

Yearⁱⁿ Review

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

**Saturday, February 8, 2020, 8:00 AM – 4:00 PM
Charlotte, North Carolina**

Faculty

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Corey J Langer, MD

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Mitchell R Smith, MD, PhD
Richard M Stone, MD
Zev Wainberg, MD, MSc

Moderator
Neil Love, MD

Research
To Practice®

Agenda

Module 1 — Lung Cancer: *Drs Langer and Riely*

Module 2 — Acute Leukemias: *Drs DiNardo and Stone*

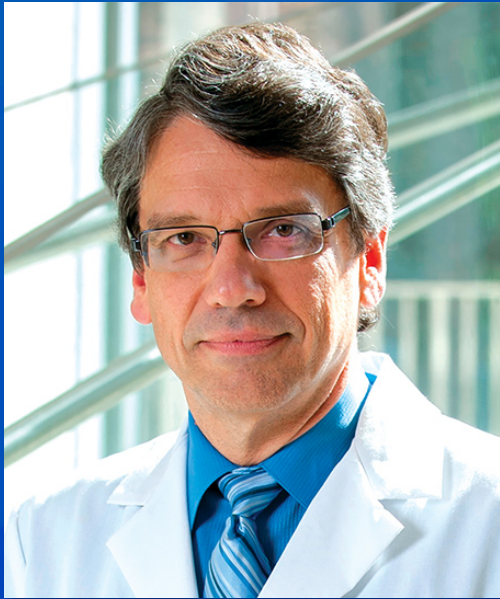
Module 3 — Lymphomas and Chronic Lymphocytic Leukemia:
Drs Abramson, LaCasce and Smith

Module 4 — Gastrointestinal Cancers: *Drs Bendell, Marshall and Wainberg*

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

Module 6 — Gynecologic Cancers: *Drs Armstrong and Liu*

Module 7 — Breast Cancer: *Drs Geyer and Krop*



Charles E Geyer Jr, MD
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Disclosures

Advisory Committee (Uncompensated)	Daiichi Sankyo Inc, Genentech, Roche Laboratories Inc, Seattle Genetics
Contracted Research	Genentech, Roche Laboratories Inc
Paid Travel	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, Roche Laboratories Inc
Writing Assistance	AbbVie Inc, Genentech, Roche Laboratories Inc



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Disclosures

Consulting Agreements	Context Therapeutics, Daiichi Sankyo Inc, Genentech, MacroGenics Inc, Roche Laboratories Inc, Taiho Oncology Inc
Contracted Research	Daiichi Sankyo Inc, Genentech, Pfizer Inc, Roche Laboratories Inc
Data and Safety Monitoring Board/Committee	Merck, Novartis

Breast Cancer — Drs Geyer and Krop

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.”

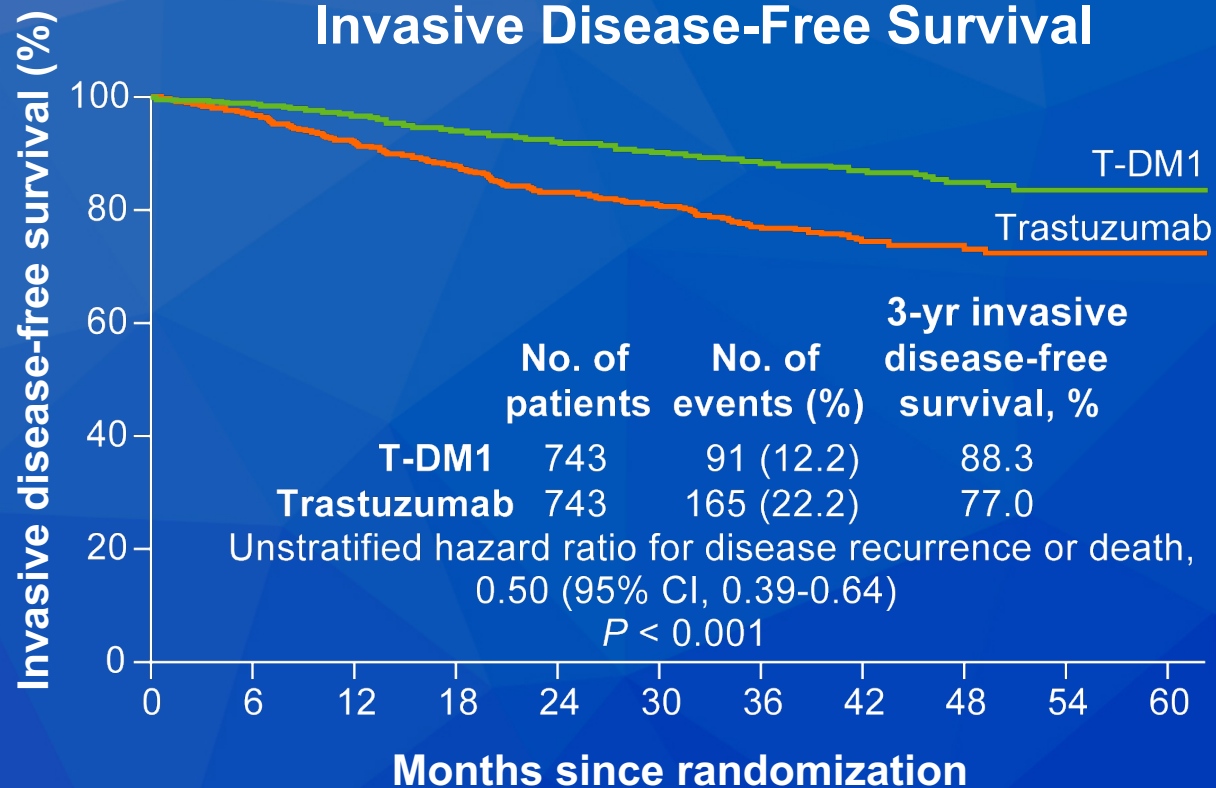
Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

