Highlights of the year

Marija Balic

March 6 th 2020

NH Hotel Vienna Airport

Dislosures

- Research funding: Celgene, Lilly, Novartis, Pfizer, Samsung
- Advisory role: Amgen, AstraZeneca, Lilly, MSD, Novartis, Pierre Fabre,Pfizer, Roche, Samsung
- Speakers buearau: Amgen, AstraZeneca, Celgene, Lilly, Novartis, Pierre Fabre, Pfizer, Roche

CECOG ACADEMY

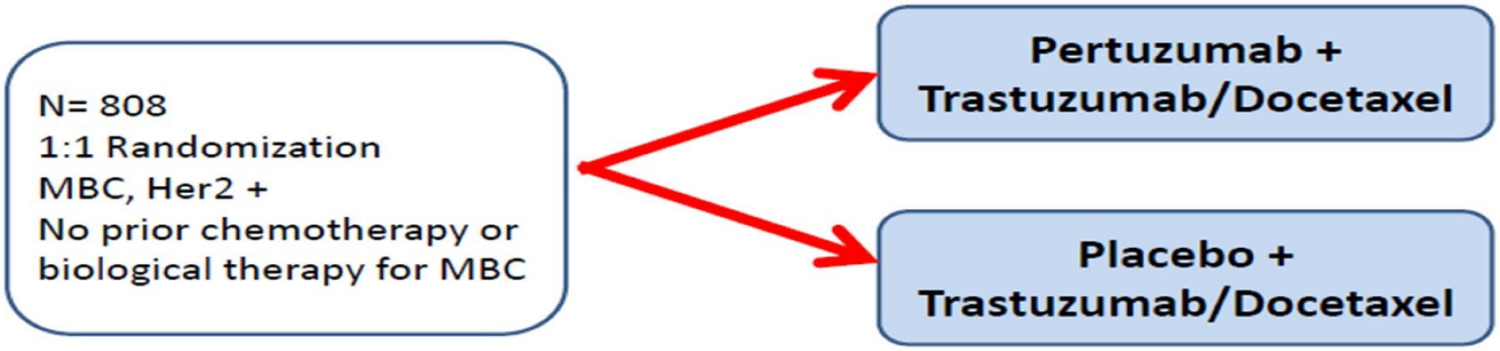
- Metastatic Breast Cancer
- Early Breast Cancer
- Translational Research

CECOG ACADEMY

- Metastatic Breast Cancer
- Early Breast Cancer
- Translational Research

CECOG ACADEMY

Her2 positive metastatic setting



Trastuzumab (8 mg /kg LD then 6 mg/ kg Q3W and Docetaxel 75 mg/m2 Q3W
Pertuzumab 840 mg LD then 420 mg Q3W

Baselga et al, NEJM 2012; Hahn O, ASCO 2019

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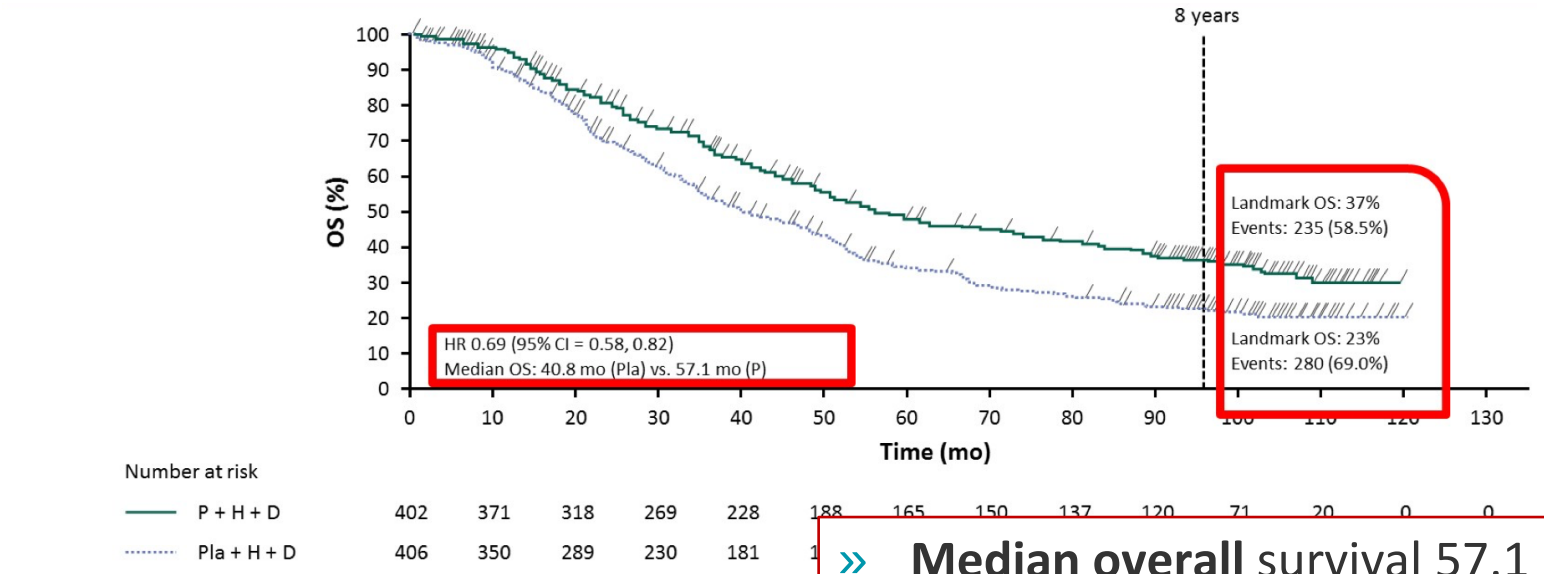
Her2 positive metastatic setting- end of treatment OS analysis Cleopatra



* Crossover pts were analyzed in the Pla arm.
OS was compared between arms using the log-rank test, stratified by prior treatment status and geographic
used to estimate median OS, and a stratified Cox proportional hazards model was used to estimate the HR a
CI, confidence interval; D, docetaxel; H, trastuzumab; HR, hazard ratio; ITT, intention-to-treat; OS, overall su

- **Median overall** survival 57.1 months vs. 40.8 = 16.3 months absolute difference
- The 8-year landmark overall survival rates were 37% and 23%

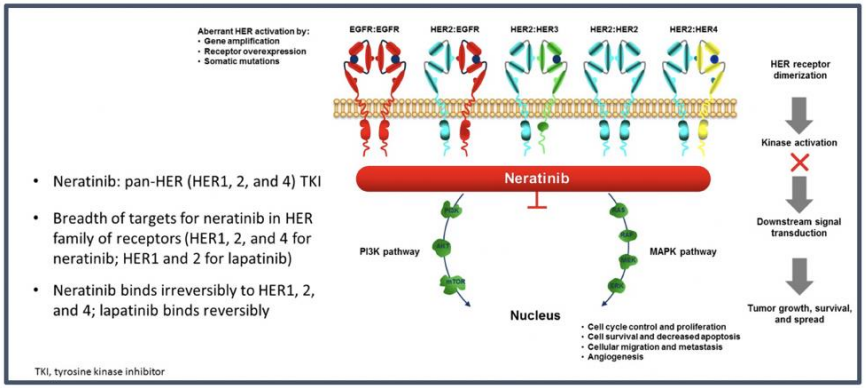
Baselga et al, NEJM 2012; Hahn O, ASCO 2019

CECOG ACADEMY

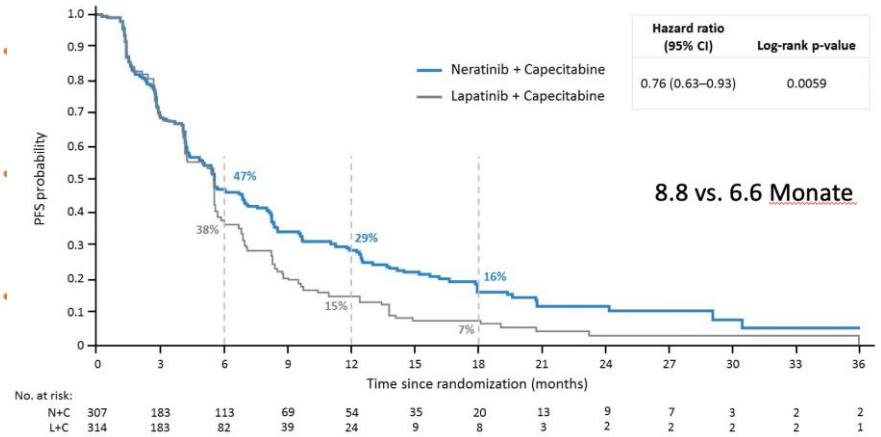
Neratinib

Neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with ≥2 HER2-directed regimens: Findings from the multinational, randomized, phase 3 NALA trial

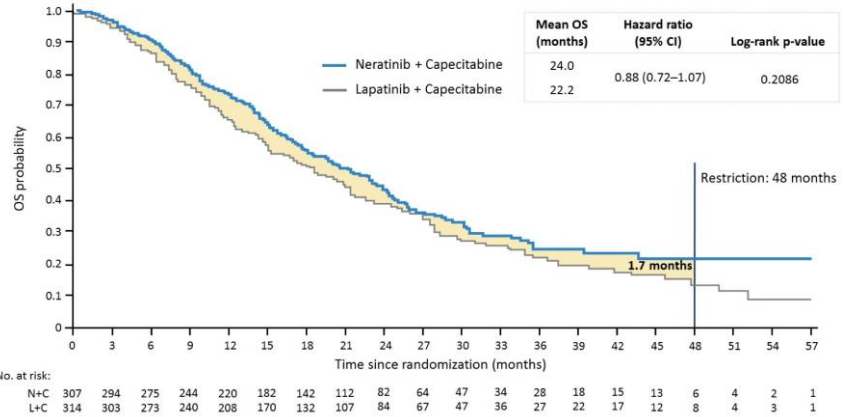
Cristina Saura, Mafalda Oliveira, Yin-Hsun Feng, Ming-Shen Dai, Sara A Hurvitz, Sung-Bae Kim, Beverly Moy, Suzette Delaloge, William Gradishar, Norikazu Masuda, Marketa Palacova, Maureen E Trudeau, Johanna Mattson, Yoon Sim Yap, Richard Bryce, Bin Yao, Judith Bebchuk, Kiana Keyvanjah, Adam Brufsky, NALA Investigators



Centrally confirmed PFS (co-primary)



OS (co-primary)



CECOG ACADEMY

Her2 climb with Tucatinib

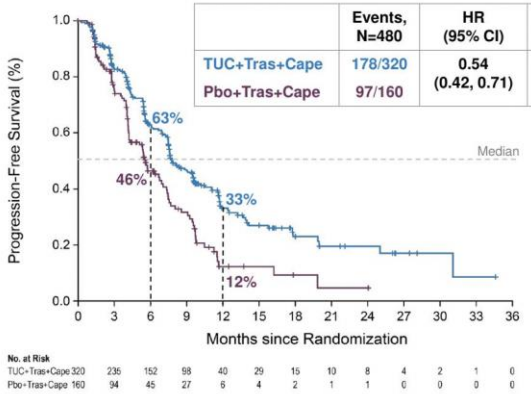
Her2CLIMB Trial

Tucatinib+ Capecitabine+Trastuzumab (N=207)

R

Placebo+ Capecitabine+Trastuzumab (N=201)

PFS



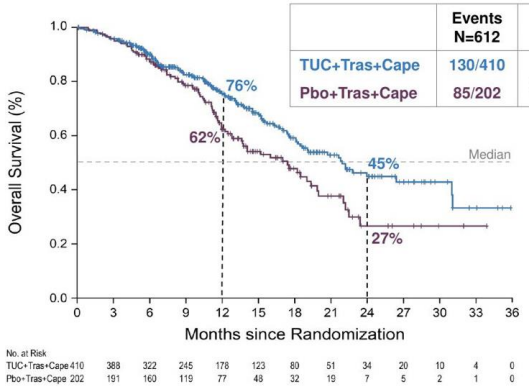
	Events, N=480	HR (95% CI)	P Value
TUC+Tras+Cape	178/320	0.54 (0.42, 0.71)	<0.00001
Pbo+Tras+Cape	97/160		

