Year in Review

A Multitumor Regional Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Saturday, January 11, 2020, 8:00 AM – 4:00 PM
Houston, Texas

Faculty

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Gregory J Riely, MD, PhD
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Moderator

Neil Love, MD

Research To Practice®

Agenda

Module 1 — Lymphomas and Chronic Lymphocytic Leukemia: *Drs Cheson, Nastoupil and Smith*

Module 2 — Breast Cancer: *Drs Hamilton and Hurvitz*

Module 3 — Acute Leukemias: *Drs Erba and Levis*

Module 4 — Gastrointestinal Cancers: *Drs Bekaii-Saab, Bendell and Philip*

Module 5 — Genitourinary Cancers: *Drs Drake and Oh*

Module 6 — Lung Cancer: *Drs Liu and Riely*

Module 7 — Gynecologic Cancers: *Drs Coleman and Moore*

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Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Black Diamond Therapeutics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Daiichi Sankyo Inc, Genentech, Lilly, Mersana Therapeutics, Novartis, Pfizer Inc, Puma Biotechnology Inc, Roche Laboratories Inc, Silverback Therapeutics
Contracted Research	AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Aravive Inc, ArQule Inc, Arvinas, AstraZeneca Pharmaceuticals LP, BerGenBio ASA, Black Diamond Therapeutics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Clovis Oncology, Curis Inc, CytomX Therapeutics, Daiichi Sankyo Inc, Deciphera Pharmaceuticals, eFFECTOR Therapeutics Inc, Eisai Inc, EMD Serono Inc, Fochon Pharmaceuticals Ltd, Fosun Orinove PharmaTech Inc, FUJIFILM Pharmaceuticals USA Inc, Genentech, H3 Biomedicine, Harpoon Therapeutics, Hutchison MediPharma, Immunomedics Inc, InventisBio, Leap Therapeutics Inc, Lilly, Lycera, MacroGenics Inc, Marker Therapeutics Inc, Medivation Inc, a Pfizer Company, Mersana Therapeutics, Merus BV, Molecular Templates, Novartis, NuCana, OncoMed Pharmaceuticals Inc, Pfizer Inc, Radius Health Inc, Regeneron Pharmaceuticals Inc, Rgenix, Roche Laboratories Inc, Seattle Genetics, Sermonix Pharmaceuticals, Silverback Therapeutics, Stemcentrx, Sutro Biopharma, Syndax Pharmaceuticals Inc, Syros Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Torque Therapeutics, Unum Therapeutics, Verastem Inc, Zenith Epigenetics Ltd, Zymeworks

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Disclosures

Grant/Support	Ambryx Inc, Amgen Inc, Bayer HealthCare Pharmaceuticals, BioMarin, Boehringer Ingelheim Pharmaceuticals Inc, Daiichi Sankyo Inc, Dignitana, Genentech, GlaxoSmithKline, Lilly, MacroGenics Inc, Medivation Inc, a Pfizer Company, Merrimack Pharmaceuticals Inc, Novartis, OBI Pharma Inc, Pfizer Inc, Pieris Pharmaceuticals, Puma Biotechnology Inc, Roche Laboratories Inc, Seattle Genetics
Paid Travel	Lilly, Novartis, OBI Pharma Inc

Breast Cancer — Drs Hamilton and Hurvitz

HER2-Positive Breast Cancer

Triple-Negative Breast Cancer

ER-Positive Breast Cancer

FDA Approves Ado-Trastuzumab Emtansine (T-DM1) as Adjuvant Treatment for HER2-Positive Early Breast Cancer

Press Release – May 3, 2019

"The Food and Drug Administration approved ado-trastuzumab emtansine for the adjuvant treatment of patients with HER2-positive early breast cancer (EBC) who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

Approval was based on the KATHERINE trial (NCT01772472), a randomized, multicenter, open-label trial of 1,486 patients with HER2-positive EBC. Breast tumor samples were required to demonstrate HER2 overexpression defined as 3+ IHC or ISH amplification ratio ≥2.0 determined at a central laboratory using the PATHWAY anti-HER2-/neu (4B5) Rabbit Monoclonal Primary Antibody or HER2 Dual ISH DNA Probe Cocktail assays.

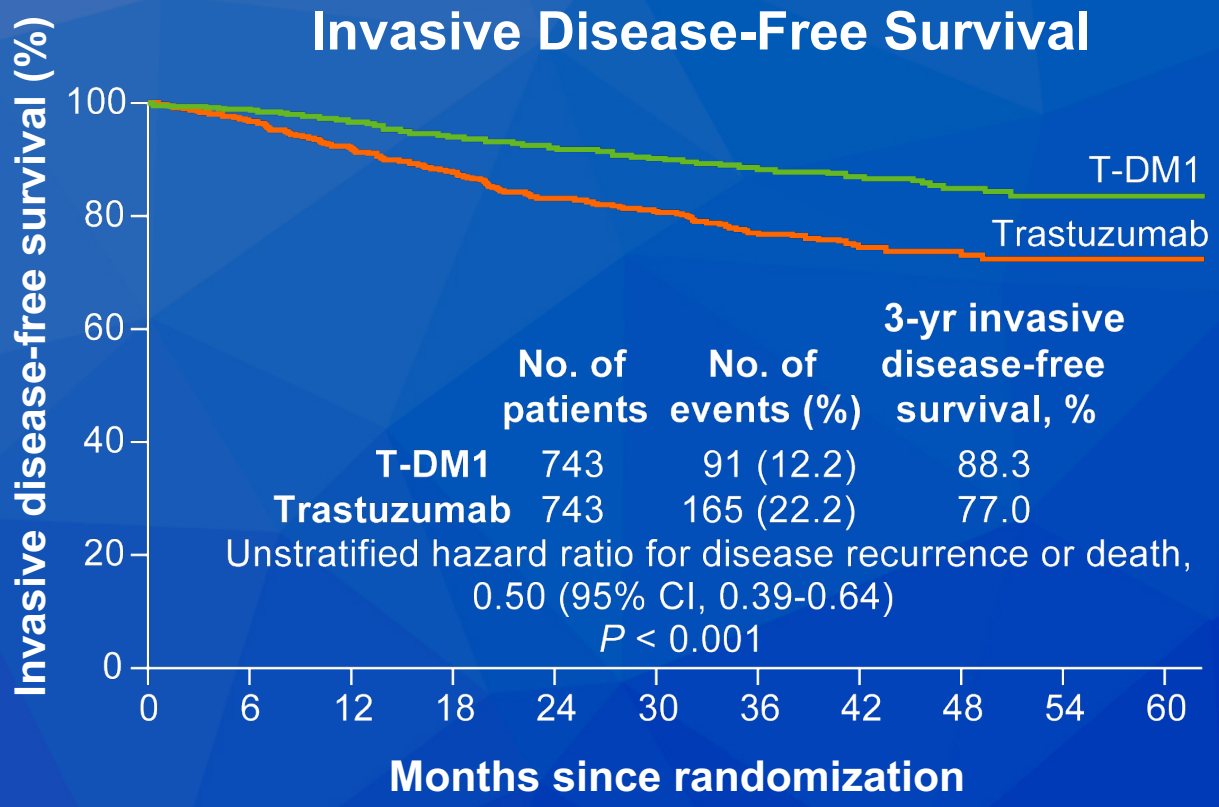
Patients were required to have had neoadjuvant taxane and trastuzumab-based therapy with residual invasive tumor in the breast and/or axillary lymph nodes."

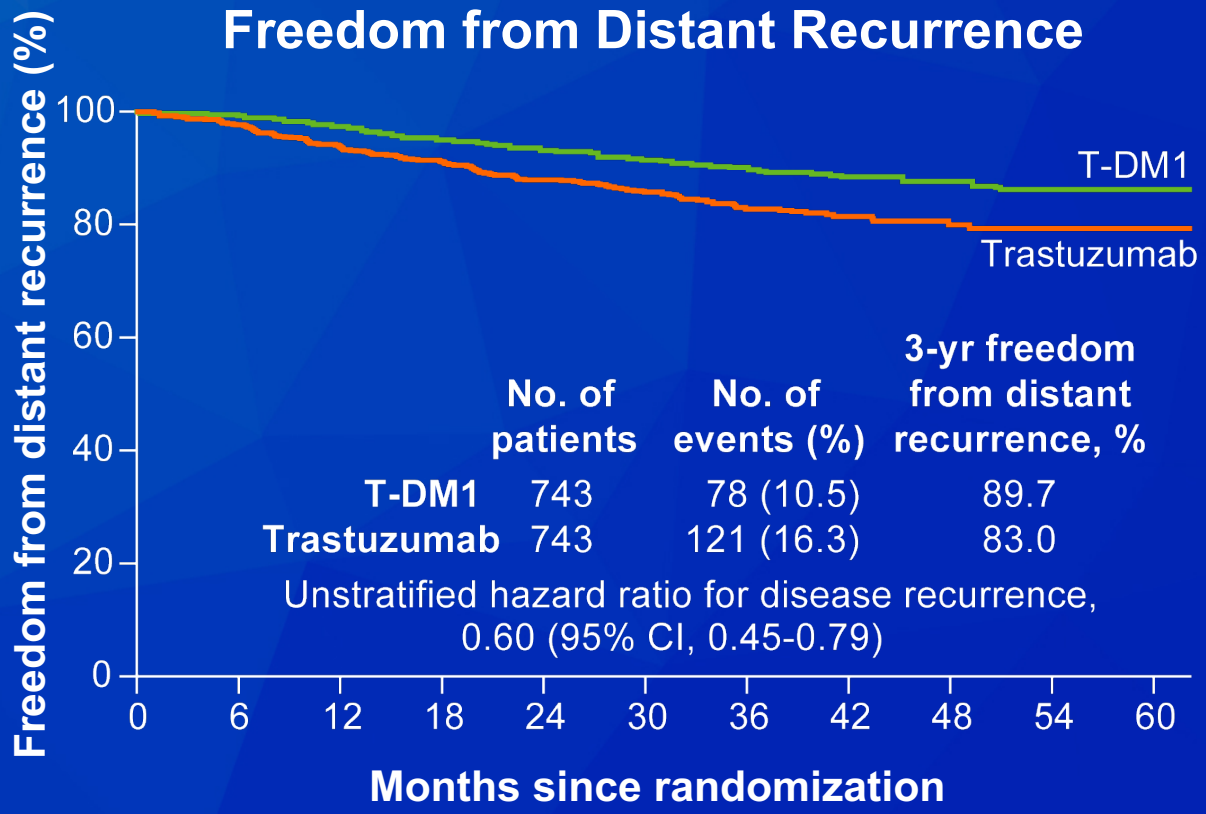
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ado-trastuzumab-emtansine-early-breast-cancer

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

von Minckwitz G et al.
N Engl J Med 2019;380(7):617-28.

KATHERINE: Invasive DFS and Freedom from Distant Recurrence

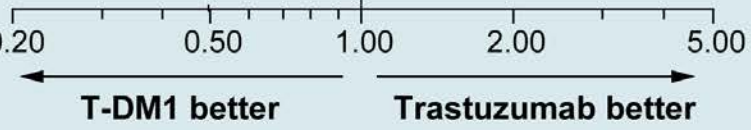




von Minckwitz G et al. *N Engl J Med* 2019;380(7):617-28.

KATHERINE: Subgroup Analyses of Invasive Disease-Free Survival

Subgroup	T-DM1	Trastuzumab	Hazard ratio for invasive-disease event	3-yr invasive disease-free survival rate	
	no. of patients with an invasive-disease event/total no.			T-DM1 %	Trastuzumab %
All patients	91/743	165/743	0.50	88.3	77.0
Age group					
<40 yr	20/143	37/153	0.50	86.5	74.9
40–64 yr	64/542	113/522	0.49	88.8	77.1
≥65 yr	7/58	15/68	0.55	87.4	81.1
Clinical stage at presentation					
Inoperable breast cancer	42/185	70/190	0.54	76.0	60.2
Operable breast cancer	49/558	95/553	0.47	92.3	82.8
Hormone-receptor status					
Negative (ER-negative and progesterone-receptor–negative or unknown)	38/209	61/203	0.50	82.1	66.6
Positive (ER-positive, progesterone-receptor–positive, or both)	53/534	104/540	0.48	90.7	80.7
Preoperative HER2-directed therapy					
Trastuzumab alone	78/600	141/596	0.49	87.7	75.9
Trastuzumab plus additional HER2-directed agent or agents	13/143	24/147	0.54	90.9	81.8
Pathological nodal status after preoperative therapy					
Node-positive	62/343	103/346	0.52	83.0	67.7
Node-negative or NE	29/400	62/397	0.44	92.8	84.6



von Minckwitz G et al. *N Engl J Med* 2019;380(7):617-28.

Editorial — Dr O'Shaughnessy

Adjuvant trastuzumab added to chemotherapy dramatically improved outcome for HER2+ early stage breast cancer patients. Yet still about 25% of patients had a disease-free survival (DFS) event, with about 16% of these representing invasive disease recurrence. The addition of adjuvant pertuzumab to trastuzumab plus chemotherapy further improved invasive DFS by 1.6% in the overall population and by 2%-3% in patients with node-positive or ER-negative disease. Because the FDA granted accelerated approval to preoperative pertuzumab before granting full approval for adjuvant pertuzumab, treating stage II and III patients with preoperative trastuzumab/pertuzumab plus chemotherapy (TPCx) became the standard of care over the past 5 years. This then enabled the conduct of the KATHERINE trial which demonstrated that treating patients who had residual disease in their breast or axillary lymph nodes following TPCx with the antibody-drug conjugate of trastuzumab linked to the potent and non-cross-resistant anti-microtubule agent maytansine, T-DM1, postoperatively dramatically improved invasive DFS in this highest risk population, regardless of ER status.

Editorial — Dr O'Shaughnessy (continued)

Overall functional status of the patients was not diminished by adjuvant T-DM1 compared with adjuvant trastuzumab, although greater neuropathy, fatigue, liver dysfunction and thrombocytopenia occurred in patients treated with T-DM1. The FDA moved quickly to approve adjuvant T-DM1 in patients with residual disease post-neoadjuvant TPCx, as did NCCN, establishing T-DM1 as a new standard of care in this high risk population.

Adjuvant Trastuzumab Emtansine (T-DM1) vs Trastuzumab (H) in Patients with Residual Invasive Disease After Neoadjuvant Therapy for HER2-Positive Breast Cancer: KATHERINE Subgroup Analysis

Mano MS et al.
San Antonio Breast Cancer Symposium 2019;Abstract P3-14-01.

Editorial — Dr Hurvitz

The phase III randomized KATHERINE study demonstrated a significant improvement in 3-year invasive disease-free survival (DFS) associated with the use of adjuvant T-DM1 (compared to trastuzumab) in patients with residual disease after standard neoadjuvant trastuzumab-based chemotherapy. A subgroup analysis was conducted to evaluate whether certain groups derived more or less benefit from T-DM1. The benefit of T-DM1 was similar in patients who received anthracycline (77%) vs. non-anthracycline (23%) chemotherapy (HR 0.51 for anthracycline; HR 0.43 for non-anthracycline). Interestingly the 3-year iDFS was numerically higher in the non-anthracycline patients (non-anthracycline 3-year iDFS T-DM1: 91.7% vs trastuzumab: 81.4%; anthracycline 3-year iDFS T-DM1: 87.4% vs trastuzumab: 75.7%).

Editorial — Dr Hurvitz (continued)

The toxicity of T-DM1 was higher in the non-anthracycline arm with higher rates of all-grade pulmonary toxicity as well as grade 3/4 adverse events including thrombocytopenia and peripheral neuropathy. Though interesting, these differences in toxicity may be related to imbalances in baseline characteristics of patients (more ECOG PS 1 and Asian patients in non-anthracycline arm and higher exposure to taxane and platinum chemotherapy). A small subset of patients (N=77) had cT1 cN0 tumors at baseline; 6 of 32 patients in the trastuzumab arm had a recurrence compared to 0 of 45 in the T-DM1 arm, suggesting benefit even in this group of patients considered to be lower risk by virtue of their original stage. Finally, this analysis demonstrated that patients who were inoperable at baseline or who had hormone receptor-negative disease with node metastases at surgery remain at particularly high risk of relapse (3-year iDFS 76%) in spite of receiving T-DM1.

Interim Overall Survival Analysis of APHINITY (BIG 4-11): A Randomized Multicenter, Double-Blind, Placebo-Controlled Trial Comparing Chemotherapy plus Trastuzumab plus Pertuzumab versus Chemotherapy plus Trastuzumab plus Placebo as Adjuvant Therapy in Patients with Operable HER2-Positive Early Breast Cancer

Piccart M et al.
San Antonio Breast Cancer Symposium 2019;Abstract GS1-04.

APHINITY: Clinical Benefit of Adjuvant Dual-HER2 Blockade with Chemotherapy

Hazard ratio for IDFS in the ITT population and subgroups based on lymph node & hormone receptor status			**IDFS at 6 years from randomization** (APHINITY updated descriptive analysis)		
Population	**Primary analysis** median FU 45.4 months; 2017	**Updated analysis** median FU 74.1 months; 2019	**Pertuzumab arm**	**Placebo arm**	**Absolute benefit**
ITT	0.81	0.76	90.6%	87.8%	2.8%
LN-positive	0.77	0.72	87.9%	83.4%	4.5%
LN-negative	1.13	1.02	95.0%	94.9%	0.1%
HR-positive	0.86	0.73	91.2%	88.2%	3.0%
HR-negative	0.76	0.83	89.5%	87.0%	2.5%

LN = lymph node; HR = hormone receptor

OS difference after 74.1 months of median FU did not yet reach statistical significance

Piccart M et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-04.

Editorial — Dr Hurvitz

At the primary analysis in 2017, the APHINITY trial showed a small but statistically significant iDFS benefit (0.9% absolute difference at 3 years) with the addition of 1 year of adjuvant pertuzumab to trastuzumab for early-stage HER2+ breast cancer. However, the benefit appeared to be restricted to those patients with lymph node positive disease. In 2019, with approximately 42% of survival events, and 74-months median follow up, the median OS was similar in the 2 arms (5.2% pertuzumab, 6.1% placebo). An updated analysis of iDFS did demonstrate more separation between the two curves, now with a 2.8% absolute iDFS benefit at 6 years with pertuzumab. Again, though, the benefit with pertuzumab was restricted to those with node-positive disease, where the absolute improvement in iDFS at 6 years was 4.5%. In contrast to early results from APHINITY as well as results from EXTENET (evaluating adjuvant neratinib), hormone receptor expression did not affect the benefit associated with pertuzumab.

Editorial — Dr Hurvitz (continued)

While these updated iDFS results strengthen the rationale to use adjuvant pertuzumab in high-risk, node-positive HER2+ breast cancer, most patients with high-risk disease are now being treated in the neoadjuvant setting, and adjuvant treatment is being determined based on whether a pathologic complete response is achieved at the time of surgery. A patient who has residual disease at the time of surgery will now typically receive adjuvant T-DM1 (based on KATHERINE). That said, for those patients who start with node-positive disease and achieve a pCR with pertuzumab/trastuzumab-based neoadjuvant therapy, the APHINITY data lend support to complete a full year of pertuzumab, though survival differences have not been observed to date.