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

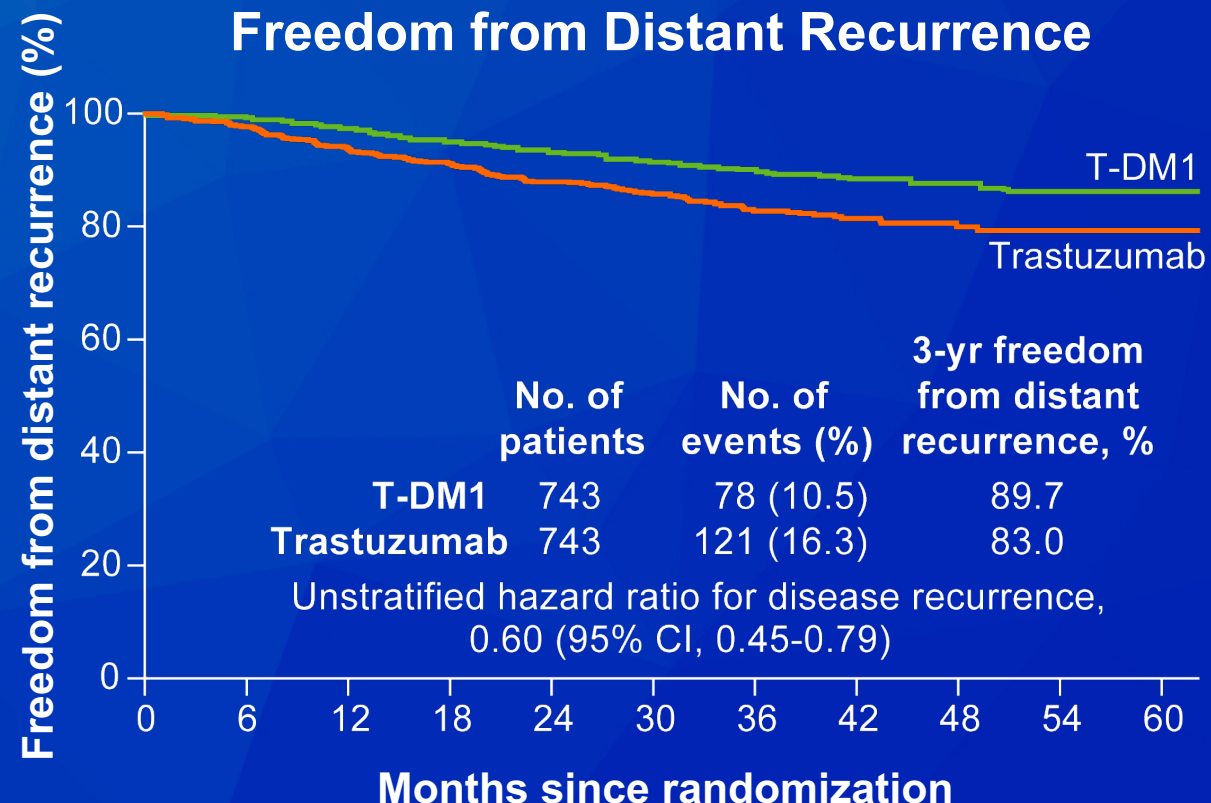


KATHERINE: Invasive DFS and Freedom from Distant Recurrence

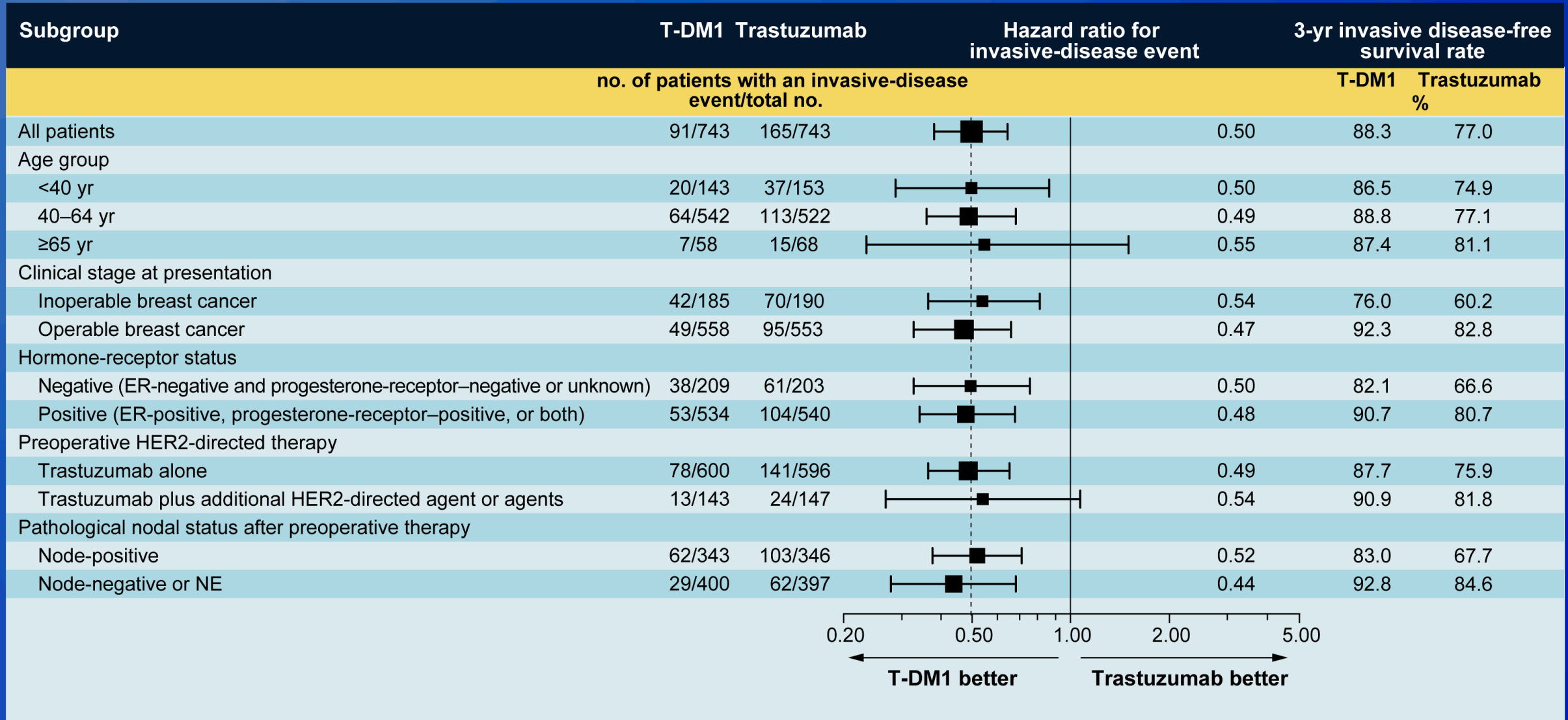
Invasive Disease-Free Survival



Freedom from Distant Recurrence



KATHERINE: Subgroup Analyses of Invasive Disease-Free Survival



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

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.

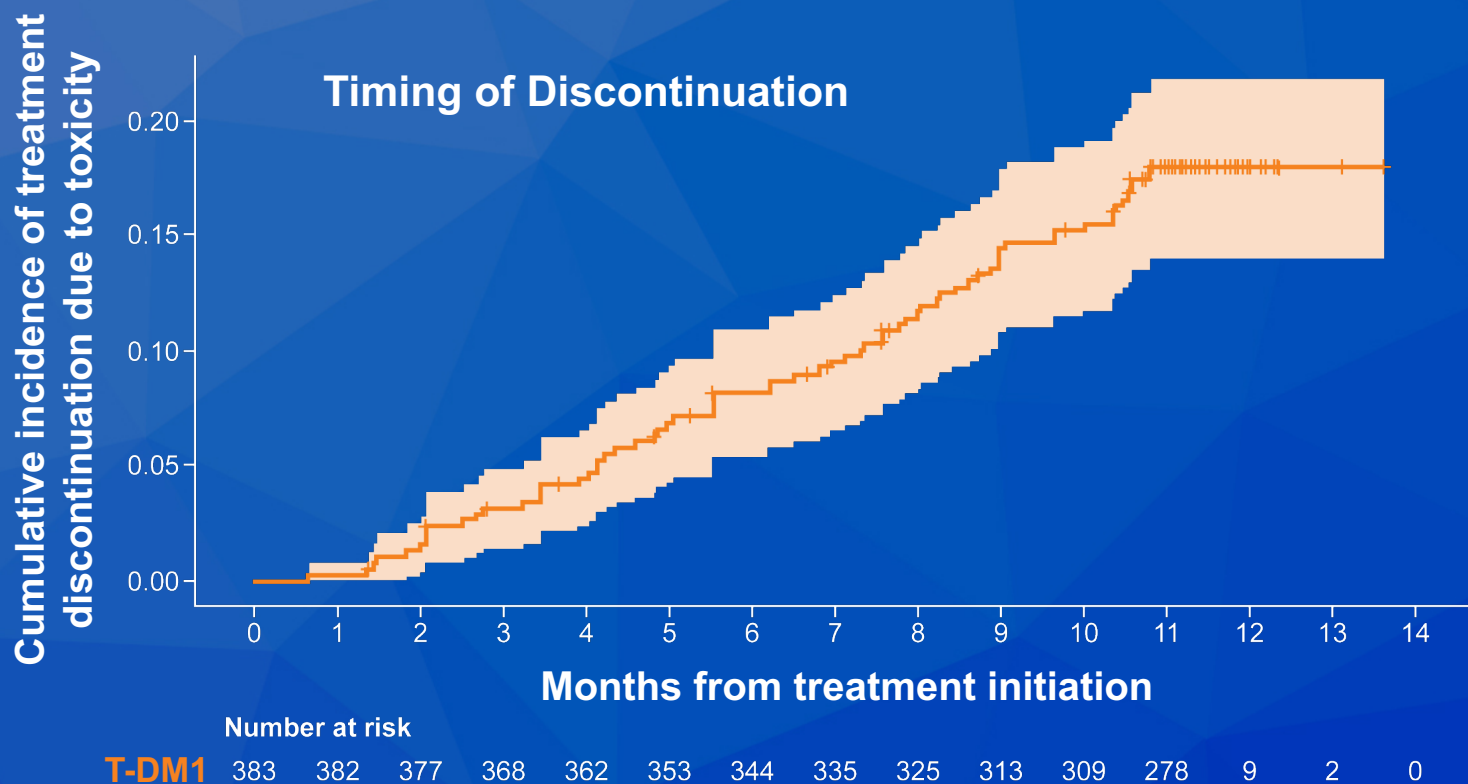
San Antonio Breast Cancer Symposium 2019;Abstract GS1-05.



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%			

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%

ATEMPT: Cardiac Toxicity



	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 ($\geq 15\%$)	5 (1.3%)	7 (6.1%)

Editorial — Dr Krop

Outcomes for even relatively high-risk patients with early stage HER2+ breast cancer are now quite favorable. One remaining challenge is to determine who needs maximum therapy and who can get by with less toxic regimens.

An update on the APHINITY trial evaluating the use of adjuvant pertuzumab helps address who benefits from the addition of pertuzumab to trastuzumab + chemotherapy. While there is a modest DFS benefit to dual therapy (ie, pertuzumab + trastuzumab) in the overall trial (but no significant OS benefit so far), this new analysis clearly showed that essentially all the benefit is in node-positive patients — node-negative patients did not benefit. Hormone receptor status did not influence pertuzumab benefit. In practice, these adjuvant findings are going to be somewhat complicated to implement because all patients with clinical stage II or higher HER2+ cancers should now be treated with neoadjuvant therapy.

Editorial — Dr Krop (continued)

One approach is to use dual antibody therapy for clinically node-positive cancers or large clinically node-negative cancers (since they are more likely to have occult nodal disease), and use trastuzumab alone (with chemotherapy) in patients with T2N0 cancers. In my opinion, dual therapy should be continued in the adjuvant setting for clinically N+ cancers even if they have a pCR, since the favorable long-term data with APHINITY used one year of therapy.

For HER2+ stage 1 cancers, data from APT established paclitaxel/trastuzumab (TH) as the standard of care, with very good outcomes. A new study, ATEMPT, explored whether we can get rid of conventional chemotherapy entirely.

ATEMPT randomized stage 1 patients to a year of T-DM1 or standard TH. It found that patients receiving T-DM1 had an extremely low risk of recurrence (3-yr DFS 97.7%).

Editorial — Dr Krop (continued)

The overall rate of clinically significant adverse events was similar between the arms, although types of AEs differed (TH had more neuropathy, neutropenia, and alopecia; T-DM1 had better QOL but more transaminase elevations and thrombocytopenia). Thus, T-DM1 cannot be considered a new standard of care for stage 1 patients but could be considered for select patients in whom the TH toxicities (ie, neuropathy) may be a particular burden.

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).”