Risk of progression or death was reduced by 46% in the primary endpoint population

One-year PFS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
33% (27, 40)	12% (6, 21)
Median PFS (95% CI):	
7.8 months (7.5, 9.6)	5.6 months (4.2, 7.1)

Prespecified efficacy boundary for PFS: P=0.05
Data cut off: Sep 4, 2019

OS



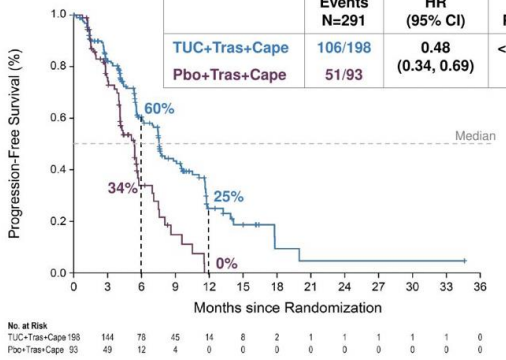
	Events N=612	HR (95% CI)	P Value
TUC+Tras+Cape	130/410	0.66 (0.50, 0.88)	0.00480
Pbo+Tras+Cape	85/202		

Risk of death was reduced by 34% in the total population

Two-year OS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
45% (37, 53)	27% (16, 39)
Median OS (95% CI):	
21.9 months (18.3, 31.0)	17.4 months (13.6, 19.9)

Prespecified efficacy boundary for OS (P=0.0074) was met at the first interim analysis.
Data cut off: Sep 4, 2019

PFS in pts with brain mets

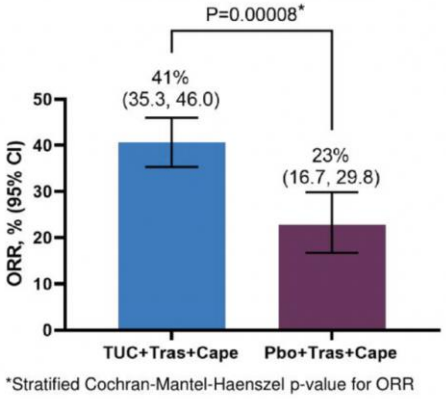


	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	106/198	0.48 (0.34, 0.69)	<0.00001
Pbo+Tras+Cape	51/93		

Risk of progression or death in patients with brain metastases was reduced by 52% in the total population

One-year PFS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
25% (17, 34)	0%
Median PFS (95% CI):	
7.6 months (6.2, 9.5)	5.4 months (4.1, 5.7)

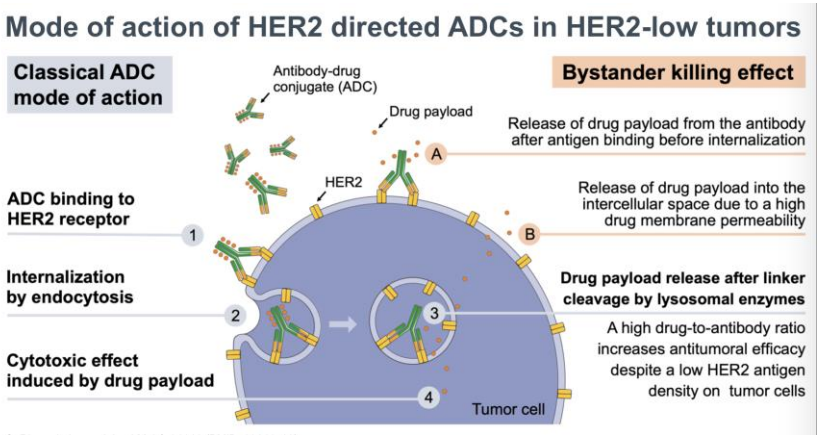
Prespecified efficacy boundary for $PFS_{BrainMets}$ (P=0.0080) was met at the first interim analysis.
Data cut off: Sep 4, 2019

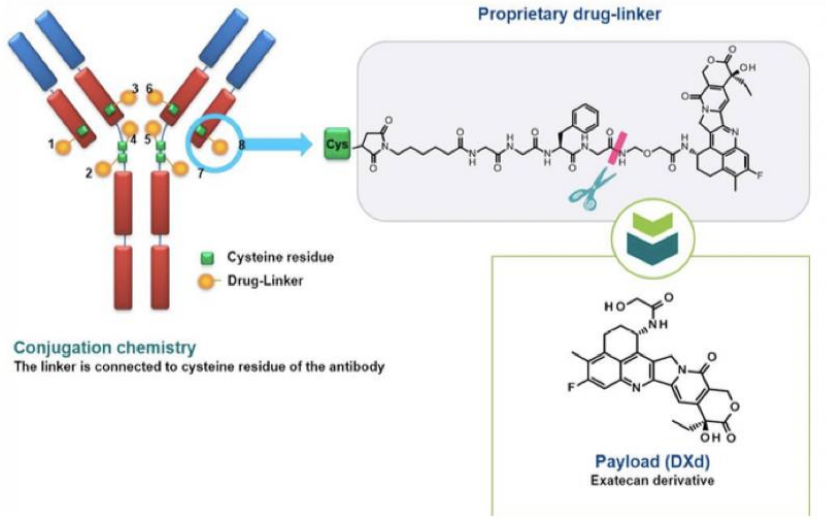


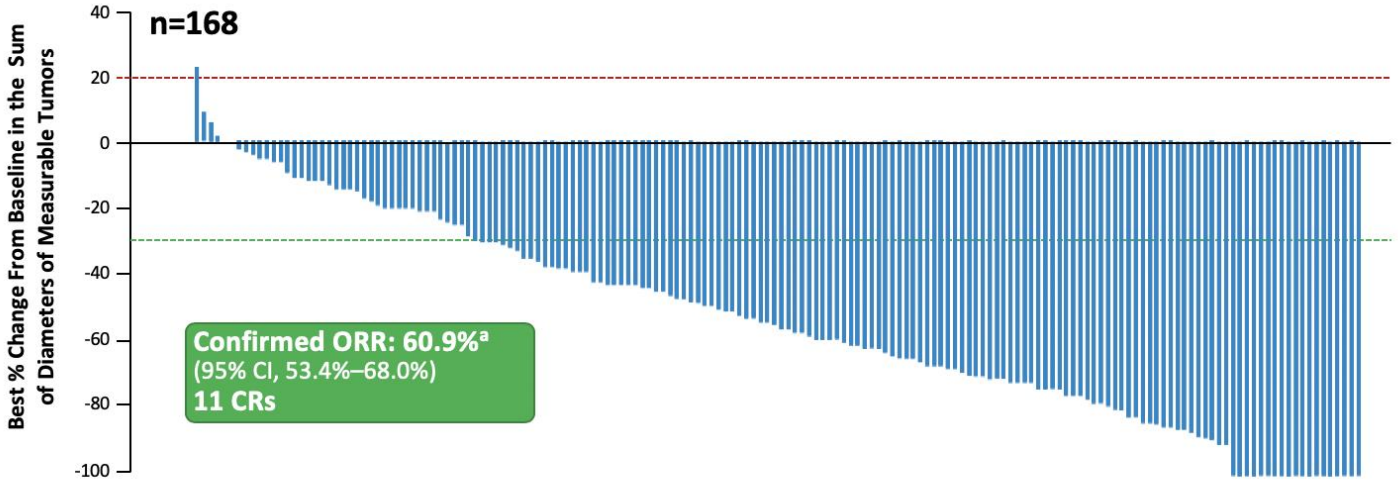
*Stratified Cochran-Mantel-Haenszel p-value for ORR

CECOG ACADEMY

Trastuzumab deruxtecan







CECOG ACADEMY

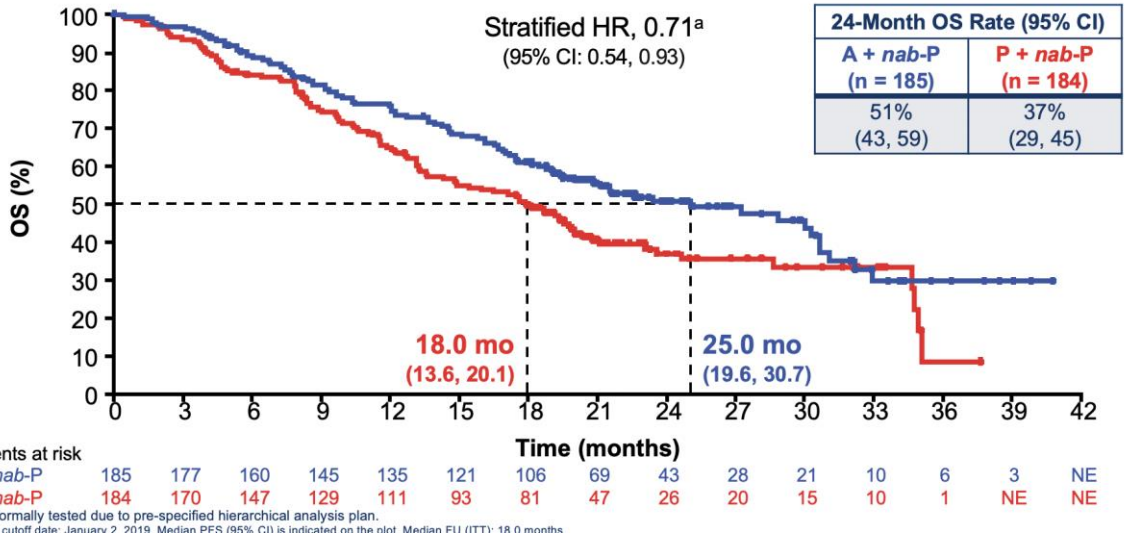
Triple negative metastatic breast cancer

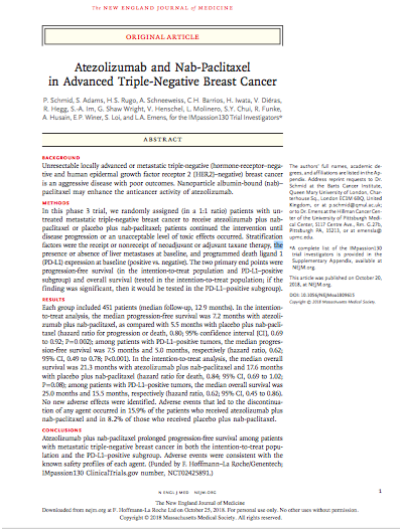
» OS in PD L1 + population

Impassion 130

R

- Atezo + nab Paclitaxel (N=451)
- Placebo+ Nab-Paclitaxel (N=451)