TBCRC 033: A Randomized Phase II Study of Adjuvant Trastuzumab Emtansine (T-DM1) vs Paclitaxel (T) in Combination with Trastuzumab (H) for Stage I HER2-Positive Breast Cancer (BC) (ATEMPT)

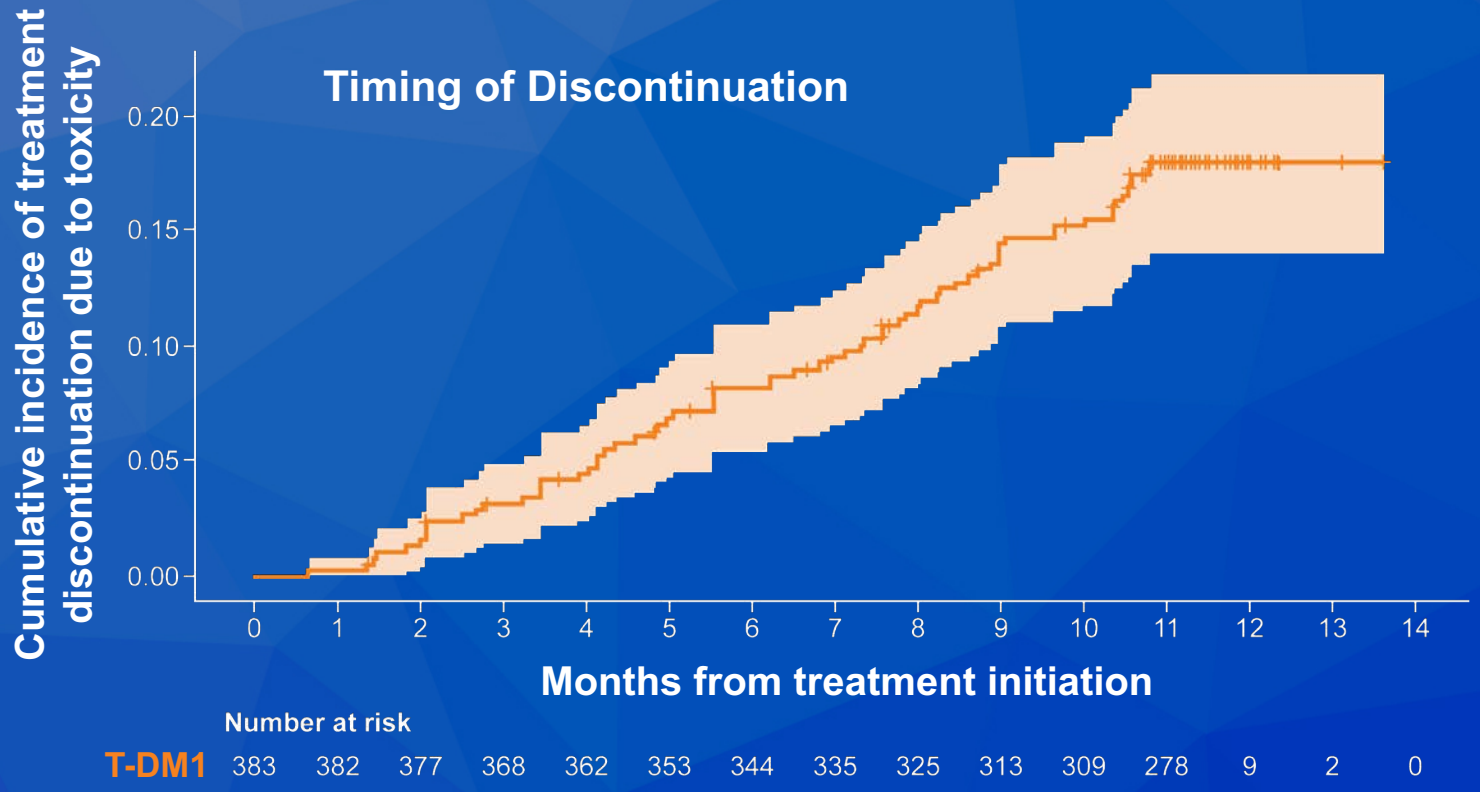
Tolaney SM et al.
San Antonio Breast Cancer Symposium 2019;Abstract GS1-05.

ATEMPT: Disease-Free Survival

	T-DM1			TH		
	N	No. of events	3-y DFS	N	No. of events	3-y DFS
Overall	**383**	**10**	**97.7%**	**114**	**7**	**92.8%**
Hormone receptor (HR) status						
HR+	289	8	97.5%	Not reported		
HR-	94	2	98.5%			
Tumor size						
T <1cm	163	2	98.5%	Not reported		
T ≥1cm	220	8	97.1%			

Tolaney SM et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-05.

ATEMPT: T-DM1 Discontinuations



	n (%)
Discontinuations for any reason	90 (23.5%)
Discontinuations for toxicity	67 (17.0%)
Discontinuations for toxicity that were protocol mandated	33 (9%)

*** 66% of patients who discontinued T-DM1 early for toxicity received further therapy with trastuzumab**

- Probability of discontinuing within 6 months: 8.2%
- Probability of discontinuing between months 6-12: 10.7%

Tolaney SM et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-05.

ATEMPT: Cardiac Toxicity

ECHO or MUGA

	Arm 1: T-DM1 (n = 383)	Arm 2: TH (n = 114)
Symptomatic congestive heart failure	3 (0.8%)	1 (0.9%)
Asymptomatic declines in LVEF (≥15%)	5 (1.3%)	7 (6.1%)

Tolaney SM et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-05.

Editorial — Dr Hurvitz

Although the benefits of HER2-targeted therapy for early-stage HER2+ disease cannot be overstated, it is not clear that all patients with early-stage disease require standard 6-8 cycles of chemo-based treatment in order to achieve a good outcome. As such, a number of studies are evaluating whether therapy can be de-escalated for lower-risk patients. One example of the uptake of this strategy is the recent acceptance of the “APT” weekly paclitaxel (12 doses) plus trastuzumab (1-year) regimen for node-negative disease based on promising results from a single-arm phase II trial (3-year DFS 98.7%). In the phase II ATEMPT study, patients with stage I disease were randomized 3:1 to receive T-DM1 (17 cycles) or the APT (“TH”) regimen. The study aimed to compare the toxicity of the 2 arms and to evaluate the 3-year DFS in the T-DM1 arm; the study was not designed to compare the DFS of T-DM1 to TH. The 3-year DFS was 97.7% in the T-DM1 arm.

Editorial — Dr Hurvitz (continued)

It was 92.8% in the TH arm. Neurotoxicity, infusion reactions, and neutropenia rates were higher in the TH arm, but more patients (17% vs 6%) discontinued T-DM1 due to toxicity and higher rates of thrombocytopenia and liver function abnormalities were observed with T-DM1. In summary, T-DM1 appears to represent a reasonable option for adjuvant treatment of patients with low-risk (stage I) disease who are not good candidates for (or are unwilling to take) chemotherapy. Longer term follow-up from this trial will be important.

FDA Breakthrough Therapy Designation for Tucatinib in mBC

Press Release – December 18, 2019

"The Food and Drug Administration has granted Breakthrough Therapy designation to tucatinib, in combination with trastuzumab and capecitabine, for treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have been treated with trastuzumab, pertuzumab, and T-DM1. The positive topline results of the pivotal HER2CLIMB clinical trial were announced in October 2019, and additional data were presented at the 2019 San Antonio Breast Cancer Symposium and were simultaneously published in the *New England Journal of Medicine*.

This Breakthrough Therapy designation was based on data from the pivotal HER2CLIMB clinical trial, which compared tucatinib in combination with trastuzumab and capecitabine to trastuzumab and capecitabine alone in patients with locally advanced unresectable or metastatic HER2-positive breast cancer. Patients had previously received trastuzumab, pertuzumab and ado-trastuzumab emtansine (T-DM1)."

https://www.biospace.com/article/releases/seattle-genetics-announces-u-s-fda-grants-breakthrough-therapy-designation-for-tucatinib-in-locally-advanced-or-metastatic-her2-positive-breast-cancer/

Tucatinib vs Placebo, Both Combined with Capecitabine and Trastuzumab, for Patients with Pretreated HER2-Positive Metastatic Breast Cancer With and Without Brain Metastases (HER2CLIMB)[1]

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer[2]

[1] Murthy R et al.
San Antonio Breast Cancer Symposium 2019;Abstract GS1-01.

[2] Murthy RK et al.
N Engl J Med 2019;[Epub ahead of print].

HER2CLIMB: Phase II Trial Schema

Key eligibility criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab and T-DM1
- ECOG performance status 0 or 1
- Brain MRI baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated progressing brain metastases not needing immediate local therapy
  - No evidence of brain metastases

R* (2:1)

N = 410

Tucatinib + trastuzumab + capecitabine
(21-day cycle)
Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg q3w (loading dose 8 mg/kg C1D1)
+
Capecitabine 1,000 mg/m^2 PO BID (days 1-14)

N = 202

Placebo + trastuzumab + capecitabine
(21-day cycle)
Placebo
+
Trastuzumab 6 mg/kg q3w (loading dose 8 mg/kg C1D1)
+
Capecitabine 1,000 mg/m^2 PO BID (days 1-14)

* Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

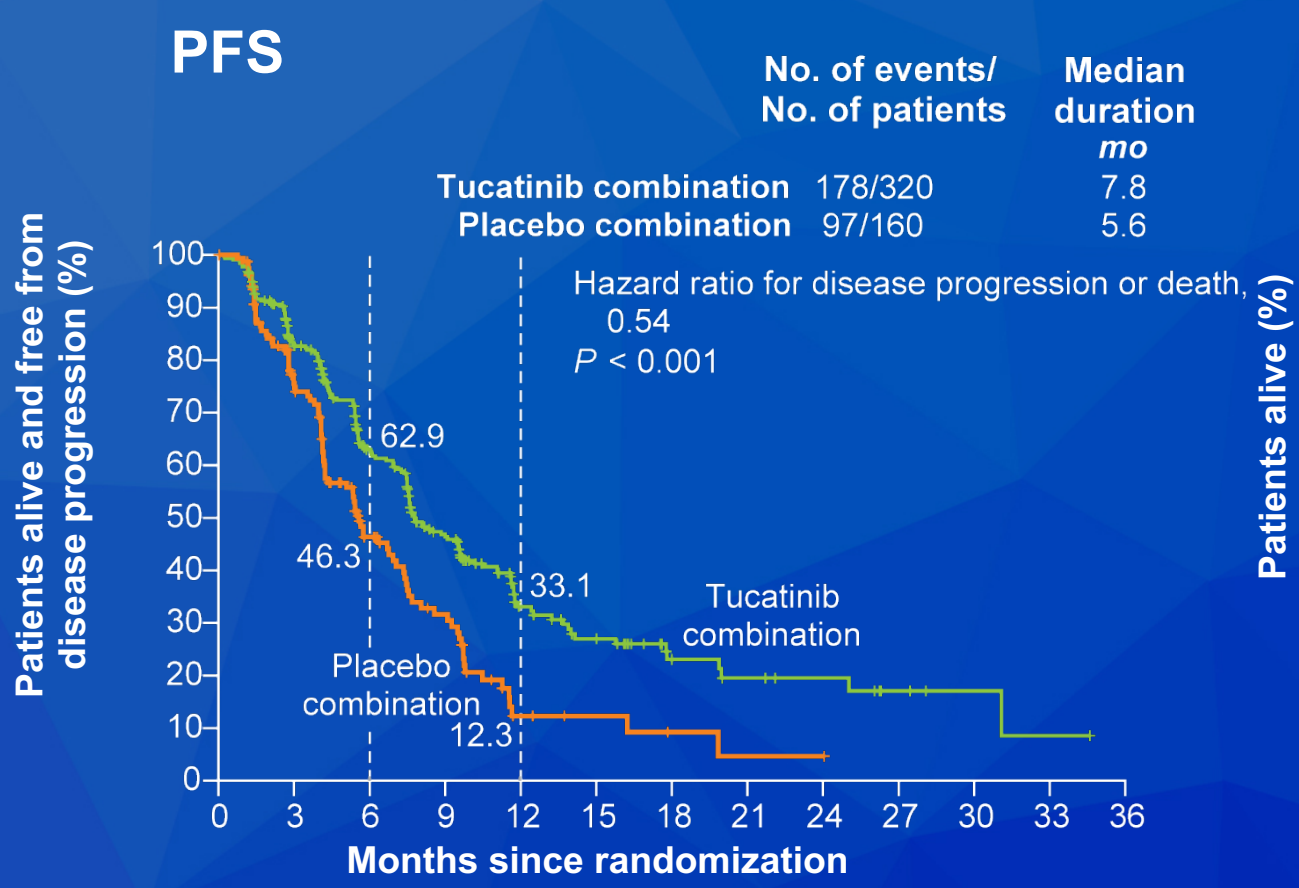
Murthy R et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-01; Murthy RK et al. *N Engl J Med* 2019;[Epub ahead of print].

HER2CLIMB: Survival Outcomes

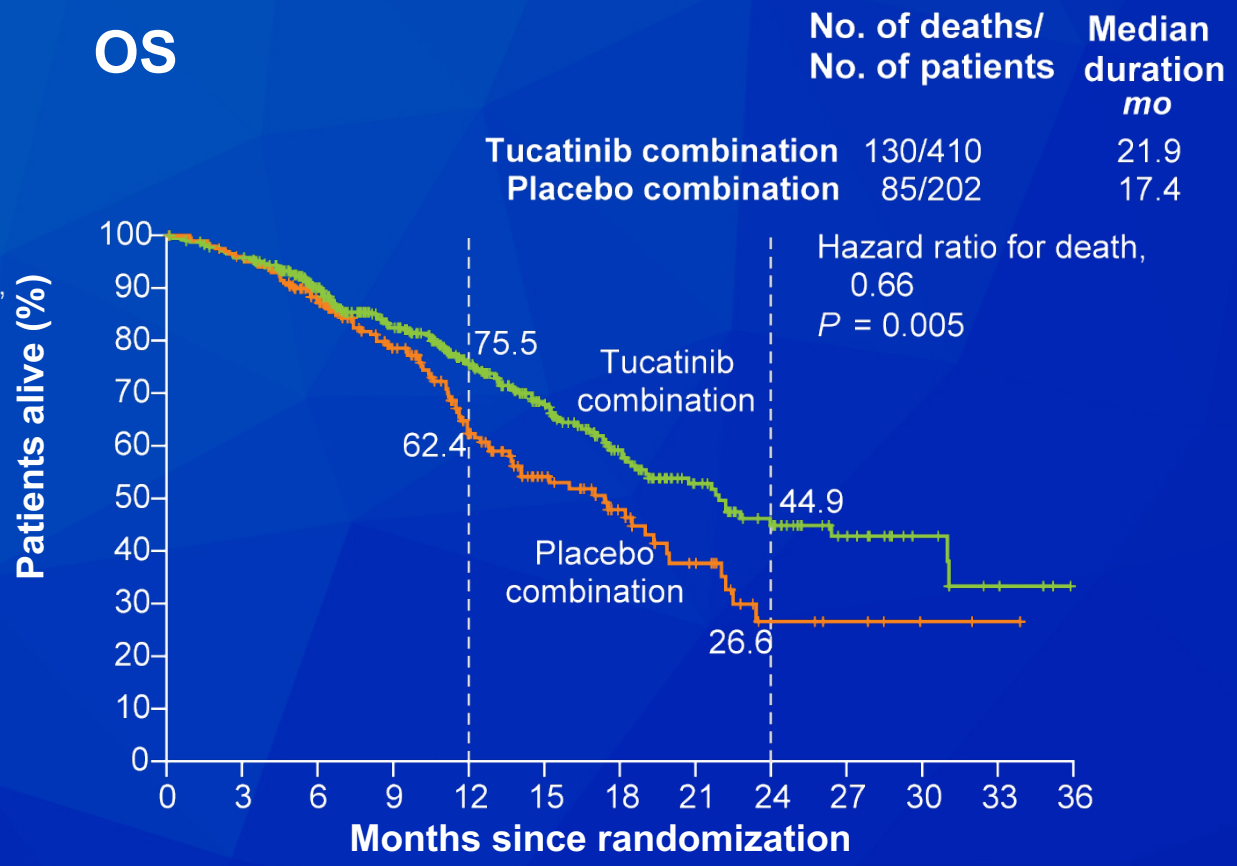
Among the patients with brain metastases:

- Median PFS = 7.6 mo (tucatinib) vs 5.4 mo (placebo)
  - HR = 0.48; $p < 0.001$
- 1-yr PFS = 24.9% (tucatinib) vs 0% (placebo)

PFS



OS



Murthy R et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-01; Murthy RK et al. *N Engl J Med* 2019;[Epub ahead of print].

HER2CLIMB: Safety Outcomes

Select AE	Tucatinib (n = 404)		Placebo (n = 197)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	99.3%	55.2%	97.0%	48.7%
Diarrhea	80.9%	12.9%	53.3%	8.6%
PPE syndrome	63.4%	13.1%	52.8%	9.1%
Nausea	58.4%	3.7%	43.7%	3.0%
Fatigue	45.0%	4.7%	43.1%	4.1%
Vomiting	35.9%	3.0%	25.4%	3.6%
Stomatitis	25.5%	2.5%	14.2%	0.5%
Increased AST	21.3%	4.5%	11.2%	0.5%
Increased ALT	20.0%	5.4%	6.6%	0.5%

Murthy R et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-01; Murthy RK et al. *N Engl J Med* 2019;[Epub ahead of print].

Editorial — Dr Hamilton

Tucatinib is a novel oral tyrosine kinase inhibitor that inhibits only HER2 and not EGFR/HER1 (a differentiator from other drugs such as lapatinib, neratinib, etc). This HER2 selectivity translates to a drug that doesn't cause rash and diarrhea, which we know are problems with the nonspecific TKIs. In HER2CLIMB, patients were treated with capecitabine/trastuzumab with or without tucatinib. We saw significant improvements in PFS, OS, ORR and PFS in the brain met population. Another truly unique aspect of this trial was the inclusion of atypical populations of patients with brain mets. Not only were the classically included patients with treated stable brain mets included, but patients were also allowed to enroll who had untreated asymptomatic mets, or mets that had been treated and had subsequently progressed. We saw a significantly improved survival with a 33% improvement in the risk of death (HR 0.66, *P* 0.0048).

