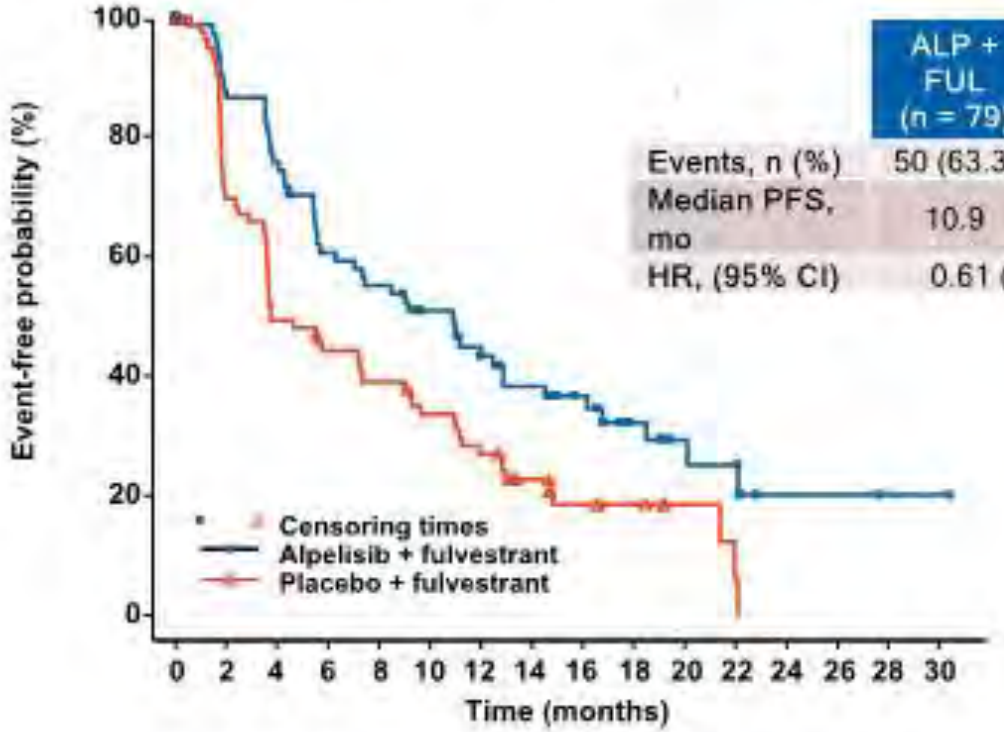
Data cut-off: Jun 12, 2018	ALP + FUL (n = 169)	PBO + FUL (n = 172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
HR (95% CI)	0.65 (0.50-0.85)	
One-sided *P* value	0.00065	

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
At final PFS analysis, superiority was declared if one-sided, stratified log-rank test *P* value was ≤ 0.0199 (Haybittle-Peto boundary).
[a] Mutation status determined from tissue biopsy.
1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

PFS by line of therapy

Second-line (n = 161)

Defined as patients whose disease progressed > 1 year after (neo)adjuvant ET and while on or after 1 line of ET for ABC or patients with newly diagnosed ABC whose disease progressed while on or after 1 line of ET



	ALP + FUL (n = 79)	PBO + FUL (n = 82)
Events, n (%)	50 (63.3)	65 (79.3)
Median PFS, mo	10.9	3.7
HR, (95% CI)	0.61 (0.42-0.89)	