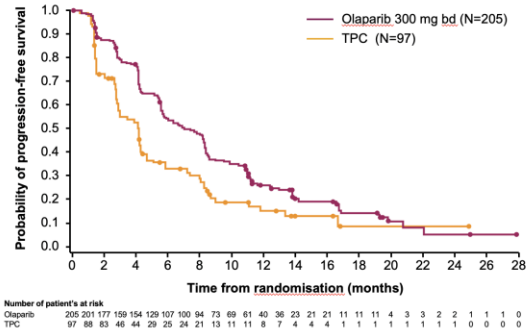




CECOG ACADEMY

PARP inhibitors in BRCA positive patients

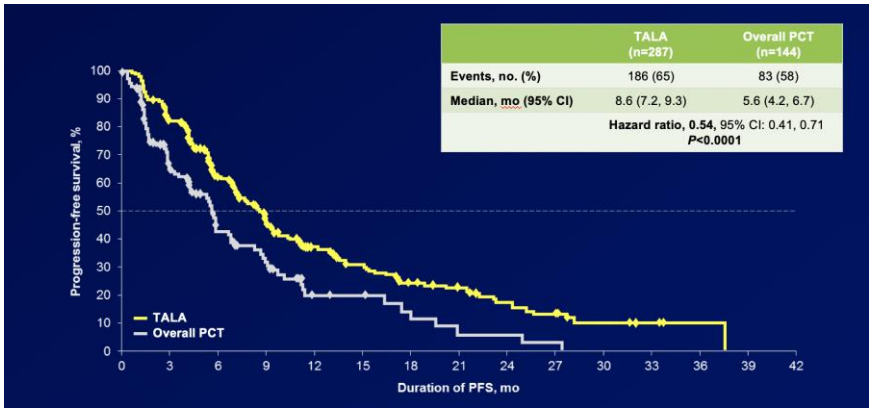
OLYMPIAD

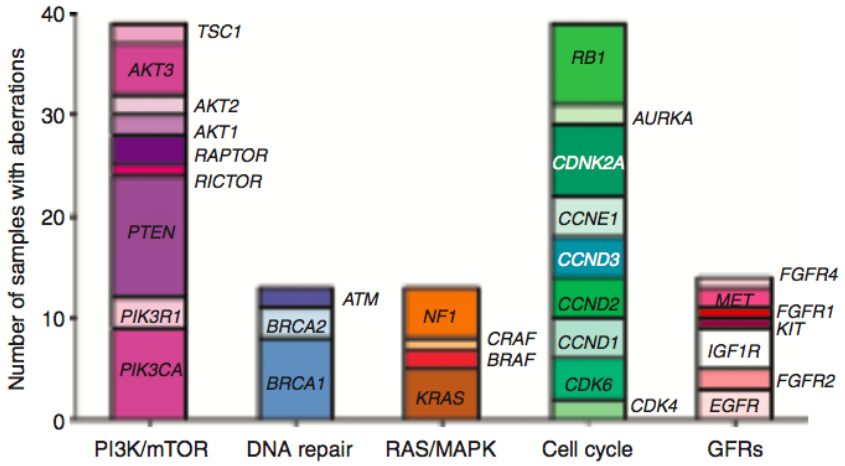


	Olaparib	TPC
n	205	97
Events (%)	163 (79.5%)	71 (73.2%)
Median (m)	7.0	4.2
	HR = 0.58 95 % CI (0.43, 0.80) p=0.0009	
PFS free at 6m (%)	54.1	32.9
PFS free at 12m (%)	25.9	15.0

Median PFS was improved by 69% with olaparib treatment compared to standard of care chemotherapy[2]

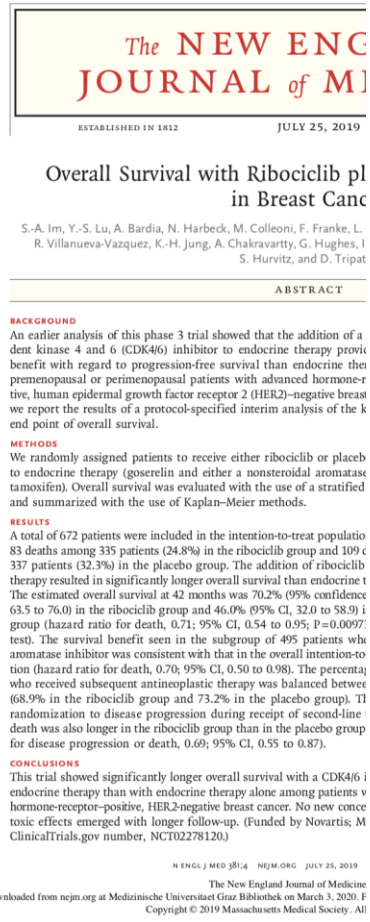
EMBRACA





CECOG ACADEMY

CDK 4/6 inhibitors and OS



The NEW ENG
JOURNAL of MI

ESTABLISHED IN 1812 JULY 25, 2019

Overall Survival with Ribociclib pl
in Breast Canc

S.-A. Im, Y.-S. Lu, A. Bardia, N. Harbeck, M. Colleoni, F. Franke, L.
R. Villanueva-Vazquez, K.-H. Jung, A. Chakravartty, G. Hughes, I
S. Hurvitz, and D. Tripat

ABSTRACT

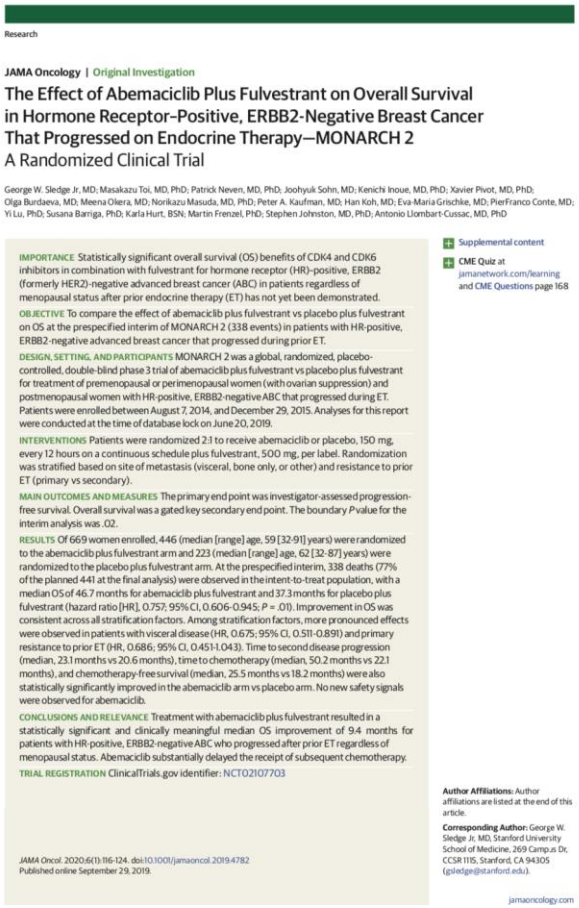
BACKGROUND
An earlier analysis of this phase 3 trial showed that the addition of a
dent kinase 4 and 6 (CDK4/6) inhibitor to endocrine therapy provi
benefit with regard to progression-free survival than endocrine the
premenopausal or perimenopausal patients with advanced hormone-r
tive, human epidermal growth factor receptor 2 (HER2)–negative breast
we report the results of a protocol-specified interim analysis of the k
end point of overall survival.

METHODS
We randomly assigned patients to receive either ribociclib or placeb
to endocrine therapy (goserelin and either a nonsteroidal aromatase
tamoxifen). Overall survival was evaluated with the use of a stratified
and summarized with the use of Kaplan–Meier methods.

RESULTS
A total of 672 patients were included in the intention-to-treat populatio
83 deaths among 335 patients (24.8%) in the ribociclib group and 109 d
337 patients (32.3%) in the placebo group. The addition of ribociclib
therapy resulted in significantly longer overall survival than endocrine t
The estimated overall survival at 42 months was 70.2% (95% confidence
63.5 to 76.0) in the ribociclib group and 46.0% (95% CI, 32.0 to 58.9) i
group (hazard ratio for death, 0.71; 95% CI, 0.54 to 0.95; P=0.0097
test). The survival benefit seen in the subgroup of 495 patients wh
aromatase inhibitor was consistent with that in the overall intention-to
tion (hazard ratio for death, 0.70; 95% CI, 0.50 to 0.98). The percentag
who received subsequent antineoplastic therapy was balanced betwee
(68.9% in the ribociclib group and 73.2% in the placebo group). Th
randomization to disease progression during receipt of second-line
death was also longer in the ribociclib group than in the placebo group
for disease progression or death, 0.69; 95% CI, 0.55 to 0.87).

CONCLUSIONS
This trial showed significantly longer overall survival with a CDK4/6 i
endocrine therapy than with endocrine therapy alone among patients v
hormone-receptor–positive, HER2-negative breast cancer. No new conce
toxic effects emerged with longer follow-up. (Funded by Novartis; M
ClinicalTrials.gov number, NCT02278120.)

N ENGL J MED 381;4 NEJM.ORG JULY 25, 2019



Research

JAMA Oncology | Original Investigation

The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2
A Randomized Clinical Trial

George W. Sledge Jr, MD; Masakazu Toi, MD, PhD; Patrick Neven, MD, PhD; Joohyuk Sohn, MD; Kenichi Inoue, MD, PhD; Xavier Pivot, MD, PhD; Olga Burdaeva, MD; Meena Okera, MD; Norikazu Masuda, MD, PhD; Peter A. Kaufman, MD; Han Koh, MD; Eva-Maria Grischke, MD; PierFranco Conte, MD; Yi Lu, PhD; Susana Barriga, PhD; Karla Hurt, BSN; Martin Frenzel, PhD; Stephen Johnston, MD, PhD; Antonio Llombart-Cussac, MD, PhD

IMPORTANCE Statistically significant overall survival (OS) benefits of CDK4 and CDK6 inhibitors in combination with fulvestrant for hormone receptor (HR)–positive, ERBB2 (formerly HER2)-negative advanced breast cancer (ABC) in patients regardless of menopausal status after prior endocrine therapy (ET) has not yet been demonstrated.

OBJECTIVE To compare the effect of abemaciclib plus fulvestrant vs placebo plus fulvestrant on OS at the prespecified interim of MONARCH 2 (338 events) in patients with HR-positive, ERBB2-negative advanced breast cancer that progressed during prior ET.

DESIGN, SETTING, AND PARTICIPANTS MONARCH 2 was a global, randomized, placebo-controlled, double-blind phase 3 trial of abemaciclib plus fulvestrant vs placebo plus fulvestrant for treatment of premenopausal or perimenopausal women (with ovarian suppression) and postmenopausal women with HR-positive, ERBB2-negative ABC that progressed during ET. Patients were enrolled between August 7, 2014, and December 29, 2015. Analyses for this report were conducted at the time of database lock on June 20, 2019.

INTERVENTIONS Patients were randomized 2:1 to receive abemaciclib or placebo, 150 mg, every 12 hours on a continuous schedule plus fulvestrant, 500 mg, per label. Randomization was stratified based on site of metastasis (visceral, bone only, or other) and resistance to prior ET (primary vs secondary).

MAIN OUTCOMES AND MEASURES The primary end point was investigator-assessed progression-free survival. Overall survival was a gated key secondary end point. The boundary *P* value for the interim analysis was .02.

RESULTS Of 669 women enrolled, 446 (median [range] age, 59 [32-91] years) were randomized to the abemaciclib plus fulvestrant arm and 223 (median [range] age, 62 [32-87] years) were randomized to the placebo plus fulvestrant arm. At the prespecified interim, 338 deaths (77% of the planned 441 at the final analysis) were observed in the intent-to-treat population, with a median OS of 46.7 months for abemaciclib plus fulvestrant and 37.3 months for placebo plus fulvestrant (hazard ratio [HR], 0.757; 95% CI, 0.606-0.945; *P* = .01). Improvement in OS was consistent across all stratification factors. Among stratification factors, more pronounced effects were observed in patients with visceral disease (HR, 0.675; 95% CI, 0.511-0.891) and primary resistance to prior ET (HR, 0.686; 95% CI, 0.451-1.043). Time to second disease progression (median, 23.1 months vs 20.6 months), time to chemotherapy (median, 50.2 months vs 22.1 months), and chemotherapy-free survival (median, 25.5 months vs 18.2 months) were also statistically significantly improved in the abemaciclib arm vs placebo arm. No new safety signals were observed for abemaciclib.

CONCLUSIONS AND RELEVANCE Treatment with abemaciclib plus fulvestrant resulted in a statistically significant and clinically meaningful median OS improvement of 9.4 months for patients with HR-positive, ERBB2-negative ABC who progressed after prior ET regardless of menopausal status. Abemaciclib substantially delayed the receipt of subsequent chemotherapy.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT02107703

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 168

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: George W. Sledge Jr, MD, Stanford University School of Medicine, 269 Campus Dr, CCSR 1115, Stanford, CA 94305 (gsledge@stanford.edu).