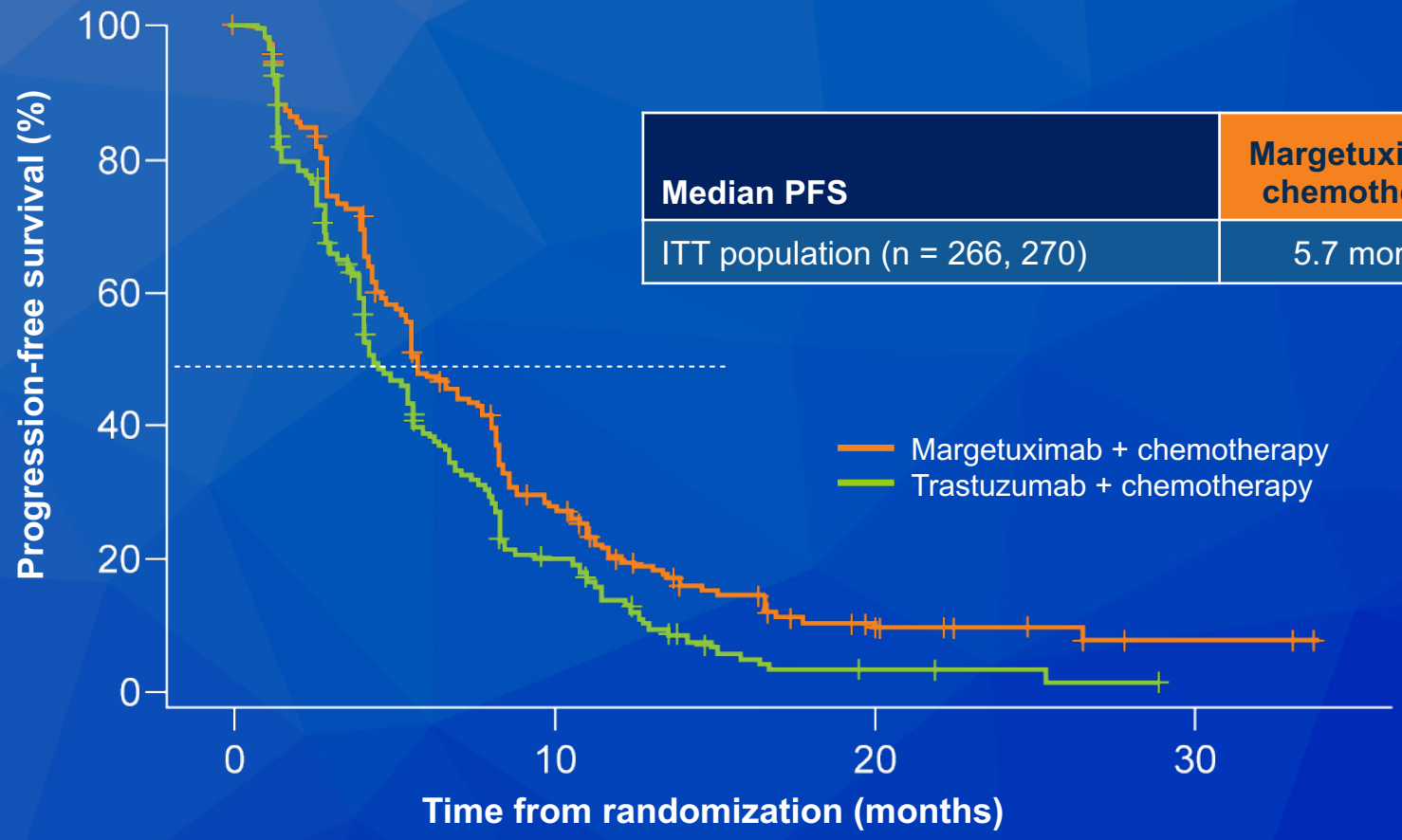
Editorial — Dr Hamilton (continued)

The triplet combination also improved PFS in all pts compared to cape/trastuzumab alone (HR 0.54, $p < 0.00001$), including those pts with brain mets (HR 0.48, $p < 0.00001$). This is the first time in a trial where we see patients with brain metastases do just as well as their counterparts without them and will significantly help this population who has few treatment options.

Phase 3 SOPHIA Study of Margetuximab + Chemotherapy vs Trastuzumab + Chemotherapy in Patients with HER2+ Metastatic Breast Cancer After Prior Anti-HER2 Therapies: Second Interim Overall Survival Analysis

Rugo HS et al.
San Antonio Breast Cancer Symposium 2019;Abstract GS1-02.

SOPHIA: Investigator-Assessed PFS and Second Interim OS Analysis with Margetuximab/Chemotherapy versus Trastuzumab/Chemotherapy for Previously Treated HER2-Positive mBC



Median PFS	Margetuximab + chemotherapy	Trastuzumab + chemotherapy	HR (*p*-value)
ITT population (n = 266, 270)	5.7 months	4.4 months	0.71 (0.0006)

- Investigator-assessed PFS – data cut-off Sept 2019
- Second interim OS analysis – data cut-off Sept 2019; not yet statistically significant
  - Median: 21.6 mo versus 19.8 mo (HR 0.89; $p = 0.326$)

Rugo HS et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-02.

FDA Approval of Trastuzumab Deruxtecan for Unresectable or Metastatic HER2-Positive BC

Press Release – December 20, 2019

"The Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki for patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

Efficacy was investigated in DESTINY-Breast01 (NCT03248492), a multicenter, single-arm trial enrolling 184 female patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2 therapies. Patients received fam-trastuzumab deruxtecan-nxki 5.4 mg/kg by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression.

The main efficacy outcome measures were confirmed objective response rate (ORR) assessed by independent central review using RECIST 1.1 and response duration. ORR was 60.3%, with a 4.3% complete response rate and a 56% partial response rate. Median response duration was 14.8 months."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2-positive-breast-cancer

[Fam-] Trastuzumab Deruxtecan (T-DXd; DS-8201a) in Subjects with HER2-Positive Metastatic Breast Cancer Previously Treated with T-DM1: A Phase 2, Multicenter, Open-Label Study (DESTINY-Breast01)[1]

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer[2]

[1] Krop IE et al.
San Antonio Breast Cancer Symposium 2019;Abstract GS1-03.

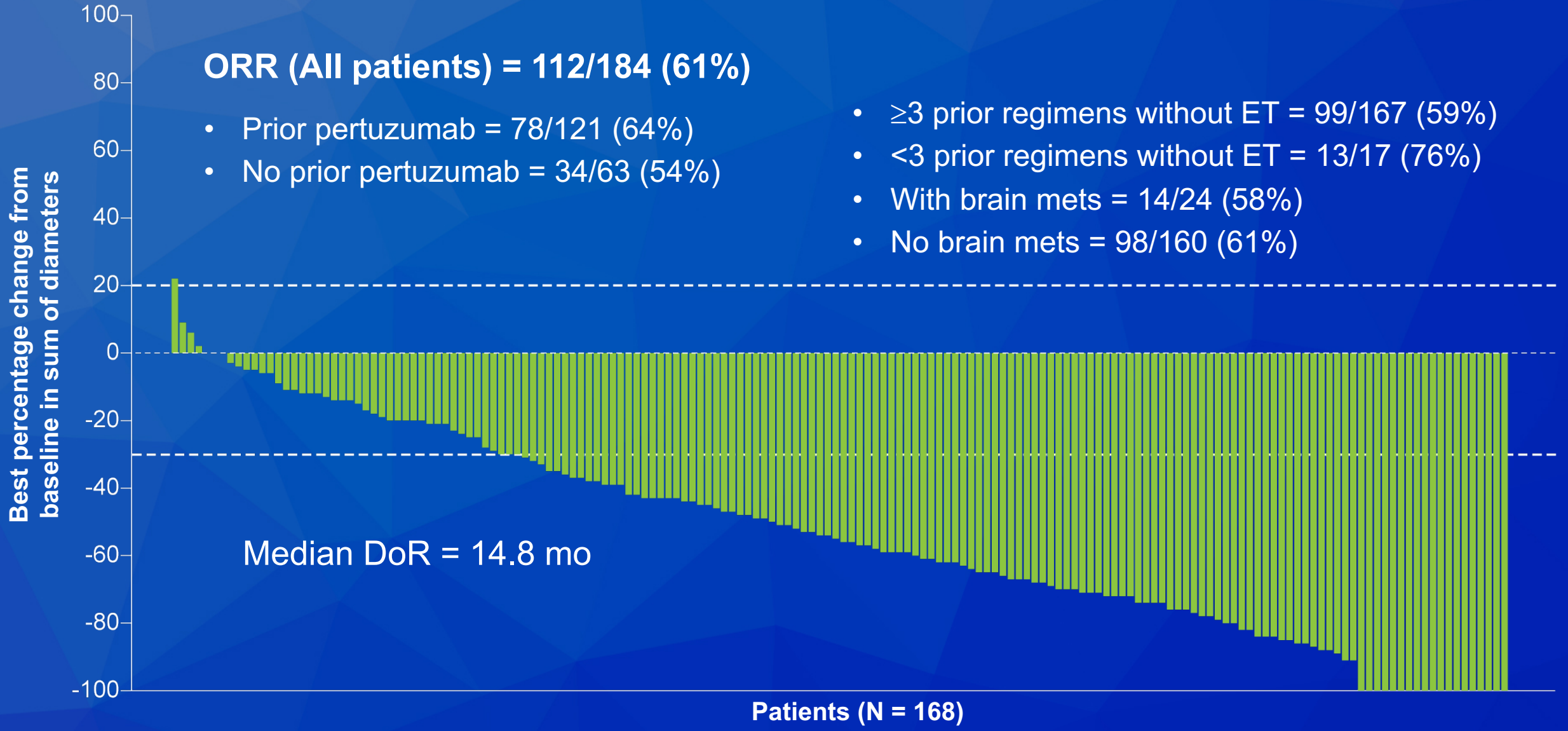
[2] Modi S et al.
N Engl J Med 2019;[Epub ahead of print].

DESTINY-Breast01: Response According to Tumor Size and Subgroup Analyses

ORR (All patients) = 112/184 (61%)

- Prior pertuzumab = 78/121 (64%)
- No prior pertuzumab = 34/63 (54%)

- ≥3 prior regimens without ET = 99/167 (59%)
- <3 prior regimens without ET = 13/17 (76%)
- With brain mets = 14/24 (58%)
- No brain mets = 98/160 (61%)



Krop IE et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-03; Modi S et al. *N Engl J Med* 2019;[Epub ahead of print].

DESTINY-Breast01: Survival and Safety

- Median duration of follow-up = 11.1 mo
- Median PFS = 16.4 mo
- Estimated 6-mo OS = 93.9%
- Estimated 12-mo OS = 86.2%
- Median OS = Not reached

AEs of special interest (n = 184)	All grades	Grades 3/4
Interstitial lung disease	25 (13.6%)	1 (0.5%)
Prolonged QT interval	9 (4.9%)	2 (1.1%)
Infusion-related reaction	4 (2.2%)	0
Decreased left ventricular ejection fraction	3 (1.6%)	1 (0.5%)

- Most common Grade ≥3 were decreased neutrophil count (21%), anemia (9%) and nausea (8%).

Krop IE et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-03; Modi S et al. *N Engl J Med* 2019;[Epub ahead of print].

Editorial — Dr Hamilton

At SABCS, we saw the data from DESTINY-Breast01. This was a phase II trial of 184 women with heavily pretreated metastatic HER2-positive breast cancer with a median of 6 priors in the metastatic setting. We saw a confirmed ORR of 60.9% with 11 CRs (wow!) and a median PFS of 16.4 months. I think it is very important to not only highlight the response rate but also highlight that for the patients who received benefit, the duration of response was very long at 14.8 months. I'm not sure we have seen anything like this in HER2+ metastatic disease before. Interstitial lung disease again was highlighted as a very important side effect to watch out for with 13.6% of patients developing during treatment, which included fatal cases in 4/184 patients. For this drug, it is recommended to hold treatment even for G1 pneumonitis seen on a CT only in the absence of symptoms until improvement.

Editorial — Dr Hamilton (continued)

Based on this study, on December 20, 2019 trastuzumab deruxtecan was granted accelerated approval by the FDA. There are several large ph III trials that remain enrolling – the 2nd line trial against T-DM1 and the 3rd line trial against capecitabine/trastuzumab or capecitabine/lapatinib. Also, recall that we have seen great activity of this drug in so-called “HER2-low patients” and there is a large clinical trial enrolling in the IHC 1+/2+ FISH-negative space.

Breast Cancer — Drs Hamilton and Hurvitz

HER2-Positive Breast Cancer

Triple-Negative Breast Cancer

ER-Positive Breast Cancer

FDA Approval of Atezolizumab for PD-L1-Positive Unresectable Advanced Triple-Negative Breast Cancer (TNBC)

Press Release – March 8, 2019

The Food and Drug Administration granted accelerated approval to atezolizumab in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test.

The FDA also approved the PD-L1 (SP142) Assay as a companion diagnostic device for selecting TNBC patients for atezolizumab.

Approval was based on IMpassion130 (NCT02425891), a multicenter, international, double-blinded, placebo-controlled, randomized trial that included 902 patients with unresectable locally advanced or metastatic TNBC who had not received prior chemotherapy for metastatic disease.

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-pd-l1-positive-unresectable-locally-advanced-or-metastatic-triple-negative

Atezolizumab and *Nab*-Paclitaxel in Advanced Triple-Negative Breast Cancer[1]

Atezolizumab plus *Nab*-Paclitaxel as First-Line Treatment for Unresectable, Locally Advanced or Metastatic Triple-Negative Breast Cancer (IMpassion130): Updated Efficacy Results from a Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial[2]

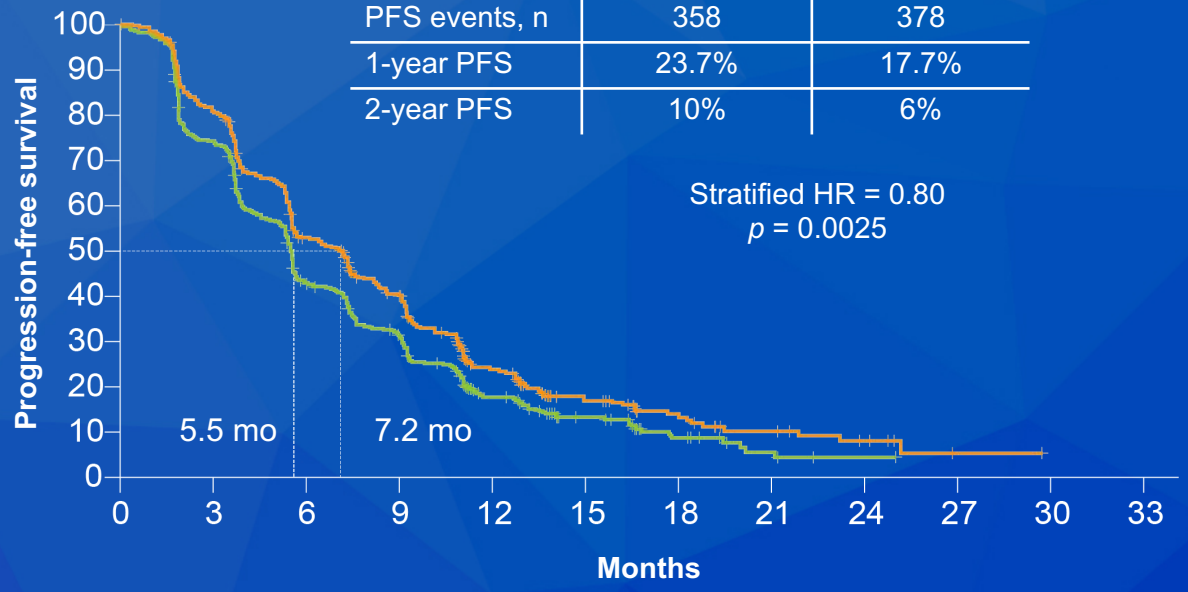
[1] Schmid P et al.
N Engl J Med 2018;379(22):2108-21.

[2] Schmid P et al.
Lancet Oncol 2020;21(1):44-59.

IMpassion130: PFS Results

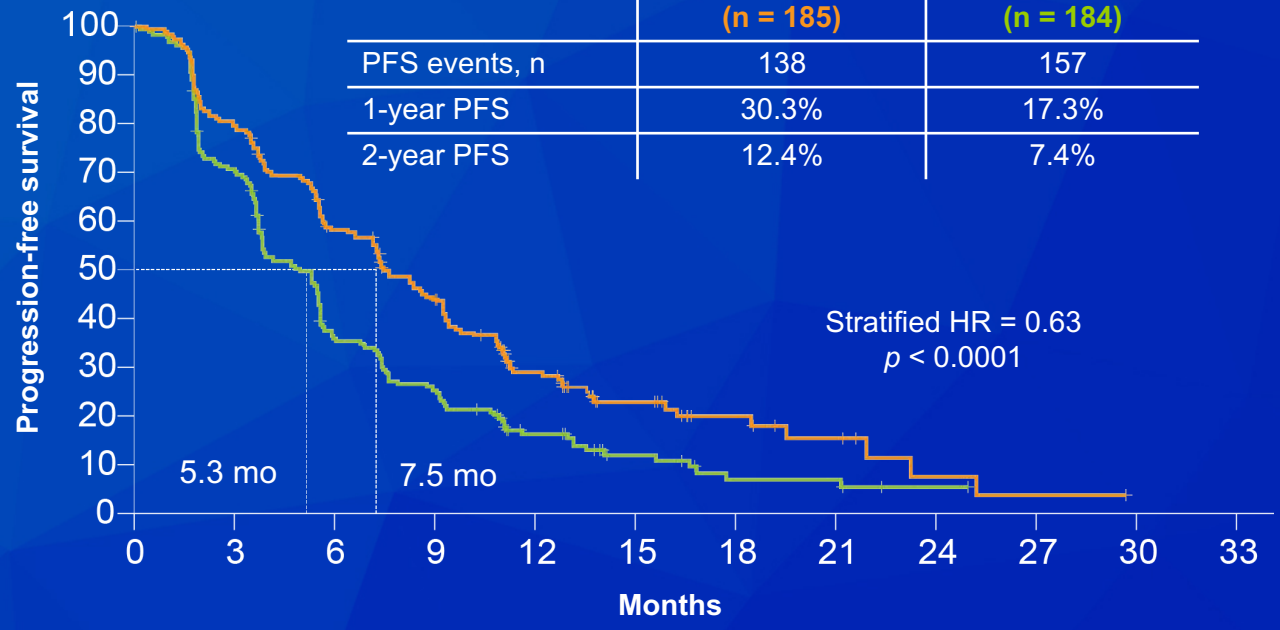
Primary PFS analysis: ITT population

	Atezo + *nab*-P (n = 451)	Plac + *nab*-P (n = 451)
PFS events, n	358	378
1-year PFS	23.7%	17.7%
2-year PFS	10%	6%



Primary PFS analysis: PD-L1+ population

	Atezo + *nab*-P (n = 185)	Plac + *nab*-P (n = 184)
PFS events, n	138	157
1-year PFS	30.3%	17.3%
2-year PFS	12.4%	7.4%



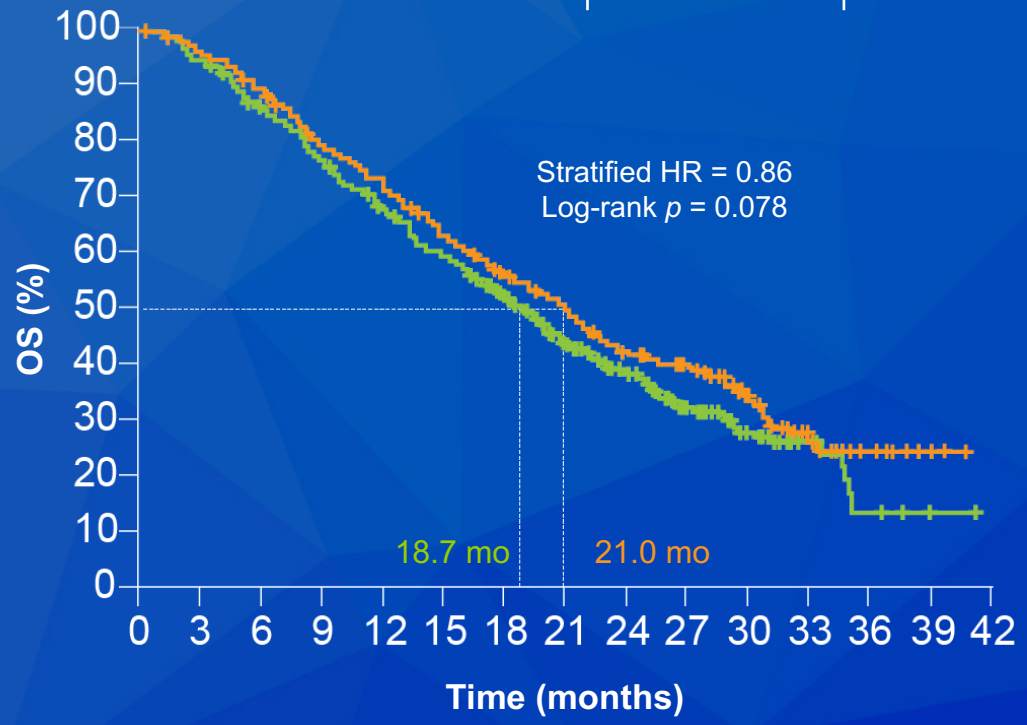
Second interim analysis median follow-up = 18.5 mo (atezo) vs 17.5 mo (placebo)

Schmid P et al. *Lancet Oncol* 2020;21(1):44-59; *N Engl J Med* 2018;379(22):2108-21; *Proc ESMO* 2018;Abstract LBA1_PR.

