Innovazione e nuove prospettive di cura nel Carcinoma della Mammella

ORIGINAL ARTICLE FREE PREVIEW

Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2

Dennis J. Slamon, M.D., Ph.D., Brian Leyland-Jones, M.D., Steven Shak, M.D., Hank Fuchs, M.D., Virginia Paton, Pharm.D., Alex Bajamonde, Ph.D., Thomas Fleming, Ph.D., Wolfgang Eiermann, M.D., Janet Wolter, M.D., Mark Pegram, M.D., Jose Baselga, M.D., and Larry Norton, M.D.*

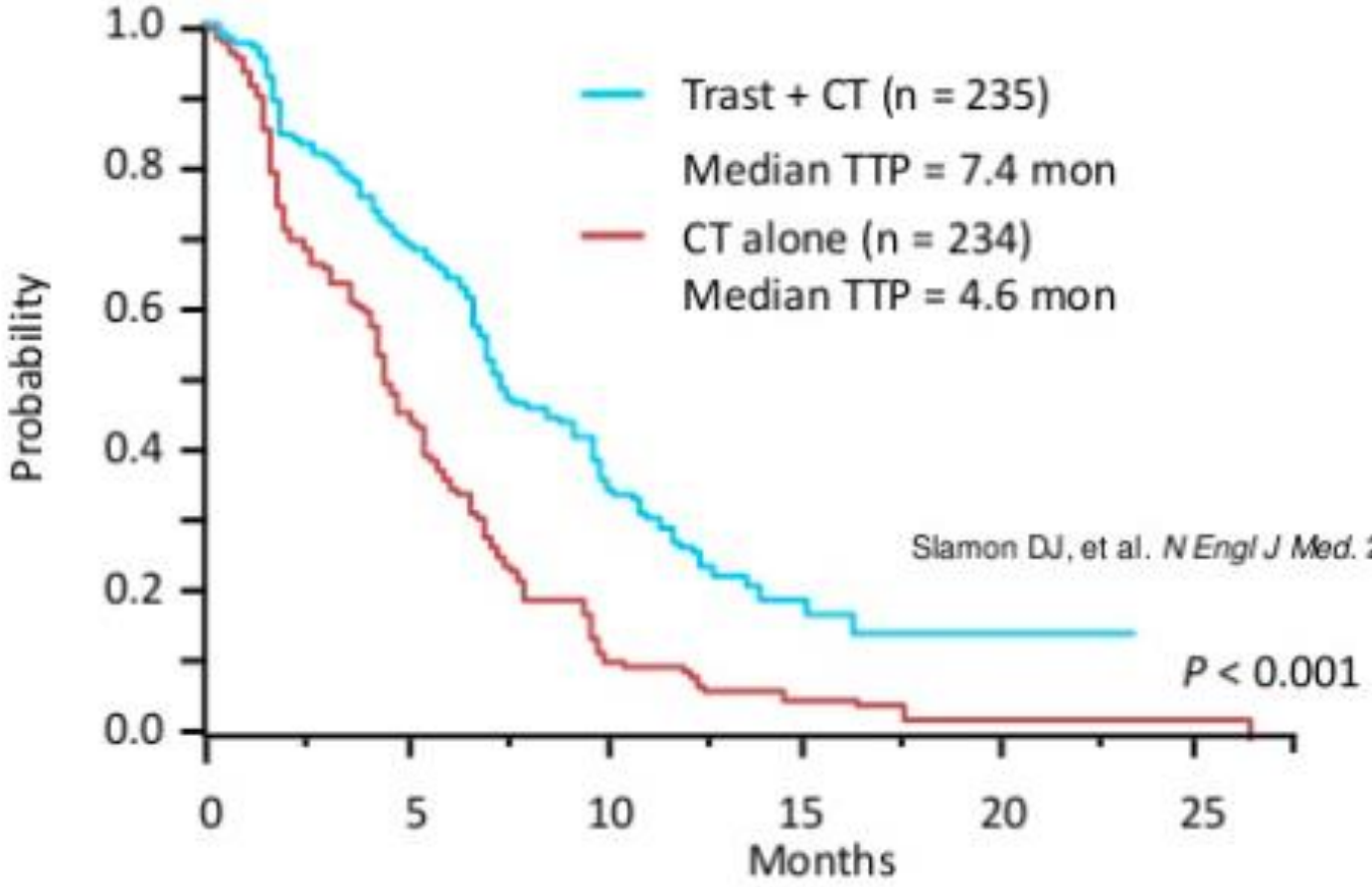
March 15, 2001
N Engl J Med 2001; 344:783-792
DOI: 10.1056/NEJM200103153441101

Abstract

BACKGROUND The *HER2* gene, which encodes the growth factor receptor HER2, is amplified and HER2 is overexpressed in 25 to 30 percent of breast cancers, increasing the aggressiveness of the tumor.

METHODS We evaluated the efficacy and safety of trastuzumab, a recombinant monoclonal antibody against HER2, in women with metastatic breast cancer that overexpressed HER2. We randomly assigned 234 patients to receive standard chemotherapy alone and 235 patients to receive standard

Chemotherapy +/- Trastuzumab: Proportion of Patients with Cancer Under Control



Slamon DJ, et al. *N Engl J Med.* 2001;344(11):783-792.

When trastuzumab was first approved based on the results above, few thought it would have such a profound effect on the course of HER2+ breast cancer

Herceptin Combination Pivotal Trial: Efficacy Summary

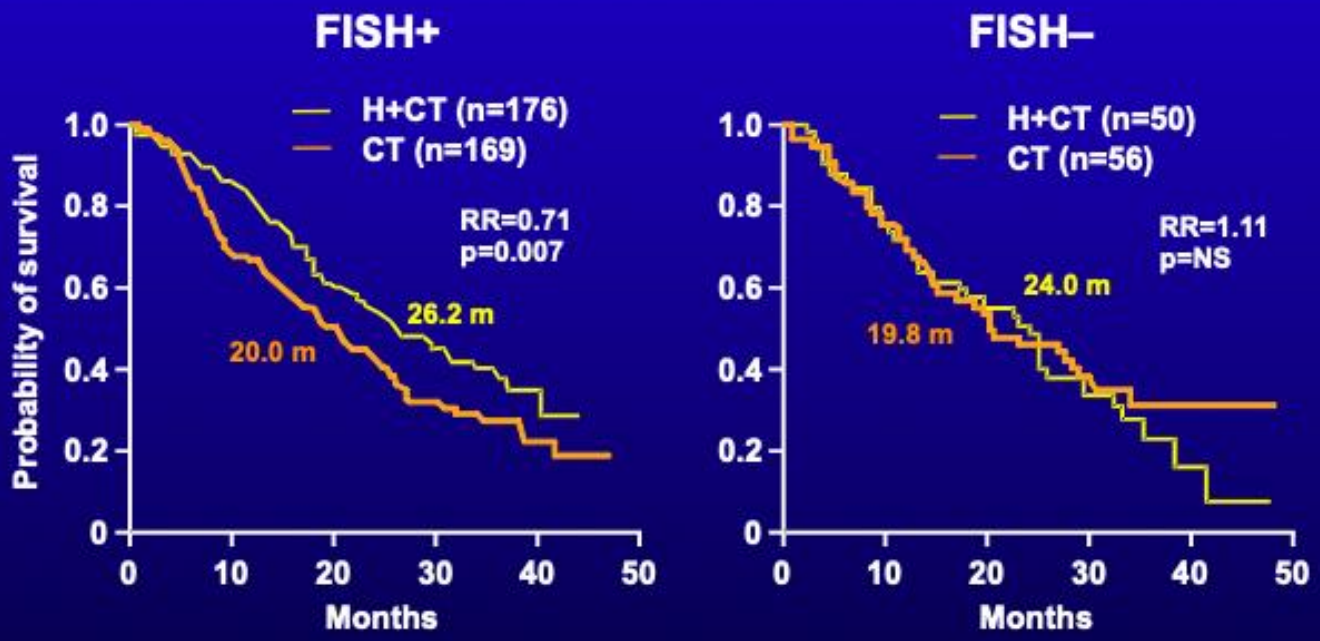
Parameter	Subgroup				Overall	
	H+AC (n=143)	AC (n=138)	H+T (n=92)	T (n=96)	H+CT (n=235)	CT (n=234)
ORR (%)	56	42	41	17	50	32
P value	<0.02		<0.001		<0.001	
Median DR (m)	9.1	6.7	10.5	4.5	9.1	6.1
P value	0.005		<0.01		<0.001	
Median TTP (m)	7.8	6.1	6.9	3.0	7.4	4.6
P value	<0.001		<0.001		<0.001	
Median survival (m) *	26.8	21.4	22.1	18.4	25.1	20.3
P value	0.16		0.17		0.046	

DR=duration of response; H=Herceptin; ORR=overall response rate; T=Taxol; TTP=time to progression; m=months; Herceptin Package Insert 2002.

Slamon D, et al. N Engl J Med 2001;344:783.

* Study was not powered to show a survival difference in subgroups.

Herceptin Combination Pivotal Trial: Overall Survival



Survival advantage was demonstrated for first-line H + CT despite 66% of CT group receiving H in second or later lines of therapy

CT=chemotherapy; NS=not significant; RR=response rate

Update of Mass R, et al. Proc Am Soc Clin Oncol 2001;20;22a:abstract 85.

