2019 ASCO® ANNUAL MEETING

MAY 31-JUNE 4, 2019

May 30-May 31: Pre-Annual Meeting Educational Programs

June 1-3: Exhibits

McCORMICK PLACE
CHICAGO, ILLINOIS | #ASCO19

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Dr. **Uirá M. Resende**, MD
médico oncologista
Goiânia, GO

Conflitos de Interesses

Uirá Resende

Médico Oncologista Clínico

De acordo com a Resolução 1595/2000 do Conselho Federal de Medicina e RDC 96/2008 da ANVISA declaro que tenho os seguintes conflitos de interesse:

Desempenhei o papel de **SPEAKER** para as seguintes empresas:

Astellas, AstraZeneca, Roche, Bristol-Myers Squibb, MSD, Novartis, Janssen, Libbs

ADVISORY BOARD:

Libbs, Janssen, Medscape, URSO Oncologia, Synapse Treinamento em Aprendizagem Ativa, Bristol-Myers Squibb

Trabalho como **ONCOLOGISTA** no: Hemolabor

Os meus pré-requisitos para participar destas atividades são a autonomia do pensamento científico, a independência de opiniões e a liberdade de expressão, critérios respeitados por todas as empresas para as quais presto serviço.

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COMO APRENDEMOS

A pirâmide de aprendizagem de William Glasser

Aprendemos...

10% quando lemos;

20% quando ouvimos;

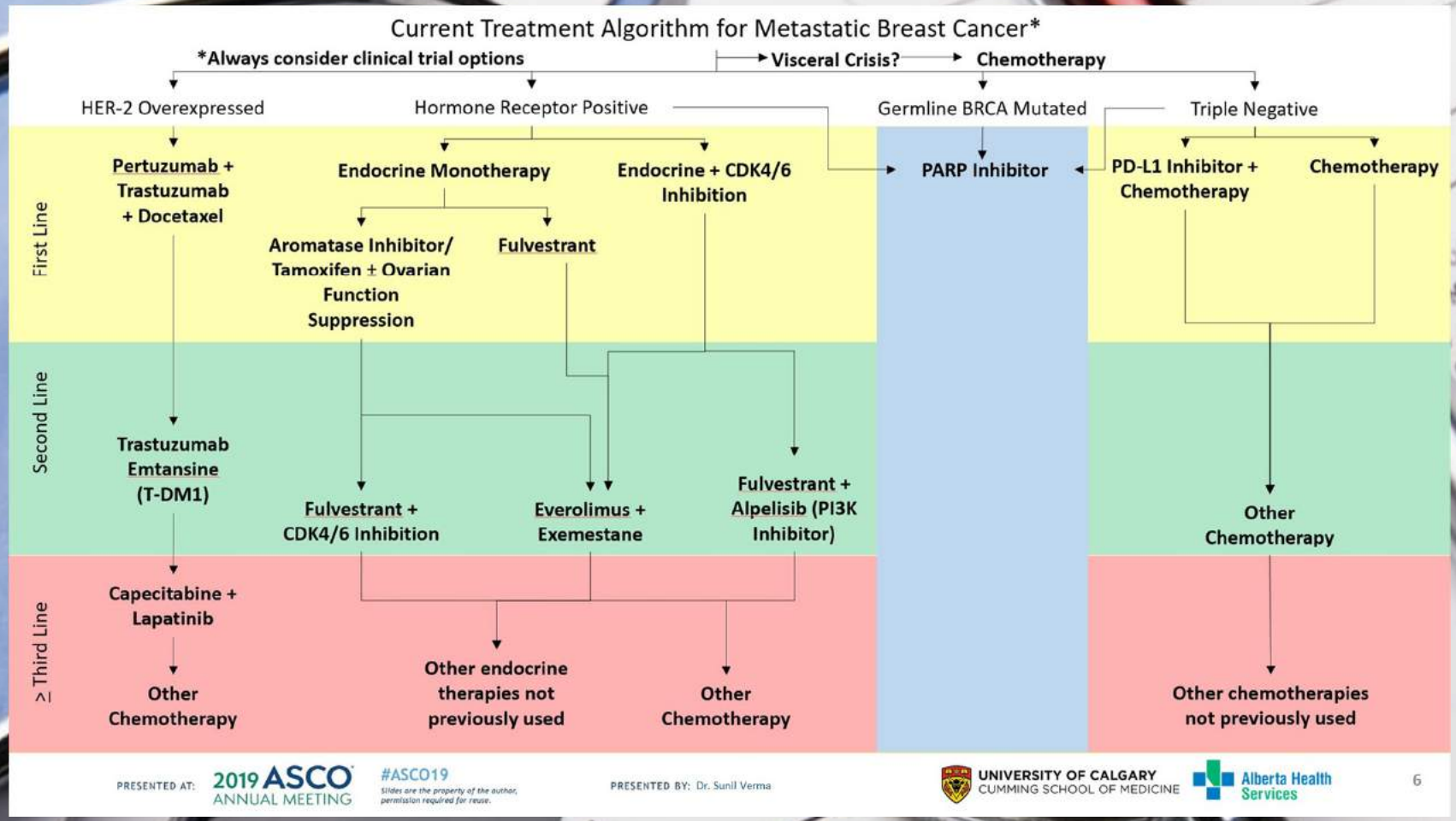
30% quando observamos;

50% quando vemos e ouvimos;

70% quando discutimos com outros;

80% quando fazemos;

95% quando ensinamos aos outros.



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Médico Oncologista Clínico
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Médico Oncologista Clínico
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Key Phase III HER2 Positive MBC Trials

	First Line	Second Line	Third Line	3rd/4th Line
Trial	CLEOPATRA[1]	EMILIA[2]	TH3RESA[3]	EGF104900[4]
Number of Patients	808	991	602	291
Treatment Comparisons	THP vs TH	T-DM1 vs XL	T-DM1 vs TPC	HL vs L
Gain in OS	16.3m (40.8 vs. 57.1)	4m (25.9 vs. 29.9)	6.9m (15.8 vs. 22.7)	4.5m (9.5 vs. 14)
Side effects	Minimally increased	Less with T-DM1	Less with T-DM1	Minimally increased
Prior Trastuzumab (anti-HER2 Rx)	Only 10% and interval of ≥12m required	100% (16% with adjuvant, disease free interval <6m)	Prior Trastuzumab and Lapatinib	100%(≥ 3 regimens)

1. Swain S, et al. ASCO 2019; 2. Diéras V, et al. Lancet Oncol 2017; 3. Krop I, et al. Lancet Oncol 2017; 4. Blackwell K, et al. J Clin Oncol 2012
Table adapted from: Rugo H, 2019

Current Approach for Advanced HER2+ Breast Cancer

First Line	Trastuzumab + Pertuzumab + Taxane (CT)	
Second Line	TDM1	Cap + **Pyrotinib**
		Cap + **Neratinib**
Third and Further Lines	Cap + Lapatinib Chemo + Trastuzumab Lapatinib + Trastuzumab Endocrine Rx + anti-HER2 Rx (HR+) Pertuzumab or TDM1 if not received earlier	CT + **Margetuximab**

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PHENIX Study Design

Pyrotinib combined with capecitabine in women with HER2+ metastatic breast caNcer previously treated with trastuzumab and taXanes: a randomized phase 3 study