PFS by prior CDK 4/6 treatment

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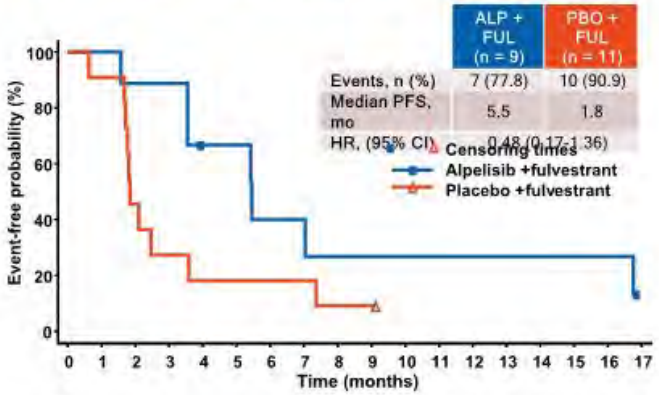
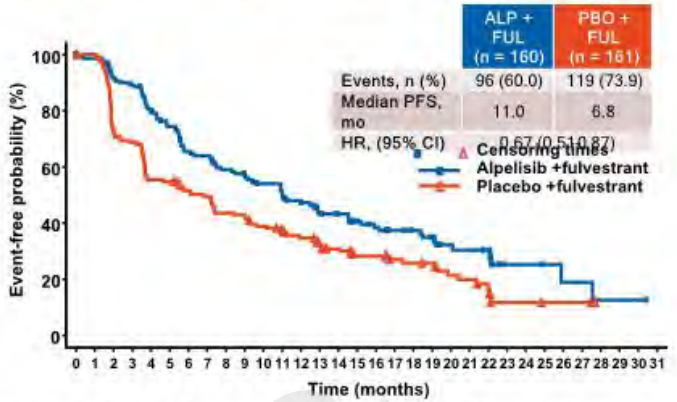
PFS by Prior CDK4/6 Inhibitor Treatment in the *PIK3CA*-mutant Cohort[a]

With Prior CDK4/6 inhibitor therapy



Without Prior CDK4/6 inhibitor therapy

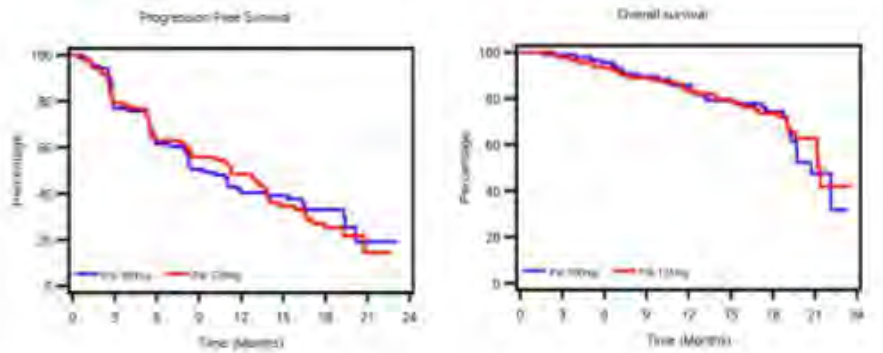


- Previous treatment with any CDK4/6 inhibitor was a stratification factor, however the number of patients enrolled who had received prior CDK4/6 inhibitor therapy was small
- Treatment benefit with alpelisib was observed regardless of prior use with a CDK4/6 inhibitor

PD1-10: Randomized Phase II Study Comparing Two Different Schedules of Palbociclib plus Second Line Endocrine Therapy

Parulekar et al

- Randomized phase II study
- N= 180
- Palbociclib 125 mg po q d 21/28 vs.
- Palbociclib 100 mg po q d continuous



- Palbociclib100 mg po daily had comparable efficacy (PFS, RR, OS) and QoL profiles compared to palbociclib125 mg po3/ 4 weeks.
- More patients in the 100 mg po daily group experienced grade 3-4 neutropenia (69 vs 53%).The rate of febrile neutropenia and discontinuation due to AE were low on both arms, and comparable.
- Planned dose intensity was lower on the 100 mg arm than the standard (41 vs 54% achieved planned dose intensity)
- QOL? Which should we recommend?

Pulling it all together….
What did we learn and what are the remaining questions?

- Bazedoxifene+ palbociclib is pretty well tolerated and has some activity in heavily pretreated. Can the correlatives predict who will respond?
- Venetoclax added to tamoxifen is tolerable and intriguing response rate. What do the correlatives tell us about how to move this forward?
- LSZ102- a RP2D has been identified, food effect and PK have been explored. Combination studies are ongoing. What is the benefit of FES PET in exploring novel endocrine therapies?

Provocative Questions

- How many new SERMs and SERDs do we need? And how should we judge them?
- Do we adequately understand the mechanisms for endocrine therapy resistance and have we targeted those?
- What is the role for continuing targeted therapy in previously treated/progressing patients?
- Scheduling nuances– at what point in drug development/ use should we study these?
- How best to bring -omics to the clinic, and what would those trials look like?