Original Article

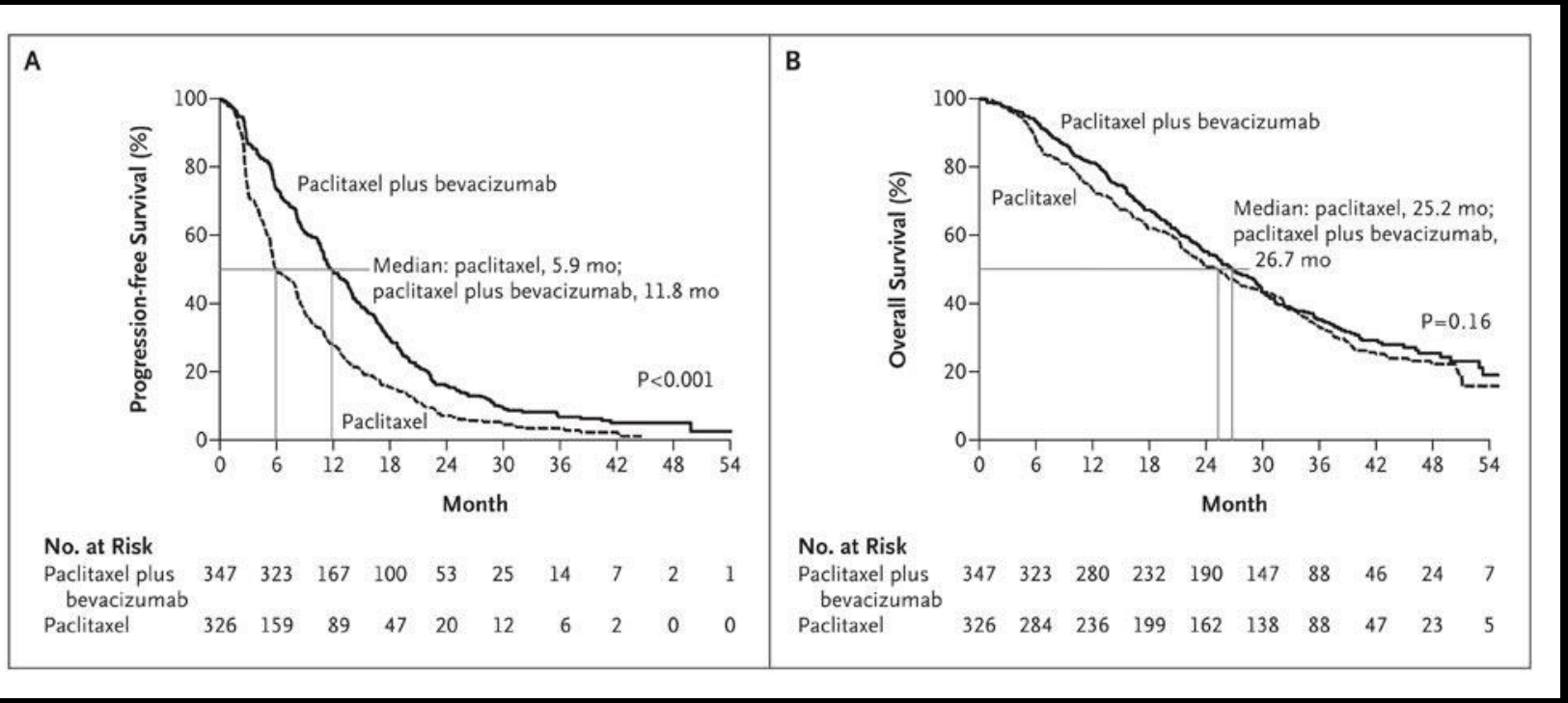
Paclitaxel plus Bevacizumab versus Paclitaxel Alone for Metastatic Breast Cancer

Kathy Miller, M.D., Molin Wang, Ph.D., Julie Gralow, M.D., Maura Dickler, M.D., Melody Cobleigh, M.D., Edith A. Perez, M.D., Tamara Shenkier, M.D., David Cella, Ph.D., and Nancy E. Davidson, M.D.

N Engl J Med
Volume 357(26):2666-2676
December 27, 2007

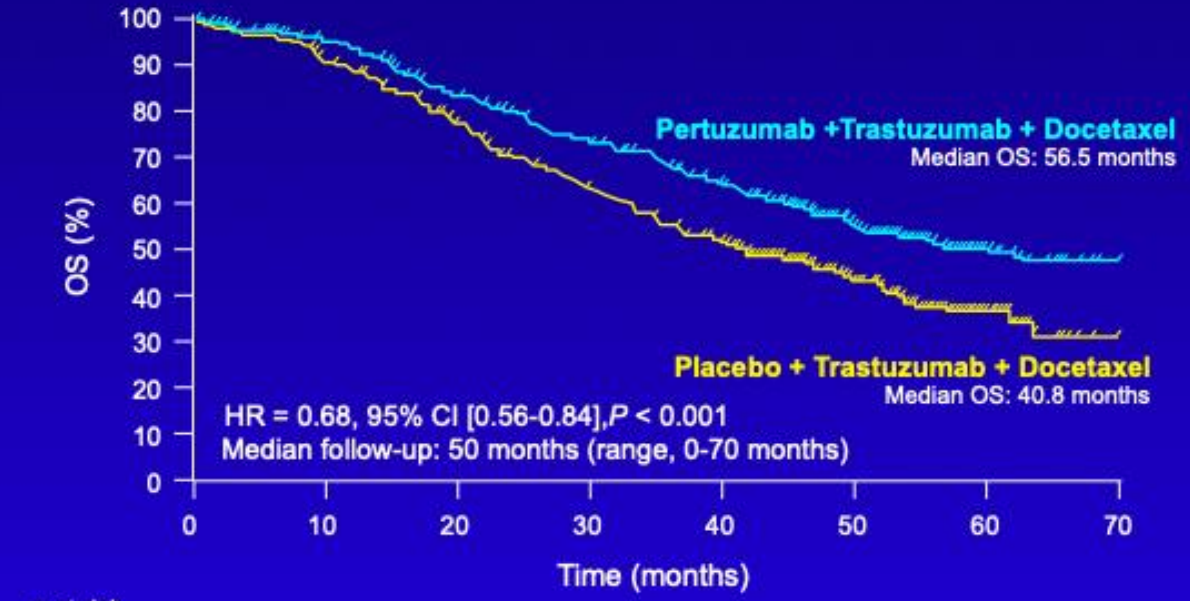
The NEW ENGLAND JOURNAL of MEDICINE

Survival Analyses



Miller K et al. N Engl J Med 2007;357:2666-2676

CLEOPATRA: OS



n at risk								
Pertuzumab	402	371	318	268	226	104	28	1
Placebo	406	350	289	230	179	91	23	0

Δ = 15.7 months

Swain SM, et al. *N Engl J Med.* 2015;372(8):724-734.

"Tonight I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes.

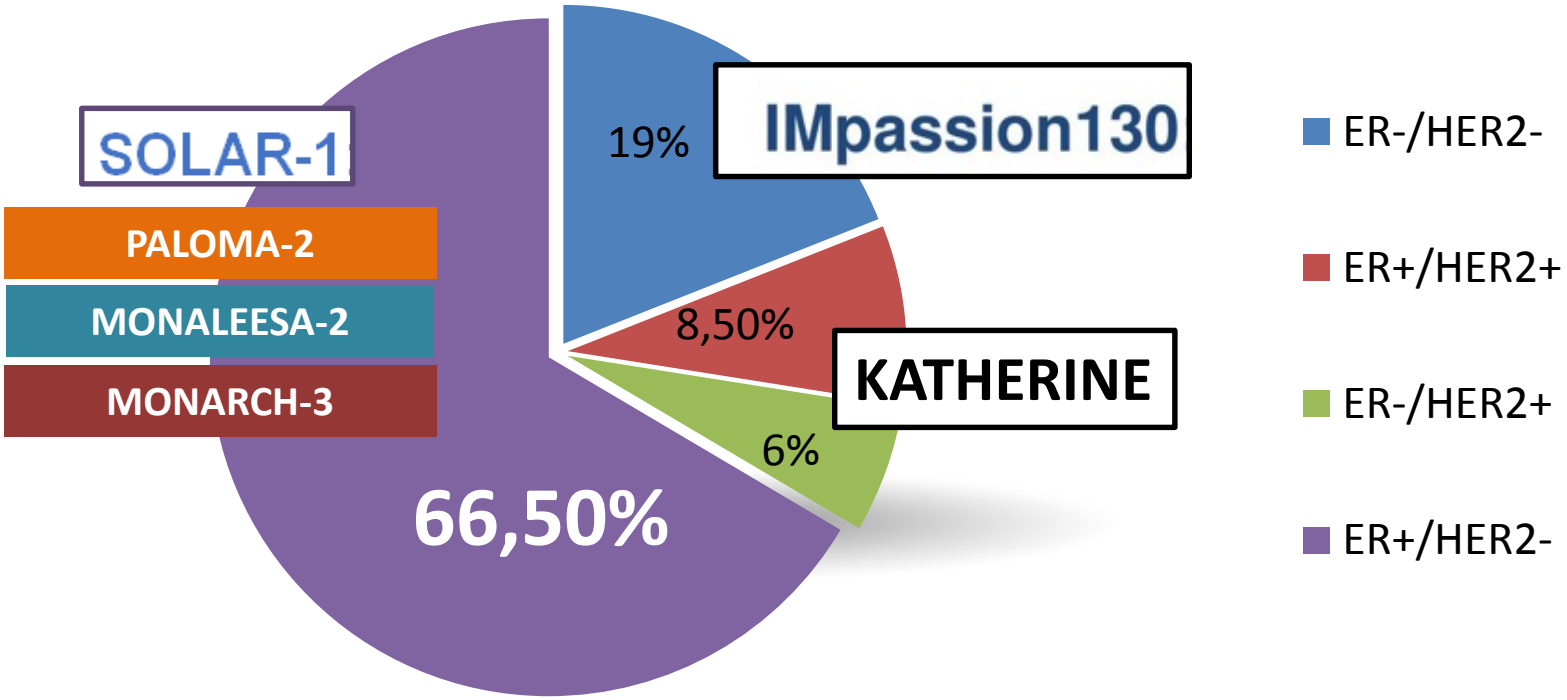
And to give us all access to the personalized information we need to keep ourselves and our families healthier."