- ☐ **Double-blinded, multicenter, randomized phase 3 trial (NCT02973737)**
- ☐ **Primary objective:** the efficacy of pyrotinib plus capecitabine after failure of trastuzumab

Key eligibility criteria:

- Pathologically confirmed HER2-positive* metastatic breast cancer
- Disease progression during or after treatment with trastuzumab#, and were not amenable or available for trastuzumab or lapatinib treatment
- Prior taxane -containing regimen
- No. of lines of prior chemotherapy in the metastatic setting ≤ 2
- At least one measurable lesion
- ECOG performance status of 0 or 1

Randomization 2:1

Pyrotinib (400 mg, orally, qd) + Capecitabine (1000 mg/m², orally, bid on days 1–14 of each 21-day cycle)

Stratification:

- Metastatic sites at screening (visceral *versus* non-visceral)
- Hormone receptor status (ER- and/or PR-positive *versus* ER- and PR-negative)

Placebo (400 mg, orally, qd) + Capecitabine (1000 mg/m², orally, bid on days 1–14 of each 21-day cycle)

At progression

Investigator's choice of pyrotinib (400 mg, orally, qd)

Treatment until disease progression, unacceptable toxicity, patient withdrawal, or investigator decision.

☐**Primary endpoint:** IRC-assessed PFS

☐**Secondary endpoints:** ORR, DoR, DCR, CBR, OS, and safety profile

*__HER2-positive:__ immunohistochemistry 3+ and/or fluorescence in situ hybridization positive; #__Progression with trastuzumab:__ ≥2 cycles in the metastatic setting, or ≥3 months in adjuvant setting)

Abbreviations: IRC, independent review committee; DoR, duration of response; DCR, disease control rate; CBR, clinical benefit rate; OS, overall survival.

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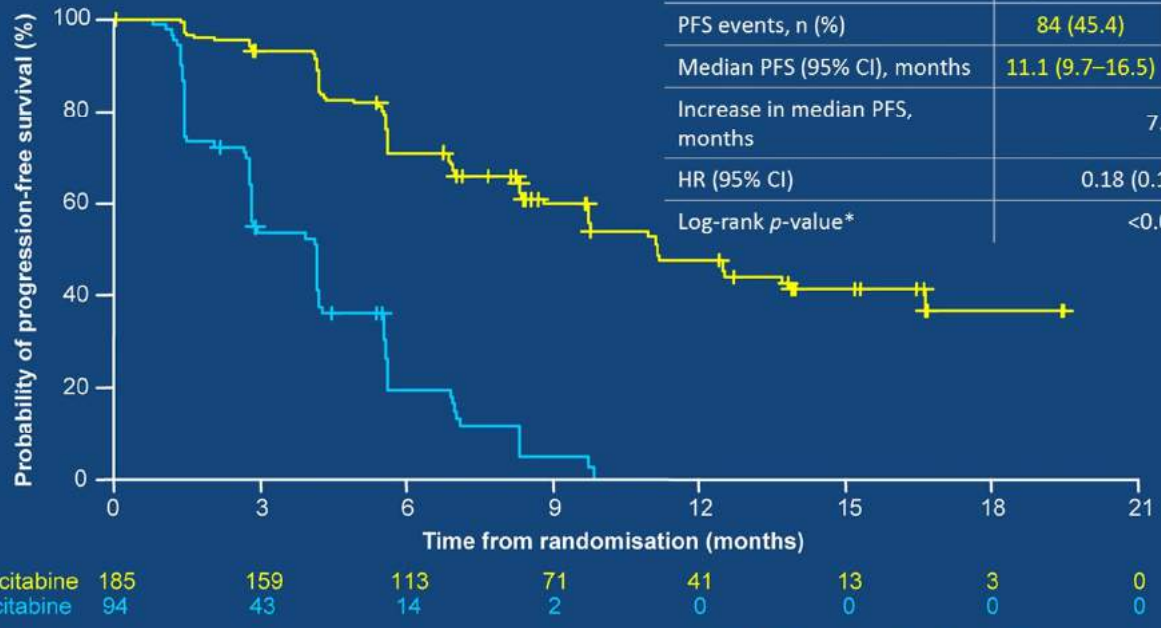
IRC-assessed PFS

FAS population, double-blind period

ORR, n (%; 95% CI)	68.6% (61.4–75.3)	16.0% (9.2–25.0)	<0.001



	Pyrotinib plus capecitabine	Placebo plus capecitabine
PFS events, n (%)	84 (45.4)	78 (83.0)
Median PFS (95% CI), months	11.1 (9.7–16.5)	4.1 (2.8–4.2)
Increase in median PFS, months	7.0	
HR (95% CI)	0.18 (0.13–0.26)	
Log-rank *p*-value*	<0.001	

No. at risk:

Pyrotinib plus capecitabine	185	159	113	71	41	13	3	0
Placebo plus capecitabine	94	43	14	2	0	0	0	0

*Stratified by metastatic sites and hormone receptor status

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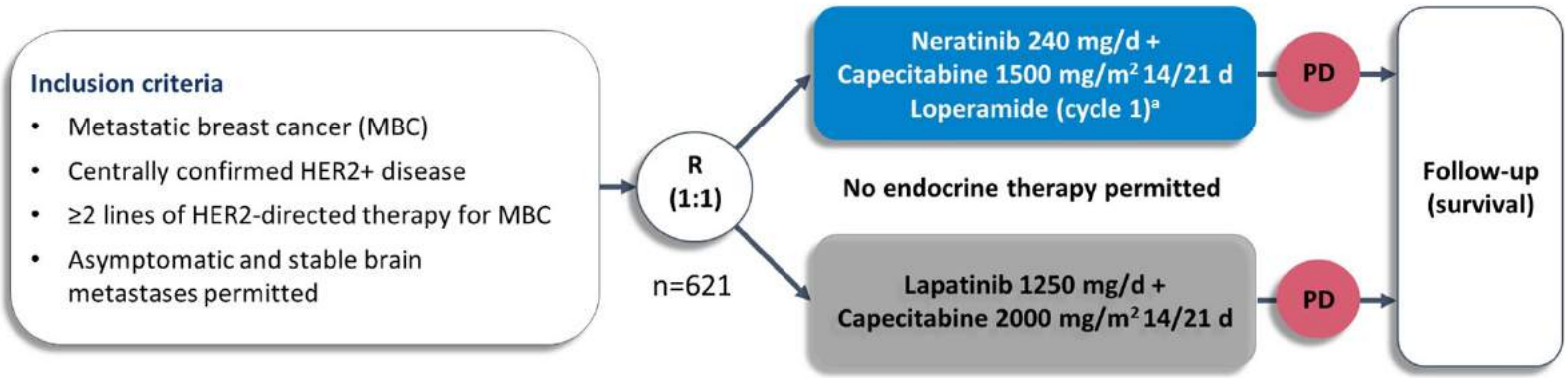
NALA Study design