IMpassion130: OS Results at Second Interim Analysis

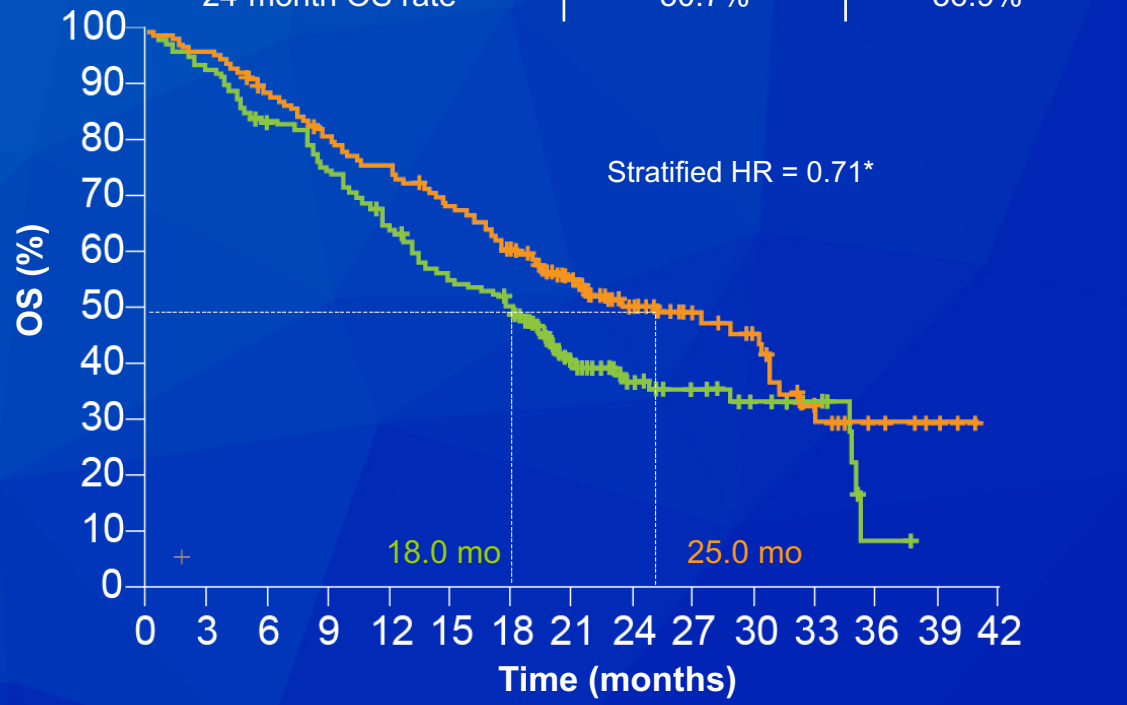
Second interim analysis of OS: ITT population

	Atezo + *nab*-P (n = 451)	Plac + *nab*-P (n = 451)
24-month OS rate	42.4%	38.7%



Second interim analysis of OS: PD-L1+ population

	Atezo + *nab*-P (n = 185)	Plac + *nab*-P (n = 184)
24-month OS rate	50.7%	36.9%



* Not formally tested because of prespecified hierarchical analysis plan

- Median OS (PD-L1-negative population): 19.7 mo (atezo) vs 19.6 mo (placebo); HR = 0.97

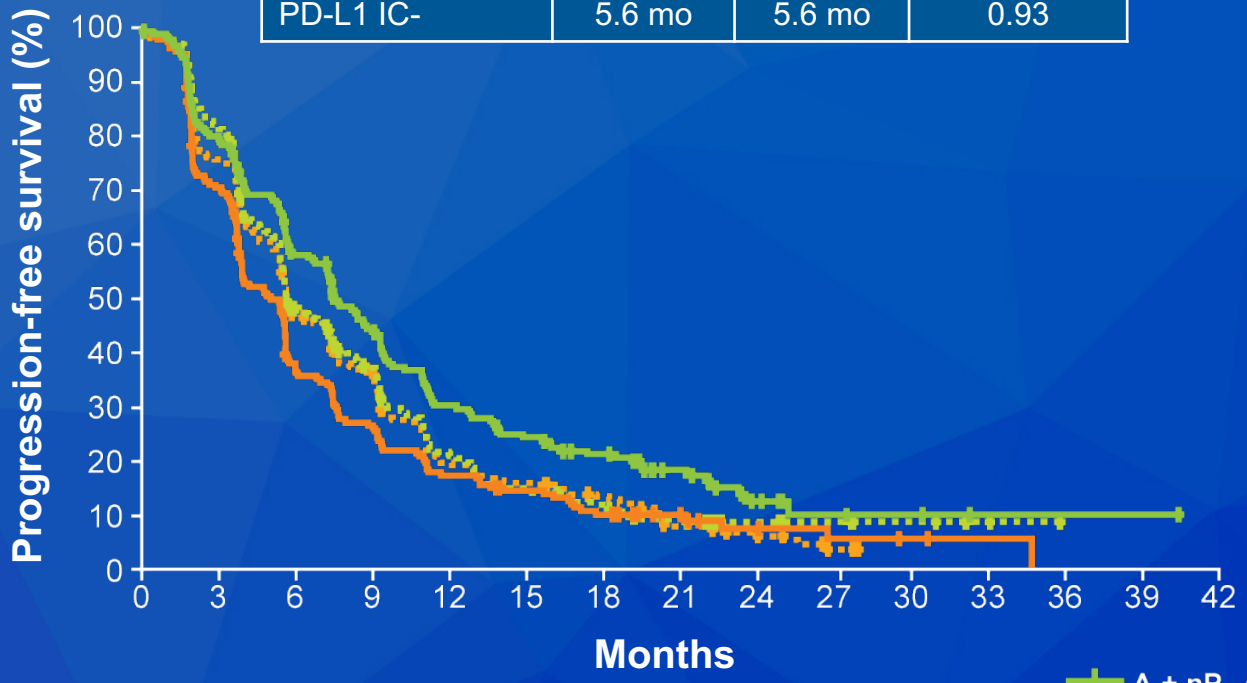
Schmid P et al. *Lancet Oncol* 2020;21(1):44-59; ASCO 2019;Abstract 1003.

Performance of PD-L1 Immunohistochemistry Assays in Unresectable Locally Advanced or Metastatic Triple-Negative Breast Cancer: Post Hoc Analysis of IMpassion130

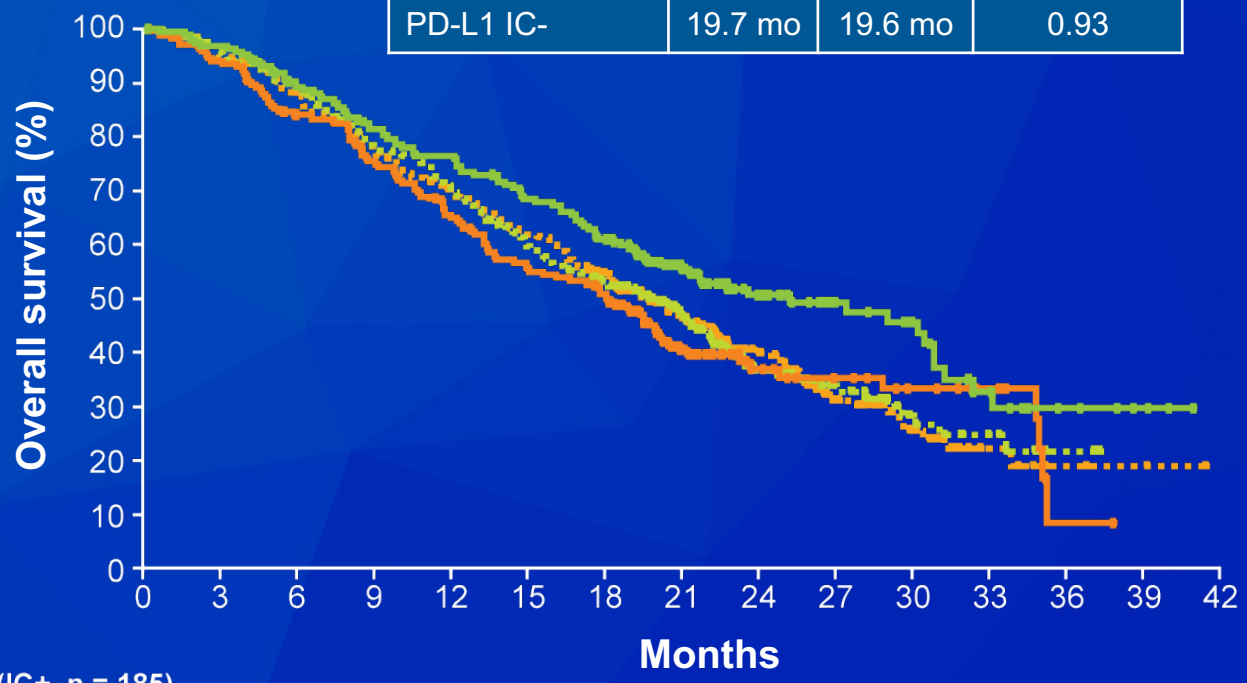
Rugo HS et al.
Proc ESMO 2019;Abstract LBA20.

IMpassion130: PD-L1 Status by SP142 Predicts PFS and OS

Population	Median PFS		HR
	A + nP	P + nP	
PD-L1 IC+	7.5 mo	5.3 mo	0.63
PD-L1 IC-	5.6 mo	5.6 mo	0.93



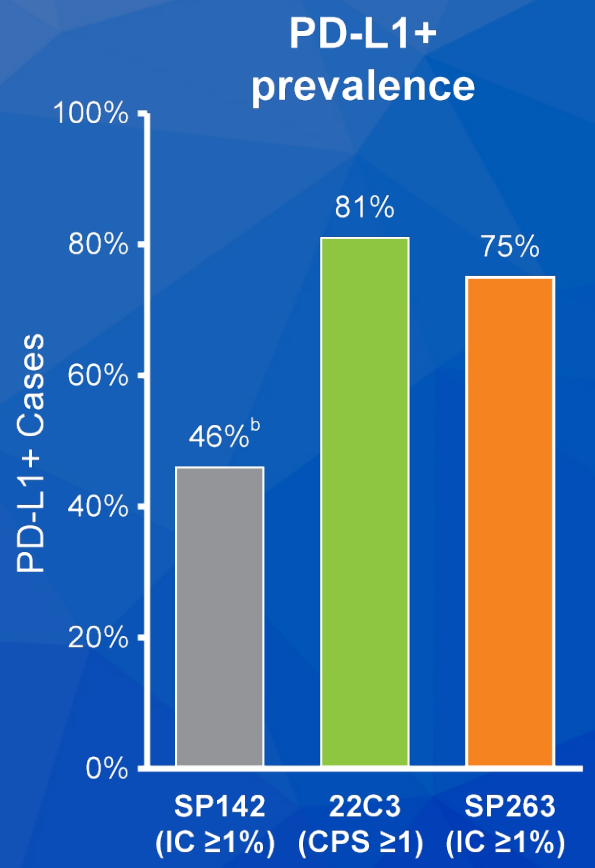
Population	Median OS		HR
	A + nP	P + nP	
PD-L1 IC+	25.0 mo	18.0 mo	0.71
PD-L1 IC-	19.7 mo	19.6 mo	0.93



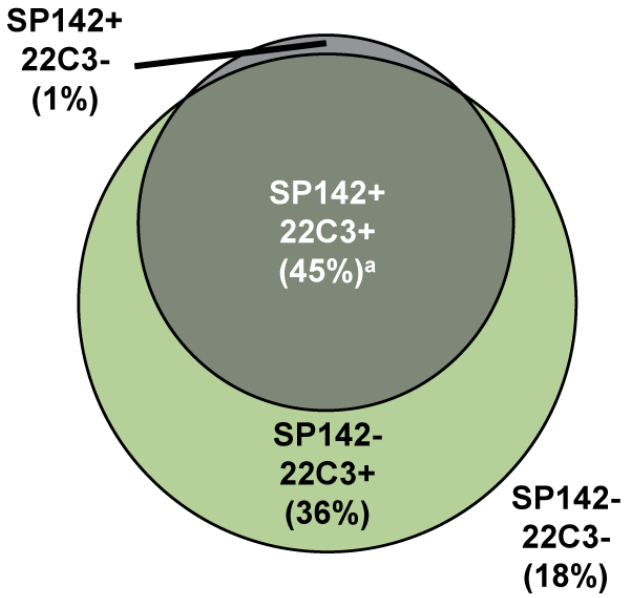
A + nP (IC+, n = 185)
P + nP (IC+, n = 184)
A + nP (IC-, n = 266)
P + nP (IC-, n = 267)

Rugo HS et al. *Proc ESMO* 2019;Abstract LBA20.

IMpassion130: PD-L1 IHC Assays (Prevalence and Concordance)

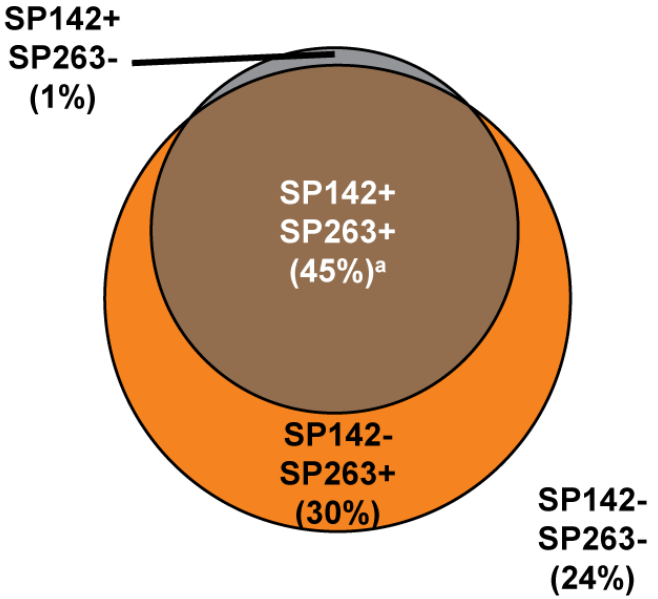


SP142 (IC 1%) and 22C3 (CPS 1)



OPA[c]	64%
PPA	98%
NPA	34%

SP142 (IC 1%) and SP263 (IC 1%)



OPA[c]	69%
PPA	98%
NPA	45%

NPA = negative percentage agreement; OPA = overall percentage agreement; PPA = positive percentage agreement
[a] >97% of SP142+ samples included in 22C3+ or SP263+ samples. [b] Compared with 41% in ITT. [C] ≥90% OPA, PPA and NPA required for analytical concordance

Rugo HS et al. *Proc ESMO* 2019;Abstract LBA20.

Editorial — Dr Hamilton

We received updated overall survival results from IMpassion130, the 1st-line study for metastatic triple-negative patients. Recall that this study enrolled both PD-L1+ and PD-L1– patients and looked at PD-L1 status via the SP142 assay on tumor *immune* cells, which is different from other tumor types that look at staining in the actual tumor tissue instead of immune cells in the tumor tissue. Again, we saw no benefit in survival amongst all comers, but a benefit among those patients that expressed at least 1% PD-L1+ on their tumor immune cells via SP142 assay. This benefit was significant but did come under some critique from a statistical standpoint. The trial had a hierarchical design, where the survival in the PD-L1+ subset was only to be looked at if the overall population was positive first. Because the overall population was negative, the critique is that looking at the PD-L1+ subset should not have been done. Regardless, I do think this is an important advance as we have no approved targeted agents for triple-negative breast cancer and finally have a win for immunotherapy in breast cancer.

KEYNOTE-522: Phase 3 Study of Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy as Neoadjuvant Treatment, Followed by Pembrolizumab versus Placebo as Adjuvant Treatment for Early Triple-Negative Breast Cancer (TNBC)[1]

KEYNOTE-522 Study of Neoadjuvant Pembrolizumab + Chemotherapy vs Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab vs Placebo for Early Triple-Negative Breast Cancer: Pathologic Complete Response in Key Subgroups and by Treatment Exposure, Residual Cancer Burden, and Breast-Conserving Surgery[2]

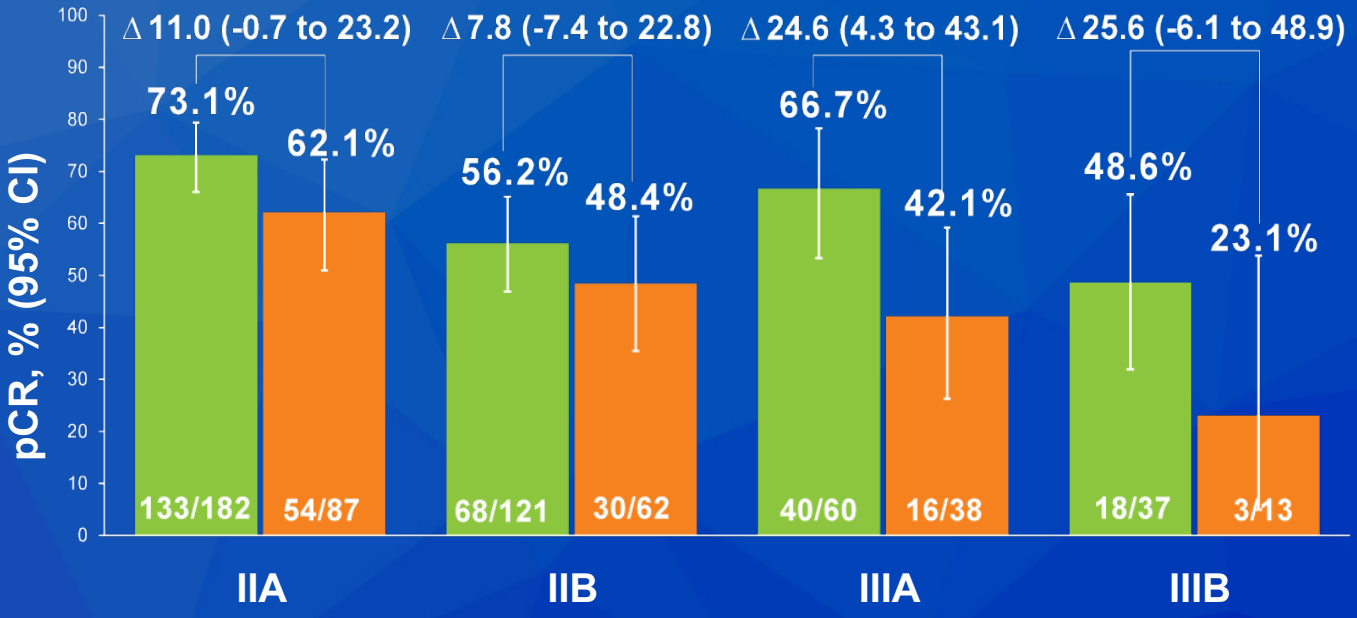
[1] Schmid P et al.
Proc ESMO 2019;Abstract LBA8.

[2] Schmid P et al.
San Antonio Breast Cancer Symposium 2019;Abstract GS3-03.