President Barack Obama
2015 State of the Union Address | January 20, 2015

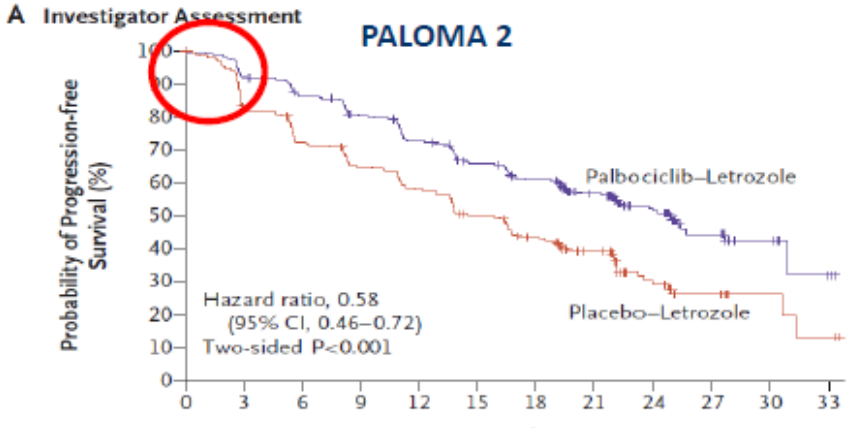
"And that's why we're here today. Because something called precision medicine … gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen."

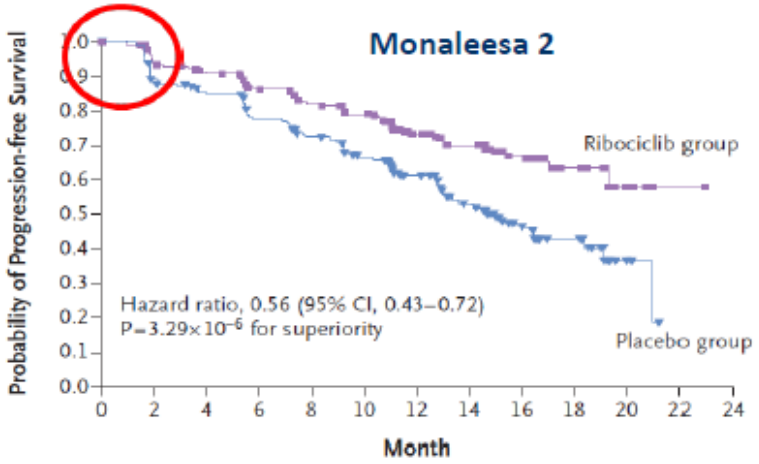
President Barack Obama
January
20, 2015

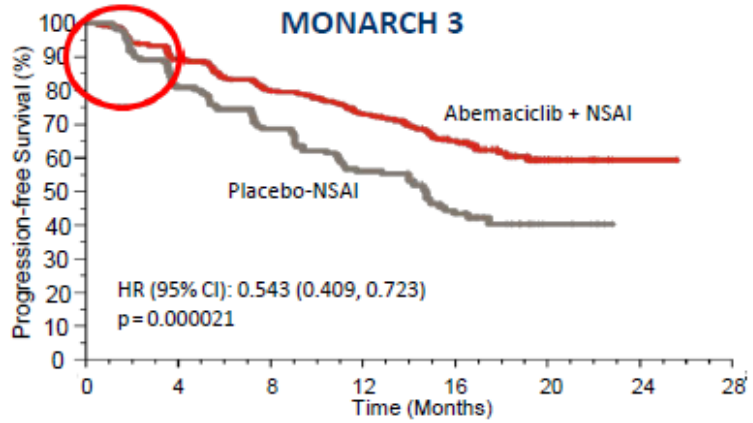
BREAKING NEWS



PALOMA 2, Monaleesa 2 & MONARCH 3- PFS







Finn R, NEJM 2016; Hortobagyi GN, NEJM 2016; DiLeo A, ESMO 2017

HR+/HER2-ve ABC:
Activity of 1st Line Endocrine Therapy with Targeted Agents

option	ORR %	CBR %
Palbociclib + letrozole	**42 %**	85 %
Ribociclib + letrozole	**41 %**	80 %
Abemaciclib + NSAI	**48 %**	78 %

AIs + CDK4/6i induce a rapid tumor shrinkage comparable to that achievable with chemotherapy

Registrative trials CDK 4/6 inhibitors

Main toxicities

	Palbociclib*	Ribociclib**	Abemaciclib***
% G3-G4 neutropenia	66	59	21
% Diarrhea	1(G3)	1(G3)	36(G2=27/G3=9)
% G3-G4 AST and/or ALT elevation	3	9	7
% G1-G4 creatinine elevation	NR	NR	19 (G3/G4=2/0)
% QTcF interval increase (>60 msec)	<1	3	NR
% Thromboembolic events	1	3	5

*Finn RS et al New Engl J Med 2016; **Hortobagyi G et al, New Engl J Med 2016; ***Goetz MP t al, J Clin Oncol 2017

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

Dejan Juric,[1]* Eva Maria Ciruelos,[2] Gabor Rubovszky,[3] Mario Campone,[4] Sibylle Loibl,[5] Hope S. Rugo,[6] 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]

[1]Massachusetts General Hospital, Boston, MA, USA; [2]Hospital Universitario 12 de Octubre, Madrid, Spain; [3]National Institute of Oncology, Budapest, Hungary; [4]Institut de Cancérologie de l'Ouest, St Herblain, France; [5]German Breast Group, Neu-Isenburg, Germany; [6]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [7]Aichi Cancer Center, Nagoya, Japan; [8]Istituto Oncologico Veneto, and University of Padua, Padua, Italy; [9]Vanderbilt University, Nashville, TN, USA; [10]Chaim Sheba Medical Center, Tel HaShomer, Israel; [11]Kanagawa Cancer Center, Yokohama, Japan; [12]National Taiwan University Hospital, Taipei, Taiwan; [13]Saitama Cancer Center, Saitama, Japan; [14]NHO Hokkaido Cancer Center, Sapporo, Japan; [15]Duna Medical Center, Budapest, Hungary; [16]Novartis Pharma S.A.S., Paris, France; [17]Novartis Pharma AG, Basel, Switzerland; [18]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [19]Gustave Roussy, Université Paris-Sud, Villejuif, France

Presenting author

The importance of the PI3K Pathway in HR+ Breast Cancer

- The PI3K pathway is frequently altered in HR+ breast cancer and has been implicated in resistance to endocrine therapies[1,2]
- Approximately 40% of HR+ breast cancers harbor a *PIK3CA* mutation, leading to hyperactivation of the PI3K pathway[3-5]
- PI3K signaling has been shown to promote estrogen-independent growth of ER+ breast cancer cells,[6,7] and this growth is inhibited by the addition of PI3K inhibitors to antiestrogens[8]

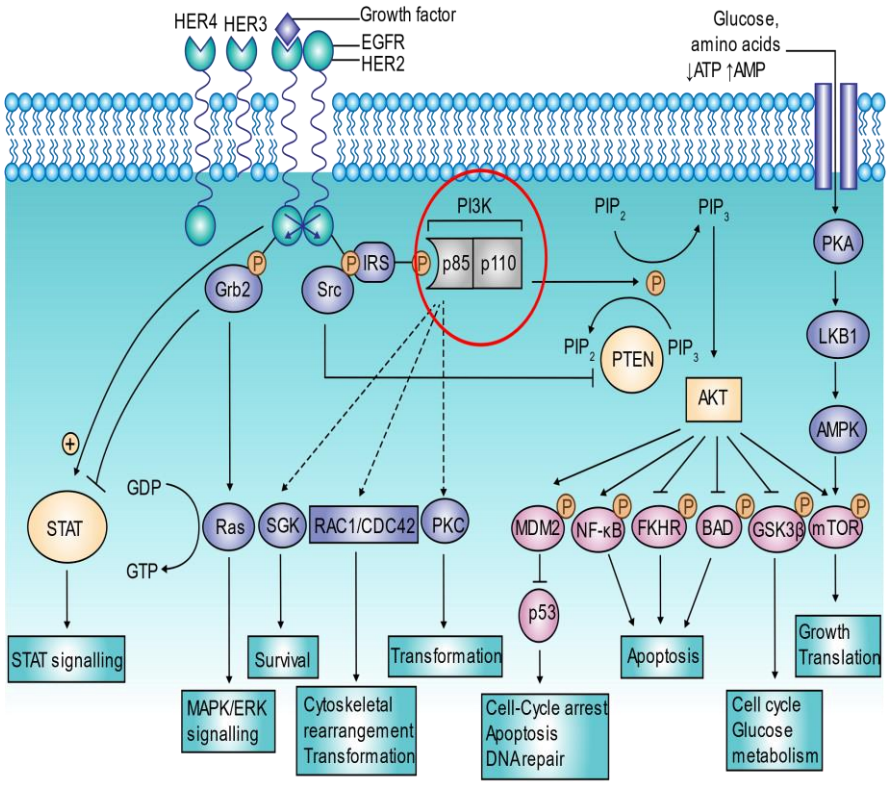
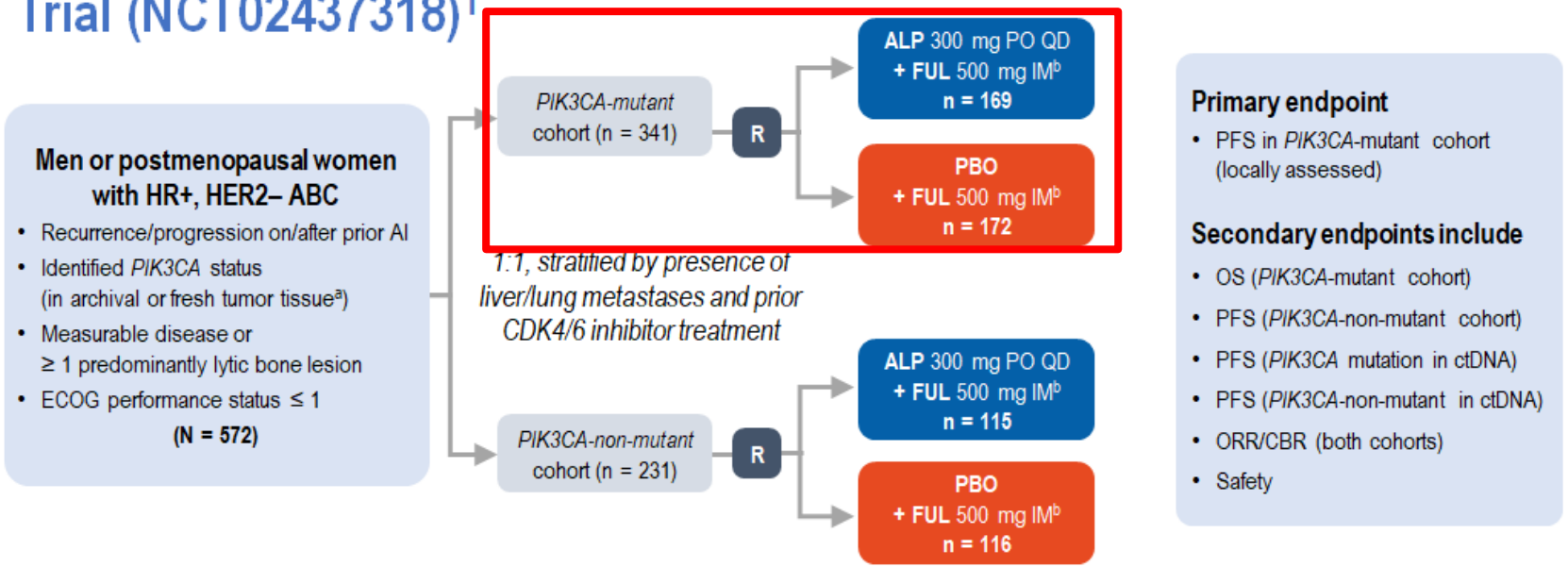