Stratification variables

- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints

- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

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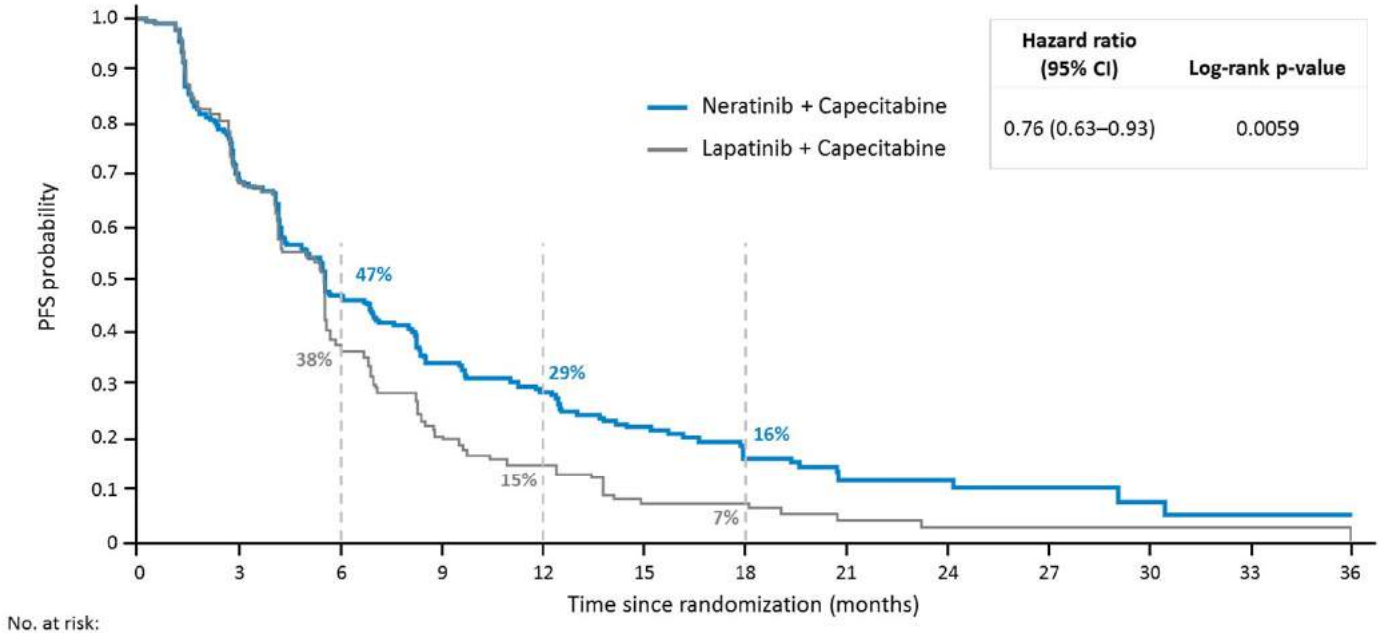
NALA

PFS (co-primary endpoint)



Hazard ratio (95% CI)	Log-rank p-value
0.76 (0.63–0.93)	0.0059

No. at risk:

N+C	307	183	113	69	54	35	20	13	9	7	3	2	2
L+C	314	183	82	39	24	9	8	3	2	2	2	2	1

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Study CP-MGAH22-04 (SOPHIA) Design[1,2]

HER2+ advanced breast cancer
- ≥2 prior anti-HER2 therapies, including pertuzumab
- 1-3 prior treatment lines in metastatic setting
- Prior brain metastasis ok if treated and stable

→ **Investigator's choice of chemotherapy** (capecitabine, eribulin, gemcitabine, or vinorelbine)

→ ***1:1 Randomization (N=536)***

→ **Arm 1**
Margetuximab (15 mg/kg Q3W) + **chemotherapy**
in 3-week cycles

→ **Arm 2**
Trastuzumab (8 mg/kg loading → 6 mg/kg Q3W) + **chemotherapy**
in 3-week cycles

Sequential Primary Endpoints	• **PFS** (by CBA; n=257; HR=0.67; α=0.05; power=90%) • **OS** (n=385; HR=0.75; α=0.05; power=80%)
Secondary Endpoints	• PFS (Investigator assessed) • Objective response rate (by CBA)
Tertiary/Exploratory Endpoints	• Clinical benefit rate (CBR), duration of response (DoR) • Safety profile, antidrug antibody • Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

Stratification:
- Chemotherapy choice
- Prior therapies (≤2 *vs* >2)
- Metastatic sites (≤2 *vs* >2)

HR=hazard ratio; CBA=central blinded analysis.

1. Rugo HS, et al. *J Clin Oncol*. 2016;34(suppl 15):TPS630. 2. Clinicaltrials.gov. NCT02492711. www.clinicaltrials.gov/ct2/show/NCT02492711. Accessed April 8, 2019.

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ITT Population: Prior Cancer Therapy

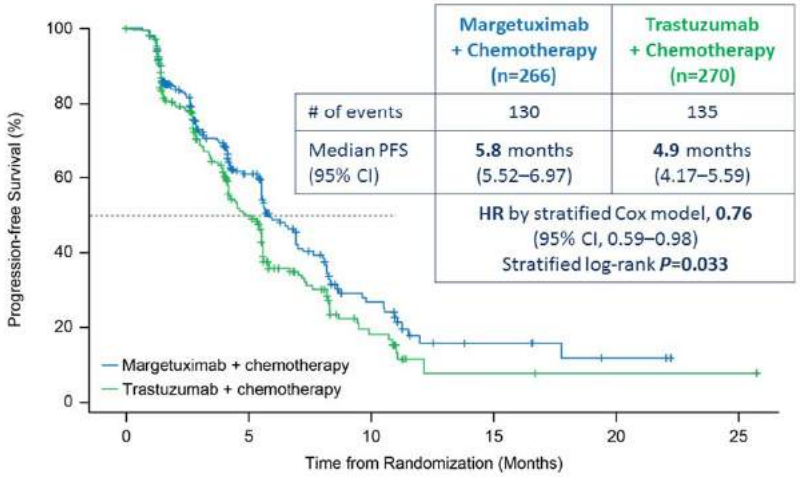
	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
Settings of prior therapy		
Adjuvant and/or neoadjuvant	**158 (59%)**	**145 (54%)**
Metastatic only	108 (41%)	125 (46%)
Prior metastatic lines of therapy		
≤2	175 (66%)	180 (67%)
>2	91 (34%)	90 (33%)
Prior anti-HER2 therapy		
Trastuzumab	**266 (100%)**	**270 (100%)**
Pertuzumab	**266 (100%)**	**269 (100%)**
T-DM1	**242 (91%)**	**247 (92%)**
Lapatinib	41 (15%)	39 (14%)
Other HER2	6 (2%)	6 (2%)
Prior chemotherapy		
Taxane	252 (95%)	249 (92%)
Anthracycline	118 (44%)	110 (41%)
Platinum	34 (13%)	40 (15%)
Prior endocrine therapy	126 (47%)	133 (49%)

Treatment arms overall balanced

ITT population: N=536.