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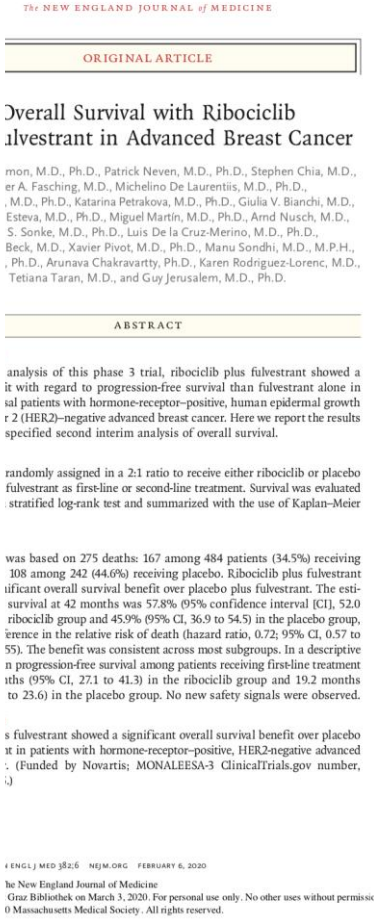

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Ribociclib
ılvestrant in Advanced Breast Cancer

mon, M.D., Ph.D., Patrick Neven, M.D., Ph.D., Stephen Chia, M.D.,
er A. Fasching, M.D., Michelino De Laurentiis, M.D., Ph.D.,
, M.D., Ph.D., Katarina Petrakova, M.D., Ph.D., Giulia V. Bianchi, M.D.,
Esteva, M.D., Ph.D., Miguel Martín, M.D., Ph.D., Arnd Nusch, M.D.,
S. Sonke, M.D., Ph.D., Luis De la Cruz-Merino, M.D., Ph.D.,
Beck, M.D., Xavier Pivot, M.D., Ph.D., Manu Sondhi, M.D., M.P.H.,
, Ph.D., Arunava Chakravartty, Ph.D., Karen Rodriguez-Lorenc, M.D.,
Tetiana Taran, M.D., and Guy Jerusalem, M.D., Ph.D.

ABSTRACT

analysis of this phase 3 trial, ribociclib plus fulvestrant showed a
it with regard to progression-free survival than fulvestrant alone in
sal patients with hormone-receptor–positive, human epidermal growth
r 2 (HER2)–negative advanced breast cancer. Here we report the results
specified second interim analysis of overall survival.

randomly assigned in a 2:1 ratio to receive either ribociclib or placebo
fulvestrant as first-line or second-line treatment. Survival was evaluated
stratified log-rank test and summarized with the use of Kaplan–Meier

was based on 275 deaths: 167 among 484 patients (34.5%) receiving
108 among 242 (44.6%) receiving placebo. Ribociclib plus fulvestrant
ificant overall survival benefit over placebo plus fulvestrant. The esti-
survival at 42 months was 57.8% (95% confidence interval [CI], 52.0
ribociclib group and 45.9% (95% CI, 36.9 to 54.5) in the placebo group,
erence in the relative risk of death (hazard ratio, 0.72; 95% CI, 0.57 to
55). The benefit was consistent across most subgroups. In a descriptive
n progression-free survival among patients receiving first-line treatment
nths (95% CI, 27.1 to 41.3) in the ribociclib group and 19.2 months
to 23.6) in the placebo group. No new safety signals were observed.

s fulvestrant showed a significant overall survival benefit over placebo
nt in patients with hormone-receptor–positive, HER2-negative advanced
. (Funded by Novartis; MONALEESA-3 ClinicalTrials.gov number,
.)

ENGL J MED 382;6 NEJM.ORG FEBRUARY 6, 2020

CECOG ACADEMY

Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial

Robert H Jones, Angela Casbard*, Margherita Carucci, Catrin Cox, Rachel Butler, Fouad Alchami, Tracie-Ann Madden, Catherine Bale, Pavel Bezecny, Johnathan Joffe, Sarah Moon, Chris Twelves, Ramachandran Venkitaraman, Simon Waters, Andrew Foxley, Sacha J Howell*

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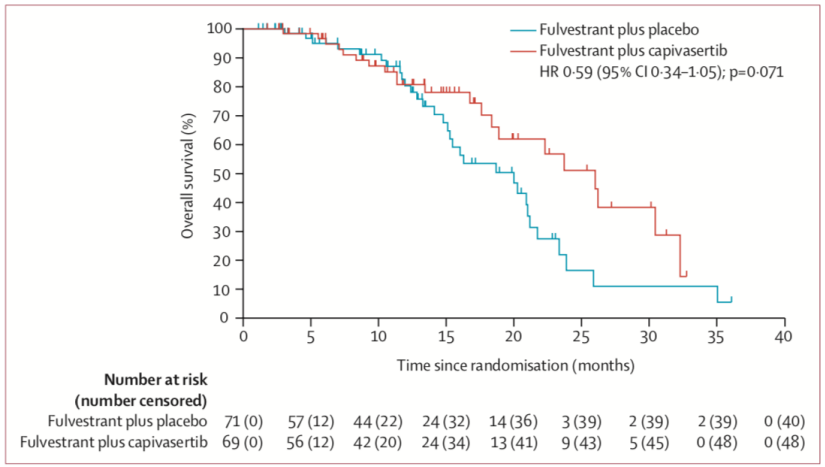
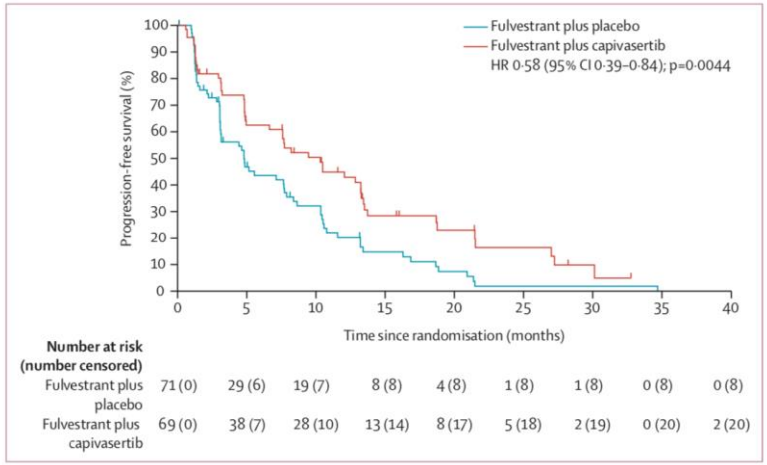
- Fulvestrant + Capivasertib (N=69)
- Fulvestrant+Placebo (N=71)

Median PFS 10.3 vs 4.8 Months



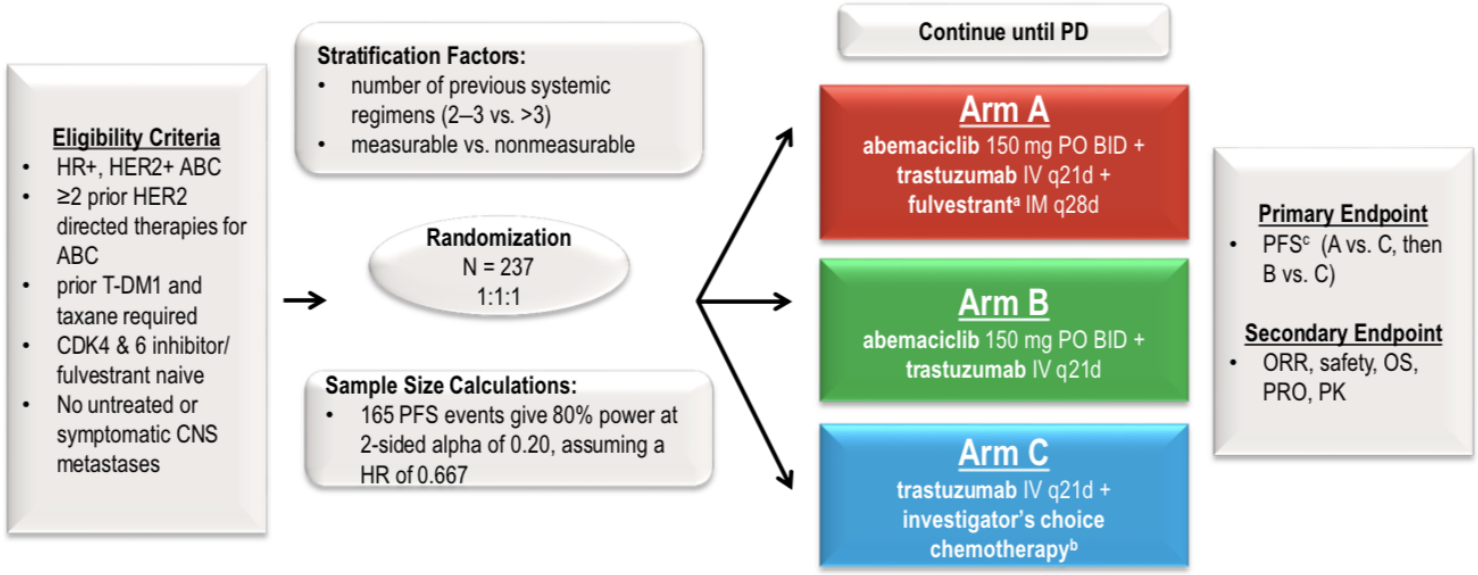
OS



CECOG ACADEMY

Triple positive breast cancer

monarcHER STUDY DESIGN



BARCELONA 2019 ESMO congress

Abbreviations: ABC = advanced breast cancer, HR+ = hormone receptor-positive, HER2(+) = human epidermal growth factor receptor-2 (positive), n = number of patients, PD = progressive disease, BID= twice daily, q21d= every 21 days, PFS = Progression Free Survival, ORR = Objective Response Rate, OS = Overall Survival, PRO = Patient Reported Outcomes, PK = pharmacokinetics

[a]Dosing per fulvestrant label

[b]Standard-of-care single-agent chemotherapy should include approved drug in breast cancer.

[c]investigator assessed

CECOG ACADEMY

MonarcHER

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

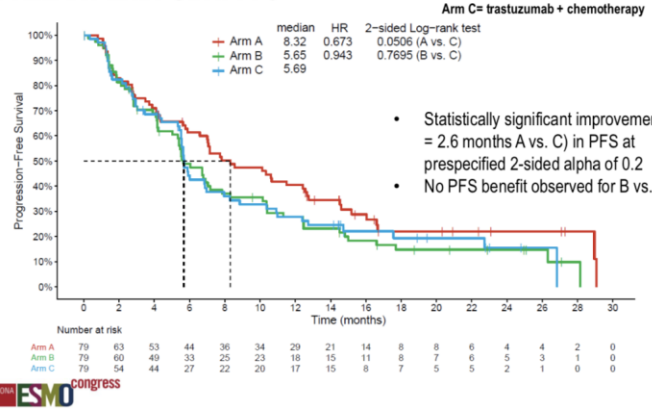
Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy

	Arm A N=79	Arm B N=79	Arm C [b] N=79
Median age, years (range)	55 (31-78)	54 (28-83)	57 (29-82)
Geographic distribution, n (%)			
Asia / Pacific	13 (16.5)	13 (16.5)	12 (15.2)
Europe	30 (38.0)	45 (57.0)	36 (45.6)
N. America	24 (30.4)	13 (16.5)	24 (30.4)
S. America	12 (15.2)	8 (10.1)	7 (8.9)
Metastatic Site, n (%)			
Visceral	58 (73.4)	56 (70.9)	48 (60.8)
Bone-only	7 (8.9)	3 (3.8)	7 (8.9)
Measurable disease, n (%)	70 (88.6)	68 (86.1)	69 (87.3)
Prior systemic therapies for ABC, n (%)			
2 to 3	35 (44.3)	44 (55.7)	40 (50.6)
More than 3	44 (55.7)	35 (44.3)	39 (49.4)
Prior endocrine therapy overall[a], n (%)	63 (79.7)	60 (75.9)	60 (75.9)
Tamoxifen in any setting	35 (44.3)	45 (57.0)	37 (46.8)
AI in any setting	46 (58.2)	42 (53.2)	42 (53.2)
Prior HER2 therapies for ABC, n (%)			
trastuzumab	77 (97.5)	76 (96.2)	79 (100.0)
trastuzumab emtansine	77 (97.5)	78 (98.7)	77 (97.5)
pertuzumab	43 (54.4)	37 (46.8)	39 (49.4)
lapatinib	35 (44.3)	37 (46.8)	31 (39.2)