Figure reprinted by permission from Springer Nature: *Nature Reviews Drug Discovery*. Exploiting the PI3K/AKT Pathway for Cancer Drug Discovery. Hennessy BT, et al. *Nat Rev Drug Discov*. 2005 Dec;4(12):988-1004. © 2005.

ER+, estrogen receptor-positive; HR+, hormone receptor-positive; P13K, phosphatidylinositol 3-kinase.

1. Miller TW, et al. *J Clin Oncol*. 2011;29(33):4452-4461. 2. Bosch A, et al. *Sci Transl Med*. 2015;7(283):283ra51. 3. Mayer IA, et al. *Clin Cancer Res*. 2017;23(1):26-34. 4. Loi S, et al. *Proc Natl Acad Sci U S A*. 2010;107(22):10208-10213.
5. Stemke-Hale K, et al. *Cancer Res*. 2008;68(15):6084-6091. 6. Miller TW, et al. *J Clin Invest*. 2010;120(7):2406-2413. 7. Crowder RJ, et al. *Cancer Res*. 2009;69(9):3955-3962. 8. Miller TW, et al. *Cancer Discovery*. 2011;1(4):338-351.

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



- 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

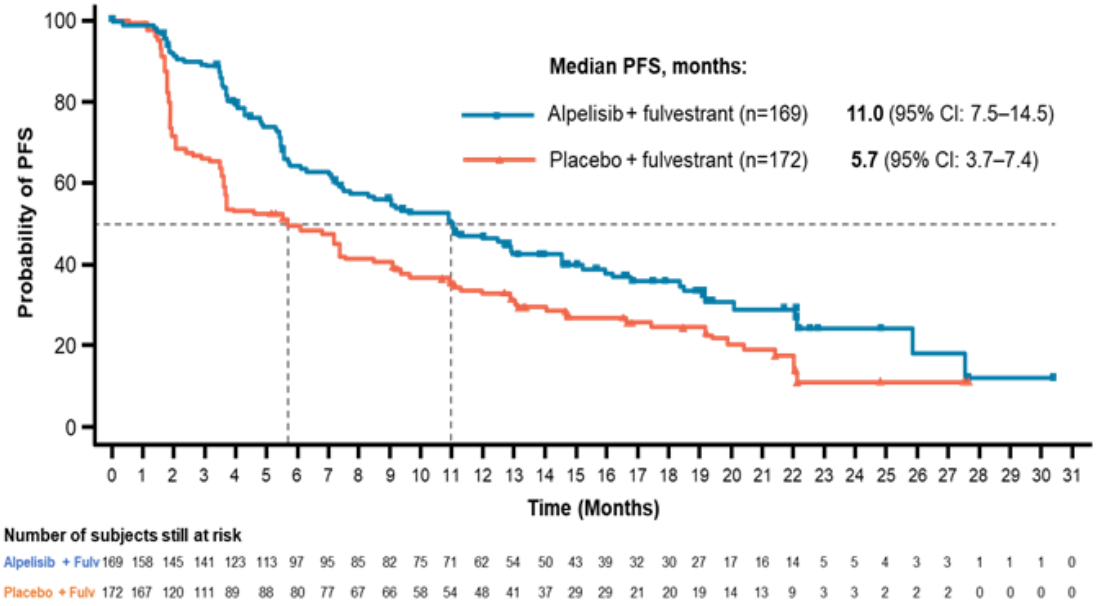
ABC, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; HER2–, human epidermal growth factor receptor-2–negative; IM, intramuscular; ORR, overall response rate; OS, overall 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].

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



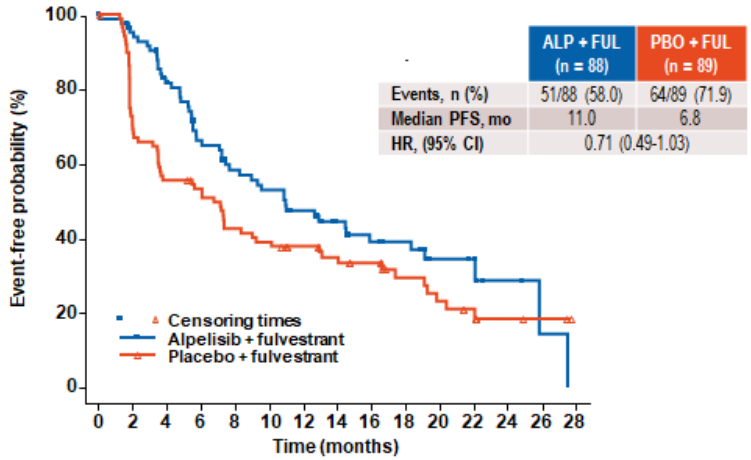
Data cut-off: Jun 12, 2018	ALP + FUL (n = 169)	PBO + FUL (n = 172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
HR (95% CI)	0.65 (0.50-0.85)	
One-sided *P* value	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 in the *PIK3CA*-mutant Cohort[a]

First-line (n = 177)

Defined as patients whose disease progressed ≤ 1 year after (neo)adjuvant ET (endocrine resistant) **or** whose disease progressed > 1 year after (neo)adjuvant ET (endocrine sensitive) (later excluded after protocol amendment)

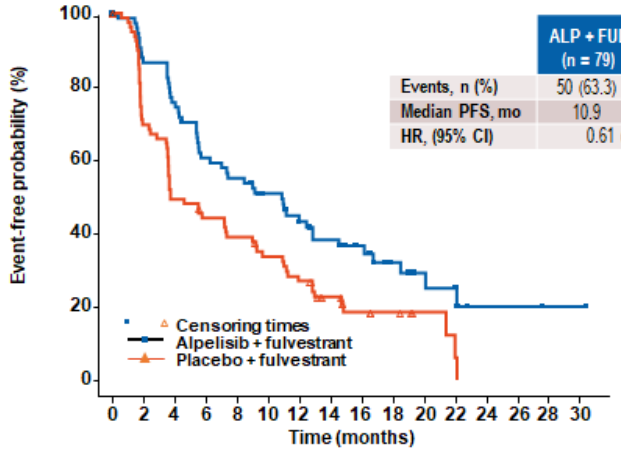


	ALP + FUL (n = 88)	PBO + FUL (n = 89)
Events, n (%)	51/88 (58.0)	64/89 (71.9)
Median PFS, mo	11.0	6.8
HR, (95% CI)	0.71 (0.49-1.03)	

	Endocrine sensitive patients		Endocrine resistant patients	
	ALP + FUL (n = 20)	PBO + FUL (n = 19)	ALP + FUL (n = 68)	PBO + FUL (n = 70)
Events, n (%)	11 (55.0)	9 (47.4)	40 (58.8)	55 (78.6)
Median PFS, mo	22.1	19.1	9.0	4.7
HR, (95% CI)	0.87 (0.35-2.17)		0.69 (0.46-1.05)	

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



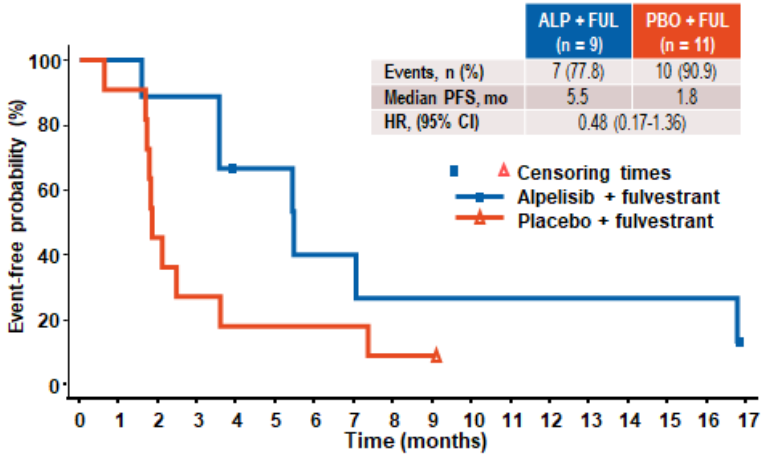
	ALP + FUL (n = 79)	PBO + FUL (n = 82)
Events, n (%)	50 (63.3)	65 (79.3)
Median PFS, mo	10.9	3.7
HR, (95% CI)	0.61 (0.42-0.89)	

ABC, advanced breast cancer; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; PFS, progression-free survival.