PFS Analysis in ITT Population

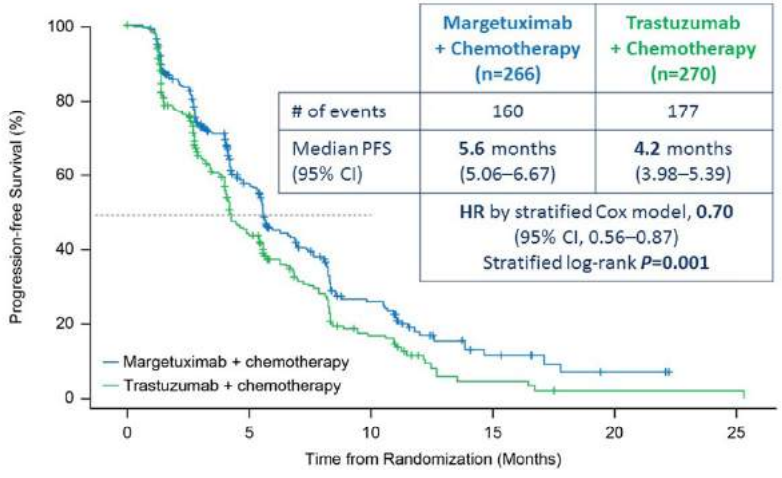
24% Risk Reduction of Disease Progression
Central Blinded Analysis (Primary Endpoint)



	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	130	135
Median PFS (95% CI)	**5.8** months (5.52–6.97)	**4.9** months (4.17–5.59)
HR by stratified Cox model, **0.76** (95% CI, 0.59–0.98) Stratified log-rank ***P*=0.033**		

Margetuximab	266	174	94	45	21	8	6	4	2	0	
Trastuzumab	270	158	74	33	13	2	2	1	1	1	1

30% Risk Reduction of Disease Progression
Investigator Assessed (Secondary Endpoint)



	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	160	177
Median PFS (95% CI)	**5.6** months (5.06–6.67)	**4.2** months (3.98–5.39)
HR by stratified Cox model, **0.70** (95% CI, 0.56–0.87) Stratified log-rank ***P*=0.001**		

Margetuximab	266	206	155	112	72	61	33	32	16	13	8	7	3	2	2	0
Trastuzumab	270	184	130	87	59	45	25	21	10	5	4	3	1	1	1	1	0

- PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred

ITT population: N=536. CI=confidence interval.

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Real World Data on OS in MBC

	Year of Diagnosis					
OS (m)	2008	2009	2010	2011	2012	2013
HR+ HER2- (N=9.908)	43.7 (40.2-46.6)	42.0 (38.9-44.6)	40.9 (38.0-43.4)	42.0 (39.2-45.0)	44.5 (41.8-47.3)	40.3 (37.8-ND)
HER2+ (N=2.861)	38.6 (33.6-44.6)	42.3 (38.3-50.8)	40.1 (35.2-45.6)	42.3 (36.5-49.8)	51.1 (46.5-ND)	Not Reached
HR- HER2- (N=2.317)	15.1 (12.7-16.4)	15.1 (13.0-17.4)	14.7 (13.2-17.0)	14.0 (11.4-15.9)	13.9 (11.4-15.9)	14.1 (12.5-15.5)

Delaloge S, et al. ASCO 2017.

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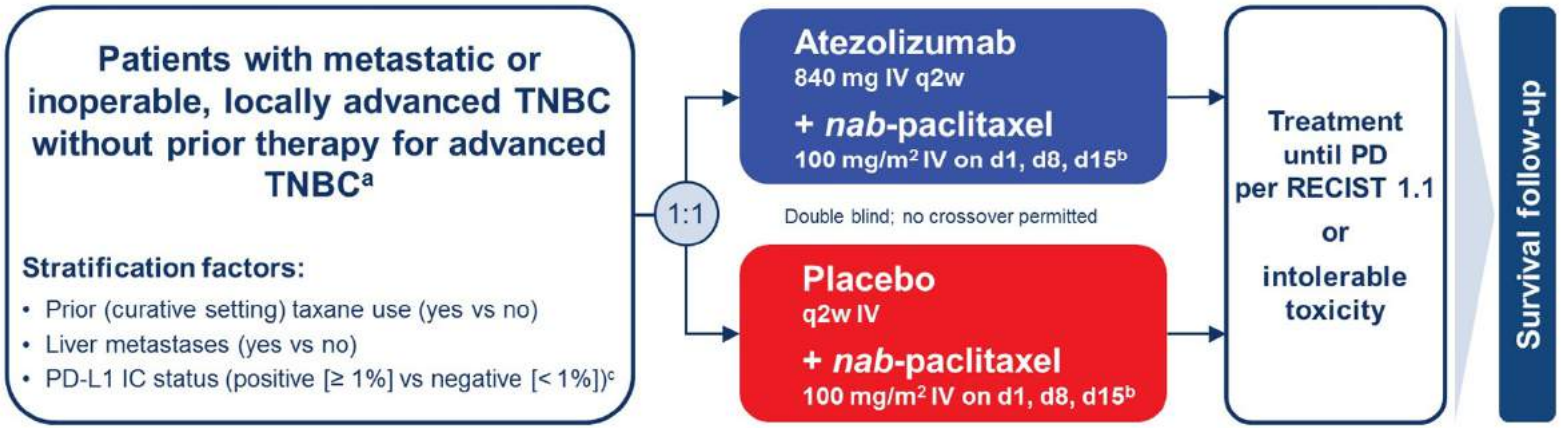
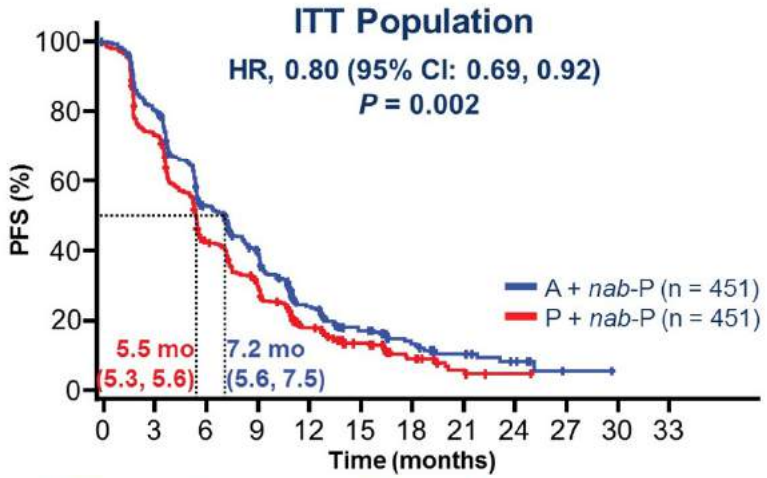
IMpassion130 Study Design

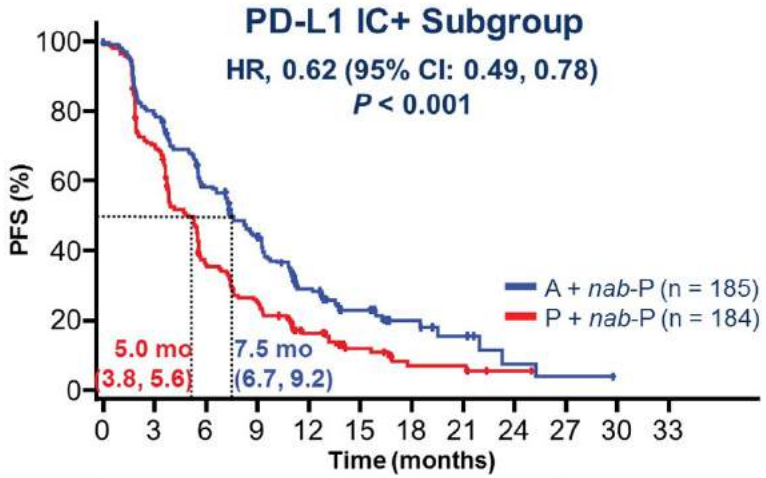


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

[a] Prior chemotherapy in the curative setting allowed if treatment-free interval ≥ 12 months. [b] 28-day cycle. [c] Centrally evaluated per VENTANA SP142 IHC assay.
[d] Efficacy endpoints assessed by investigators per RECIST 1.1. NCT02425891.