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 Cancer²

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

N = 410

R*
(2:1)

N = 202

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/m² PO BID (days 1-14)

Placebo + trastuzumab + capecitabine

(21-day cycle)

Placebo

+

Trastuzumab 6 mg/kg q3w (loading dose 8 mg/kg C1D1)

+

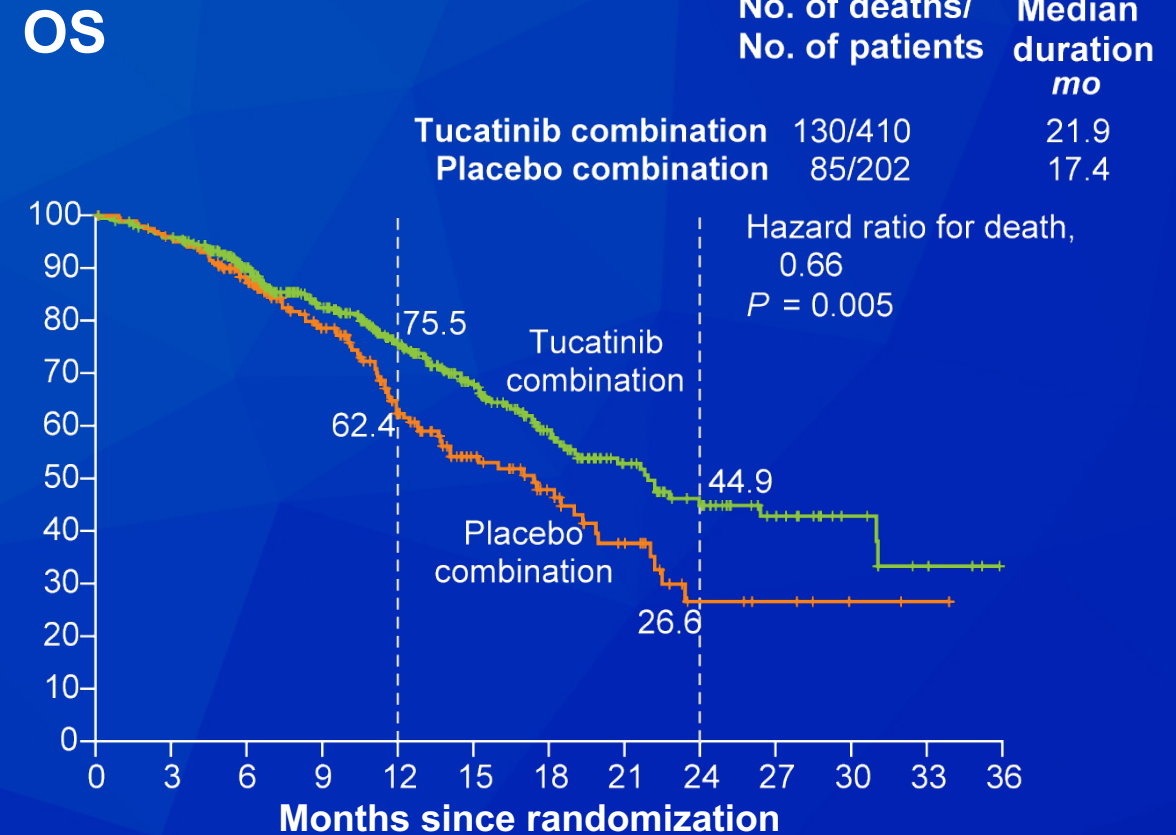
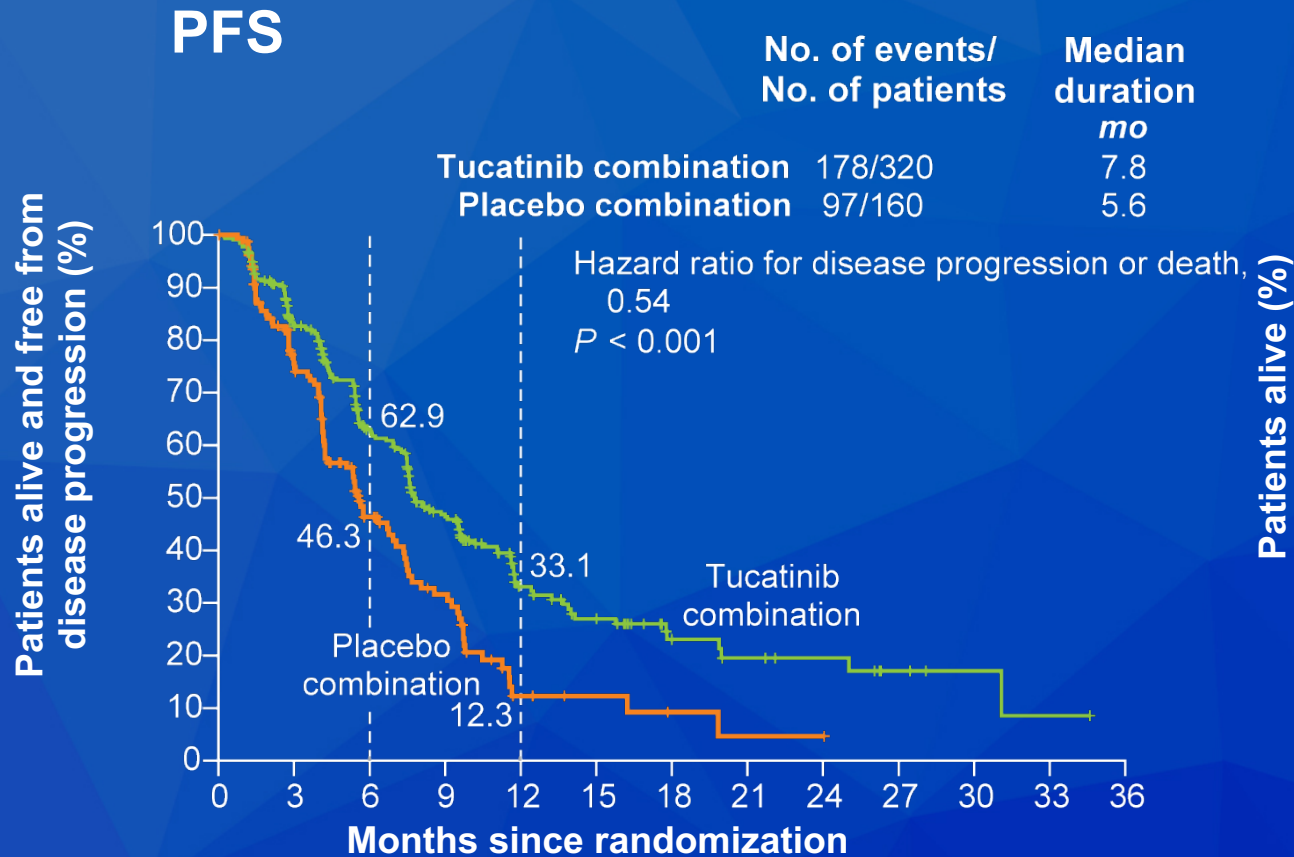
Capecitabine 1,000 mg/m² PO BID (days 1-14)

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

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)



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 Krop

Use of HER2 tyrosine kinase inhibitors (TKI) like lapatinib and neratinib have been limited by their EGFR-mediated toxicity (diarrhea and rash). Tucatinib is a new TKI that is unique in that it is almost completely HER2 selective and thus has much less EGFR-mediated toxicity. It also crosses the blood-brain barrier well. The phase 3 HER2CLIMB trial evaluated whether adding tucatinib to capecitabine and trastuzumab improved outcomes in patients with advanced HER2-positive breast cancer previously treated with T-DM1, trastuzumab and pertuzumab. Importantly, this trial was the first to allow patients with untreated or progressive brain metastases.

The study showed that the addition of tucatinib significantly improved both progression-free and overall survival in the ITT population and specifically in the patients with brain metastases. Tucatinib was associated with modest increases in diarrhea, PPE, and nausea.

Editorial — Dr Krop (continued)

Based on these data, capecitabine, trastuzumab and tucatinib is likely to receive FDA approval and should become a standard of care for third- or later-line HER2-positive patients.