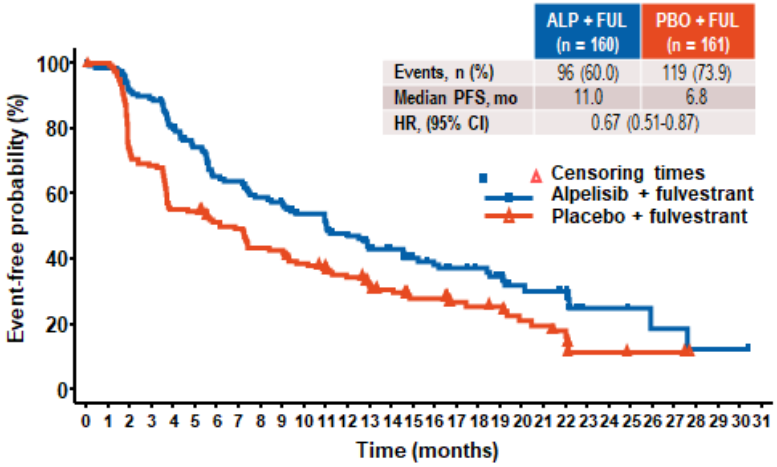
[a] Mutation status determined from tissue biopsy.

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

ABC, advanced breast cancer; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; PFS, progression-free survival.
[a] Mutation status determined from tissue biopsy.

Juric et al 2018- SABCS 2018, Oral presentation

Conclusions

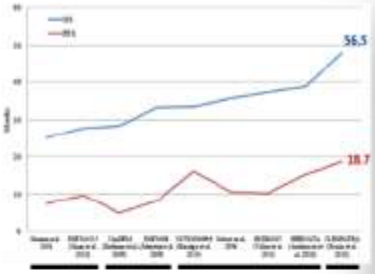
- SOLAR-1 met its primary endpoint; a statistically significant and clinically meaningful **prolongation of median PFS was observed with the addition of alpelisib to fulvestrant in patients with *PIK3CA*-mutant disease**
- The majority of patients in the study were endocrine resistant; subgroup analyses demonstrated the benefit of alpelisib, **regardless of line of therapy or prior CDK4/6 inhibitor treatment**
- OS data at the first interim analysis in patients with a *PIK3CA* mutation were immature (52% of planned events); the median OS was not reached in the alpelisib arm
- Hyperglycemia, an on-target AE, can be easily identified (most commonly within the first 2 weeks of treatment) and managed with oral anti-diabetic agents
- PFS was significantly prolonged in patients with plasma ctDNA-determined mutational status, demonstrating the clinical utility of the ctDNA test in selecting patients with a *PIK3CA* mutation and confirming the robustness of the primary endpoint results

Juric.Dejan@mgh.harvard.edu

Targeting HER2+ Breast Cancer : major clinical advances

Phase II Randomized trial of T-DM1

Phase III Pertuzumab



Need effective HER2 blockade

1998	2007	2012	2013	2017
FDA Approval				
Trastuzumab	Lapatinib	Pertuzumab	T-DM1	Neratinib [HER2 + BC, extended adj]

What's the next?

Pivotal Trials: Targeting HER2

CLEOPATRA	EMILIA	TH3RESA
Trastuzumab-Pertuzumab dual inhibition HER2+, 1st line, MBC	T-DM1 vs. Lapatinib + Capecitabine HER2+, 2nd line, ABC	T-DM1 vs. TPC HER2+, 3rd line, MBC

On-going clinical trials

Several ADCs | pan-HER inhibitors | HER3 targeting

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ORIGINAL ARTICLE

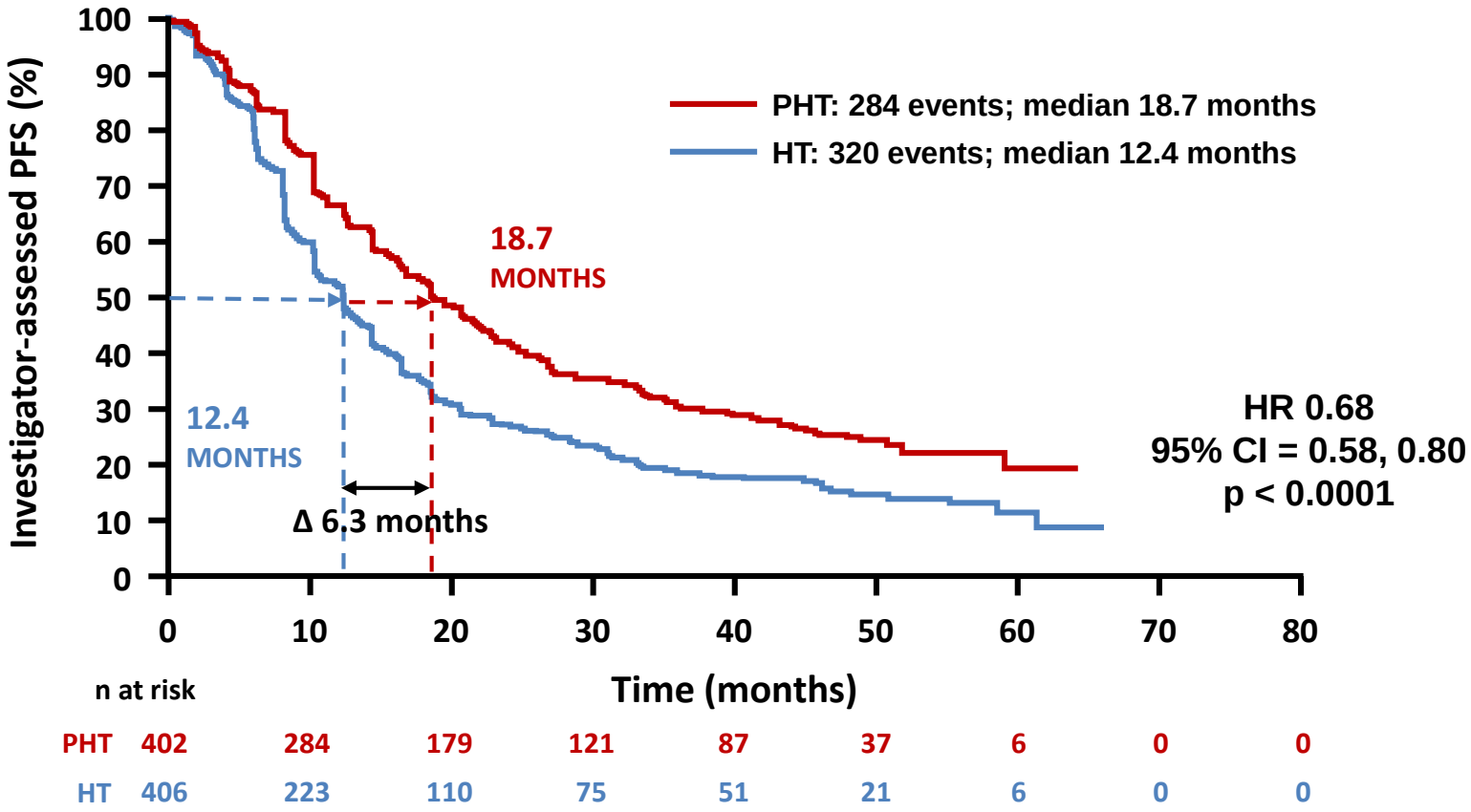
Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer

Sandra M. Swain, M.D., José Baselga, M.D., Sung-Bae Kim, M.D., Jungsil Ro, M.D., Vladimir Semiglazov, M.D., Mario Campone, M.D., Eva Ciruelos, M.D., Jean-Marc Ferrero, M.D., Andreas Schneeweiss, M.D., Sarah Heeson, B.Sc., Emma Clark, M.Sc., Graham Ross, F.F.P.M., Mark C. Benyunes, M.D., and Javier Cortés, M.D., for the CLEOPATRA Study Group*

N ENGL J MED 372;8 NEJM.ORG FEBRUARY 19, 2015

CLEOPATRA:

P + H + T increased median PFS* by 6.3 months vs. H + T alone[1]



Data cut-off: February 2014.

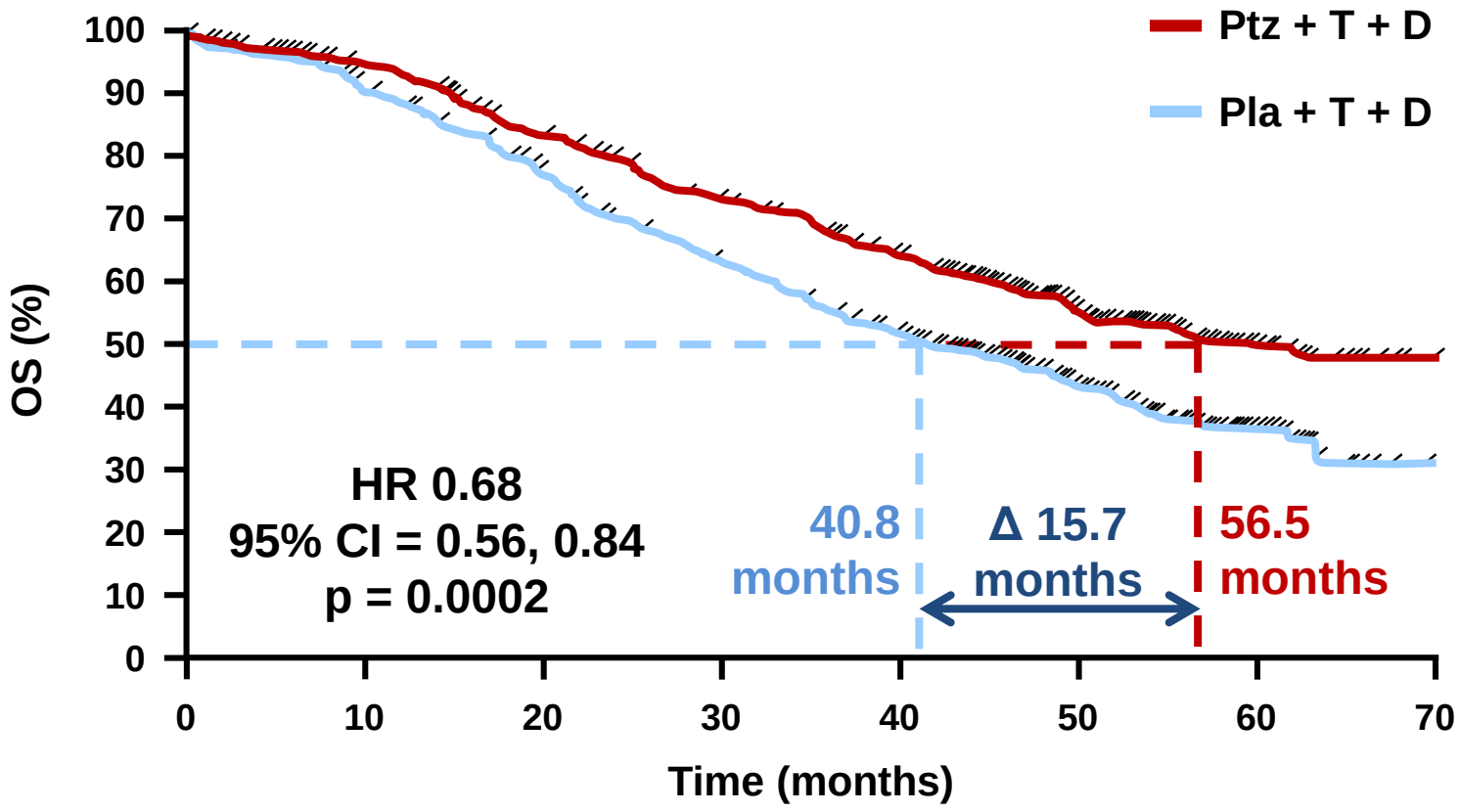
**Investigator-assessed PFS. The pre-specified number of events for IRF-assessed PFS (primary endpoint) was reached in the primary analysis; further data were not obtained for the primary endpoint.[2]*