Primary PFS Analysis in the ITT and PD-L1 IC+ Subgroup



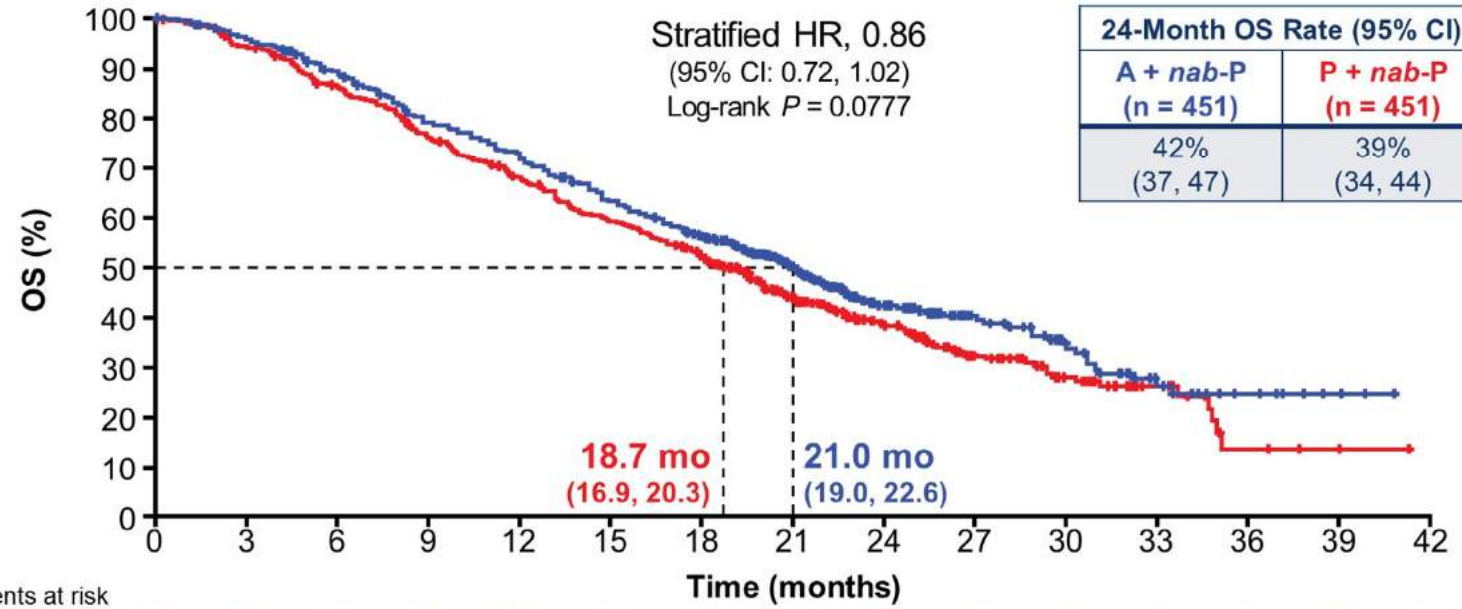


- PFS benefit driven by PD-L1 IC+ patients, as a treatment effect was not observed in PD-L1 IC− patients[1]
- Based on these data,[2] atezolizumab + *nab*-paclitaxel received accelerated approval by the FDA[3] and is recommended for patients with PD-L1 IC+ mTNBC in the NCCN[4] and AGO[5] guidelines

Data cutoff: April 17, 2018. Median follow-up (ITT): 12.9 months.

1. Emens SABCS 2018. 2. Schmid *New Engl J Med.* 2018. 3. Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2019.
4. NCCN Clinical Practice Guidelines. Breast Cancer. V1.2019. 5. AGO Guidelines Breast Version 2019.1.

OS in ITT Population



24-Month OS Rate (95% CI)	
A + *nab*-P (n = 451)	P + *nab*-P (n = 451)
42% (37, 47)	39% (34, 44)

Patients at risk

A + *nab*-P	451	426	389	342	312	270	235	162	88	56	35	19	8	3	NE
P + *nab*-P	451	420	376	329	291	252	216	145	87	51	33	17	4	1	NE

NE, not estimable. Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 mo.

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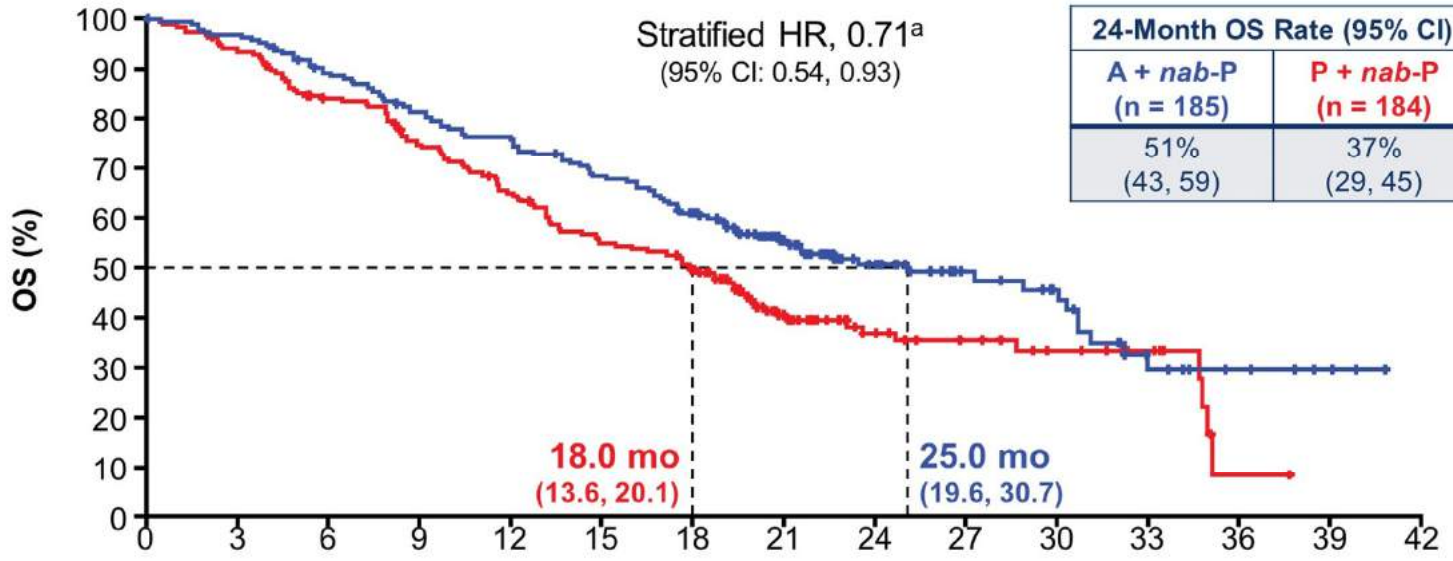
OS in PD-L1+ Population



24-Month OS Rate (95% CI)	
A + *nab*-P (n = 185)	P + *nab*-P (n = 184)
51% (43, 59)	37% (29, 45)

Patients at risk

A + *nab*-P	185	177	160	145	135	121	106	69	43	28	21	10	6	3	NE
P + *nab*-P	184	170	147	129	111	93	81	47	26	20	15	10	1	NE	NE

[a] Not formally tested due to pre-specified hierarchical analysis plan.
Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 months.