[a]any of the following: letrozole, anastrozole, exemestane, tamoxifen
[b]most common chemotherapy: Vinorelbine (37.5%) , Capecitabine (26.4%) , Eribulin (16.7%), Gemcitabine (11.1%)

PRIMARY ENDPOINT: PFS

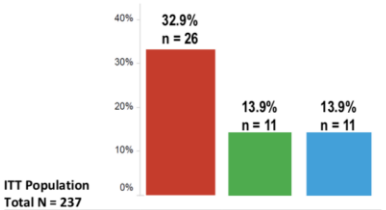
Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy



- Statistically significant improvement (Δ = 2.6 months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

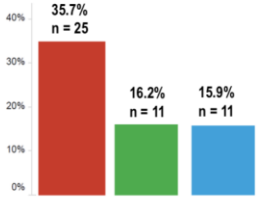
CONFIRMED BEST OVERALL RESPONSE RATE

Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy



ITT Population
Total N = 237

	Arm A N=79	Arm B N=79	Arm C N=79
95% CI (%)	(22.5-43.3)	(6.3-21.6)	(6.3-21.6)
Stratified 2-sided p-value (vs Arm C)	0.0042	1.0000	-
Duration of Response, months	12.5	9.5	not reached



Measurable Disease
Total N = 207

	Arm A N=70	Arm B N=68	Arm C N=69
95% CI (%)	(24.5-46.9)	(7.4-24.9)	(7.3-24.6)
Stratified 2-sided p-value (vs Arm C)	0.0111	1.0000	-
Duration of Response, months	10.4	9.5	not reached

Toalaney et al, ESMO 2019

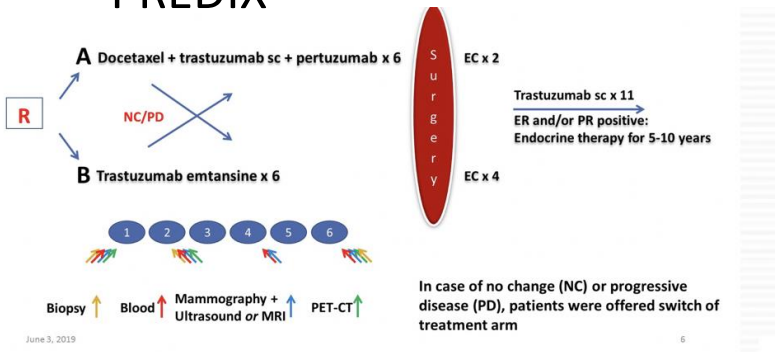
CECOG ACADEMY

- Metastatic Breast Cancer
- Early Breast Cancer
- Translational Research

CECOG ACADEMY

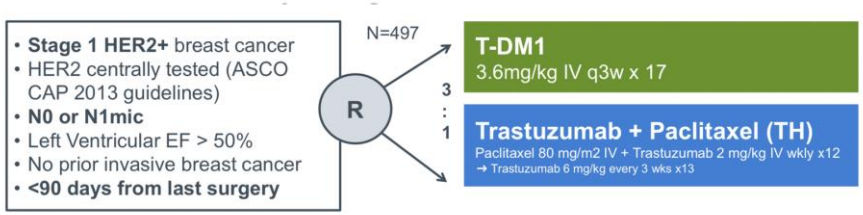
Deescalation neo/adjuvant

PREDIX

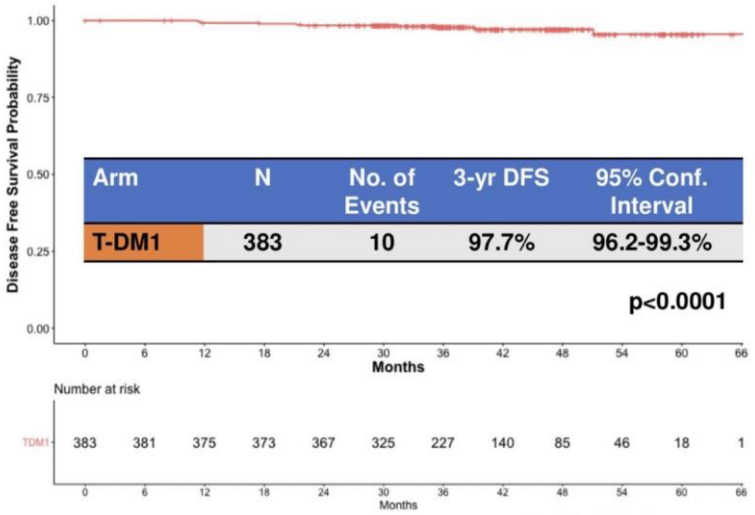


All patients	Docetaxel, trastuzumab, pertuzumab N = 99 (%)	Trastuzumab emtansine N = 98 (%)	
pCR	46 (47)	44 (45)	Chi² 2.049
No pCR (SD or PR)	53 (54)	52 (53)	p = 0.359
(PD by radiology)	0	2 (2)	
ER and PR negative	**N = 33 (%)**	**N = 39 (%)**	
pCR	22 (67)	23 (59)	Chi² 0.451
No pCR	11 (33)	16 (41)	p = 0.502
ER and/or PR positive	**N = 66 (%)**	**N = 59 (%)**	
pCR	24 (36)	21 (36)	Chi² 0.008
No pCR	42 (64)	38 (64)	p = 0.929

ATEMPT

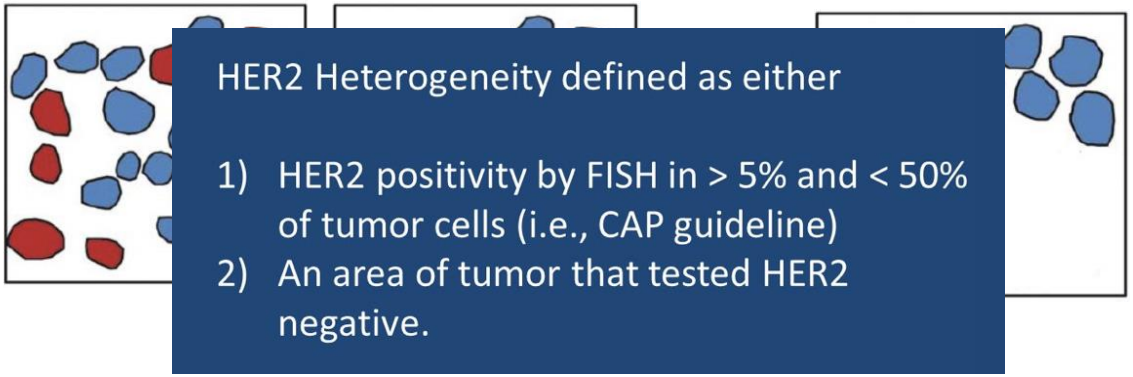


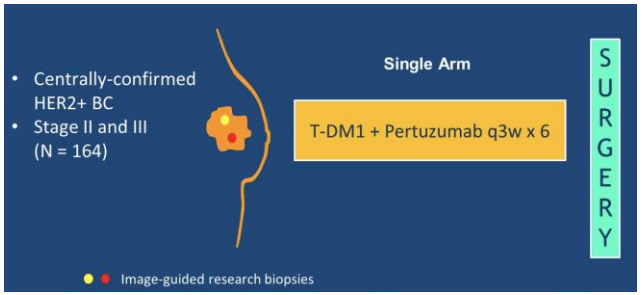
Co-primary Endpoints:
Evaluate **3 year** DFS in the T-DM1 arm
Compare the incidence of clinically relevant toxicities between the 2 arms



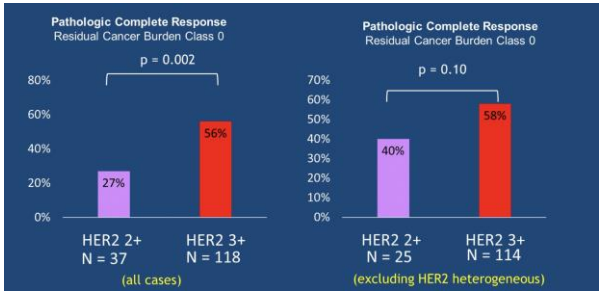
CECOG ACADEMY

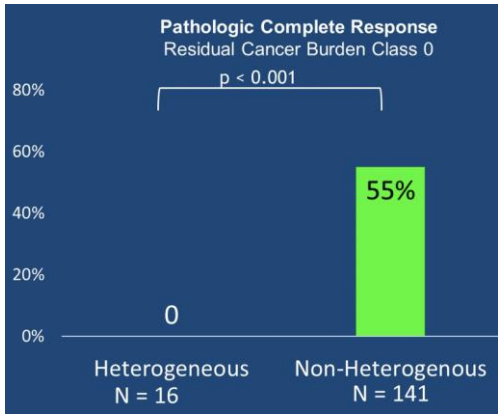
Phase II evaluating Her2heterogeneity as a predictor of response to neoadjuvant T-DM1