H, trastuzumab; HR, hazard ratio; IRF, independent review facility; P, pertuzumab; PFS, progression-free survival; T, docetaxel.

Adapted from 1. Swain SM, et al. ESMO 2014 (Abstract 350O_PR); 2. Swain et al. Lancet Oncol 2013; 14(6): 461-471.

Final OS Analysis

Median follow-up 50 months (range 0–70 months)



n at risk								
Ptz + T + D	402	371	318	268	226	104	28	1
Pla + T + D	406	350	289	230	179	91	23	0

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Swain S, et al. NEJM 2015

The NEW ENGLAND JOURNAL of MEDICINE

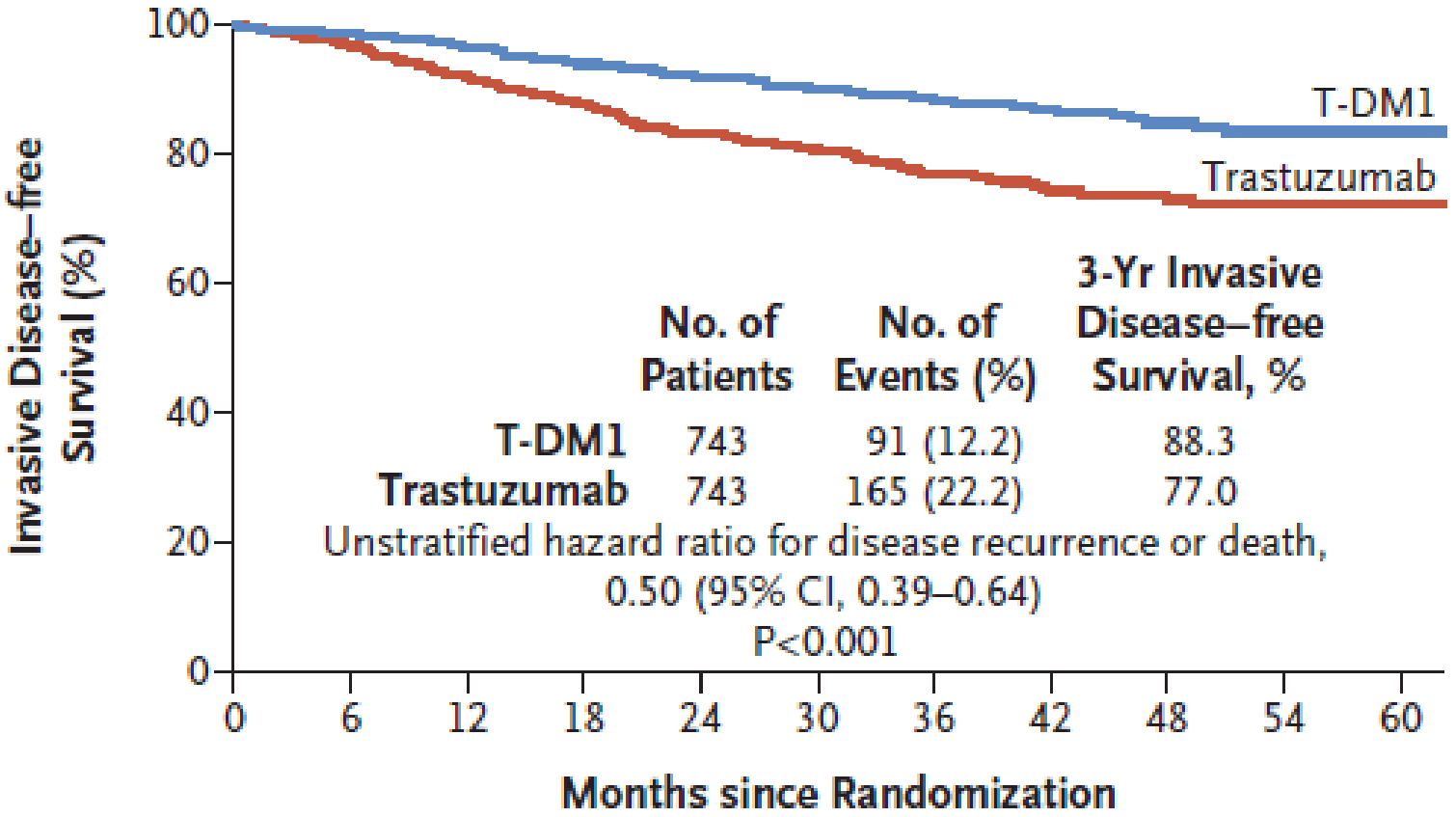
ORIGINAL ARTICLE

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. Lam, D. Tesarowski, M. Smitt, H. Douthwaite, S.M. Singel, and C.E. Geyer, Jr., for the KATHERINE Investigators*

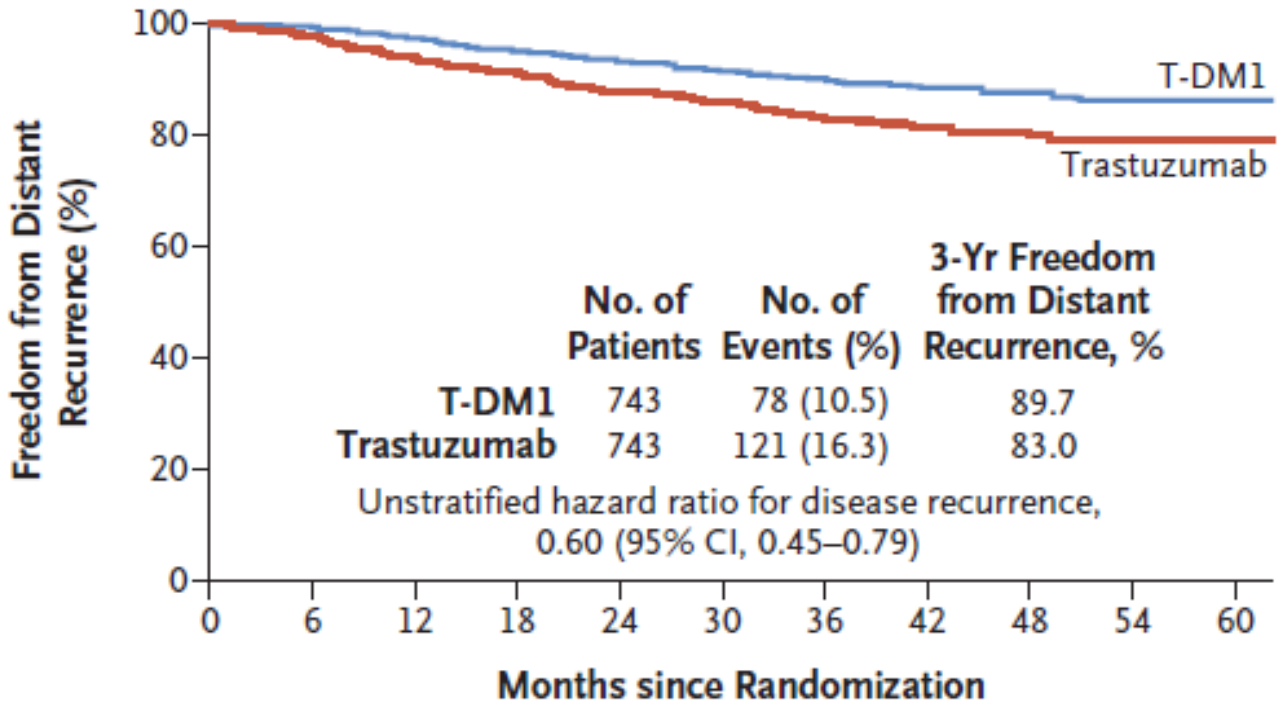
This article was published on December 5, 2018, at NEJM.org.

A



No. at Risk											
T-DM1	743	707	681	658	633	561	409	255	142	44	4
Trastuzumab	743	676	635	594	555	501	342	220	119	38	4

B



No. at Risk											
T-DM1	743	707	682	661	636	564	412	254	143	45	4
Trastuzumab	743	679	643	609	577	520	359	233	126	41	4

CONCLUSIONS

Among patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone. (Funded by F. Hoffmann–La Roche/Genentech; KATHERINE ClinicalTrials.gov number, NCT01772472.)