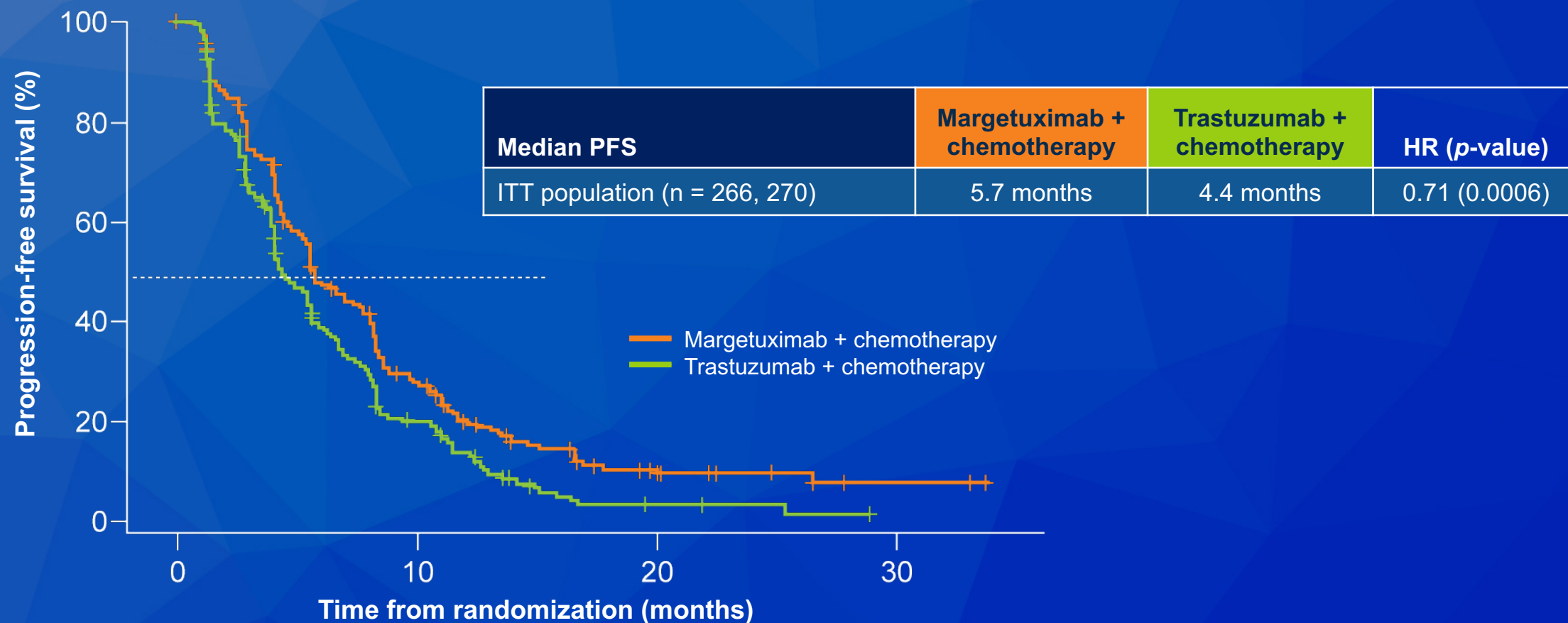
We will soon have multiple third-line options available, including trastuzumab deruxtecan in addition to tucatinib, and we will have to determine how to optimally sequence these agents. To me, it is clear that for patients who have progressive brain metastases or those who have had trouble with recurrent brain metastases, the tucatinib combination would be preferred. Another phase 3 trial is now under way evaluating the addition of tucatinib to T-DM1 in the second-line setting. A study of tucatinib in the post-neoadjuvant setting is also being considered.

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



- 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)

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.”

[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

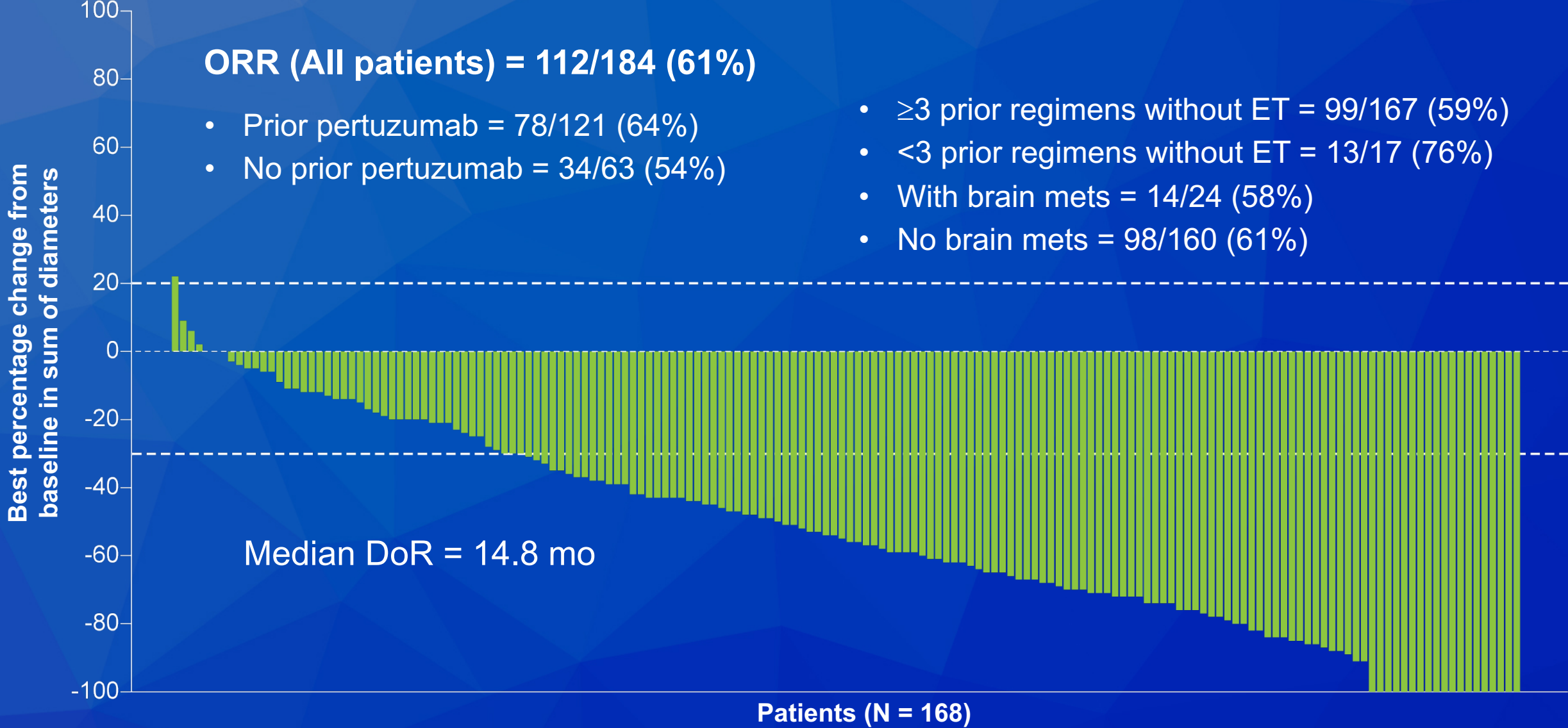
Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer²

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



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%).

Editorial — Dr Krop

The success of T-DM1, with its substantial efficacy and very favorable toxicity profile, proved that antibody-drug conjugates can be very effective in HER2+ breast cancer. However, not all patients respond to T-DM1, and in those that do respond, resistance eventually develops. Trastuzumab deruxtecan is a new antibody-drug conjugate that was designed to improve upon the efficacy of T-DM1. While it shares a similar HER2-specific antibody backbone, it differs from T-DM1 in that trastuzumab deruxtecan uses a very potent topoisomerase 1 inhibitor payload (rather than the microtubule inhibitor of T-DM1), there are twice as many payload molecules per antibody, and the payload is membrane permeable, which allows it to kill neighboring tumor cells irrespective of HER2 expression.

Editorial — Dr Krop (continued)

The Destiny breast 01 trial was a phase 2 study of trastuzumab deruxtecan in a very heavily pretreated population (median 6 prior lines of metastatic therapy) of patients with HER2+ advanced breast cancer. The drug showed a very high rate of durable responses (ORR 60.9%, PFS 16.4 mo), markedly higher than any previous study in pretreated HER2+ disease. Low grade fatigue and nausea were the most common toxicities, and alopecia occurred in about 50% of patients. In addition, pneumonitis was observed in 13.6% of patients. While the pneumonitis was mostly low grade, 2.2% of patients had fatal pneumonitis. Thus, the use of this agent requires careful monitoring for signs and symptoms of pneumonitis and prompt intervention with steroids when it occurs. Trastuzumab deruxtecan is now approved for patients with HER2+ advanced breast cancer that has progressed on at least 2 prior lines of therapy.

Breast Cancer — Drs Geyer and Krop

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 $\geq 1\%$ 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.

Atezolizumab and *Nab*-Paclitaxel in Advanced Triple-Negative Breast Cancer¹

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 Trial²

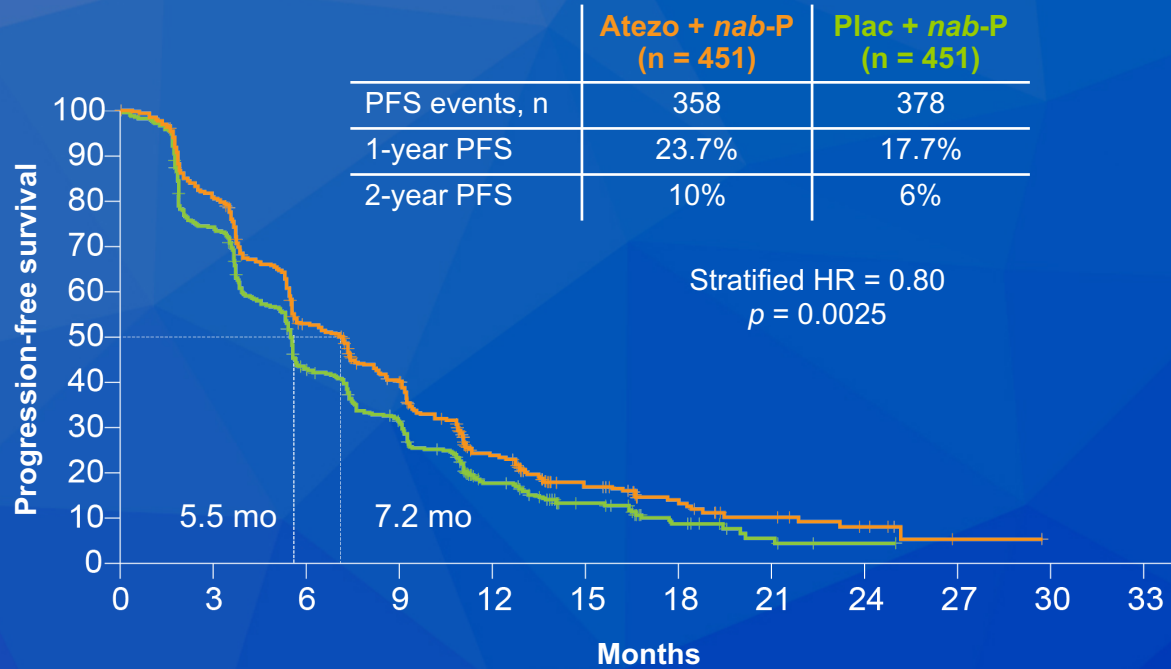
¹ Schmid P et al.
N Engl J Med 2018;379(22):2108-21.