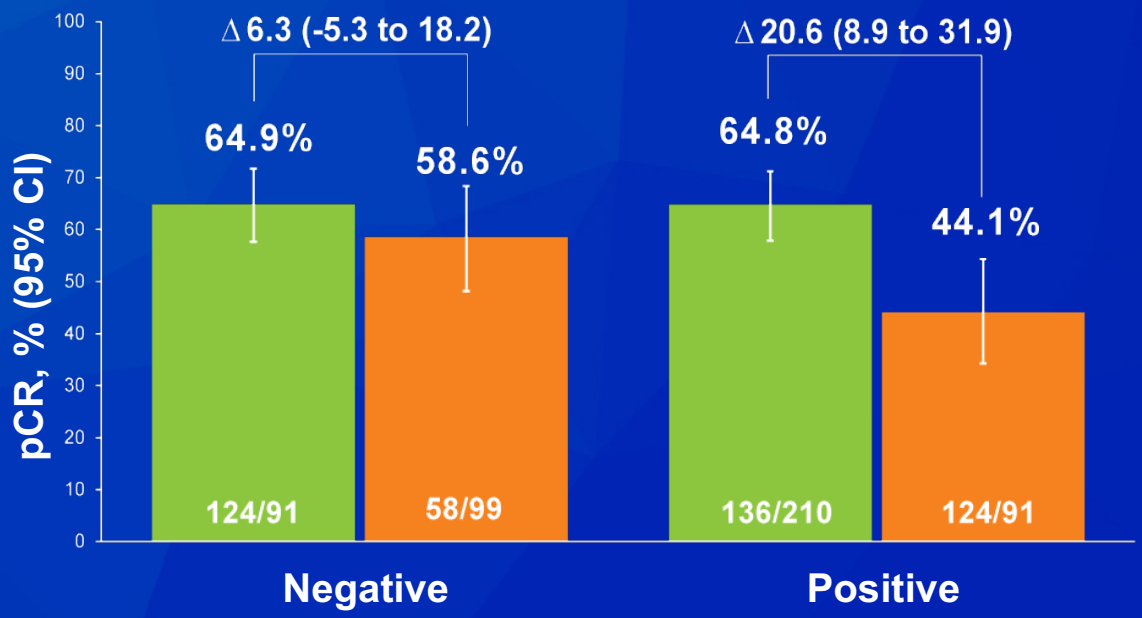
KEYNOTE-522: pCR by Disease Stage and Lymph Node Involvement

Pembro + chemo
Placebo + chemo

pCR by Disease Stage



pCR by Lymph Node Involvement

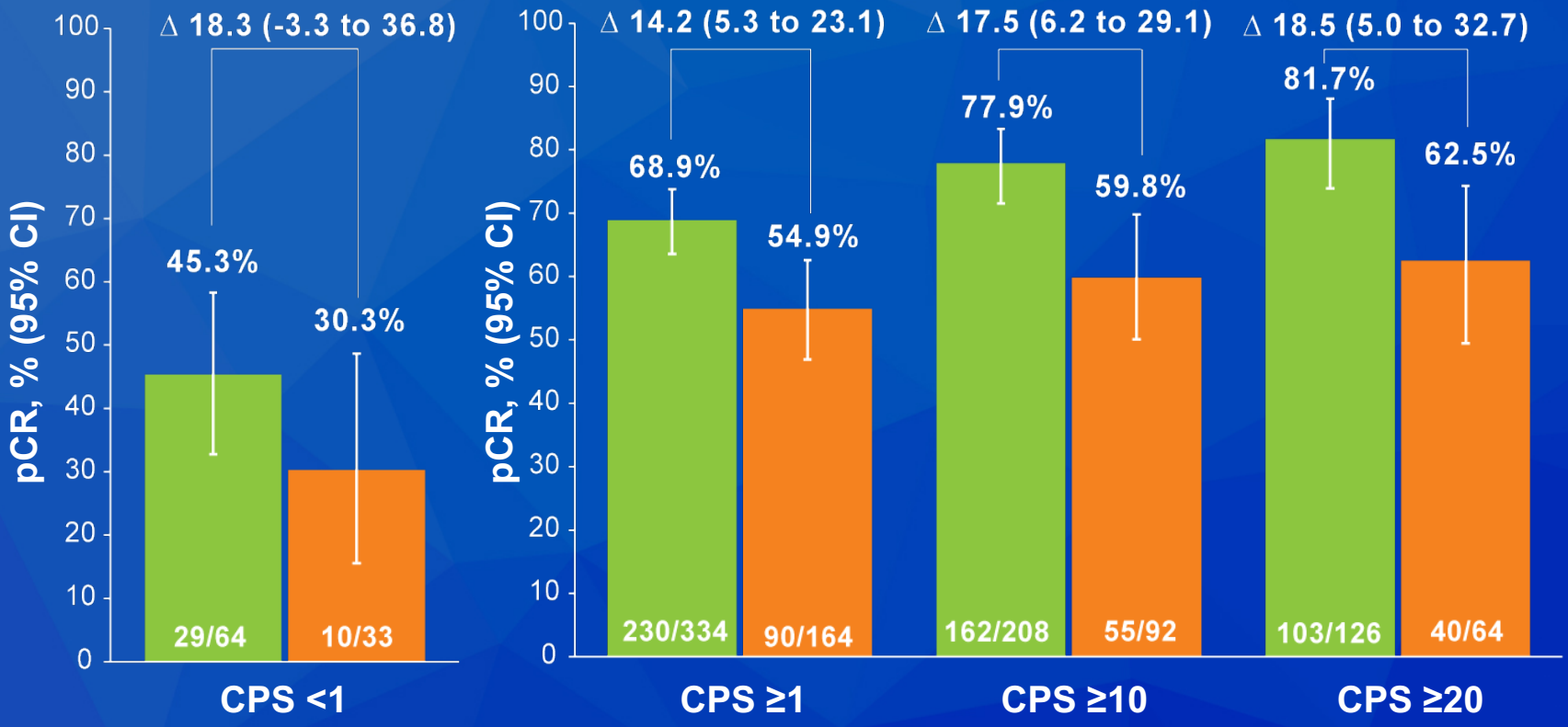


Schmid P et al. San Antonio Breast Cancer Symposium 2019;Abstract GS3-03.

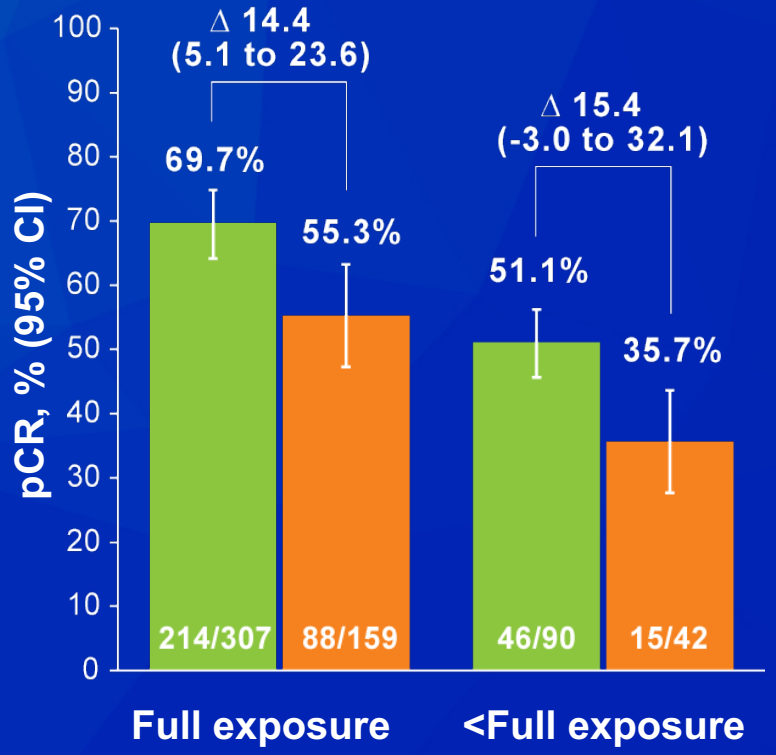
KEYNOTE-522: pCR by PD-L1 Expression and Exposure to Chemotherapy

Pembro + chemo
Placebo + chemo

pCR by PD-L1 Expression Level



pCR by Exposure to Chemotherapy



Schmid P et al. San Antonio Breast Cancer Symposium 2019;Abstract GS3-03.

Editorial — Dr Hamilton

The KEYNOTE-522 trial was a phase III trial with almost 1,200 patients who were randomized to neoadjuvant paclitaxel/carboplatin followed by anthracycline combo (AC or EC) with pembrolizumab given throughout the chemotherapy or placebo. The press release from the end of July indicated that they did meet their primary endpoint of improvement in pCR. We await these full results. There are multiple other trials ongoing looking at immunotherapy for triple-negative breast cancer in the early-stage settings. There is a neoadjuvant as well as an adjuvant study with atezolizumab with various chemo backbones, for example. This is certainly a very exciting realm, especially now having positive immunotherapy data in the first-line metastatic setting, and I hope we find ways we can use these drugs in the earlier-stage settings. Across phases, grade 3 or higher treatment-related AE rates were 78.0% in the pembro + chemo group and 73.0% in the pbo + chemo group (death incidence, 0.4% vs 0.3%, respectively).

Editorial — Dr Hamilton

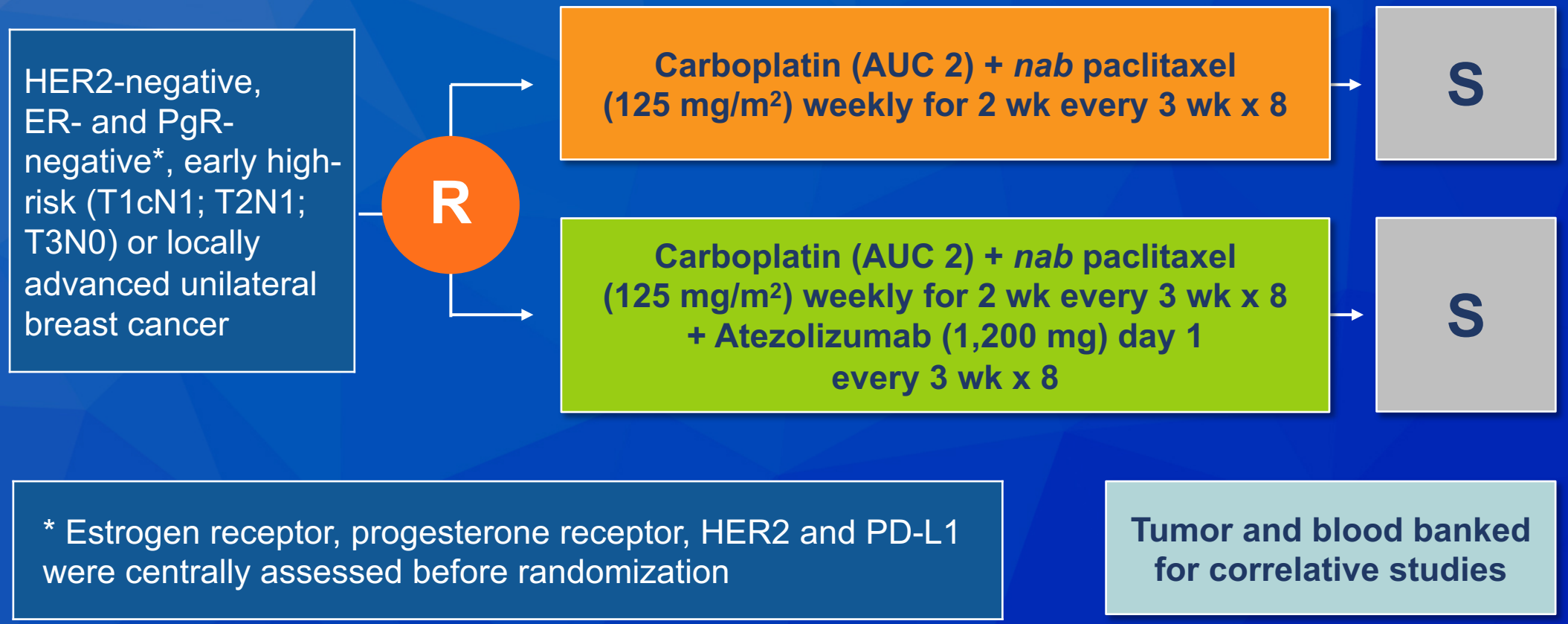
Interestingly, the improvement in pCR in this trial was seen both in the ITT population as well as the PD-L1+ subset. The assay and cut-off used to define PD-L1 expression differ in this trial as compared to the IMpassion130 trial.

Pathologic Complete Response (pCR) to Neoadjuvant Treatment with or without Atezolizumab in Triple Negative, Early High-Risk and Locally Advanced Breast Cancer. NeoTRIPaPDL1 Michelangelo Randomized Study

Gianni L et al.

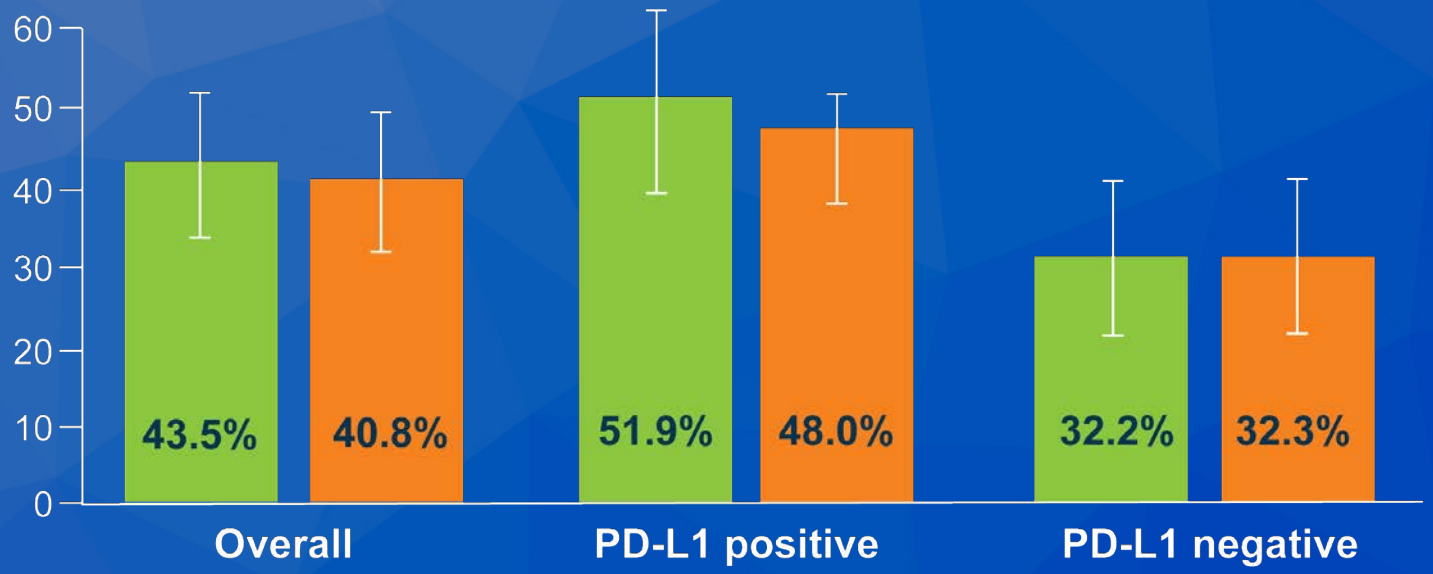
San Antonio Breast Cancer Symposium 2019;Abstract GS3-04.

NeoTRIP: Trial Schema



Gianni L et al. San Antonio Breast Cancer Symposium 2019;Abstract GS3-04.

NeoTRIP: pCR Rate by PD-L1 Expression and Disease Stage



With atezo (n = 138)

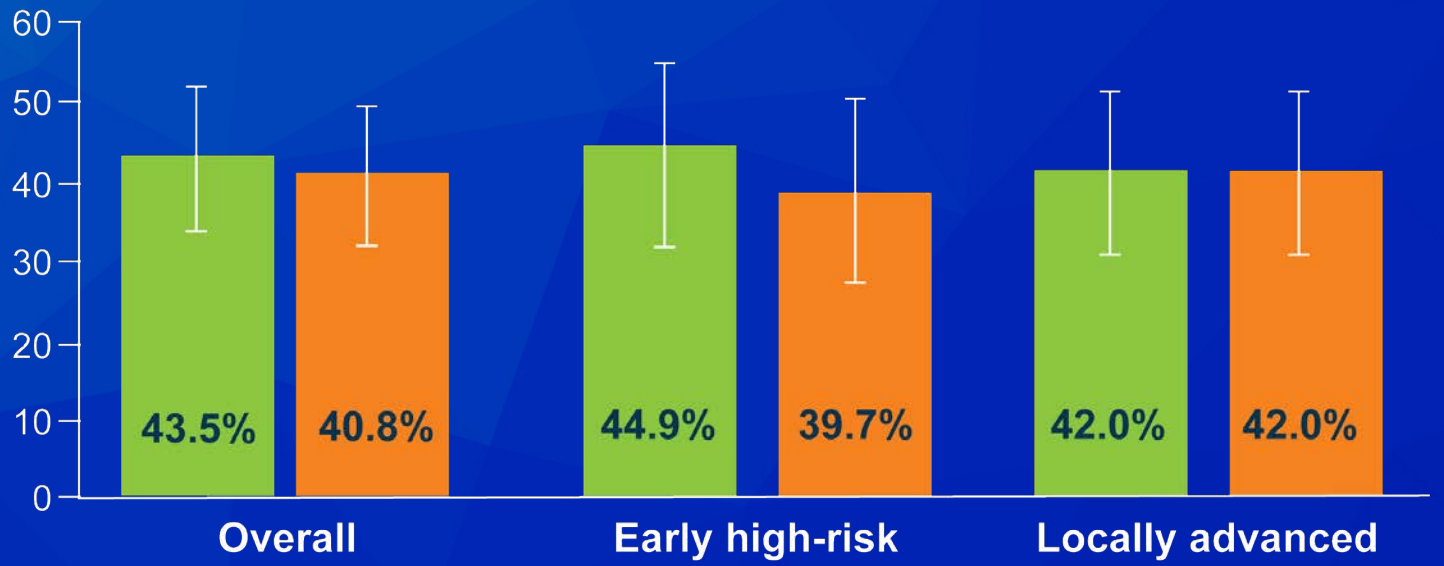
No atezo (n = 142)

Clinical overall response

- With atezo = 76.1%
- No atezo = 68.3%

Clinical complete response

- With atezo = 29.0%
- No atezo = 26.1%



Gianni L et al. San Antonio Breast Cancer Symposium 2019;Abstract GS3-04.

Editorial — Dr Hurvitz

The anti-PD-L1 antibody, atezolizumab, was shown to improve PFS and OS for PD-L1-positive metastatic triple-negative breast cancer when added to taxane chemotherapy (IMpassion130), leading to the first FDA approval of an immune checkpoint inhibitor for breast cancer. Whether or not immune therapy will improve outcomes for early stage disease still remains an outstanding question. At ESMO 2019, initial results from the KEYNOTE-522 study demonstrated an improvement in the pCR rate by adding pembrolizumab, a PD-1-targeted antibody, to neoadjuvant chemotherapy for triple-negative breast cancer, though the event-free survival rates were not yet significantly different. The addition of atezolizumab to standard taxane/platinum neoadjuvant chemotherapy for triple-negative breast cancer was evaluated in NeoTRIPaPDL1 with a primary aim to evaluate the 5-year EFS.

Editorial — Dr Hurvitz (continued)

At SABCS 2019, the key secondary endpoint, pCR rate in breast and lymph nodes, was reported. In contrast to results from KEYNOTE-522 with pembrolizumab, no significant improvement in pCR was observed with atezolizumab in the overall population or in patients with PD-L1-positive disease, though on multivariate analysis, patients with PD-L1+ tumors had a better chance of achieving pCR. A higher risk of significant adverse events and liver transaminase abnormalities were observed with atezolizumab. Based on these data, atezolizumab should not be used in the curative setting until and unless the 5-year EFS ends up showing a longer-term benefit with the use of this agent.