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

IMpassion130: Efficacy in immune biomarker subgroups from the global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + *nab*-paclitaxel in patients with treatment-naive, locally advanced or metastatic triple-negative breast cancer

Leisha A. Emens,[1] Sherene Loi,[2] Hope S. Rugo,[3] Andreas Schneeweiss,[4] Véronique Diéras,[5] Hiroji Iwata,[6] Carlos H. Barrios,[7] Marina Nechaeva,[8] Luciana Molinero,[9] Anh Nguyen Duc,[10] Roel Funke,[9] Stephen Y Chui,[9] Amreen Husain,[10] Eric P. Winer,[11] Sylvia Adams,[12] Peter Schmid[13]

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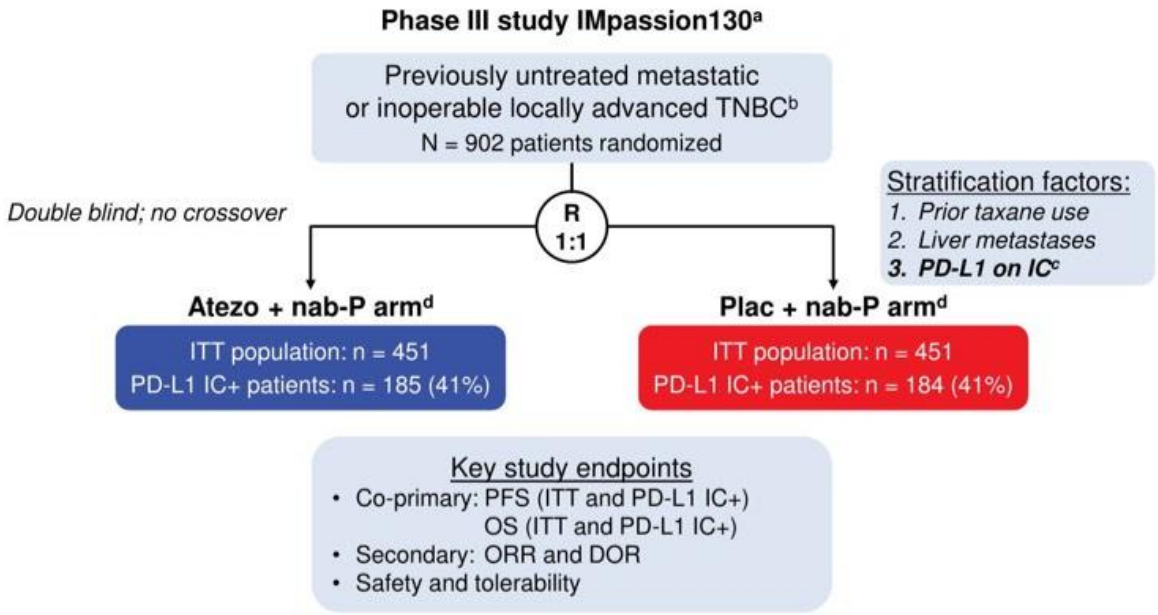
IMpassion130 study design: Prespecified analyses in the ITT and PD-L1 IC+ population



[a] NCT02425891. [b] Locally evaluated per ASCO-CAP guidelines. Prior chemotherapy in the curative setting, including taxanes, allowed if treatment-free interval ≥ 12 mo.
[c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status, PD-L1+: PD-L1 on ≥ 1% of IC). [d] Atezolizumab or placebo 840 mg IV on days 1 and 15 + *nab*-paclitaxel 100 mg/m² IV on days 1, 8 and 15 of 28-day cycle until RECIST v1.1 PD. 1. Schmid *N Engl J Med* 2018.

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The NEW ENGLAND JOURNAL of MEDICINE

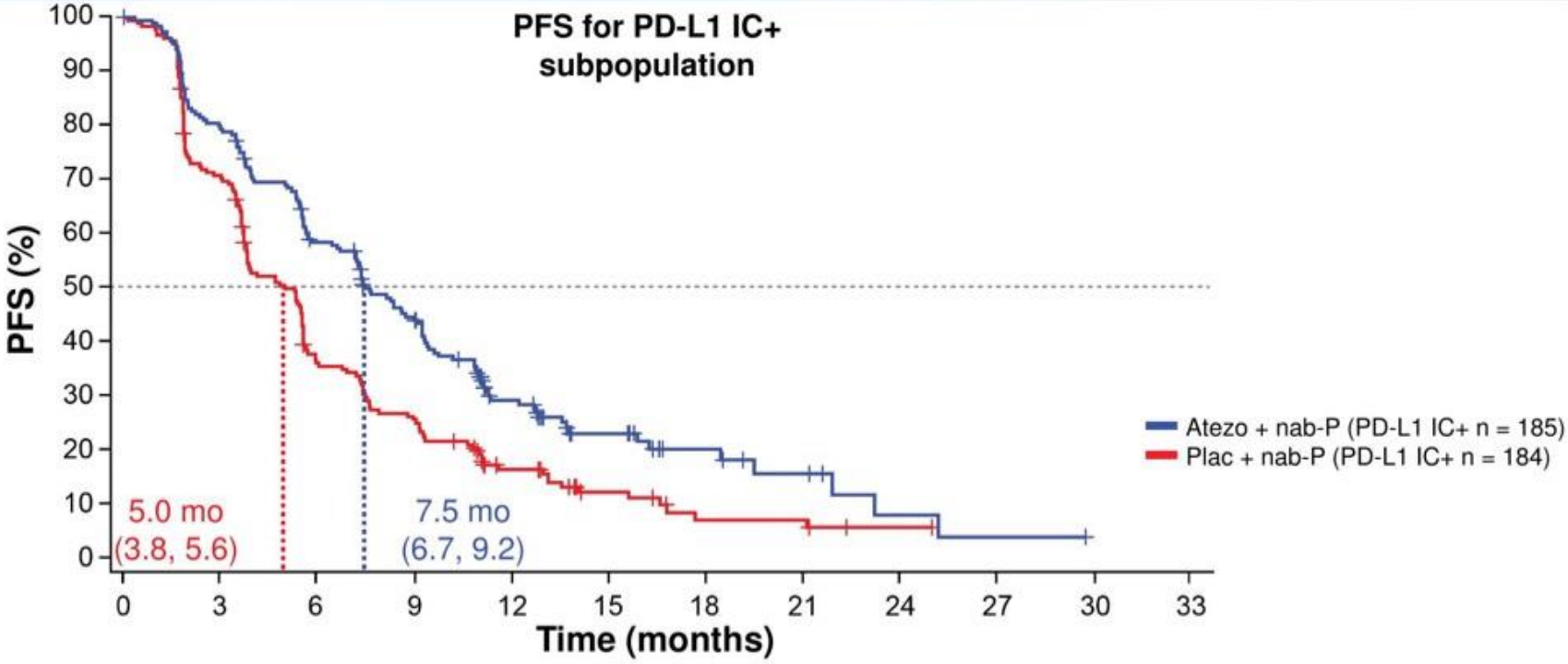
ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras,

N ENGL J MED 379;22 NEJM.ORG NOVEMBER 29, 2018

PD-L1 IC status (positive vs negative) predicts PFS benefit with atezolizumab + *nab*-paclitaxel



Median PFS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values except for PD-L1 IC+ PFS are nominal *P* values. Data cutoff: April 17, 2018.

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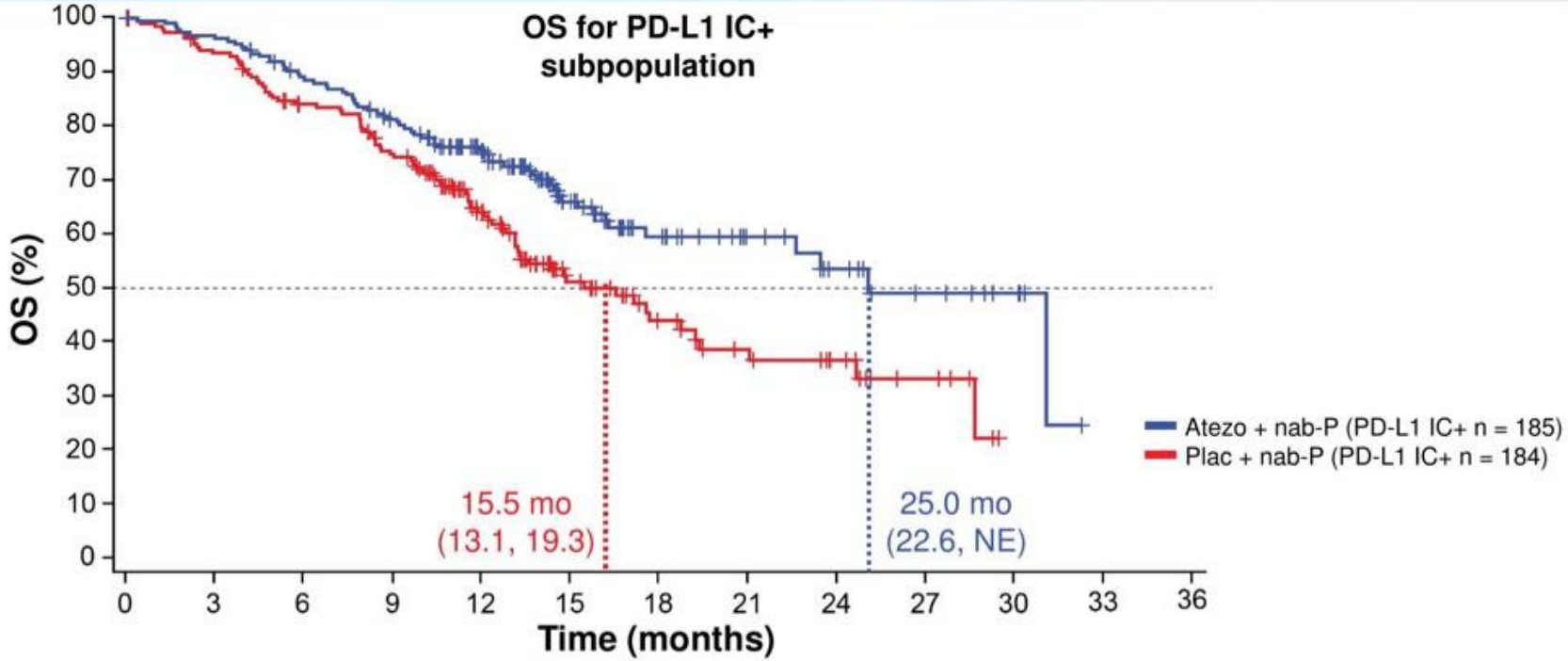
PD-L1 IC status (positive vs negative) predicts OS benefit with atezolizumab + *nab*-paclitaxel



- A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant
- PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + *nab*-paclitaxel

Median OS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values are nominal. Data cutoff: April 17, 2018.