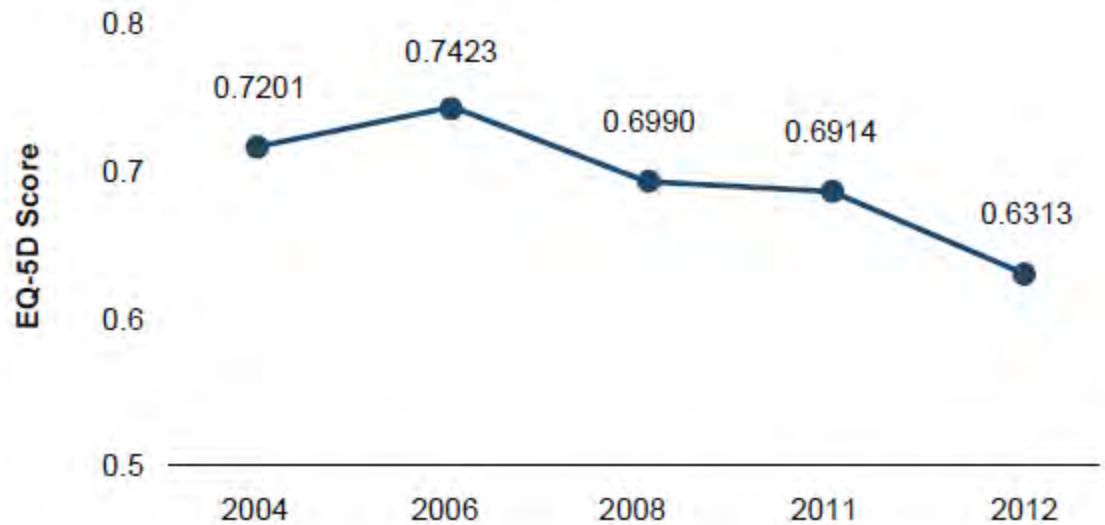
Quality of life in MBC as a chronic disease

SECTION I *Continued*

GUIDELINE STATEMENT	LoE	Consensus
Strong consideration should be given to the use of validated PROMs (patient-reported outcome measures) for patients to record the symptoms of disease and side effects of treatment experienced as a regular part of clinical care. These PROMs should be simple, and user-friendly to facilitate their use in clinical practice, and thought needs to be given to the easiest collection platform, e.g. tablets or smartphones. Systematic monitoring would facilitate communication between patients and their treatment teams by better characterizing the toxicities of all anticancer therapies. This would permit early intervention of supportive care services enhancing quality of life	1 C	Voters: 39 Yes: 87.1% (34) Abstain: 5.1% (2)
As survival is improving in many patients with ABC, consideration of survivorship issues should be part of the routine care of these patients. Health professionals should therefore be ready to change and adapt treatment strategies to disease status, treatment adverse effects and quality of life, patients' priorities and life plans. Attention to chronic needs for home and family care, job and social requirements, should be incorporated in the treatment planning and periodically updated.	Expert opinion	Voters: 40 Yes: 95% (38) Abstain: 5% (2)

Analysis suggests **limited improvement in quality of life** for patients with mBC over the last decade

Quality of life in patients with mBC as assessed by EQ-5D, 2004-2012, Generic (non-Cancer Specific) Health Utility Score[2]



- An analysis of the trends in quality of life for mBC* indicates that there has **not been significant improvement** over the past decade[2]
- In fact, there has been a **slight decrease** in quality of life[2]