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

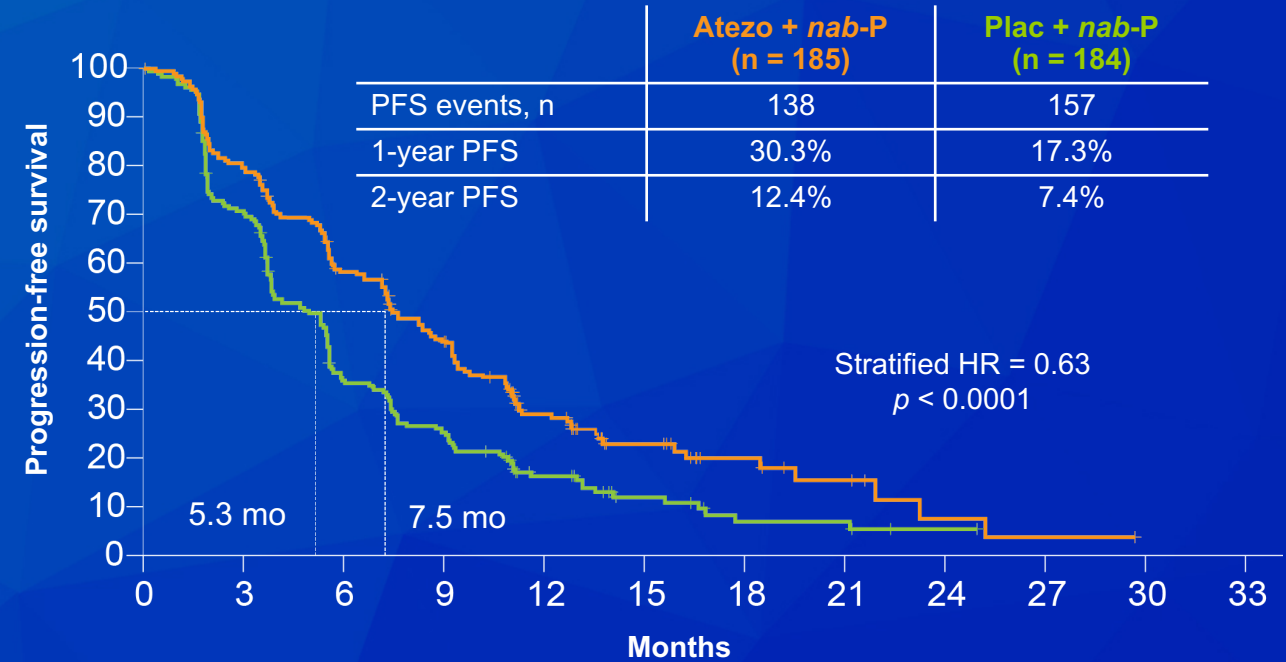


IMpassion130: PFS Results

Primary PFS analysis: ITT population



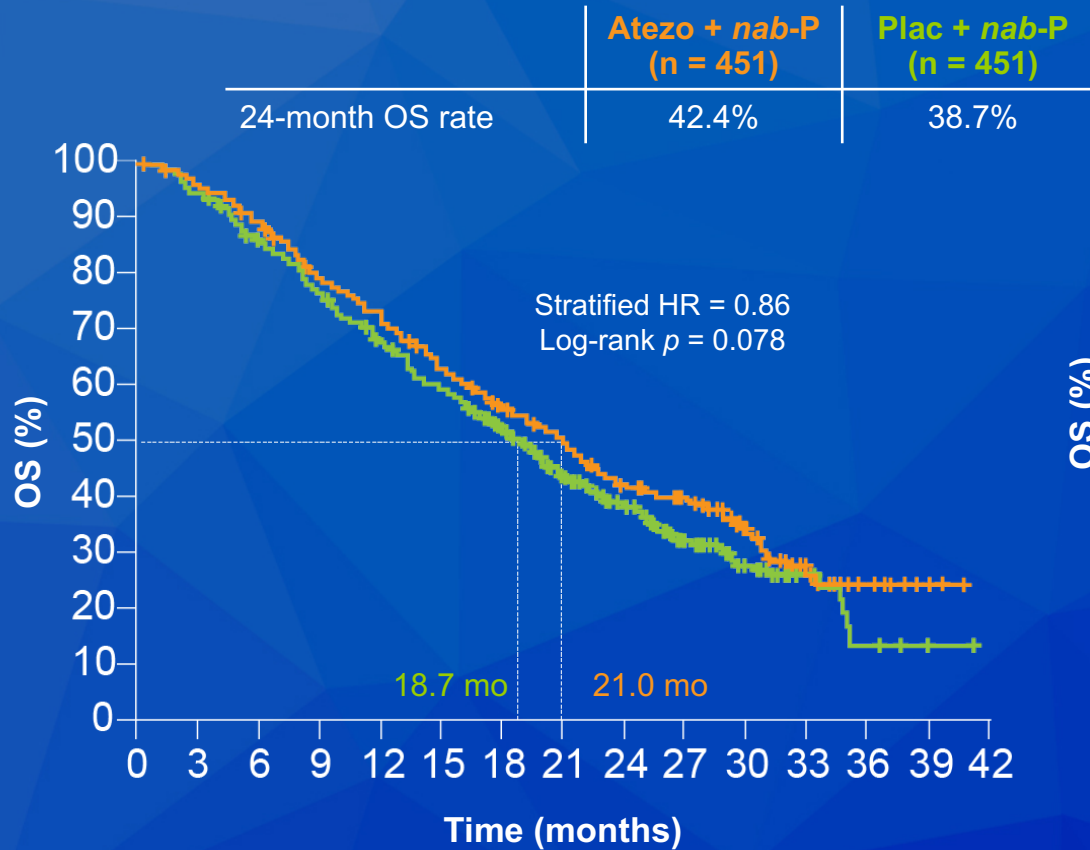
Primary PFS analysis: PD-L1+ population



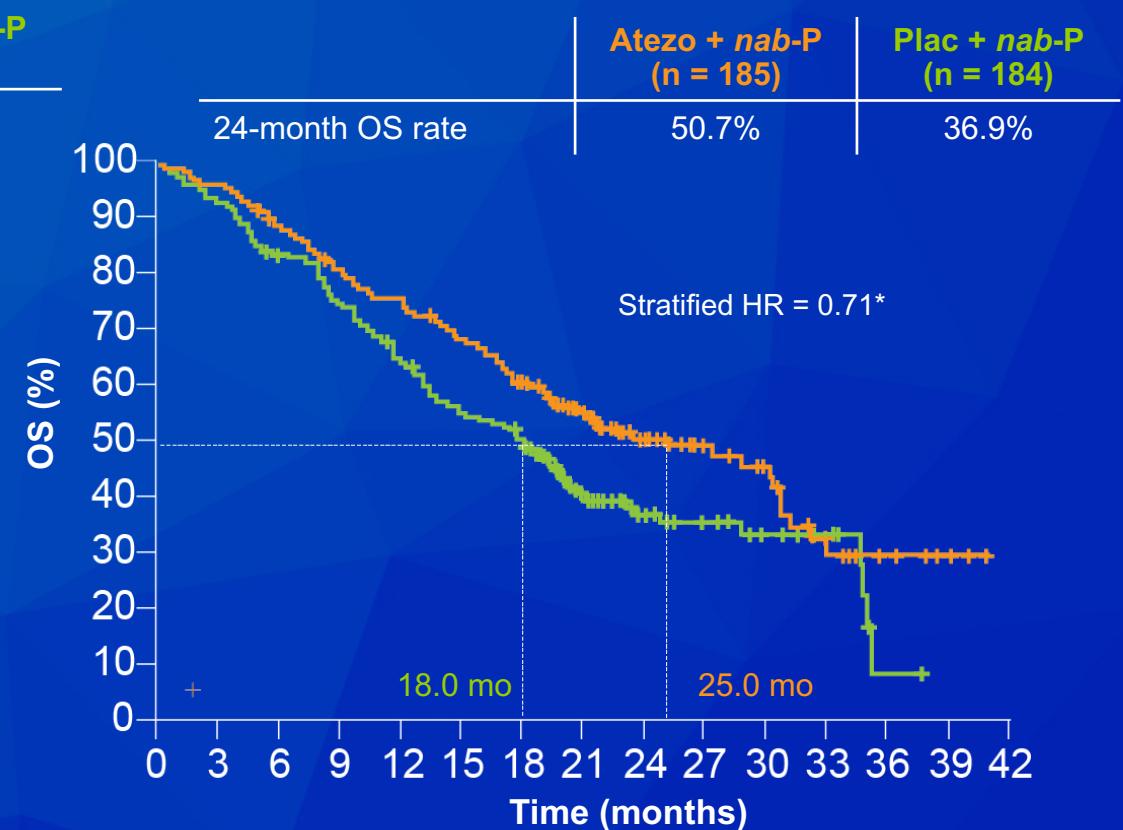
Second interim analysis median follow-up = 18.5 mo (atezo) vs 17.5 mo (placebo)