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ORIGINAL ARTICLE

Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer

S.-A. Im, Y.-S. Lu, A. Bardia, N. Harbeck, M. Colleoni, F. Franke, L. Chow, J. Sohn, K.-S. Lee, S. Campos-Gomez, R. Villanueva-Vazquez, K.-H. Jung, A. Chakravartty, G. Hughes, I. Gounaris, K. Rodriguez-Lorenc, T. Taran, S. Hurvitz, and D. Tripathy

ABSTRACT

BACKGROUND

An earlier analysis of this phase 3 trial showed that the addition of a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor to endocrine therapy provided a greater benefit with regard to progression-free survival than endocrine therapy alone in premenopausal or perimenopausal patients with advanced hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer. Here

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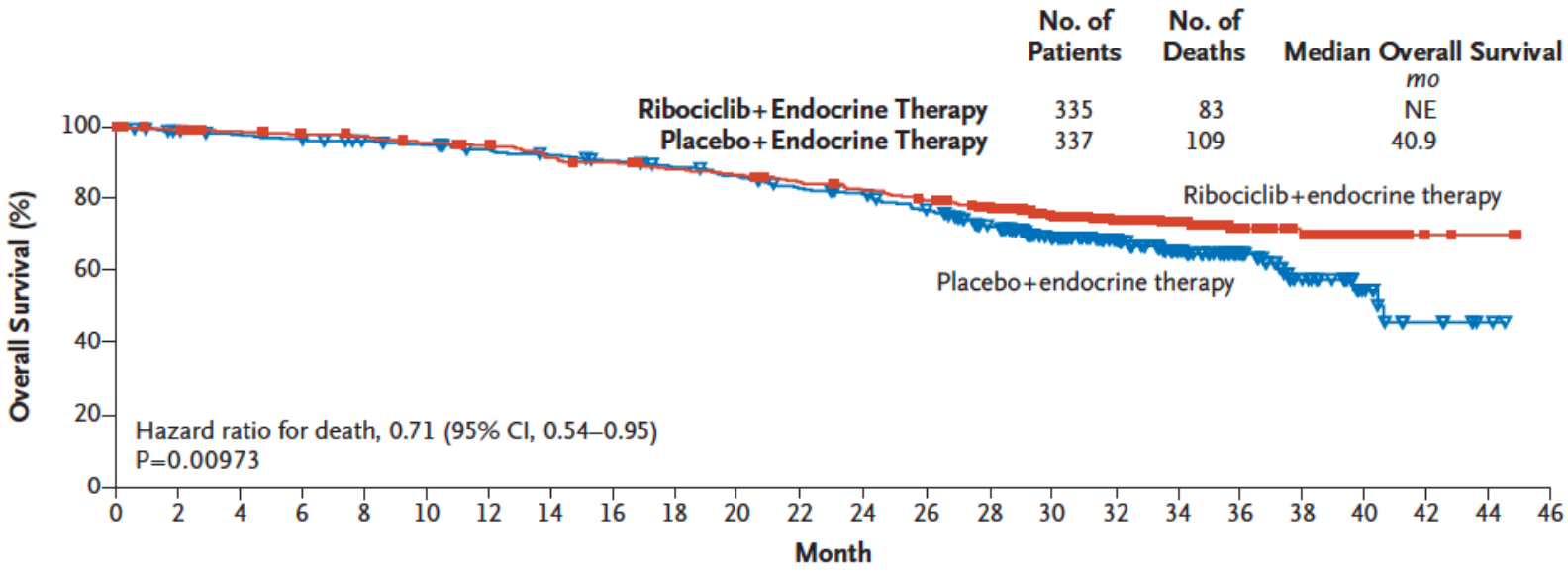
A All Patients



No. at Risk

Ribociclib	335	330	325	320	316	309	304	292	287	279	274	266	258	249	236	193	155	110	68	43	25	7	3	0
Placebo	337	330	325	321	314	309	301	295	288	280	272	258	251	235	210	166	122	92	62	33	19	7	2	0

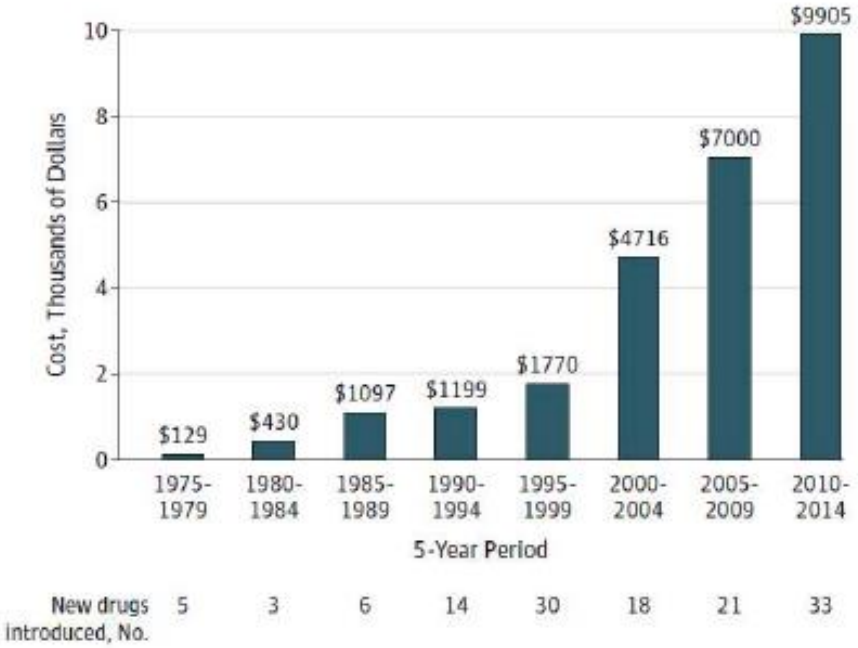
These drugs cost too much.

EDITORIAL

Perspectives on Cost and Value in Cancer Care

Leonard B. Saltz, MD

Figure. Cancer Drugs Hit Market at Ever-Higher Prices



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ART OF ONCOLOGY

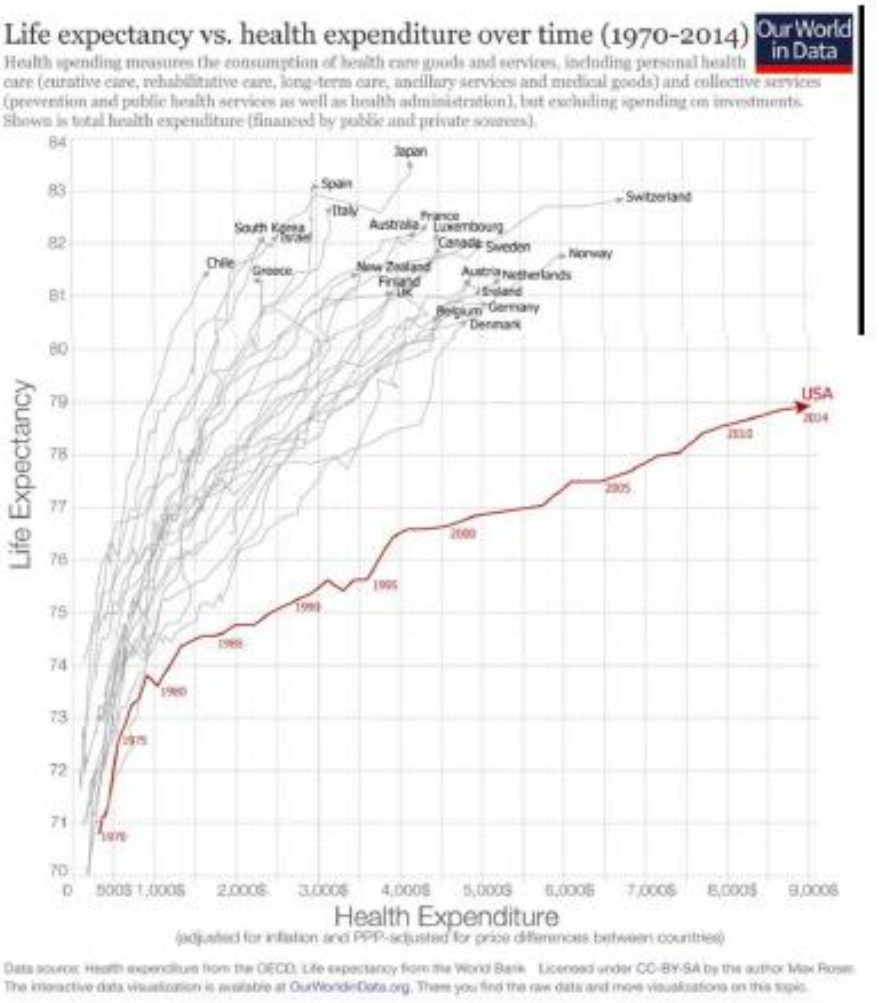
Reporting and Grading Financial Toxicity

Nandita Khera

Her questions are difficult and thought provoking: "Will I have to sell my home? Should I declare bankruptcy? Do I need to stop spending money on food and utilities to be able to pay for medical care? Will I have to go to hospice when I am unable to pay any more? Does hospice charge very much?" These questions make me uncomfortable and aware of the fact that I am not really prepared to manage this adverse effect of cancer treatment.

E’ un problema statunitense…

- Lo sapevamo già
- Ma noi siamo Europei…
- Antica e solida civiltà
- E’ tutta un’altra storia…



E’ tutta un’altra storia?