OlympiAD Final Overall Survival and Tolerability Results: Olaparib versus Chemotherapy Treatment of Physician's Choice in Patients with a Germline BRCA Mutation and HER2-Negative Metastatic Breast Cancer[1]

OlympiAD Extended Follow-Up for Overall Survival and Safety: Olaparib versus Chemotherapy Treatment of Physician's Choice in Patients with a Germline BRCA Mutation and HER2-Negative Metastatic Breast Cancer[2]

[1] Robson ME et al.
Ann Oncol 2019;30(4):558-66.

[2] Robson M et al.
San Antonio Breast Cancer Symposium 2019;Abstract PD4-03.

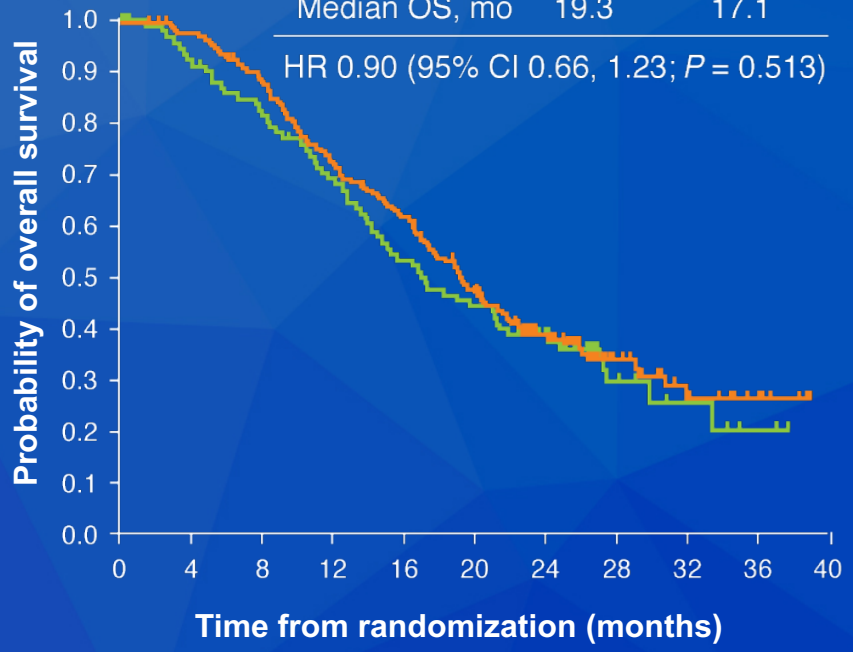
OlympiAD: Final OS Results

Overall Survival

Full Population (n = 205, 97)

	Olaparib	TPC
Deaths, n (%)	130 (63)	62 (64)
Median OS, mo	19.3	17.1

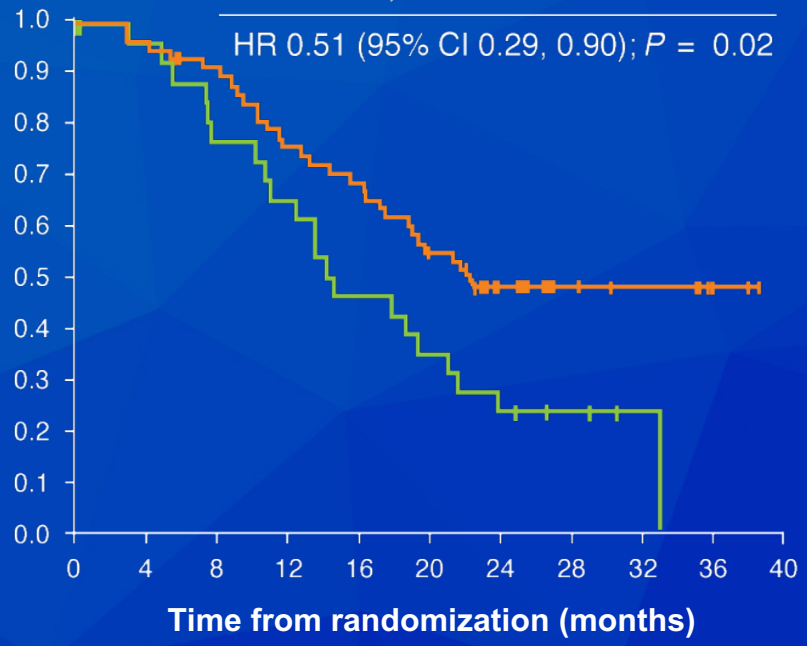
HR 0.90 (95% CI 0.66, 1.23; *P* = 0.513)



No Prior Chemo (1L) (n = 59, 28)

	Olaparib	TPC
Deaths, n (%)	30 (50.8)	21 (75.0)
Median OS, mo	22.6	14.7

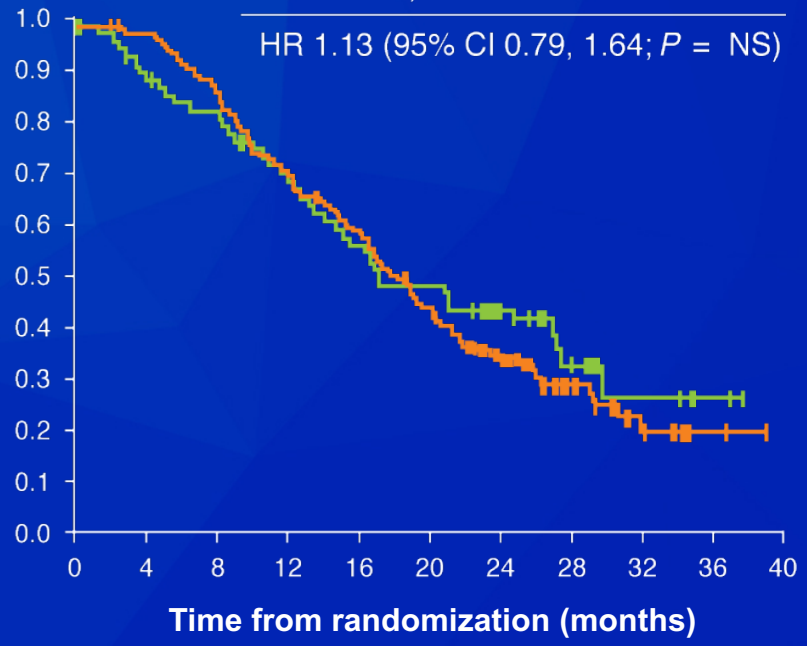
HR 0.51 (95% CI 0.29, 0.90); *P* = 0.02



Prior Chemo (2/3L) (n = 146, 69)

	Olaparib	TPC
Deaths, n (%)	100 (68.5)	41 (59.4)
Median OS, mo	18.8	17.2

HR 1.13 (95% CI 0.79, 1.64; *P* = NS)



Robson ME et al. *Ann Oncol* 2019;30(4):558-66; Robson M et al. San Antonio Breast Cancer Symposium 2019;Abstract PD4-03.

OlympiAD: Extended Follow-Up for OS

48-Month OS	Olaparib	TPC	HR
All patients (n = 205, 97)	18.9%	14.2%	0.84
ER/PR-positive (n = 103, 49)	23.1%	17.4%	0.79
TNBC (n = 102, 48)	15.4%	11.9%	0.87
No prior chemo for mBC (n = 59, 28)	24.6%	12.8%	0.54
Prior chemo for mBC (n = 146, 69)	17.1%	14.8%	1.00
Prior platinum (n = 60, 26)	16.8%	Not calculable	0.74
Without prior platinum (n = 145, 71)	20.4%	16.3%	0.86

- Median follow-up = 18.9 mo (olaparib) vs 15.5 mo (TPC)
  - For censored patients = 40.7 mo (olaparib) vs 29.2 mo (TPC)

Robson M et al. San Antonio Breast Cancer Symposium 2019;Abstract PD4-03.

Editorial — Dr Hamilton

We continue to get more data solidifying PARP inhibitors as a great treatment option for patients with germline or somatic BRCA alterations. We have known that the progression-free survival with PARP compares favorably against chemotherapy with 2-3 months improvement, however we have not yet seen that translate to overall survival. We now have the final survival data from OlympiAD with olaparib vs. chemotherapy, and for all comers the OS benefit was not statistically significant. In subgroup analysis, however, for chemotherapy-naïve patients (or 1st-line patients), this was statistically significant. This suggests to me that we may want to use this drug earlier in people's disease course, which I think is quite reasonable as in most situations the side-effect profile compares favorably with chemotherapy. Olaparib and talazoparib have performed quite similarly, and I really use these interchangeably.

Editorial — Dr Hamilton

We also saw some data at ASCO from GeparOLA with neoadjuvant olaparib compared to carboplatin and paclitaxel, and again PARP performed equally as well with a pCR rate of 55% compared to 47% with chemotherapy. I hope we can find a way to use these drugs in earlier-stage disease for appropriate patients as well, and it may allow them to receive less chemotherapy if they have a good response.

Breast Cancer — Drs Hamilton and Hurvitz

HER2-Positive Breast Cancer

Triple-Negative Breast Cancer

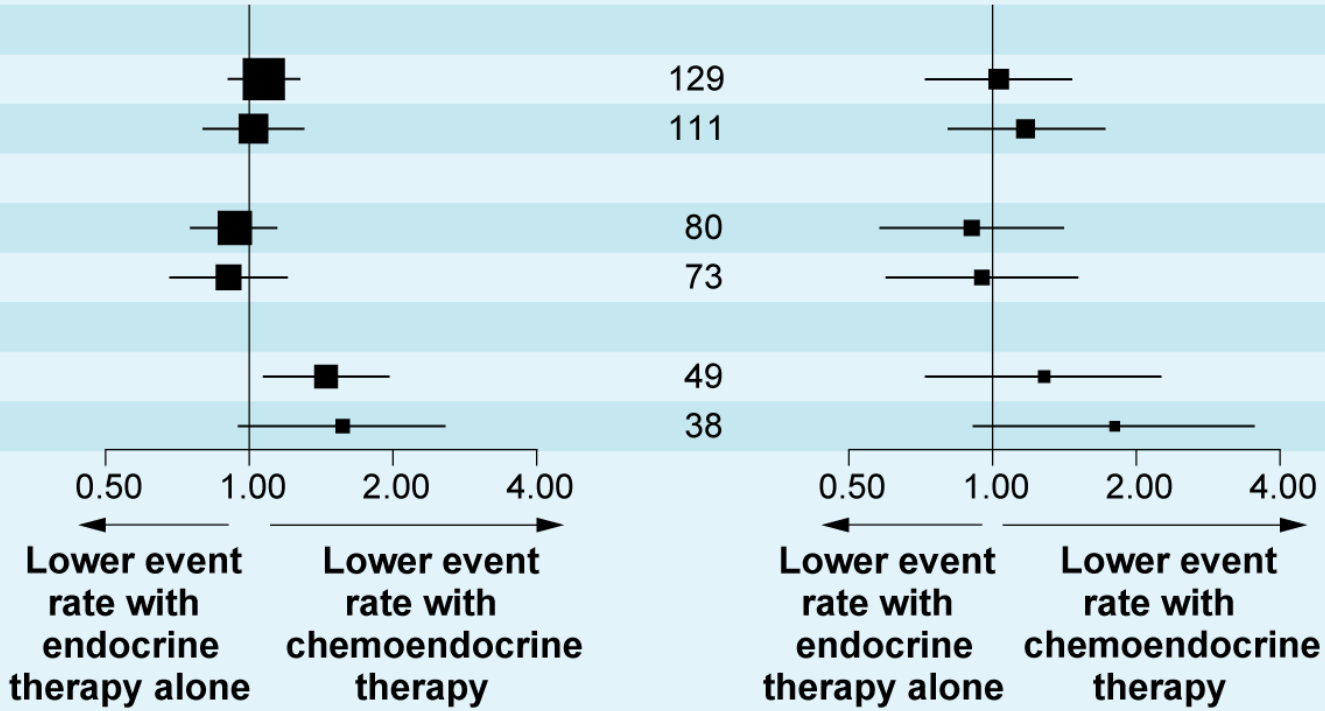
ER-Positive Breast Cancer

Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer

Sparano JA et al.
N Engl J Med 2019;380(25):2395-405.

Effect of Clinical Risk on Prediction of Chemotherapy Benefit Stratified by Age (Recurrence Score 11-25)

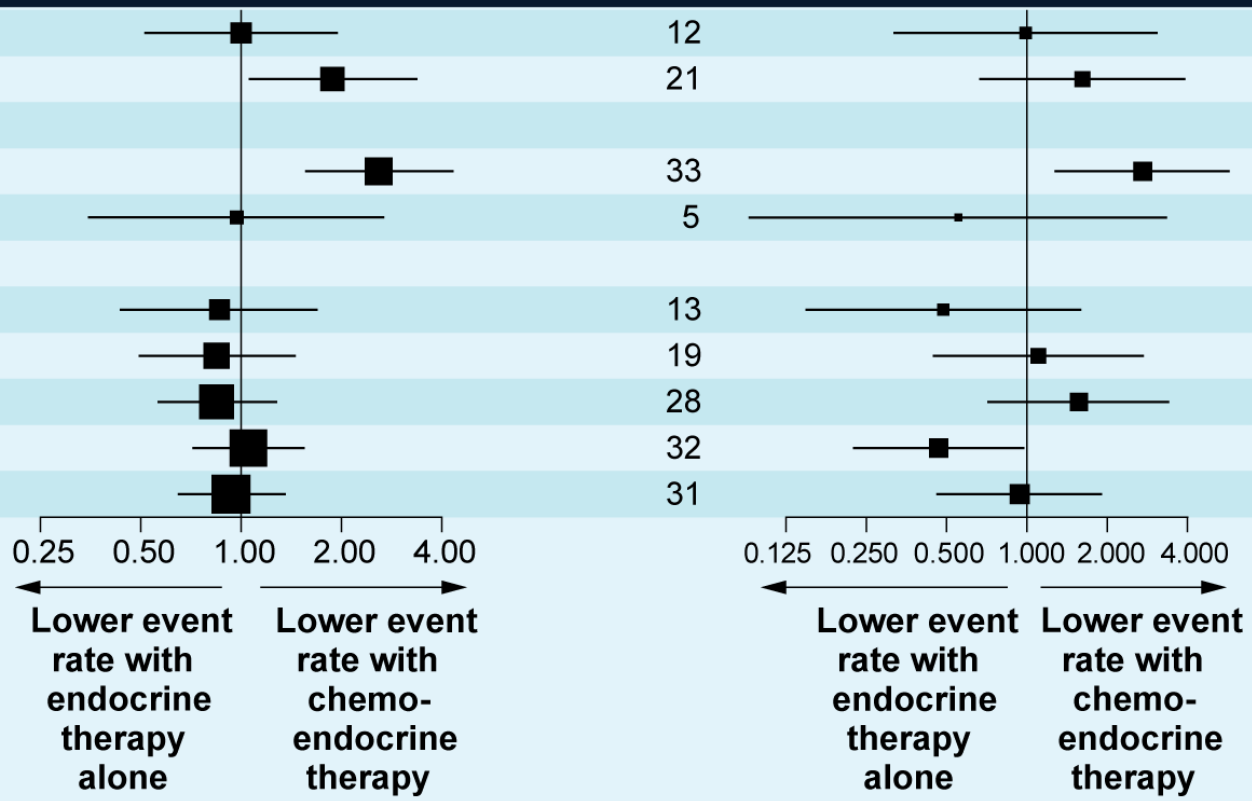
Subgroup	No. of patients	No. of events	Hazard ratio for recurrence, second primary cancer or death (95% CI)	No. of distant recurrences	Hazard ratio for distant recurrence (95% CI)
All patients					
Low clinical risk	4,799	541		129	
High clinical risk	1,697	270		111	
>50 years of age					
Low clinical risk	3,173	361		80	
High clinical risk	1,180	204		73	
≤50 years of age					
Low clinical risk	1,626	180		49	
High clinical risk	517	66		38	



Sparano JA et al. *N Engl J Med* 2019;380(25):2395-405.

Effect of Age and Menopausal Status on Chemotherapy Benefit (Recurrence Score 16-25)

Subgroup	No. of patients	No. of events	No. of distant recurrences
≤40 years of age	203	35	12
41–45 years of age	441	51	21
46–50 years of age			
Before menopause	630	69	33
After menopause	141	15	5
51–55 years of age			
Before menopause	287	34	13
After menopause	472	54	19
56–60 years of age	826	94	28
61–65 years of age	710	109	32
>65 years of age	628	117	31



Sparano JA et al. *N Engl J Med* 2019;380(25):2395-405.

Validation of the Clinical Treatment Score Post 5 Years (CTS5) in Women with Hormone Receptor Positive, HER2-Negative, Node-Negative Disease from the TAILORx Study

Sestak I et al.
San Antonio Breast Cancer Symposium 2019;Abstract GS4-03.

TAILORx: CTS5 in All Patients and According to Subgroups

CTS5	RS	Treatment	HR	*p*-value
All patients (n = 7,353)	0-100	ET/CET	1.57	<0.0001
Arm A (n = 1,323)	0-10	ET	1.34	0.19
Arm B (n = 2,746)	11-25	ET	1.50	0.002
Arm C (n = 2,655)	11-25	CET	1.56	0.0003
Arm D (n = 629)	26-100	CET	1.90	0.004
Age ≤50 years (n = 2,259)	0-100	ET/CET	1.35	0.046
Age >50 years (n = 5,094)	0-100	ET/CET	1.78	<0.0001

ET = endocrine therapy; CET = chemo-ET

- Overall, CTS5 was highly prognostic for late distant recurrence (DR) stratified for assigned chemotherapy arm (HR = 1.57, $p < 0.0001$).
- Looking at each arm separately, CTS5 did not predict late DR in women with RS 0-10 and ET (arm A), but provided strong prognostic information for late DR in arms B (RS 11-25, ET), C (RS 11-25, CET), and D (RS 26-100, CET).
- CTS5 strongly predicted late DR in women >50 years (HR = 1.78, $p < 0.0001$), but to a lesser extent in women aged 50 years or younger (HR = 1.35, $p = 0.046$).

Sestak I et al. San Antonio Breast Cancer Symposium 2019;Abstract GS4-03.

Editorial — Dr O'Shaughnessy

The 2018 publication of TAILORx demonstrated that patients with node-negative, ER-positive breast cancer did not benefit from adjuvant chemotherapy if they were over age 50 with a 21-gene Recurrence Score (RS) of 25 or less, or if they were age 50 or under and had a RS less than 16. The 2019 report of secondary analyses of TAILORx incorporated the MINDACT trial-defined clinical high vs low risk (based on tumor size and histologic grade) into the analyses of degree of benefit from adjuvant chemotherapy by age and RS. What was found is practice changing. As Hunter and Longo state in their *NEJM* editorial on the 2019 secondary analyses TAILORx publication, these new data suggest that recommendations about adjuvant chemotherapy should not be based on RS alone but rather on RS together with assessment of clinical risk. The main findings were unchanged in patients over 50: there was no benefit from adjuvant chemotherapy regardless of clinical risk or value of the RS between 11 to 25.

Editorial — Dr O'Shaughnessy (continued)

In patients 50 years or age or younger, those with high clinical risk and a RS of 16-25 benefited from adjuvant chemotherapy as did those with both high and low clinical risk with a RS of 21-25. Dr Sparano showed that chemotherapy likely had an ovarian suppression/ablation effect in women age 50 and under such that substituting an LHRH agonist for chemotherapy in high risk premenopausal patients with a RS of 16-20 could be considered.

Ontario Cancer Care and ASCO have endorsed adjuvant chemo-endocrine therapy recommendations in response to and in keeping with the above findings. The 2019 St Gallen's Consensus panelists, however, mainly concluded that all node-negative, ER+ patients with a RS of 11 to 25 did not benefit from chemotherapy, based on the 2018 primary analysis of TAILORx.