IMpassion130: OS Results at Second Interim Analysis

Second interim analysis of OS: ITT population



Second interim analysis of OS: PD-L1+ population



* 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

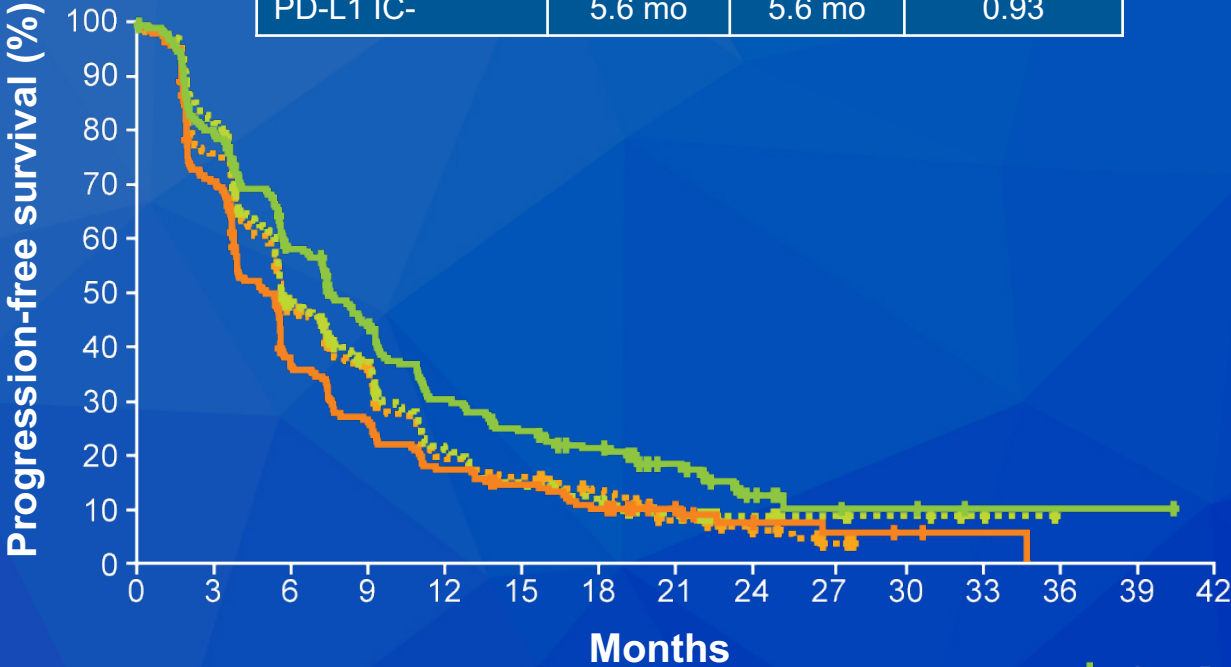
Performance of PD-L1 Immunohistochemistry Assays in Unresectable Locally Advanced or Metastatic Triple-Negative Breast Cancer: Post Hoc Analysis of IMpassion130

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



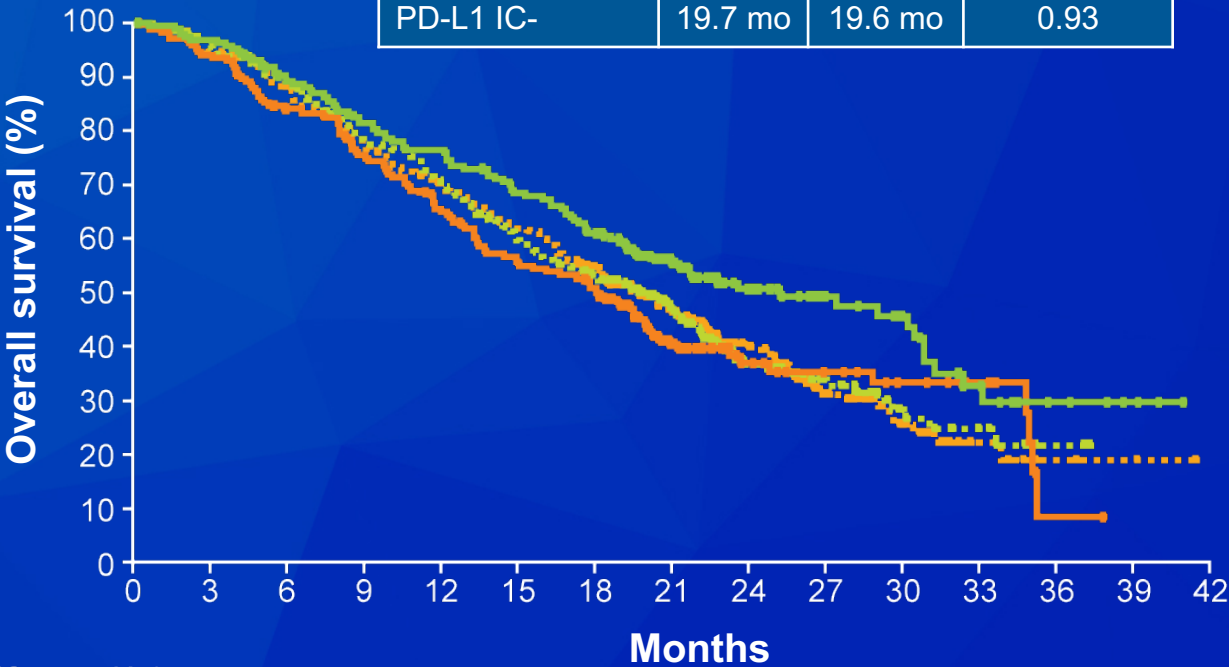
IMpassion130: PD-L1 Status by SP142 Predicts PFS and OS

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

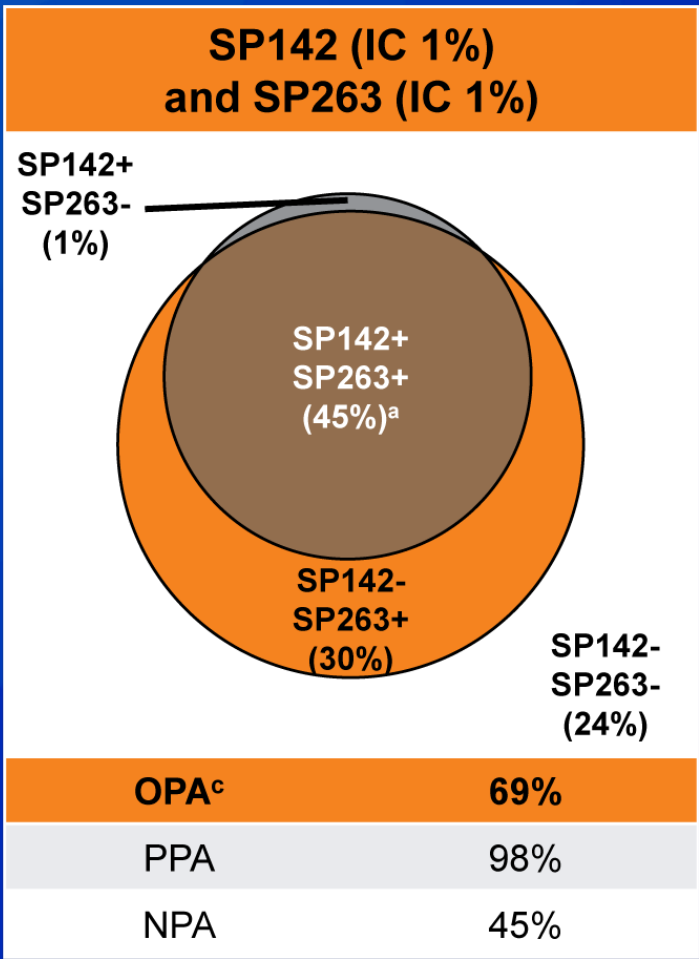
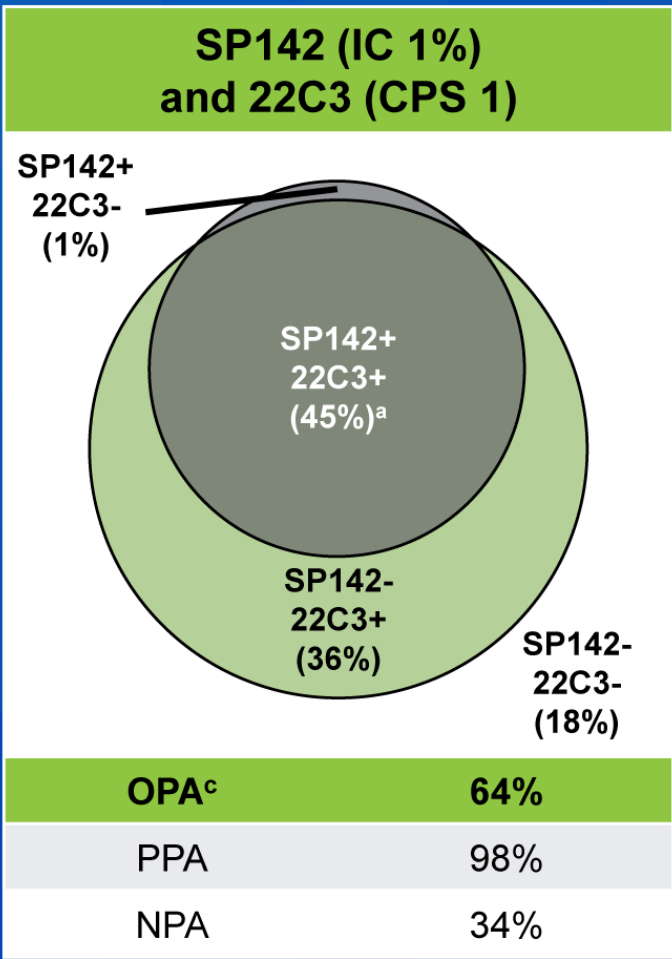
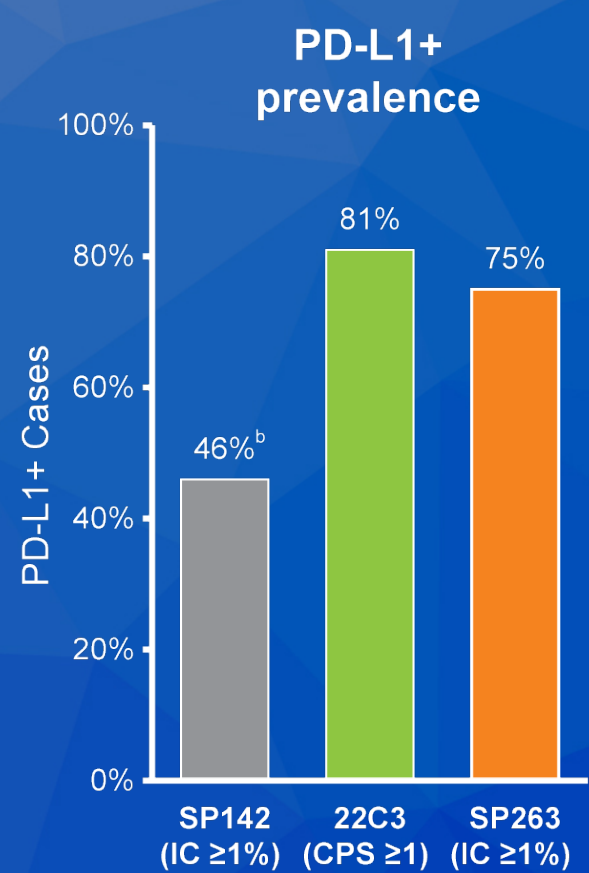