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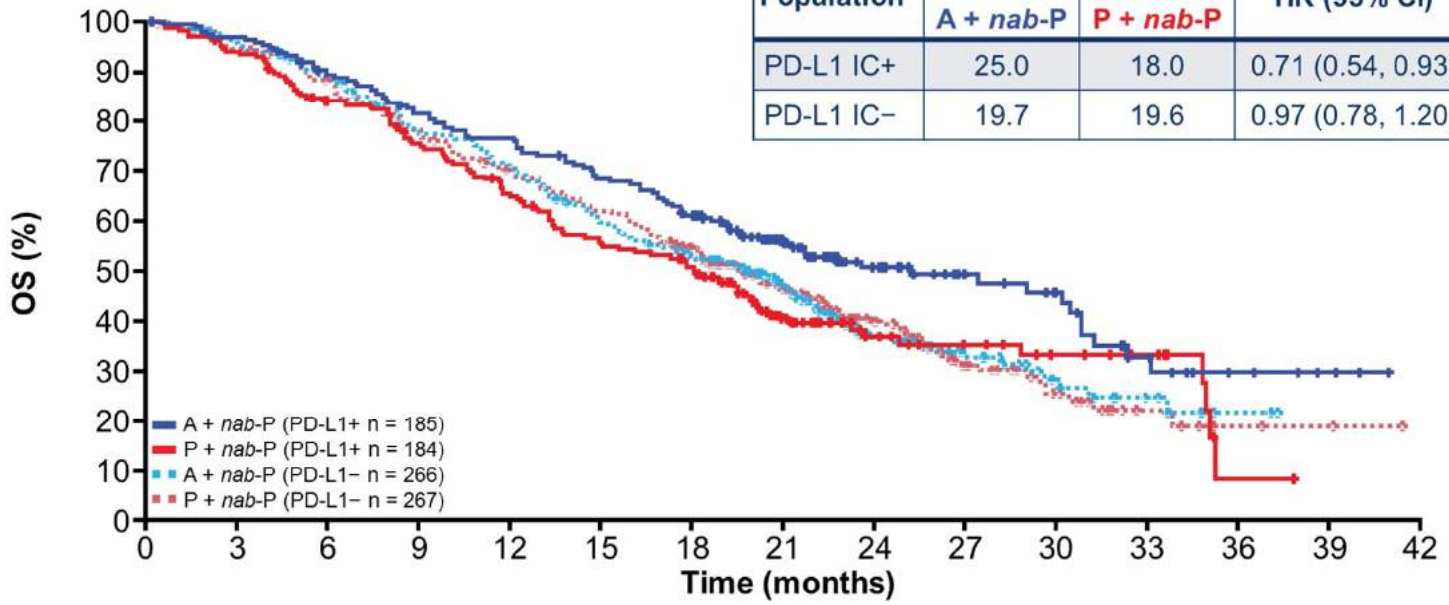
Comparison of OS in PD-L1+ and PD-L1− Populations

Population	Median OS, mo		HR (95% CI)
	A + *nab*-P	P + *nab*-P	
PD-L1 IC+	25.0	18.0	0.71 (0.54, 0.93)
PD-L1 IC−	19.7	19.6	0.97 (0.78, 1.20)



Clinical cutoff date: January 2, 2019.

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Advancing our knowledge in ER Positive Breast Cancer

Komal Jhaveri, MD FACP

Attending, Breast Medicine Service and Early Drug Development Service
Memorial Sloan Kettering Cancer Center/Evelyn H. Lauder Breast And Imaging Center
Assistant Professor, Weil Cornell Medical College

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MONALEESA-7 Study Design

First Phase III trial with a CDK4/6 inhibitor exclusively in premenopausal patients

Pre/perimenopausal women[a] with HR+/HER2− ABC

No prior ET for ABC[b]
≤ 1 prior CT for ABC

N = 672

Randomized 1:1

Ribociclib
600 mg/day;
3 weeks on/1 week off
+
NSAI/TAM[c] + GOS[d]
n = 335

Placebo
3 weeks on/1 week off
+
NSAI/TAM[c] + GOS[d]
n = 337

Primary endpoint
- PFS (local)

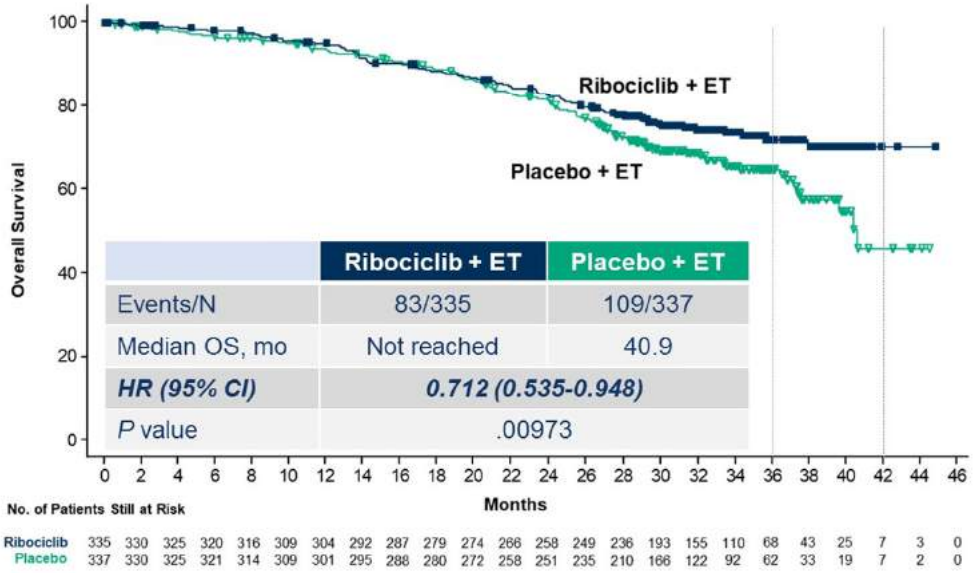
Key secondary endpoint
- OS

Select secondary endpoints
- HRQOL
- ORR
- TTDD of ECOG PS
- Safety

Stratification Factors
- Liver/lung metastasis (yes/no)
- Prior chemotherapy (yes/no)
- Combination partner (NSAI/TAM)

ANA, anastrozole; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FSH, follicle-stimulating hormone; GOS, goserelin; HRQOL, health-related quality of life; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; TAM, tamoxifen; TTDD, time to definitive deterioration.
*Premenopausal status was defined as either patient had last menstrual period ≤ 12 months ***or*** if receiving TAM or toremifene for ≤ 14 days, plasma estradiol and FSH must be in normal premenopausal range ***or*** in the case of induced amenorrhea, plasma estradiol and FSH must be in normal premenopausal range. Perimenopausal status was defined as neither premenopausal nor postmenopausal (prior bilateral oophorectomy, age ≥ 60 years, or FSH and plasma estradiol levels in normal postmenopausal range). Patients could not be ≥ 60 years of age. [b] Patients who received ≤ 14 days of NSAI/TAM ± GOS were allowed. [c] TAM and NSAI were administered daily orally. TAM dose was 20 mg, LET dose was 2.5 mg. and ANA dose was 1 mg. [d] GOS 3.6 mg was administered by subcutaneous injection.