Editorial — Dr O’Shaughnessy (continued)

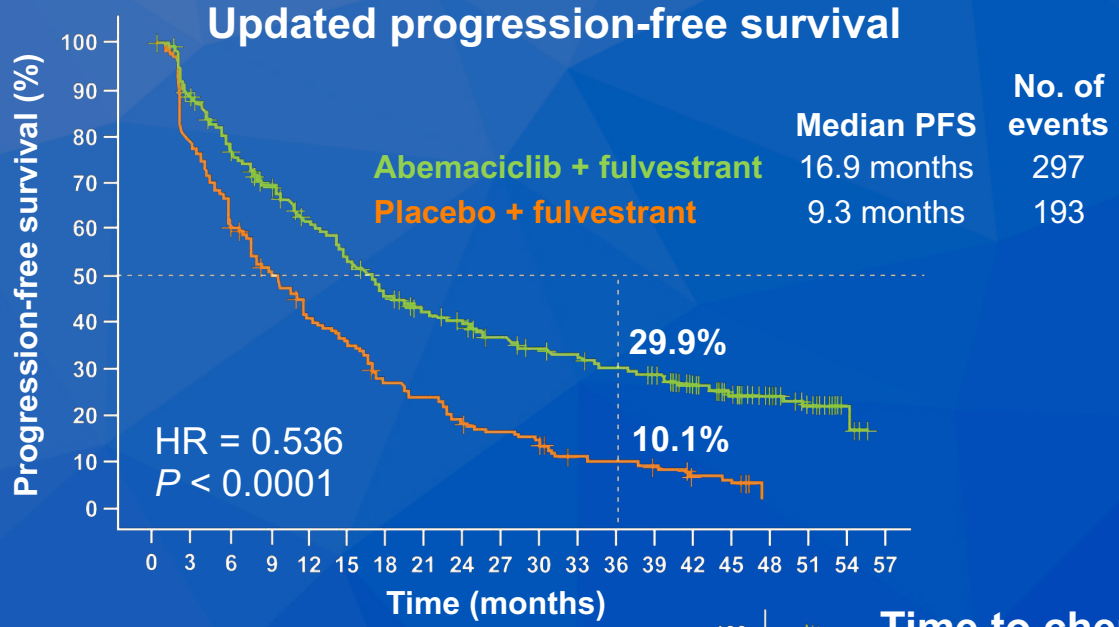
There was no consensus about whether chemotherapy should be recommended for women 50 or under with high clinical risk and RS 16-25. The 2019 St Gallen’s panel also endorsed the use of genomic assays to identify patients with ER+ low node positive tumor burden who are not likely to benefit from chemotherapy.

MONARCH 2: Overall Survival of Abemaciclib plus Fulvestrant in Patients with HR+, HER2- Advanced Breast Cancer

Sledge GW et al.
Proc ESMO 2019;Abstract LBA6.

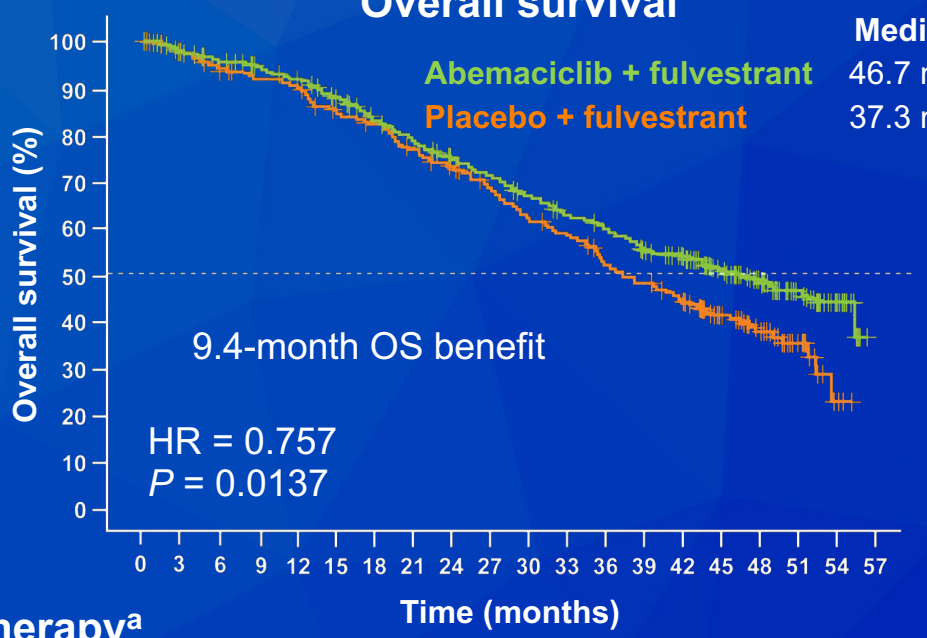
MONARCH 2: Survival Analysis and Time to Treatment with Chemotherapy

Updated progression-free survival



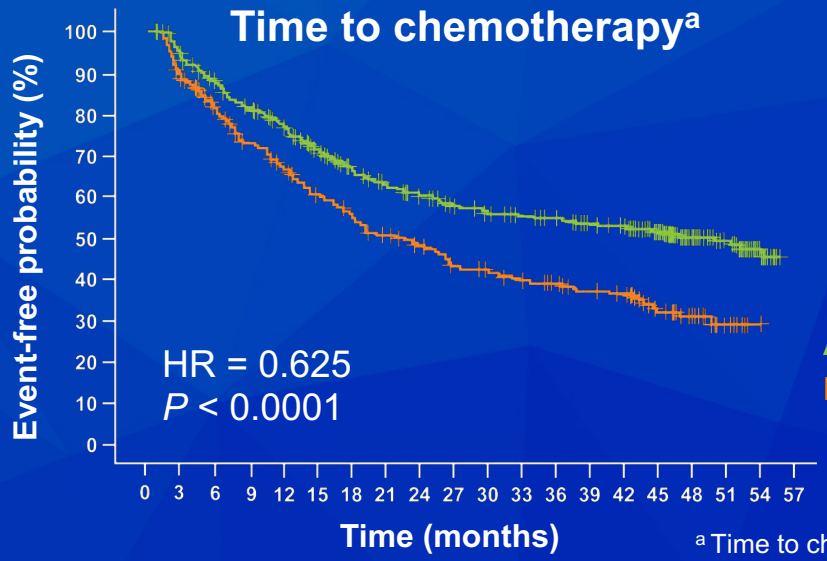
	Median PFS	No. of events
Abemaciclib + fulvestrant	16.9 months	297
Placebo + fulvestrant	9.3 months	193

Overall survival



	Median OS	No. of events
Abemaciclib + fulvestrant	46.7 months	211
Placebo + fulvestrant	37.3 months	127

Time to chemotherapy[a]



	Median OS	No. of events
Abemaciclib + fulvestrant	50.2 months	200
Placebo + fulvestrant	22.1 months	135

Sledge GW. *Proc ESMO* 2019;Abstract LBA6.

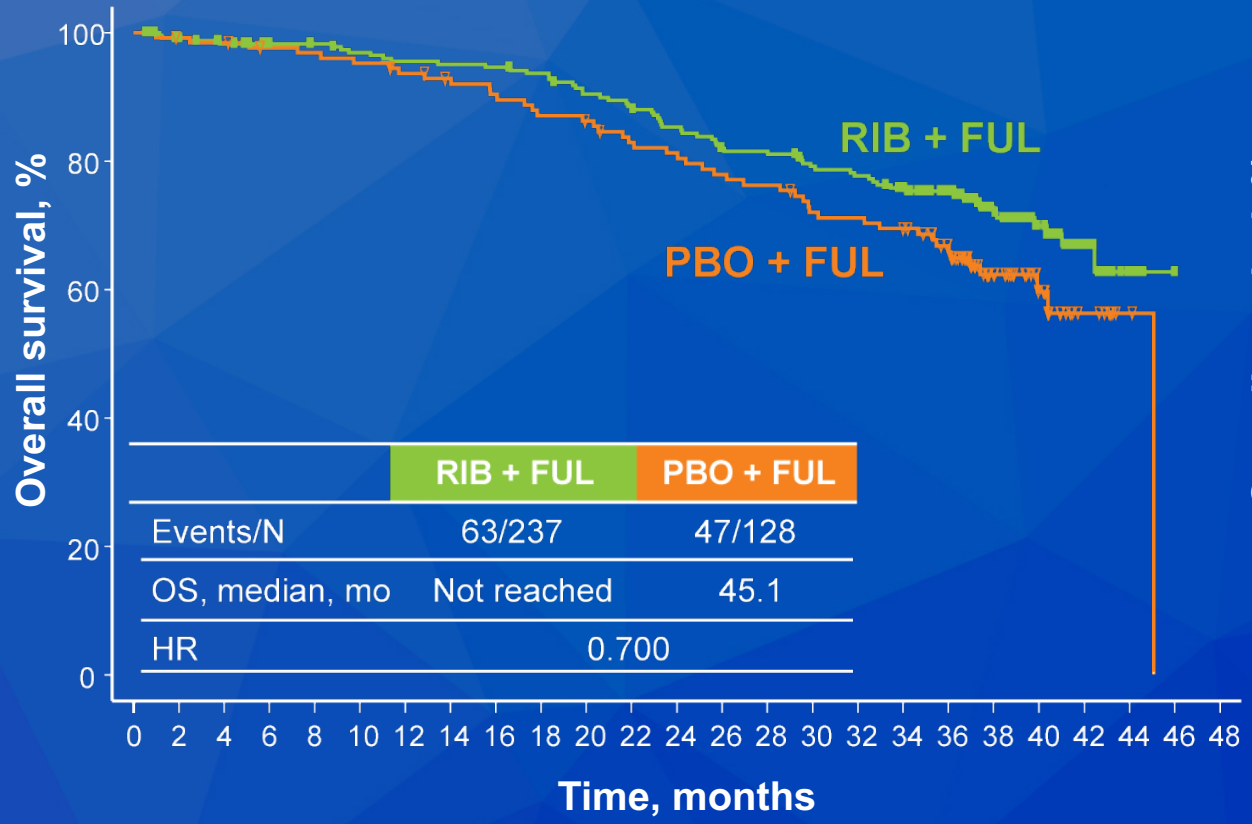
[a] Time to chemotherapy was analyzed from randomization to initiation of first post-discontinuation chemotherapy (censoring patients who died prior to initiation of chemotherapy)

Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer

Slamon DJ et al.
N Engl J Med 2019;[Epub ahead of print].

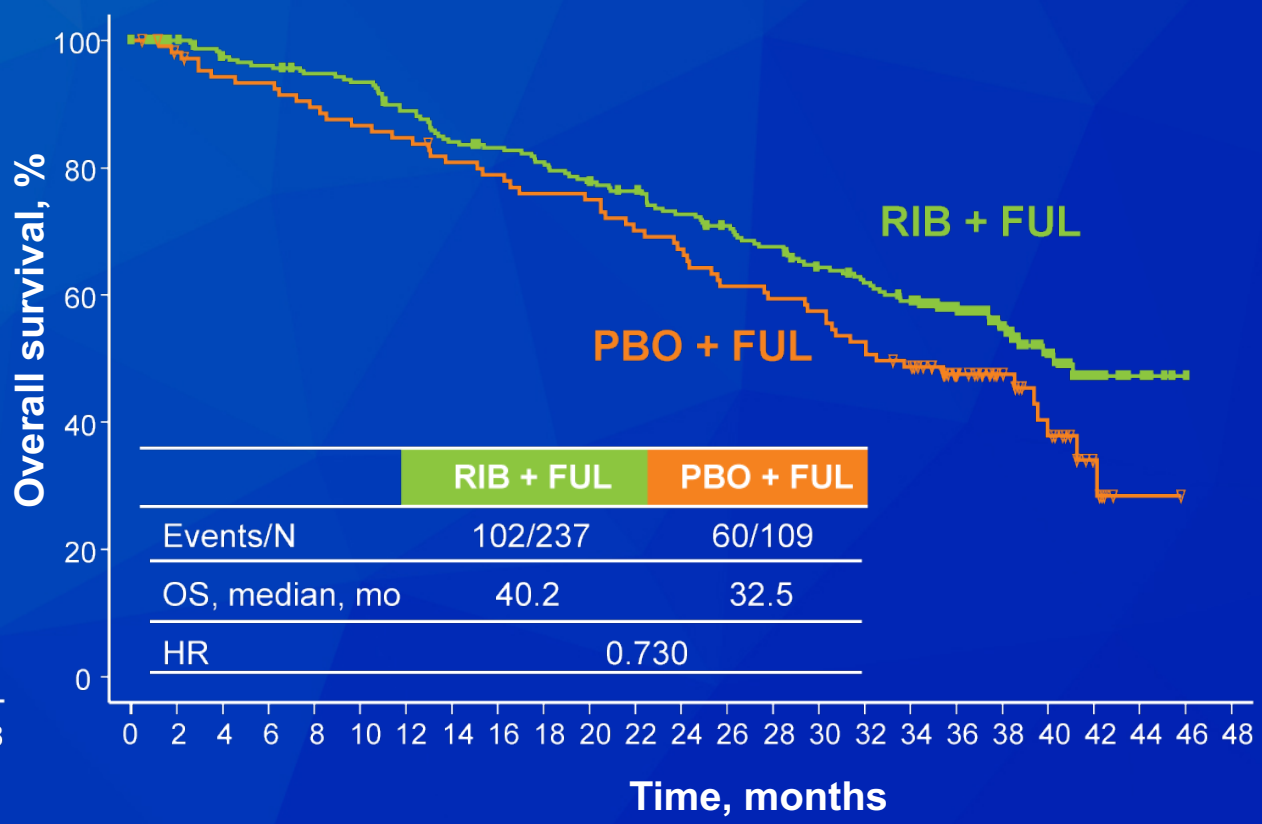
MONALEESA-3: Overall Survival Results

Pts receiving first-line tx



	RIB + FUL	PBO + FUL
Events/N	63/237	47/128
OS, median, mo	Not reached	45.1
HR	0.700	

Pts with early relapse or receiving second-line tx



	RIB + FUL	PBO + FUL
Events/N	102/237	60/109
OS, median, mo	40.2	32.5
HR	0.730	

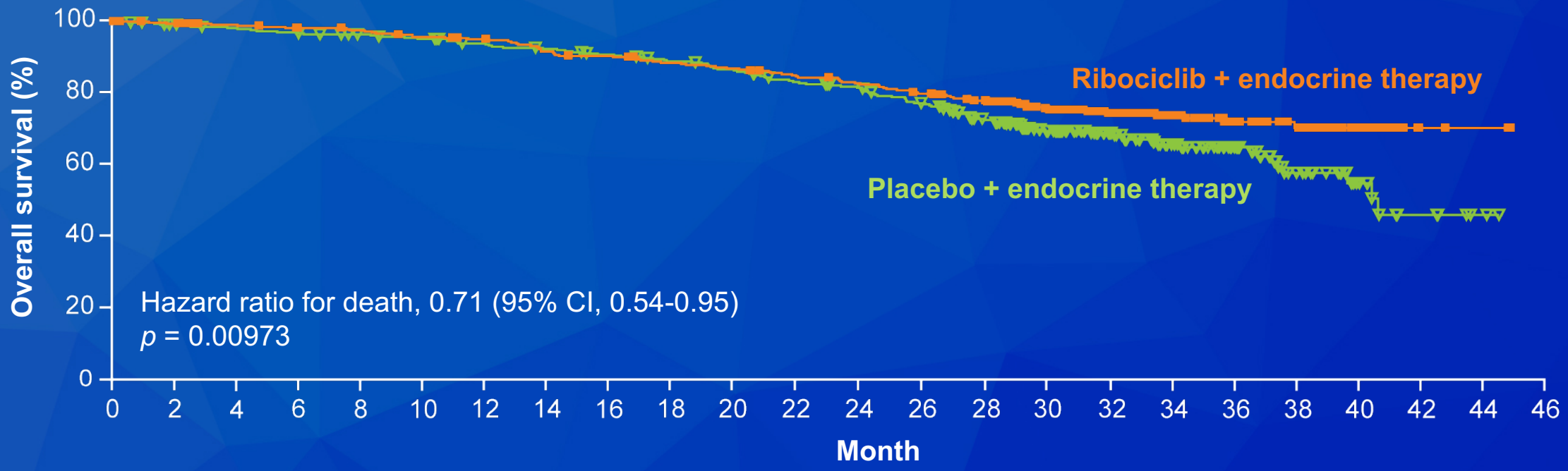
Slamon DJ et al. *N Engl J Med* 2019;[Epub ahead of print].

Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer

Im SA et al.
N Engl J Med 2019;381(4):307-16.

MONALEESA-7: Overall Survival Results

	No. of patients	No. of deaths	Median overall survival *mo*
Ribociclib + endocrine therapy	335	83	NE
Placebo + endocrine therapy	337	109	40.9



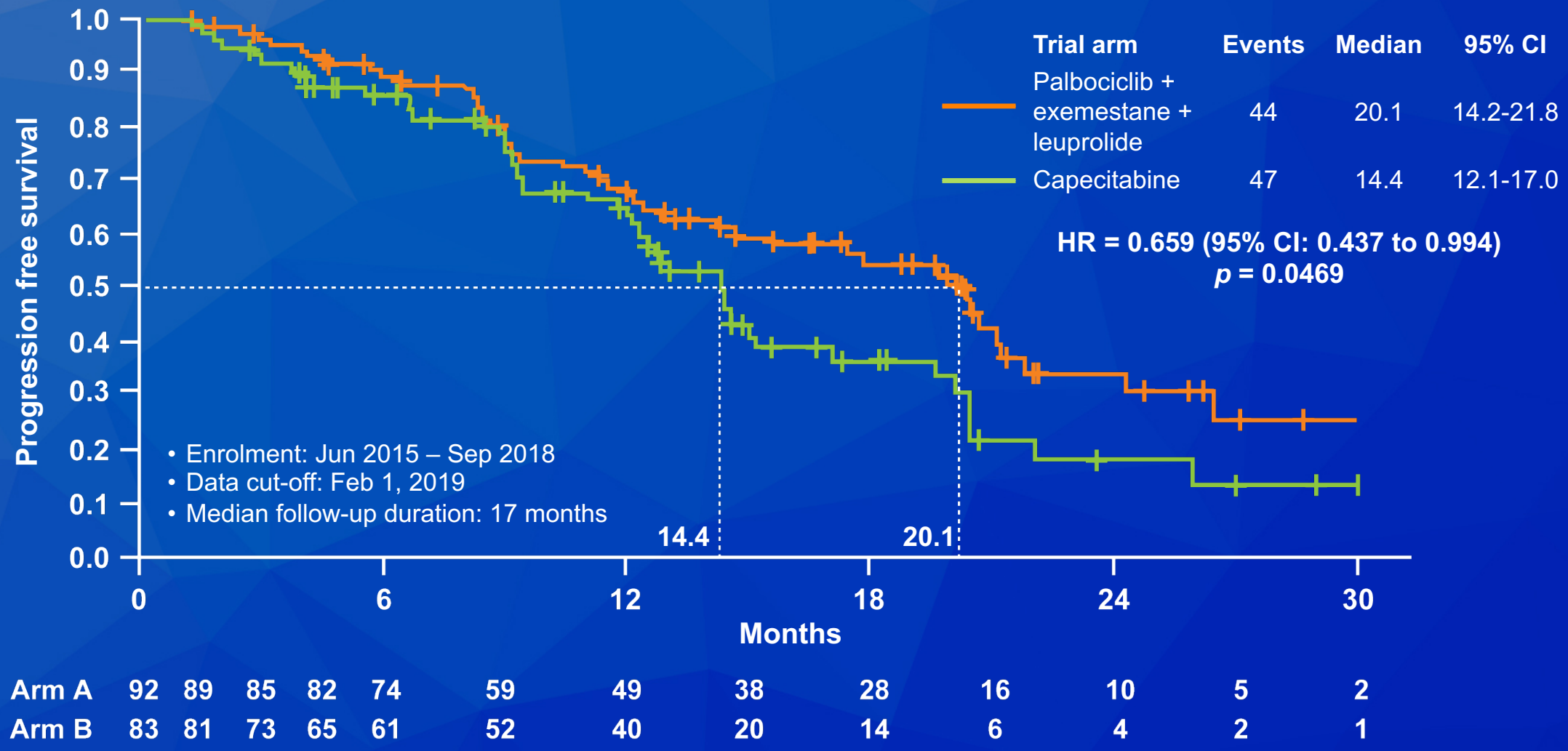
No. at Risk																							
Ribociclib	335	330	325	320	316	309	304	292	287	279	274	266	258	249	236	193	155	110	68	43	25	7	3	0
Placebo	337	330	325	321	314	309	301	295	288	280	272	258	251	235	210	166	122	92	62	33	19	7	2	0

Im SA et al. *N Engl J Med* 2019;381(4):307-16.