— A + nP (IC+, n = 185)
— P + nP (IC+, n = 184)
... A + nP (IC-, n = 266)
... P + nP (IC-, n = 267)

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



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



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

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 Surgery²

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

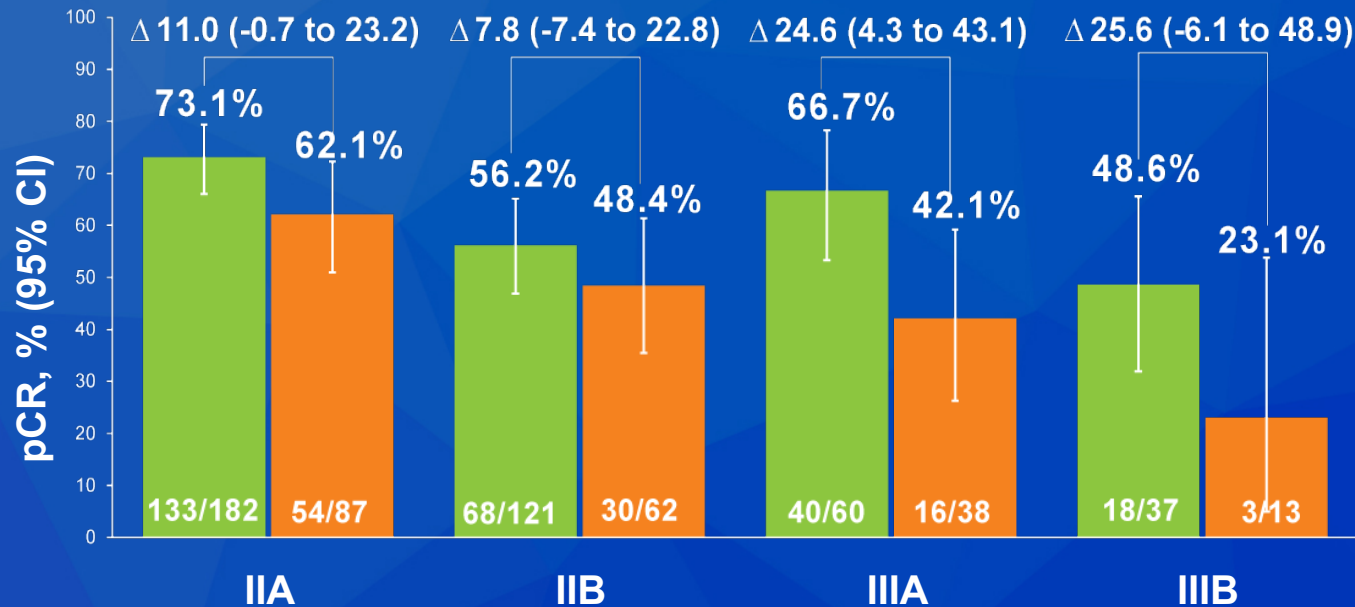
² Schmid P et al.
San Antonio Breast Cancer Symposium 2019;Abstract GS3-03.



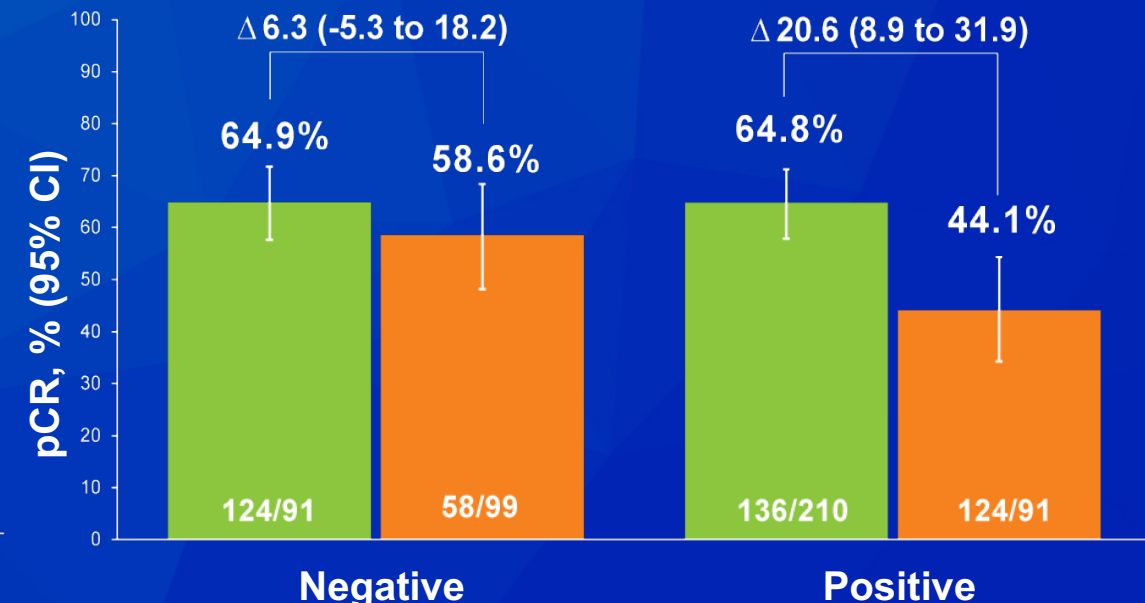
KEYNOTE-522: pCR by Disease Stage and Lymph Node Involvement