Overall Survival



	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	***0.712 (0.535-0.948)***	
P value	.00973	

- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	71.9%	64.9%
42 months	***70.2%***	***46.0%***

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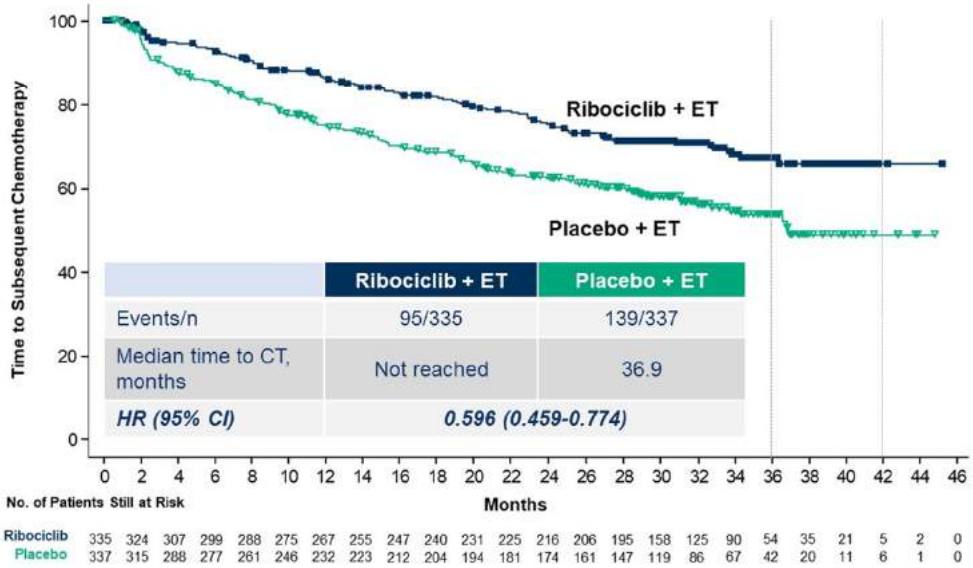
Time to First Subsequent Chemotherapy



	Ribociclib + ET	Placebo + ET
Events/n	95/335	139/337
Median time to CT, months	Not reached	36.9
HR (95% CI)	***0.596 (0.459-0.774)***	

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	67.2%	53.8%
42 months	65.8%	49.0%

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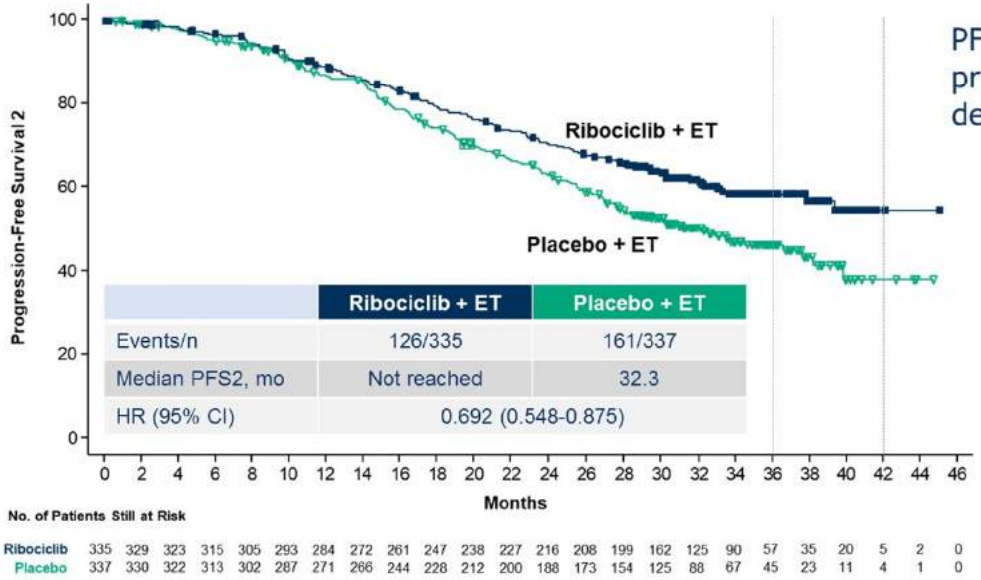
Progression-Free Survival 2