A Randomized Phase II Study of Palbociclib plus Exemestane with GNRH Agonist versus Capecitabine in Premenopausal Women with Hormone Receptor-Positive Metastatic Breast Cancer (KCSG-BR 15-10, NCT02592746)

Park YH et al.
Proc ASCO 2019;Abstract 1007.

KCSG-BR 15-10: Investigator-Assessed PFS



Park YH et al. *Proc ASCO* 2019;Abstract 1007.

Results from PEARL study (GEICAM/2013-02_CECOG/BC.1.3.006): A Phase 3 Trial of Palbociclib (PAL) in Combination with Endocrine Therapy (ET) versus Capecitabine (CAPE) in Hormonal Receptor (HR)-Positive/Human Epidermal Growth Factor Receptor (HER) 2-Negative Metastatic Breast Cancer (MBC) Patients (pts) Whose Disease Progressed on Aromatase Inhibitors (AIs)

Martin M et al.

San Antonio Breast Cancer Symposium 2019;Abstract GS2-07.

PEARL: Efficacy and Safety Results

Outcome	Cohort 2 (median follow-up: 13.5 mo) (n = 305)		Cohort 1 + Cohort 2 (ESR1 wt) (median follow-up: 19 mo) (n = 601)	
	PAL + FUL	**CAPE**	**PAL + ET**	**CAPE**
Median PFS	7.5 mo	10.0 mo	8.0 mo	10.6 mo
Adjusted HR (*p*-value)	1.09 (0.537)		1.08 (0.526)	
ORR	26.7%	33.3%	27.8%	36.9%
Median PFS (subgroup analysis)	**PAL + FUL**	**CAPE**	**PAL + ET**	**CAPE**
Luminal tumors	7.5 mo	10.0 mo	9.3 mo	11.0 mo
Adjusted HR (*p*-value)	1.07 (0.684)		1.02 (0.913)	
Nonluminal tumors	4.4 mo	14.8 mo	2.7 mo	13.7 mo
Adjusted HR (*p*-value)	2.39 (0.116)		3.19 (0.013)	

FUL = fulvestrant; ET = exemestane (EXE) or FUL

- Most frequent Grade ≥3 AEs with EXE+PAL, FUL+PAL and CAPE respectively were neutropenia (57.4%, 55.7% and 5.5%) with febrile neutropenia (1.3%, 0.7% and 1.4%), hand/foot syndrome (0%, 0% and 23.5%) and diarrhea (1.3%, 1.3% and 7.6%)

Martin M et al. San Antonio Breast Cancer Symposium 2019;Abstract GS2-07.

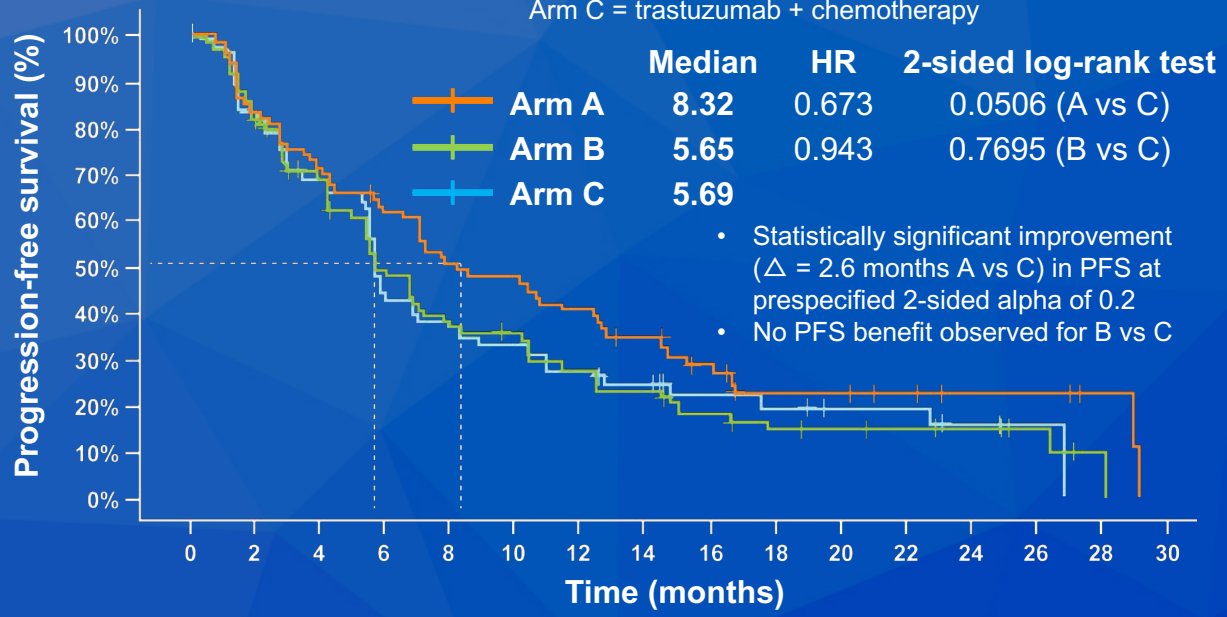
monarcHER: A Randomized Phase 2 Study of Abemaciclib plus Trastuzumab with or without Fulvestrant vs Trastuzumab + Standard-of-Care Chemotherapy in Women with HR+, HER2+ Advanced Breast Cancer (ABC)

Tolaney SM et al.
Proc ESMO 2019;Abstract LBA23.

monarcHER: Progression-Free Survival and Safety Summary

Primary endpoint: PFS

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



	Median	HR	2-sided log-rank test
Arm A	8.32	0.673	0.0506 (A vs C)
Arm B	5.65	0.943	0.7695 (B vs C)
Arm C	5.69		

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

This is the first Phase II study of a CDK4/6 inhibitor and ET versus standard chemotherapy, together with HER2-directed treatment in HR+, HER2+ ABC to report positive results

	Arm A N = 78	Arm B N = 77	Arm C N = 72
Duration of treatment, median (cycles)	10.0	8.0	7.5[a]
Patients with ≥1 CTCAE Grade ≥3 TRAE, n (%)[b]	44 (56.4)	29 (37.7)	24 (33.3)
Patients with ≥1 SAE, n (%)[b]	8 (10.3)	4 (5.2)	5 (6.9)
Deaths due to AE on study treatment, n (%)[c]	2 (2.6)	1 (1.3)	1 (1.4)
Patients with treatment discontinuation due to AE	6 (7.7)	11 (14.3)	6 (8.3)
Due to diarrhea	0	1 (1.3)	0
Due to neutropenia	1 (1.3)	1 (1.3)	0

CTCAE = Common Terminology Criteria for Adverse Events

[a] Most common chemotherapy: vinorelbine (37.5%), capecitabine (26.4%), eribulin (16.7%), gemcitabine (11.1%)

[b] Related to study treatment

[c] Deaths on study treatment due to AE: Arm A (cardio-pulmonary arrest, adult respiratory distress syndrome), Arm B (pulmonary fibrosis), Arm C (febrile neutropenia)

Tolaney SM et al. *Proc ESMO* 2019;Abstract LBA23.

FDA Safety Announcement on Possible Severe Lung Inflammation Associated with CDK4/6 Inhibitors

Press Release – September 13, 2019

"The US Food and Drug Administration (FDA) is warning that palbociclib, ribociclib, and abemaciclib used to treat some patients with advanced breast cancers may cause rare but severe inflammation of the lungs. New warnings about this risk [have been approved for] the prescribing information and Patient Package Insert for the entire class of these cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor medicines. The overall benefit of CDK 4/6 inhibitors is still greater than the risks when used as prescribed.

Health care professionals should monitor patients regularly for pulmonary symptoms indicative of interstitial lung disease (ILD) and/or pneumonitis. Signs and symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams in patients in whom infectious, neoplastic, and other causes have been excluded. Interrupt CDK 4/6 inhibitor treatment in patients who have new or worsening respiratory symptoms, and permanently discontinue treatment in patients with severe ILD and/or pneumonitis."

https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-severe-lung-inflammation-ibrance-kisqali-and-verzenio-breast-cancer

Editorial — Dr O'Shaughnessy

Survival data are now emerging from the multiple phase III trials of the 3 CDK4/6 inhibitors in patients with ER+ HER2- MBC. At ASCO 2019 and published in the *NEJM*, the MONALEESA-7 trial of ribociclib plus an LHRH agonist plus tamoxifen or an aromatase inhibitor in pre- and peri-menopausal women showed a substantial survival advantage with the addition of ribociclib. Two press releases have foreshadowed data that will be presented at ESMO 2019 reporting that both abemaciclib and ribociclib added to fulvestrant in endocrine therapy-pretreated MBC patients improves overall survival. The PALOMA-3 trial was presented at ESMO 2018 and published in the *NEJM* and showed a non-significant improvement in OS in the ITT population who received palbociclib plus fulvestrant (compared with fulvestrant/placebo), and a strong survival improvement in the 80% of patients whose breast cancers had not been primary-refractory to endocrine therapy.

Editorial — Dr O'Shaughnessy (continued)

As we await the other CDK4/6 inhibitor plus aromatase inhibitor first-line trial results, the positive/encouraging survival data from the 4 trials above support administering a CDK4/6 inhibitor with the first-line endocrine therapy for most MBC patients. Park et al from the Korean Cancer Study Group reported at ASCO 2019 results of the Young PEARL randomized phase II trial of capecitabine vs palbociclib plus exemestane plus an LHRH agonist as first-line therapy for premenopausal ER+ MBC patients. They showed that median PFS was significantly longer in patients who received this optimized endocrine therapy compared with chemotherapy, suggesting that a CDK4/6 inhibitor should be the preferred first-line standard of care for MBC patients, even those with more aggressive and visceral disease.

FDA Approves Alpelisib for Metastatic Breast Cancer

Press Release – May 24, 2019

“The Food and Drug Administration approved alpelisib in combination with fulvestrant for postmenopausal women, and men, with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

The FDA also approved the companion diagnostic test, PIK3CA RGQ PCR Kit to select patients who have PIK3CA mutations in tumor tissue specimens and/or in circulating tumor DNA (ctDNA) isolated from plasma specimens. If the test is negative for PIK3CA mutations in plasma, patients should undergo testing for PIK3CA mutations in tumor tissue.

Approval was based on SOLAR-1 (NCT02437318), a phase 3, randomized, double-blind, placebo-controlled trial of alpelisib plus fulvestrant versus placebo plus fulvestrant in 572 patients including postmenopausal women, and men, with HR-positive, HER2-negative, advanced or metastatic breast cancer whose disease had progressed or on or after receiving an aromatase inhibitor.”

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-alpelisib-metastatic-breast-cancer

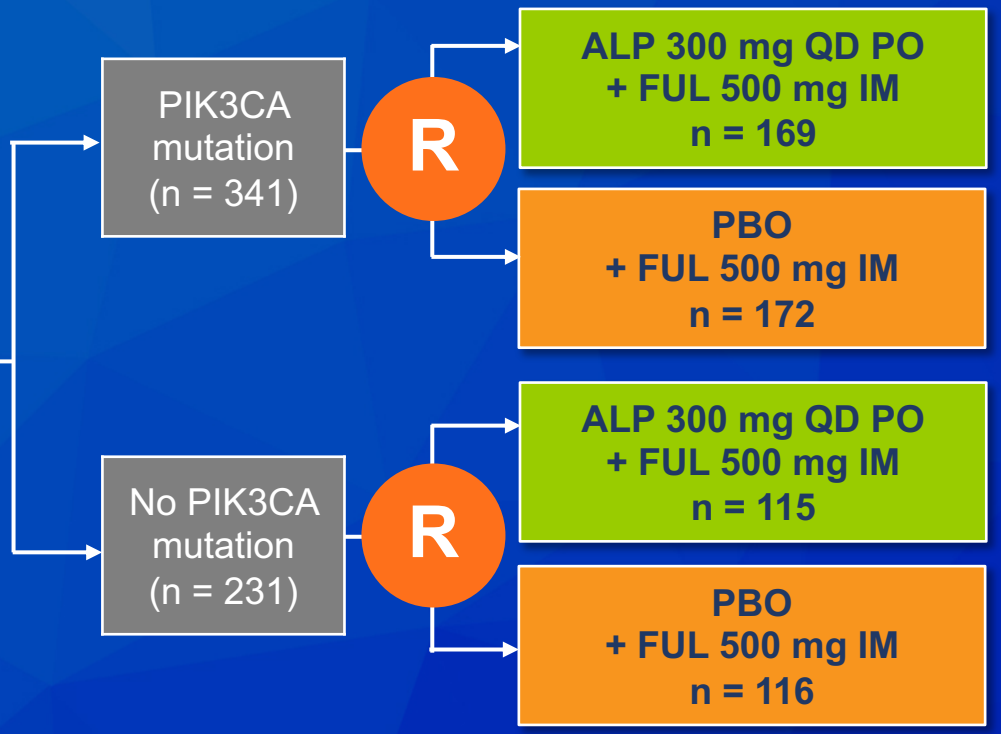
Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer

André F et al.
N Engl J Med 2019;380(20):1929-40.

SOLAR-1 Phase III Study Design

Men or postmenopausal women with HR+, HER2-neg advanced breast cancer (N = 572)

- Recurrence/progression on/after prior aromatase inhibitor
- Identified PIK3CA status (in archival or fresh tumor tissue)
- ECOG performance status ≤1

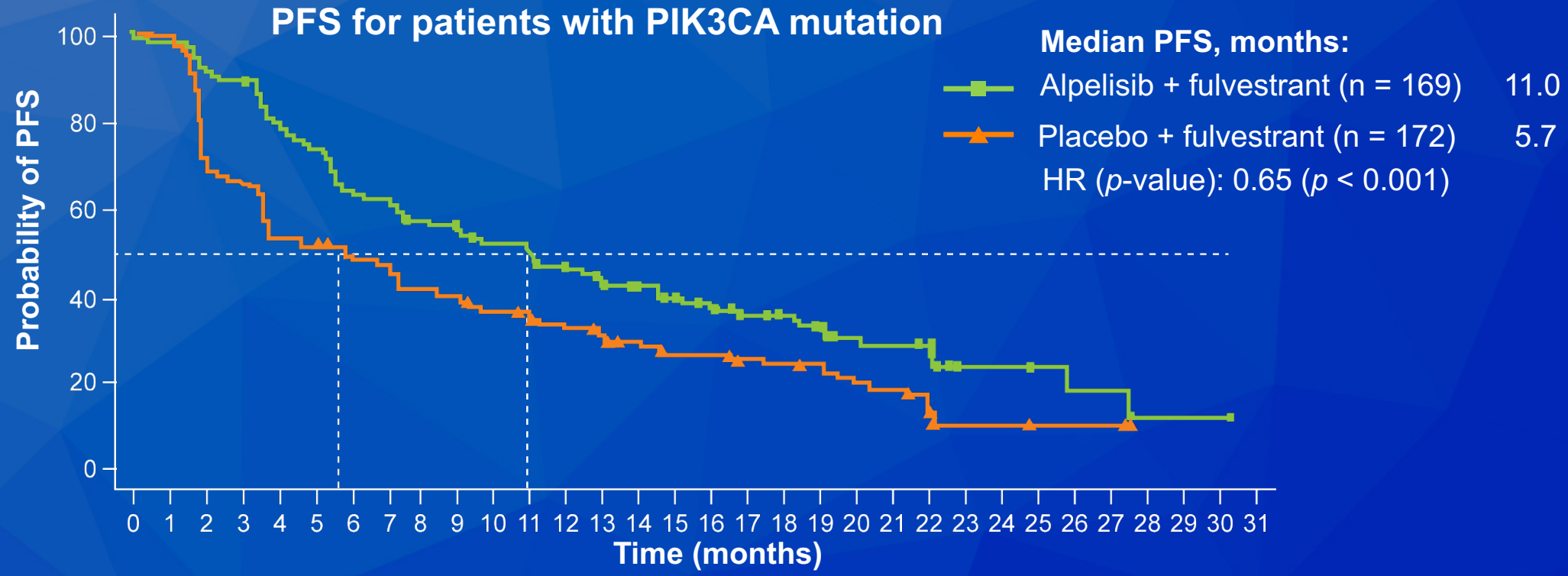


IM = intramuscular

Primary endpoint: Locally assessed PFS in PIK3CA mutation cohort

André F et al. *N Engl J Med* 2019;380(20):1929-40; André F et al. *Proc ESMO* 2018;Abstract LBA3_PR.

SOLAR-1: Alpelisib/Fulvestrant for Patients with Advanced Breast Cancer After Prior AI – Efficacy and Safety



Select adverse events	Alpelisib and fulvestrant (n = 284)	Placebo and fulvestrant (N = 287)
Any Grade 3 or 4 adverse event	76%	36%
Hyperglycemia	37%	<1%
Rash	10%	<1%

André F et al. *N Engl J Med* 2019;380(20):1929-40; André F et al. *Proc ESMO* 2018;Abstract LBA3_PR.

Editorial — Dr O'Shaughnessy

PIK3CA mutations occur in about 40% of patients with ER+ HER2- MBC and are believed to be a mechanism of resistance to endocrine therapy for metastatic disease. PIK3CA mutations are generally found in the primary breast cancer but may be "acquired" in approximately 10% of patients in the metastatic setting, as ascertained by ctDNA. The FDA approved alpelisib for patients with aromatase inhibitor-pretreated ER+, HER2-, PIK3CA-mutant MBC in May 2019 based on the results of the phase III SOLAR-1 trial, which showed that adding alpelisib to fulvestrant almost doubled the median PFS from 5.7 to 11 months. Only 6% of patients had been pretreated with a CDK4/6 inhibitor in the SOLAR-1 trial, so we don't know whether or not alpelisib will be as active following progression on a CDK4/6 inhibitor.

Editorial — Dr O'Shaughnessy (continued)

The key treatment-limiting toxicities of alpelisib are hyperglycemia and rash, which can be prevented/reduced by avoiding the use of alpelisib in patients with a HgbA1C more than 6.4%, careful monitoring of fasting glucose levels with early introduction of metformin for hyperglycemia, and with the use of a non-drowsy antihistamine twice a day, starting on day 1. Other toxicities included fatigue, liver dysfunction, elevated creatinine, stomatitis, and diarrhea, which were manageable with dose reduction as needed. The FDA also approved a companion diagnostic to test for the presence of a PIK3CA mutation in tissue, and recommended obtaining ctDNA to assess for a PIK3CA mutation in the metastatic setting, and to then test primary or metastatic tissue for the mutation if ctDNA is negative.

Editorial — Dr O’Shaughnessy (continued)

It is likely we will recommend alpelisib and fulvestrant to patients whose PIK3CA-mutant disease is progressing on a CDK4/6 inhibitor, as preclinical studies have shown that signaling through the PI3K pathway is likely an important mechanism of resistance to CDK4/6 inhibitors.