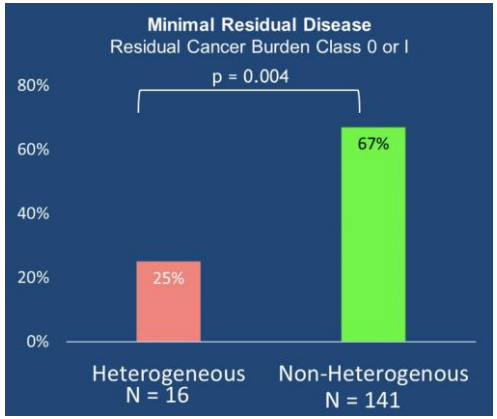




16/157 (10%) pts w heterogenous Her2
13 (81%) ER+ and 3(19%) ER-





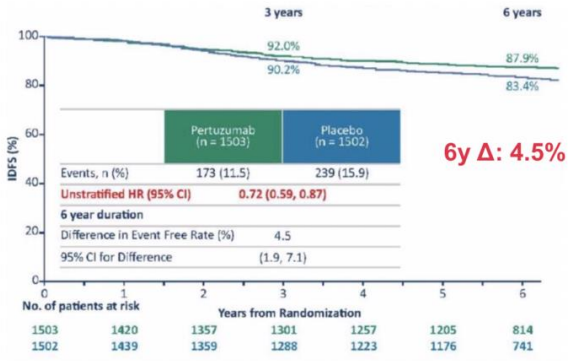


Metzger et al ASCO 2019

CECOG ACADEMY

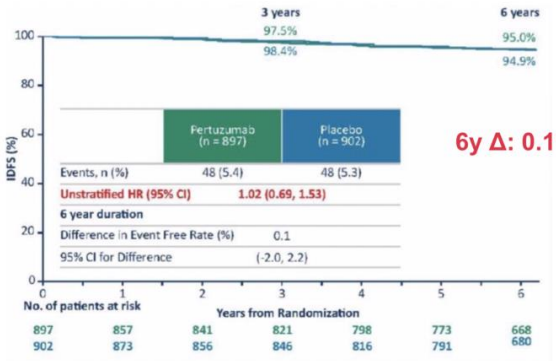
Aphinity update

LK positive



6y Δ: 4.5%

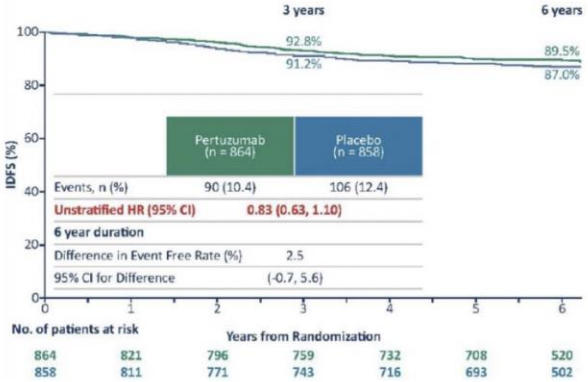
LK negative



6y Δ: 0.1%

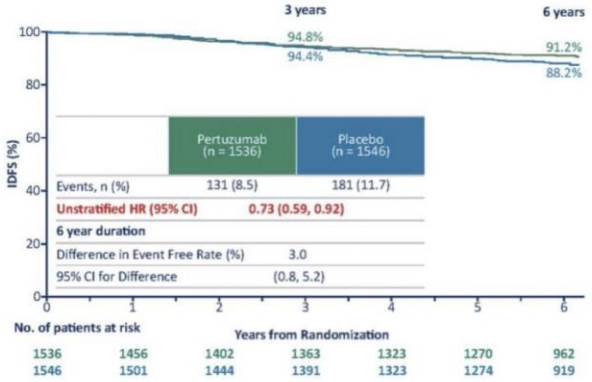
HR negative cohort

ITT population



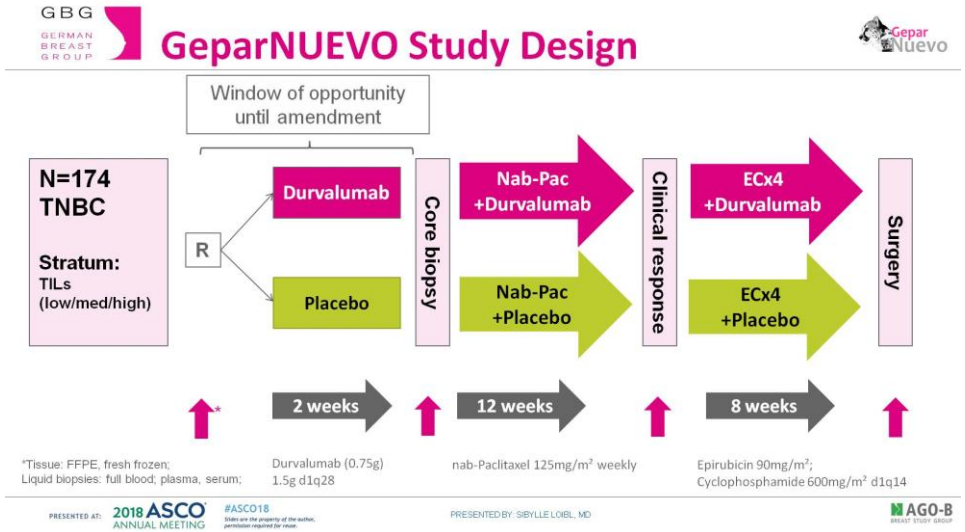
HR positive cohort

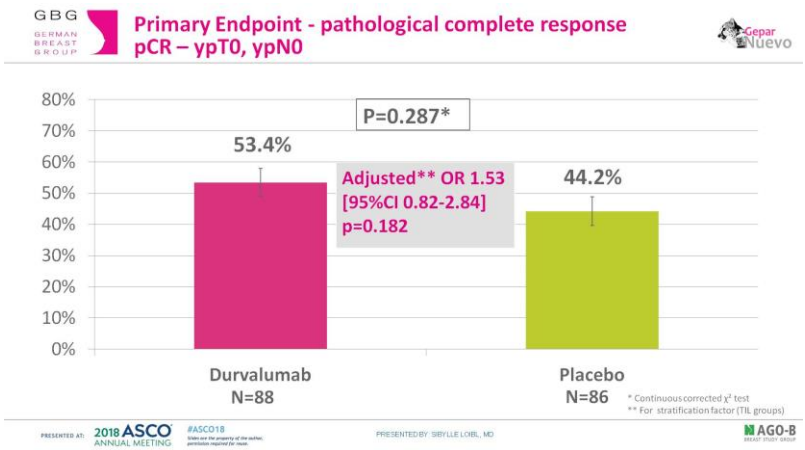
ITT population



CECOG ACADEMY

Immunotherapy in triple negative breast cancer neoadjuvant





NeoTRIPaPDL1 Michelangelo

*HER-2 negative, ER and PgR negative early high-risk (T1cN1; T2N1; T3N0) or locally advanced unilateral breast cancer

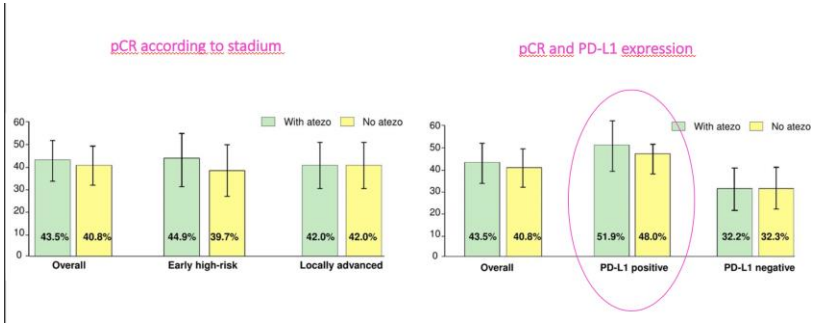
R

Carboplatin (AUC2) + *nab*-paclitaxel (125 mg/m²) weekly for 2 wks every 3; 8 cy → S

Carboplatin (AUC2) + *nab*-paclitaxel (125 mg/m²) weekly for 2 wks every 3; 8 cy **+ Atezolizumab (1200 mg)** day 1 every 3 wks for 8 cycles → S

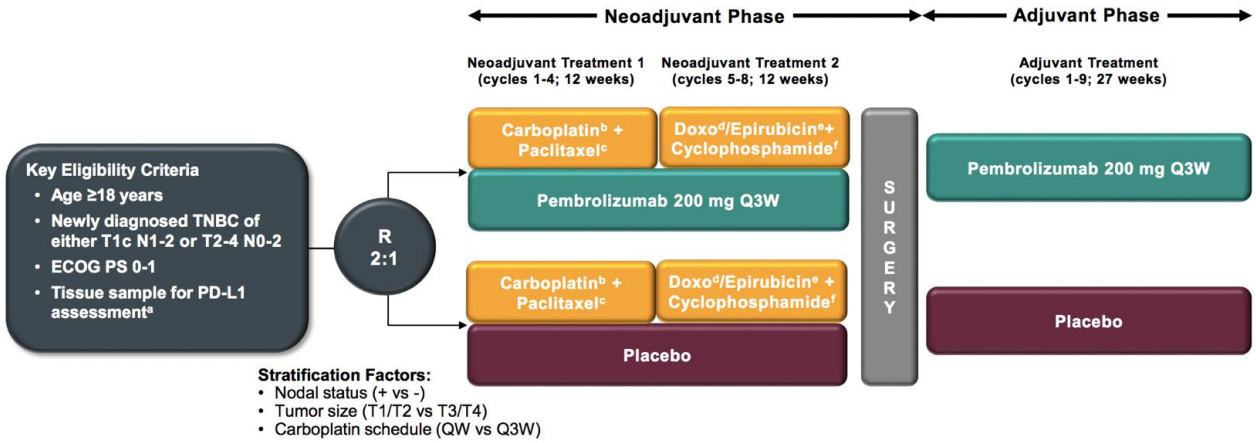
4 cycles of an anthracycline regime of investigetor choisce

No anthracyclines



CECOG ACADEMY

Immunotherapy in triple negative breast cancer neoadjuvant- KEYNOTE 522

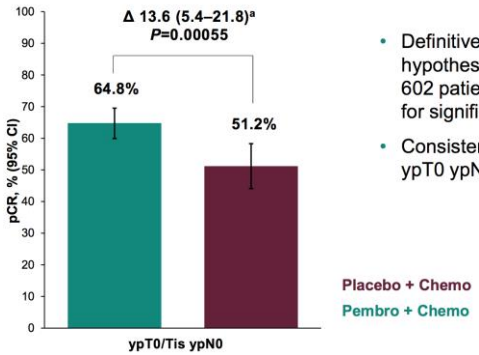


Primary EP:
pCR (ypT0/Ti) ypN0),
Event-free Survival (EFS)

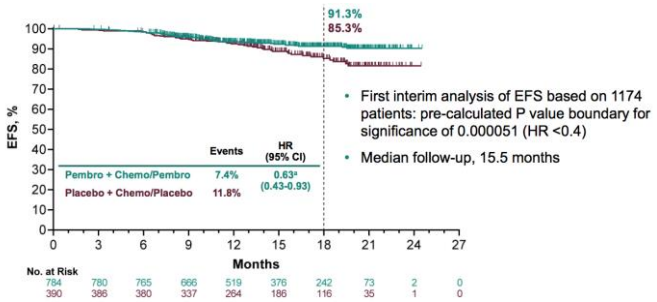
Sek. Eps
OS; pCR/EFS/OS in PD-L1 +

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)



- Definitive pCR analysis to test primary hypothesis of pCR based on prespecified first 602 patients (pre-calculated P value boundary for significance of 0.003)
- Consistent benefit seen with pCR defined as ypT0 ypN0 and ypT0/Tis



- First interim analysis of EFS based on 1174 patients: pre-calculated P value boundary for significance of 0.000051 (HR <0.4)
- Median follow-up, 15.5 months

CECOG ACADEMY

- Metastatic Breast Cancer
- Early Breast Cancer
- Translational Research

CECOG ACADEMY

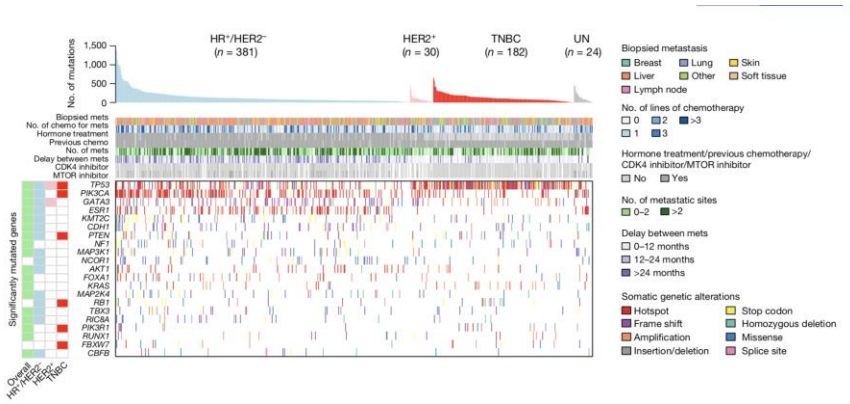
LETTER

Corrected: Author Correction

https://doi.org/10.1038/s41586-019-1056-z

Genomic characterization of metastatic breast cancers

François Bertucci[1,25], Charlotte K. Y. Ng[2,3,24,25], Anne Patsouris[4,5,25], Nathalie Droin[6,7,8], Salvatore Piscuoglio[2,3], Nadine Carbuccia[1], Jean Charles Soria[9,10], Alicia Tran Dien[11], Yahia Adnani[11], Maud Kamal[12], Séverine Garnier[1], Guillaume Meurice[11], Marta Jimenez[13], Semih Dogan[14], Benjamin Verret[14], Max Chaffanet[1], Thomas Bachelot[15], Mario Campone[4,5], Claudia Lefeuvre[16], Herve Bonnefoi[17], Florence Dalenc[18], Alexandra Jacquet[13], Maria R. De Filippo[2], Naveen Babbar[19], Daniel Birnbaum[1], Thomas Filleron[18,26], Christophe Le Tourneau[20,21,22,26] & Fabrice André[9,14,23,26]*