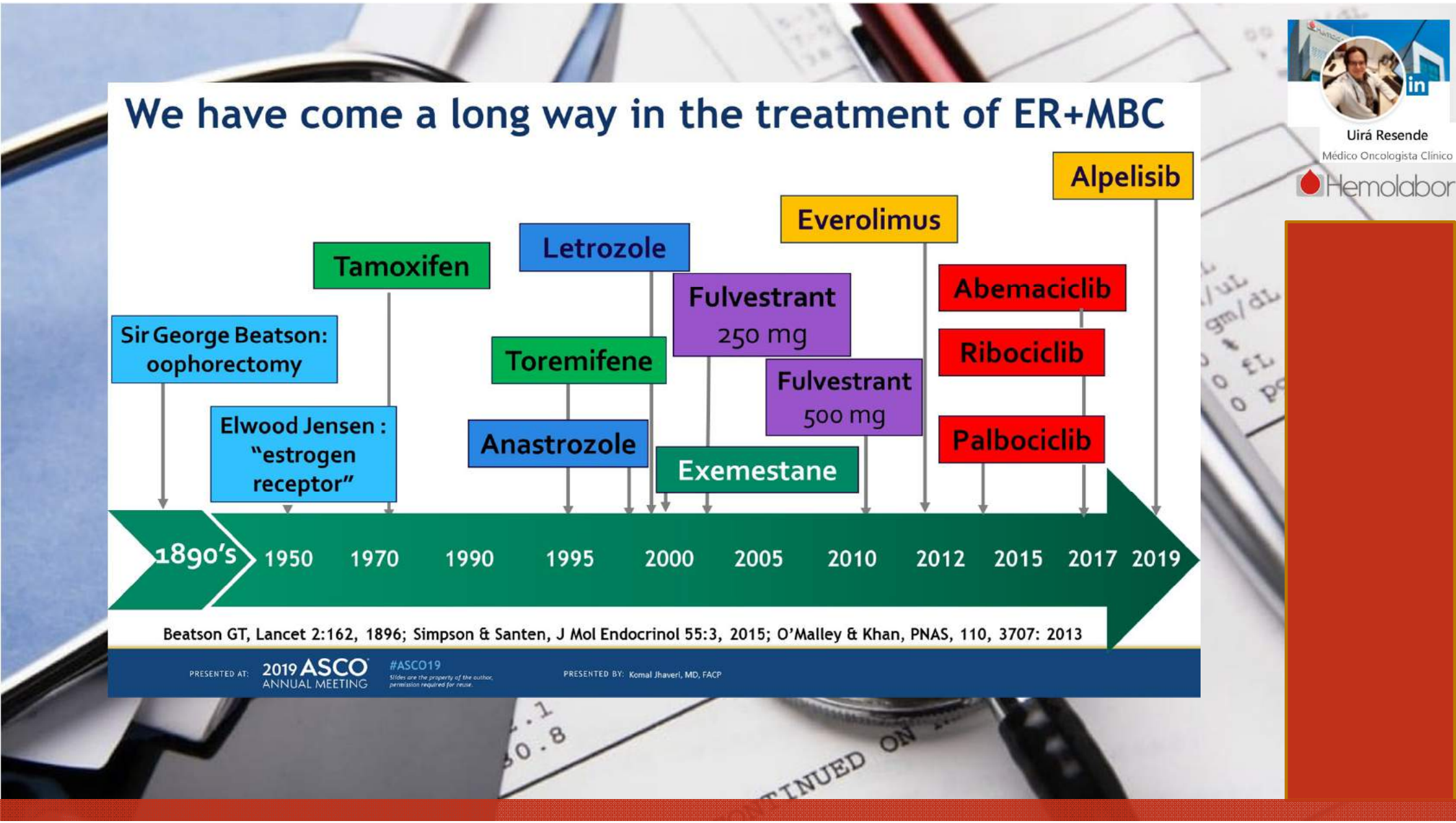


	Ribociclib + ET	Placebo + ET
Events/n	126/335	161/337
Median PFS2, mo	Not reached	32.3
HR (95% CI)	0.692 (0.548-0.875)	

PFS 2: time from randomization to progression on the next line of therapy or death

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	58.4%	46.2%
42 months	54.6%	37.8%



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My thoughts…
What do we need to know?

Results from TRINITI-1 single arm phase 2 trial of continuing a CDK 4/6i + BOLERO-2 like regimen are encouraging

Next Step: Randomized trial- Ribociclib + ET + Everolimus vs ET + Everolimus

- Data from Phase 2 MAINTAIN (PI Kevin Kalinsky; NCT02632045)
- Data from Phase 2 PACE (PI Erica Mayer; NCT03147287)
- Data from Phase 2 PALMIRA (NCT03809988)
- Data from Phase 2 BYLieve trial PIK3CA mutant tumors (NCT03056755)

Biomarker analyses are hypothesis generating and need validation

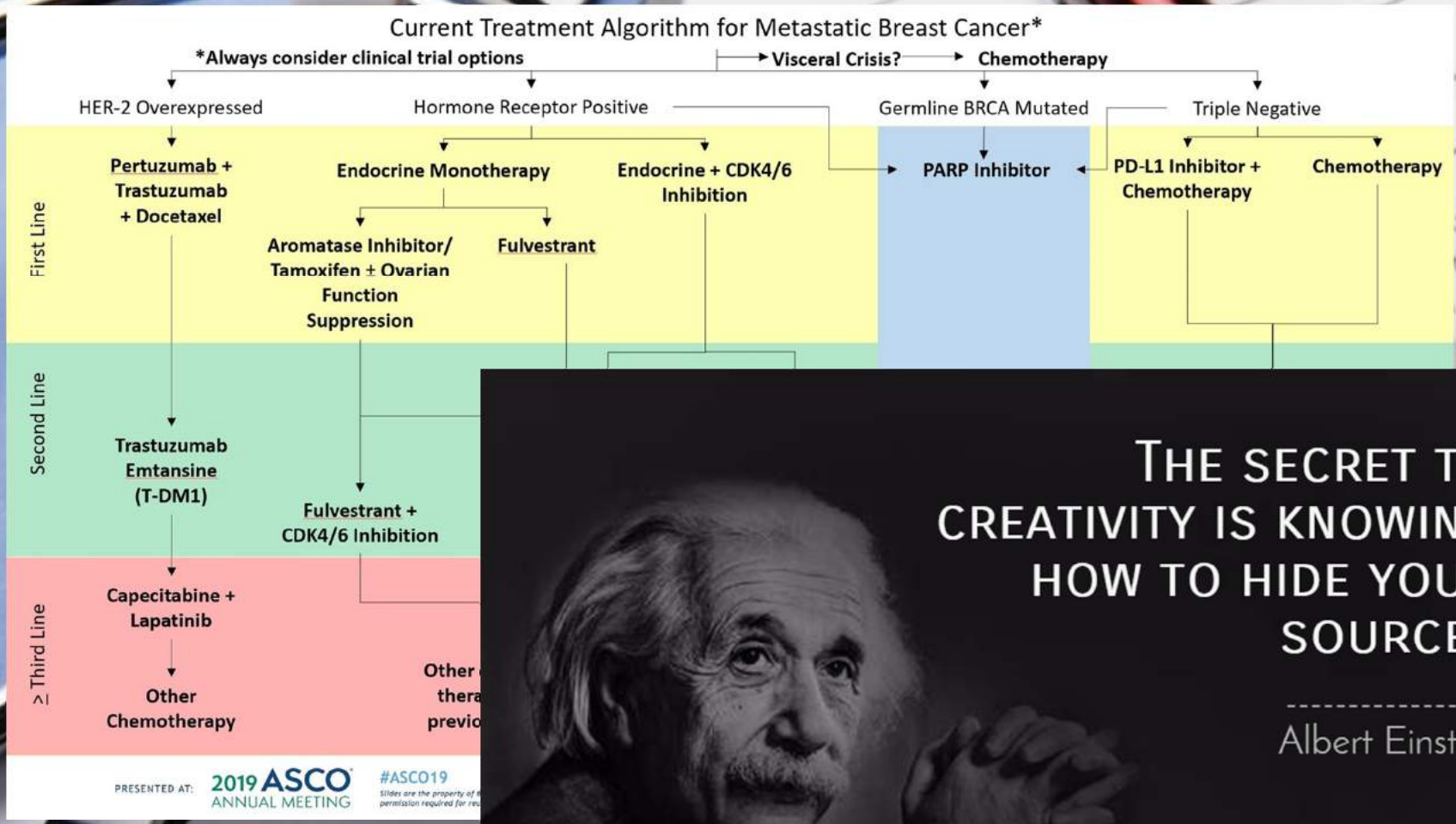
- Shorter PFS in patients with mutations in cfDNA could be a reflection of ?aggressive tumor ? high tumor burden
- ESR1 mutants: choice of SERD as ET partner

BOTTOM LINE: CDK4/6i should NOT be used beyond progression outside of clinical trials until we have results from ongoing randomized studies

O'Leary et al. Cancer Discovery 2019; Dhakal et al ASCO 2018, Abstract 1064; Cook et al ASCO 2019, Abstract 1058

Uirá Resende
Médico Oncologista Clínico
Hemolabor

Take Home Message:



Uirá Resende
Médico Oncologista Clínico
Hemolabor


TODOS
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