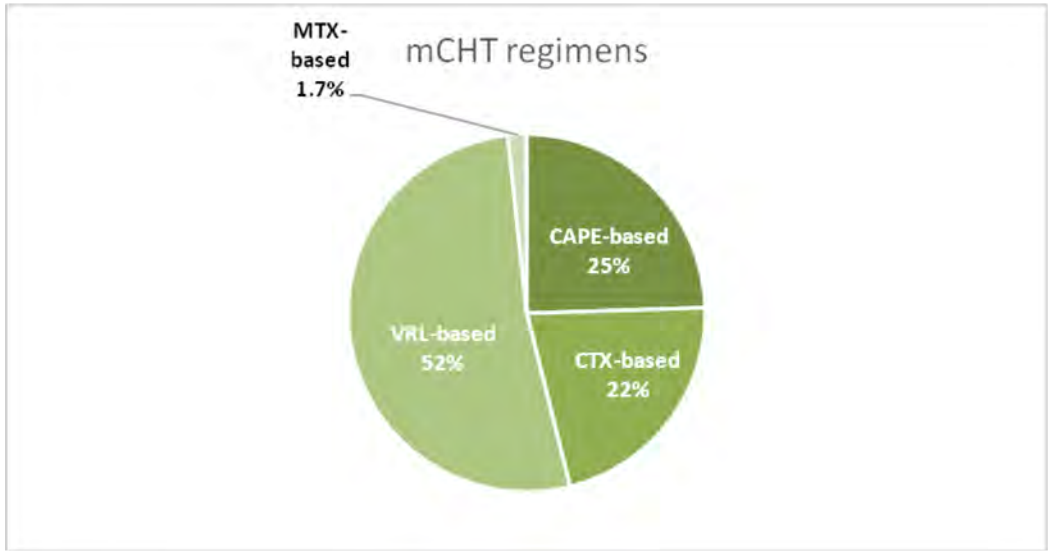
METRONOMIC CHEMOTHERAPY FOR ADVANCED BREAST CANCER PATIENTS IN THE REAL WORLD PRACTICE: FINAL RESULTS OF THE VICTOR-6 STUDY

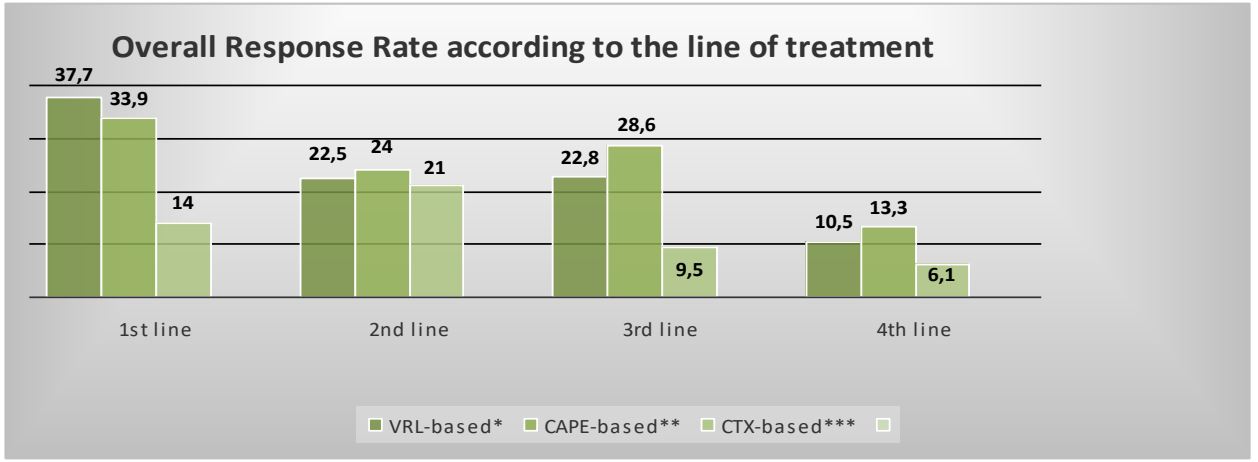
Table 1 – Patients and tumour characteristics at mCHT start

Characteristic	N	(%)
Median age (range), years	65 (30-98)	
PS (frequency missing=2)		
0	345	(59.3)
1	190	(32.6)
2	42	(7.2)
3	5	(0.9)
HR status		
ER+/PgR+	374	(64.0)
ER+/PgR-	113	(19.3)
TNBC	97	(16.6)
Metastatic sites		
- Bone	396	(67.8)
- Liver	229	(39.2)
- Lung	182	(31.2)
- Soft tissue	110	(18.7)
- CNS	24	(4.1)
- Other	192	(32.9)
Number of metastatic sites (frequency missing=10)		
- ≥ 3	130	(22.1)
- 2	238	(40.7)
- 1	206	(35.3)
Number of treatments before mCHT*		
- 0	111	(19.0)
- 1	117	(20.0)
- 2	123	(21.1)
- ≥ 3	233	(40.0)
Typology of treatments prior to mCHT		
- No CHT, and NO ET (naive)	111	(19.0)
- ET only (1st line)	143	(24.3)
- CHT only	106	(18.2)
- CHT and ET	224	(38.4)
Key prior CHT		
- Taxane-based	218	(37.3)
- Anthra-based	103	(17.5)
- VRL-CAPE based	133	(22.8)
Key prior endocrine treatments		
AIs	307	(52.3)
TAM	51	(8.7)
Everolimus	49	(8.3)

mCHT=metronomic chemotherapy; ET= Endocrine therapy; CHT= Chemo therapy;VRL=Vinorelbine; CAPE=capecitabine; AIs=aromatase inhibitors; TAM=tamoxifen