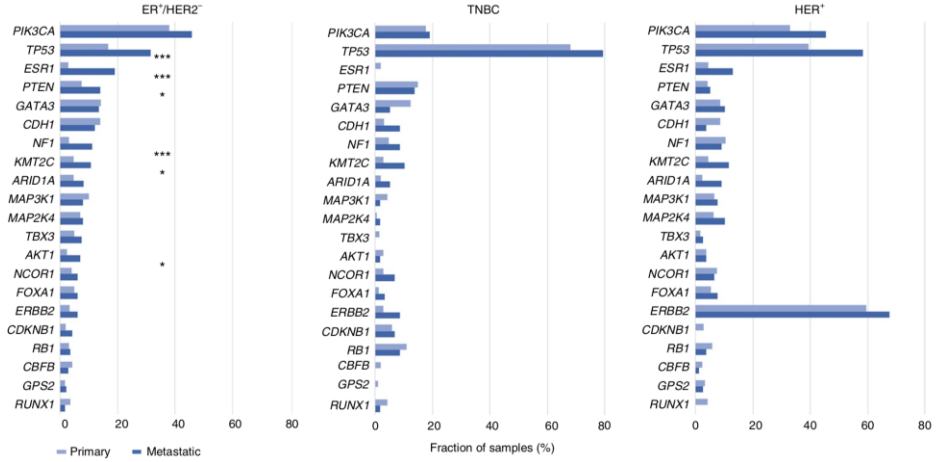
ARTICLES

https://doi.org/10.1038/s41588-019-0507-7

nature genetics

The genomic landscape of metastatic breast cancer highlights changes in mutation and signature frequencies

Lindsay Angus[1], Marcel Smid[1], Saskia M. Wilting[1], Job van Riet[1,2,3], Arne Van Hoeck[4], Luan Nguyen[4], Serena Nik-Zainal[5], Tessa G. Steenbruggen[6], Vivianne C. G. Tjan-Heijnen[7], Mariette Labots[8], Johanna M. G. H. van Riel[9], Haiko J. Bloemendal[10,11], Neeltje Steeghs[6,11], Martijn P. Lolkema[1,11], Emile E. Voest[6,11], Harmen J. G. van de Werken[2,3], Agnes Jager[1], Edwin Cuppen[4,12], Stefan Sleijfer[1,11] and John W. M. Martens[1,11]*



CECOG ACADEMY

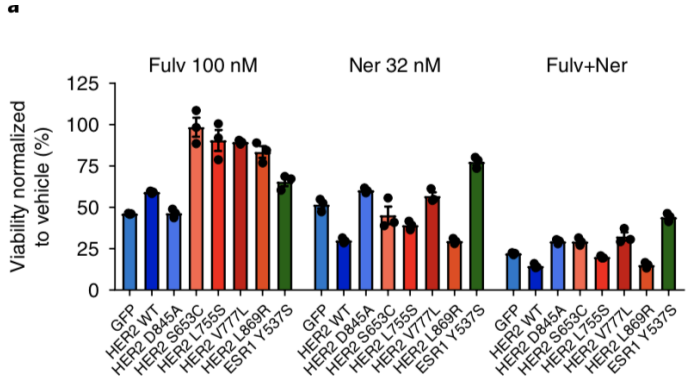
nature genetics

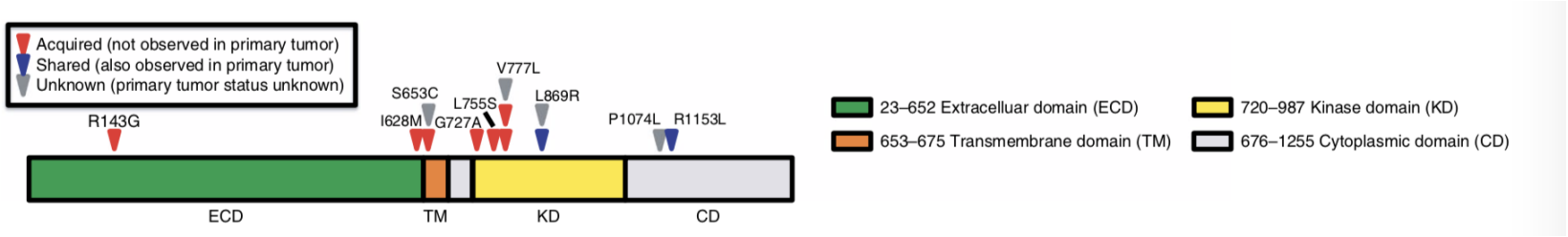
LETTERS

https://doi.org/10.1038/s41588-018-0287-5

Acquired HER2 mutations in ER+ metastatic breast cancer confer resistance to estrogen receptor–directed therapies

Utthara Nayar[1,2,3,4,9], Ofir Cohen[1,2,3,4,9], Christian Kapstad[1,2,4], Michael S. Cuoco[5], Adrienne G. Waks[1,2,3,4,6], Seth A. Wander[1,2,3,4,6], Corrie Painter[4], Samuel Freeman[2,3,4], Nicole S. Persky[4], Lori Marini[1,2], Karla Helvie[1,2], Nelly Oliver[1,2], Orit Rozenblatt-Rosen[5], Cynthia X. Ma[7], Aviv Regev[5,8], Eric P. Winer[2,3,6], Nancy U. Lin[2,3,6] and Nikhil Wagle[1,2,3,4,6]*

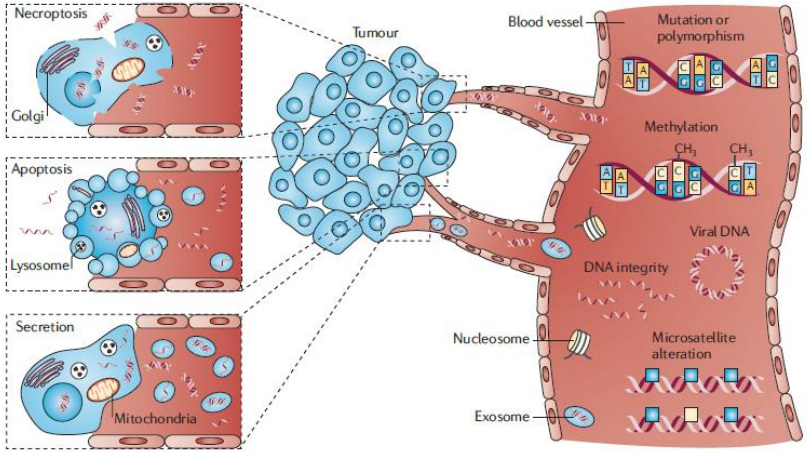




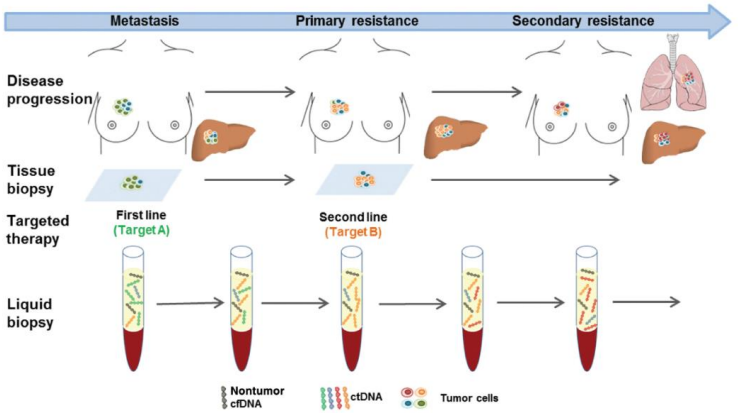
- ***ERBB2* mutations in 7% of metastatic biopsies** of ER+ breast cancer
- Most were acquired. No concurrent *ESR1* mutations
- ERBB2 and *ESR1* mutations virtually mutually exclusive (Project GENIE database)
- ERBB2 mutations (but not wt) render MCF7/T47D cells resistant to estrogen deprivation. ER signalling pathways suppressed
- Neratinib sensitive. Lower doses of neratinib induce fulvestrant sensitivity.

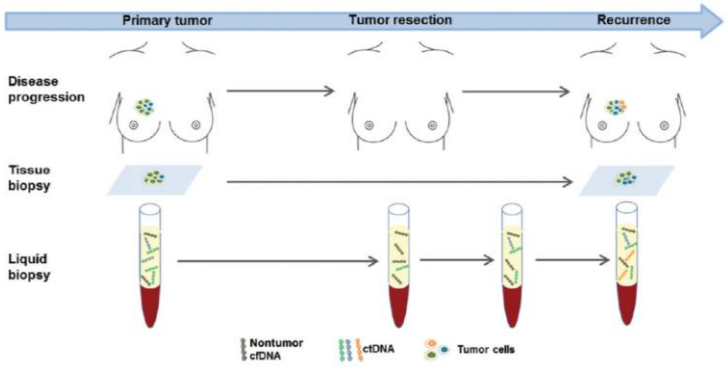
CECOG ACADEMY

Circulating cell free tumor DNA



Schwarzenbach H. et al, Nat Rev Cancer 2011



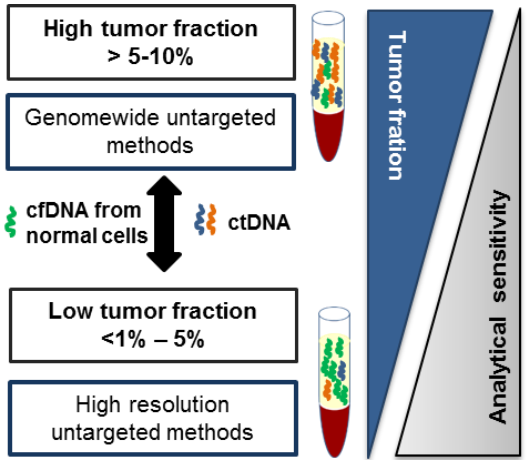


- ✓ **Analysis of biomarkers from easily accessible biofluids might be beneficial compared to tissue biopsy as repeated sampling is easily achievable**
- ✓ **ctDNA reflects tumor-specific changes from different tumor locations**
- ✓ **There is a surrogate marker for the entire tumor genome**

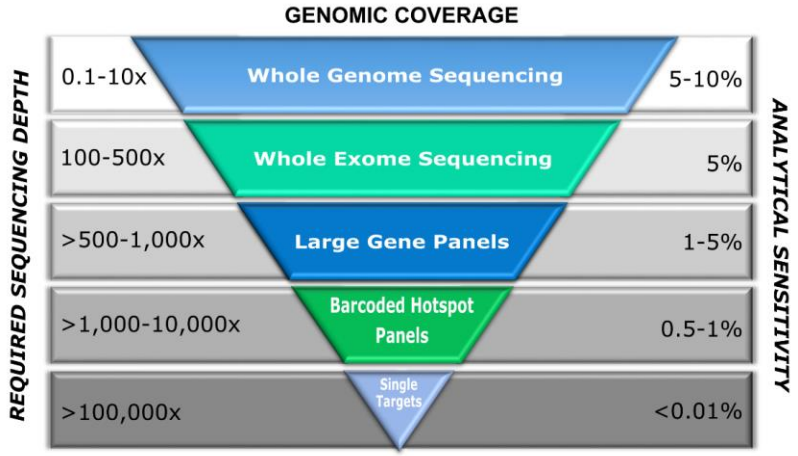
CECOG ACADEMY

Heitzer E. e

Sensitivity/ specificity of methods for cfDNA analysis



- WGS (LOD 5-10%)
- Whole methylome (LOD 5-10%)
- Plasma-Seq (LOD 5-10%)
- WES (LOD 5%)
- Tam-Seq (LOD 2%)
- CAPP-Seq (LOD <0.1%)
- Safe-SeqS (LOD <0.1%)
- BEAMing (LOD <0.01%)
- dPCR (LOD <0.01%)



Perakis et al, Advances in clinical chemistry 2017

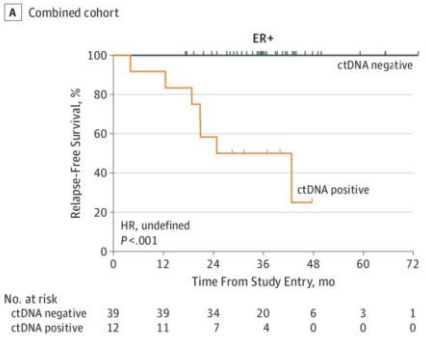
- Increasing genomic coverage comes with decreasing sensitivity
- Hotspot/single gene approaches can be analyzed with high resolution
- Genome-wide approaches require a tumor fraction of >5%

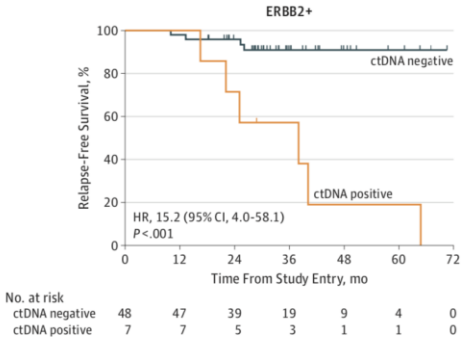
CECOG ACADEMY

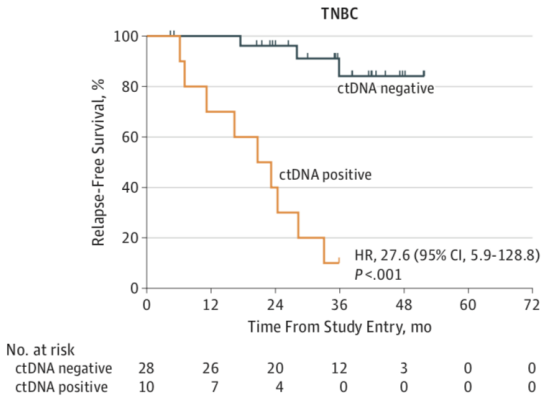
JAMA Oncology | Brief Report

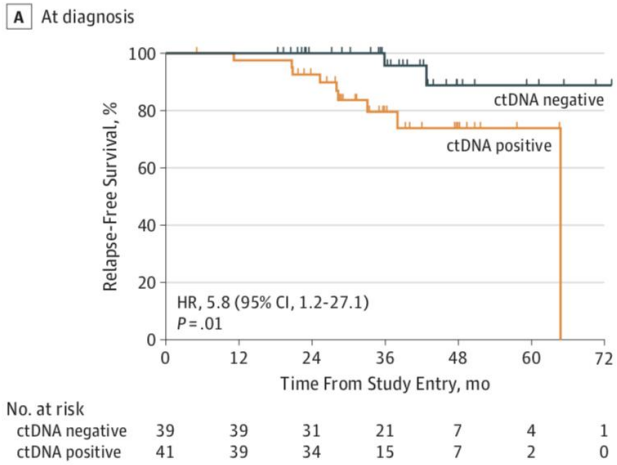
Assessment of Molecular Relapse Detection in Early-Stage Breast Cancer

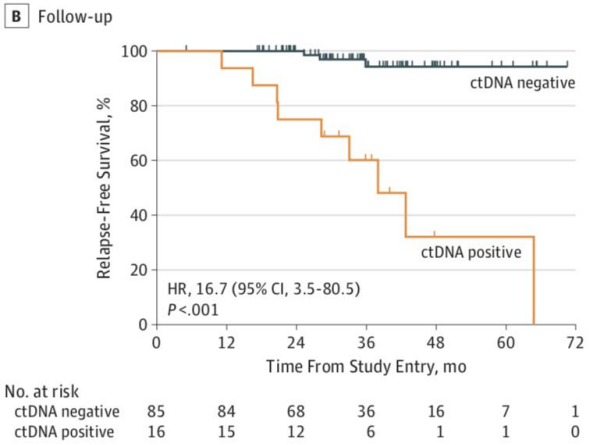
Isaac Garcia-Murillas, PhD; Neha Chopra, MD; Iñaki Comino-Méndez, PhD; Matthew Beaney, BSc; Holly Tovey, BSc; Rosalind J. Cutts, PhD; Claire Swift, BSc; Divya Kriplani, MD; Maria Afentakis, BSc; Sarah Hrebien, BSc; Giselle Walsh-Crestani, BSc; Peter Barry, MS; Stephen R. D. Johnston, PhD; Alistair Ring, MD; Judith Bliss, MSc; Simon Russell, MD; Abigail Evans, MD; Anthony Skene, MS; Duncan Wheatley, MD; Mitch Dowsett, PhD; Ian E. Smith, MD; Nicholas C. Turner, PhD











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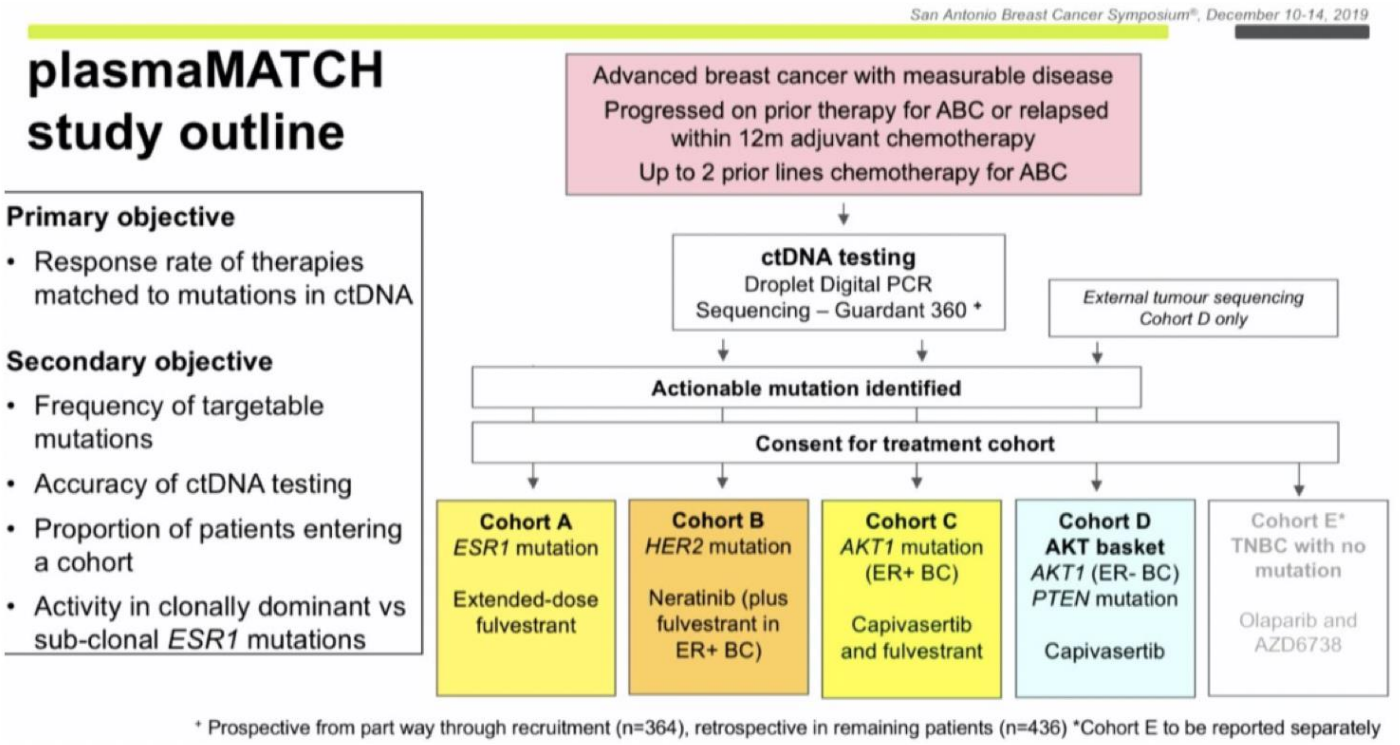
Plasma MATCH Trial



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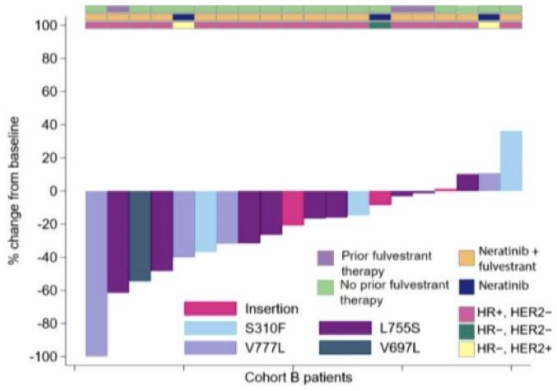
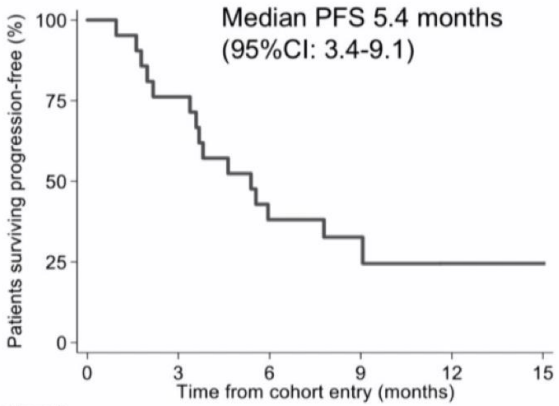
ctDNA testing

- 1044 patients registered for ctDNA testing between December 2016 and 26 April 2019 from 18 UK centres, with ctDNA results in 98.9% patients (1033/1044)
- Median time from registration to results
  - Digital PCR 13 days (IQR:11-15, n=1025)
  - Sequencing 10 days (IQR:8-11, n=364)
- Mutation frequencies by digital PCR *ESR1* 27.7%, *HER2* 2.7%, *AKT1* 4.2%
- Accuracy of ctDNA testing and will be covered in the next presentation
- Proportion of patients with a mutation in ctDNA who entered treatment cohort
  - 38% *ESR1*, 58% *HER2*, 54% *AKT1*

Cohort B: Neratinib ± fulvestrant with *HER2* mutation

Confirmed response rate 25.0% (5/20, 95%CI: 8.7-49.1)



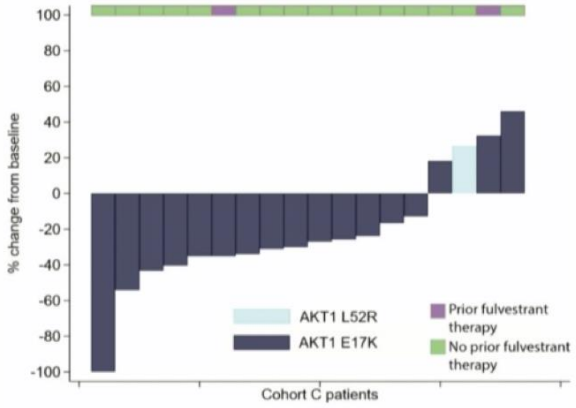


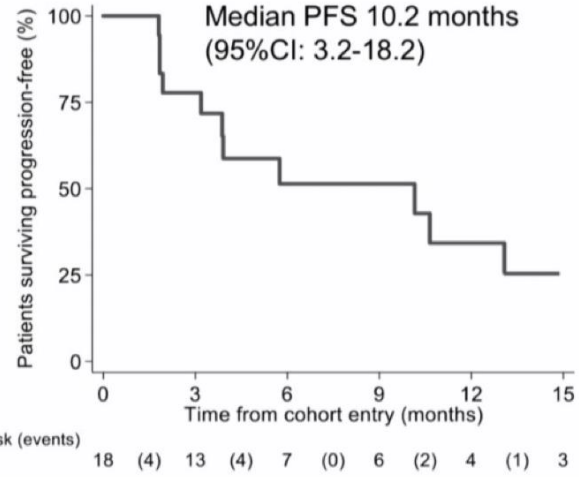
First 16 patients: RR=25.0% (4/16, 95%CI: 7.3-52.4)
HR+, HER2-: RR=23.5 (4/17, 95%CI:6.8-49.9)

San Antonio Breast Cancer Symposium®, December 10-14, 2019

Cohort C: Capivasertib + fulvestrant with *AKT1* mutation

Confirmed response rate 22.2% (4/18, 95%CI: 6.4-47.6)





First 16 patients: RR=18.8% (3/16, 95%CI: 4.0-45.6)

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THANK YOU

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