* both ET and CHT





Cazzaniga ME et Al, submitted

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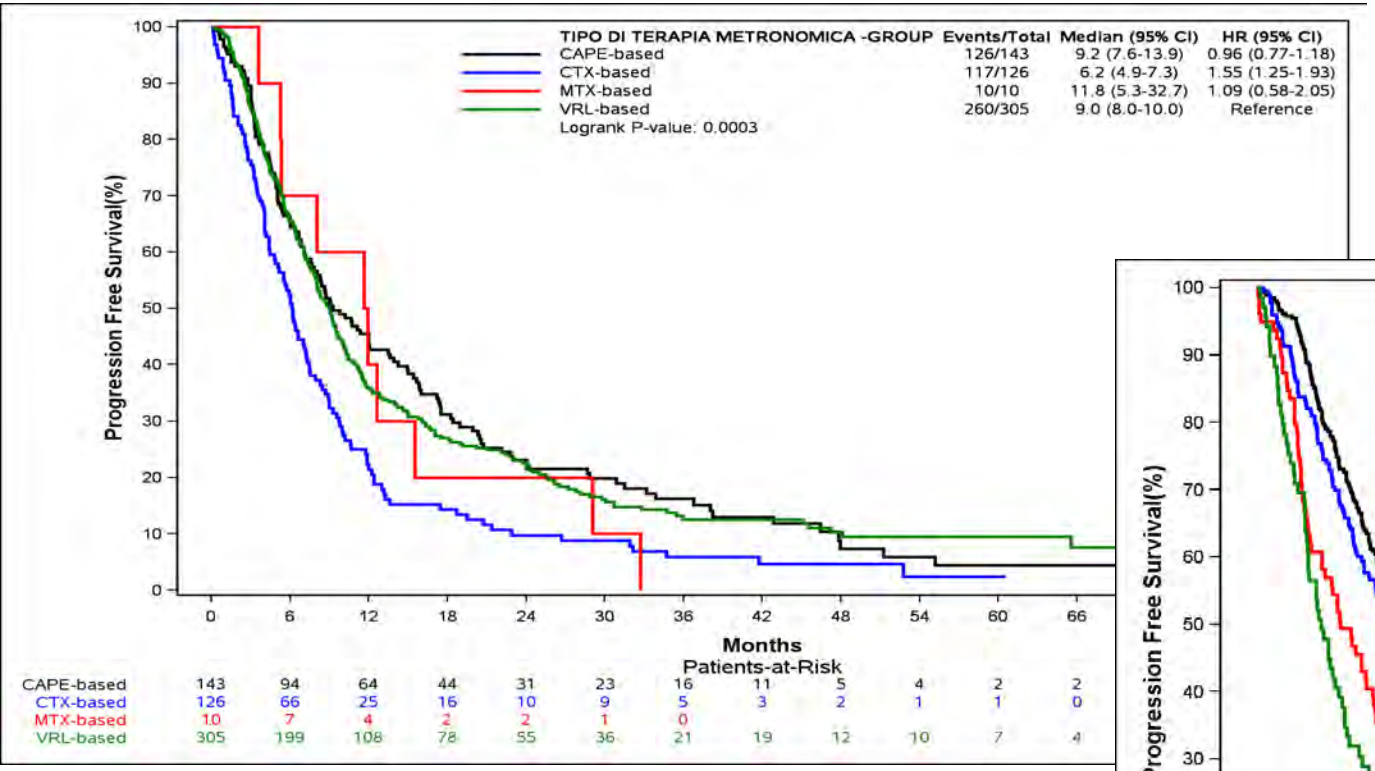
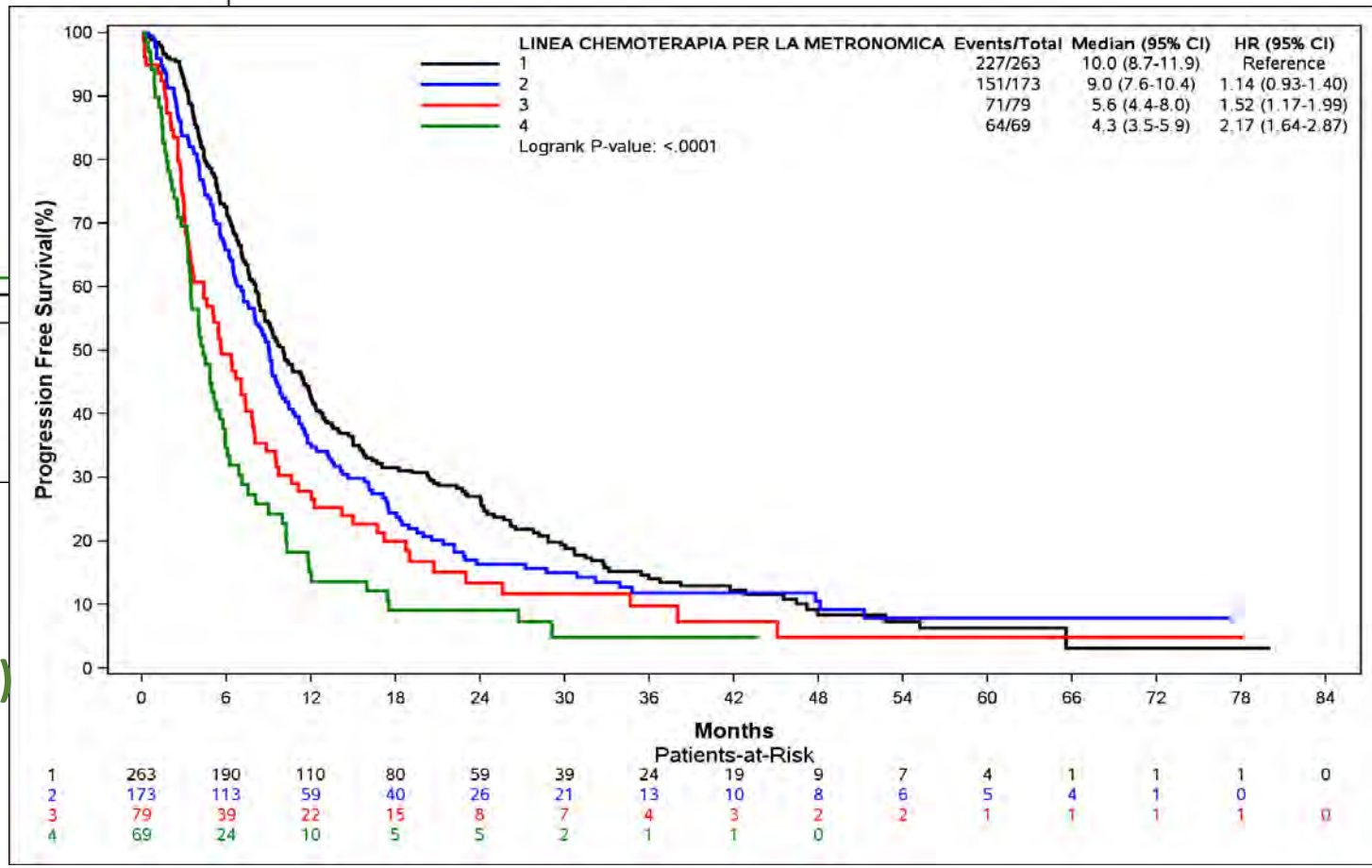


PFS according to the type of mCHT

PFS according to the line of treatment



Median SPP was 12.0 months (95% CI: 10.4 – 15.4)

Cazzaniga ME et Al, submitted

OS is no longer and End Point required by FDA

OS is a mix of prolongation of life & drug safety

Richard Pazdur, director of the FDA's Oncology Center of Excellence (OCE), which leverages the combined skills of the FDA's regulatory scientists and reviewers with expertise in drugs, biologics and devices to expedite the development of novel cancer products

What the patients want
is different
from clinical trials End Points

It’s our duty to define the standard of care