Pembro + chemo
Placebo + chemo

pCR by Disease Stage



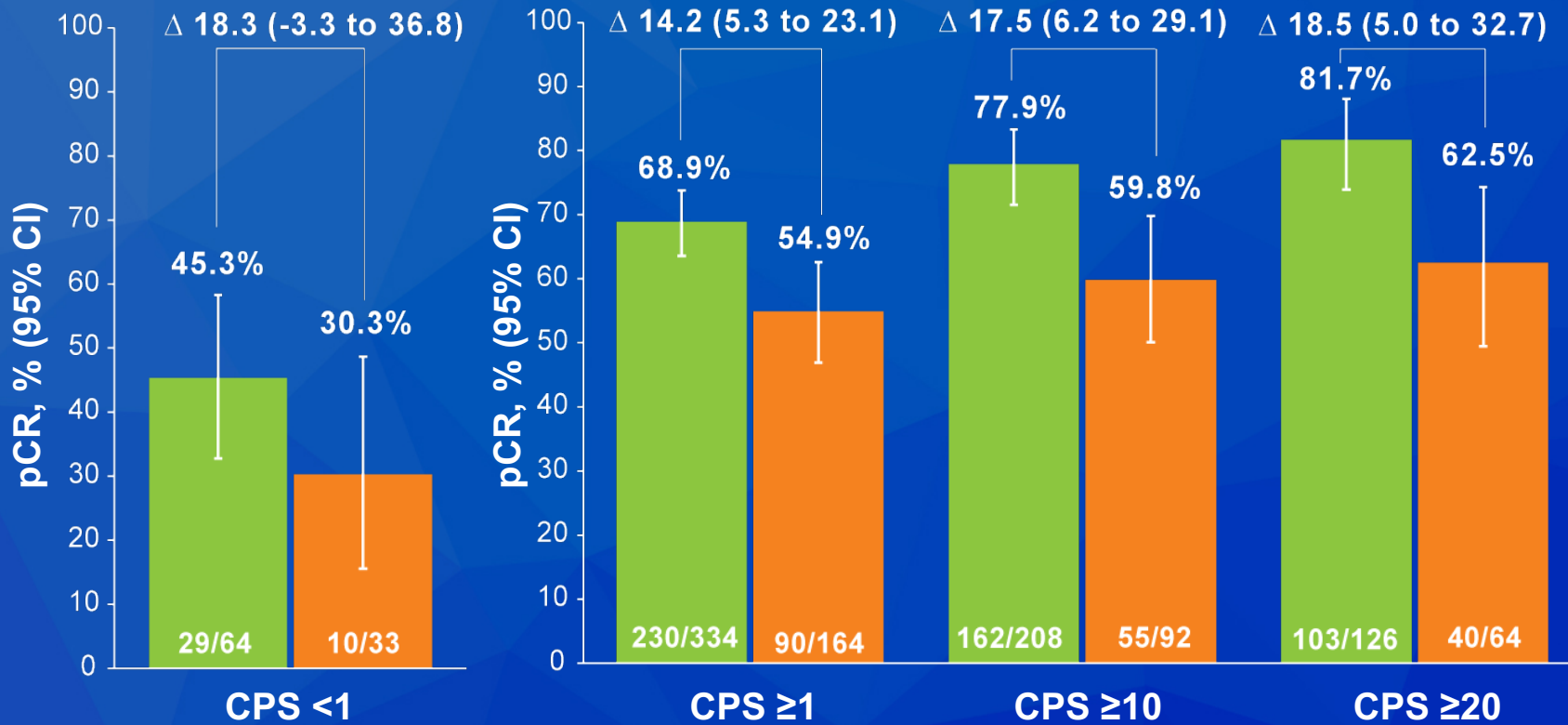
pCR by Lymph Node Involvement



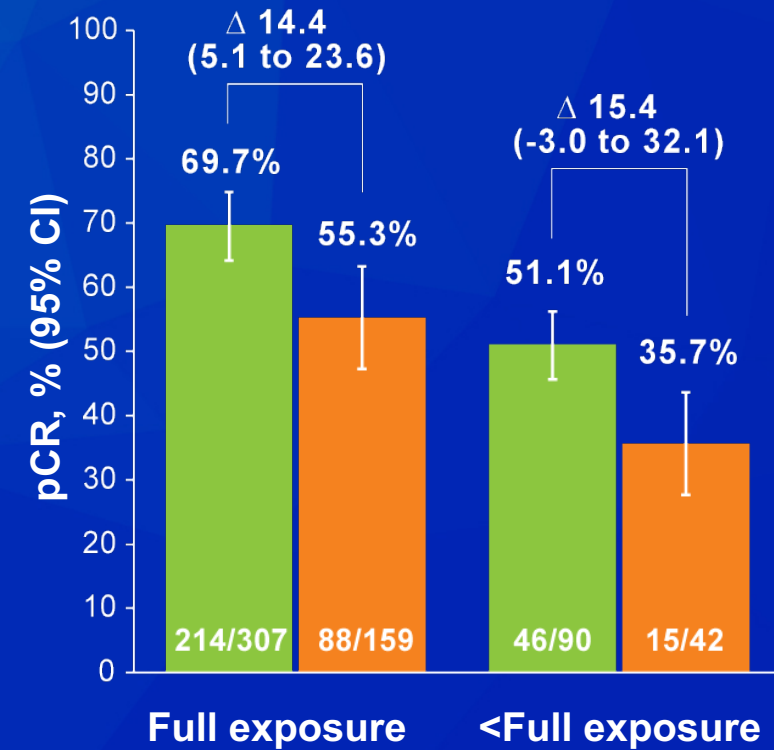
KEYNOTE-522: pCR by PD-L1 Expression and Exposure to Chemotherapy

Pembro + chemo
Placebo + chemo

pCR by PD-L1 Expression Level



pCR by Exposure to Chemotherapy



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.

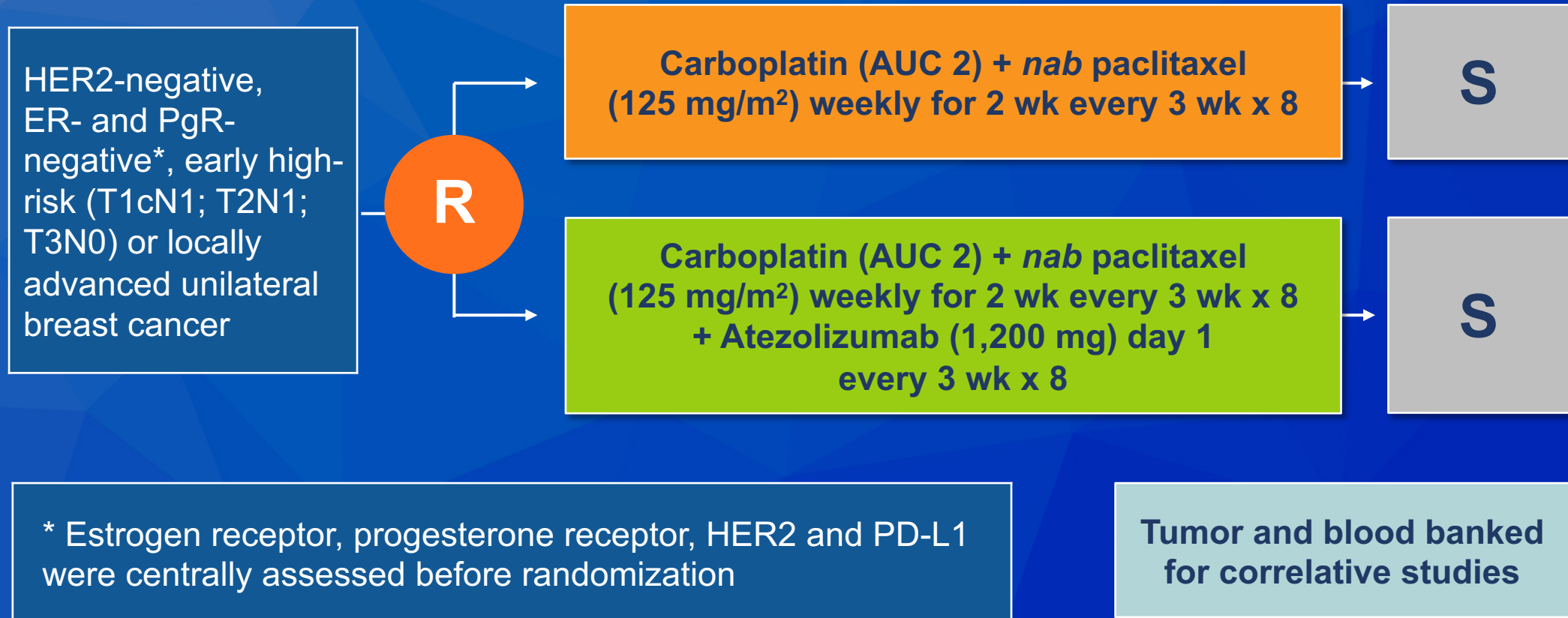
Pathologic Complete Response (pCR) to Neoadjuvant Treatment with or without Atezolizumab in Triple Negative, Early High-Risk and Locally Advanced Breast Cancer. NeoTRIPaPDL1 Michelangelo Randomized Study

Gianni L et al.

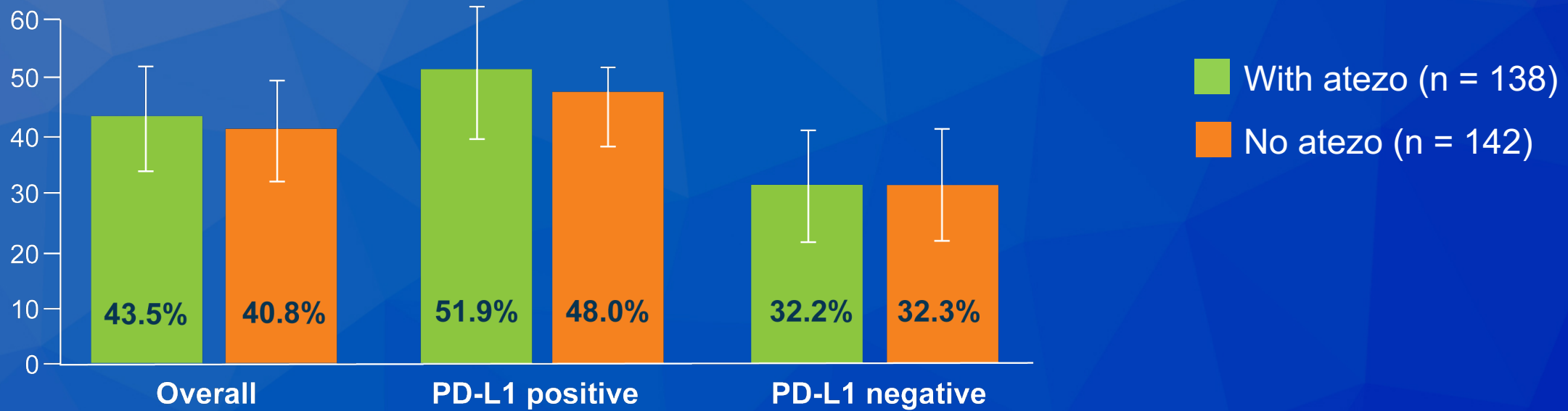
San Antonio Breast Cancer Symposium 2019;Abstract GS3-04.



NeoTRIP: Trial Schema



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

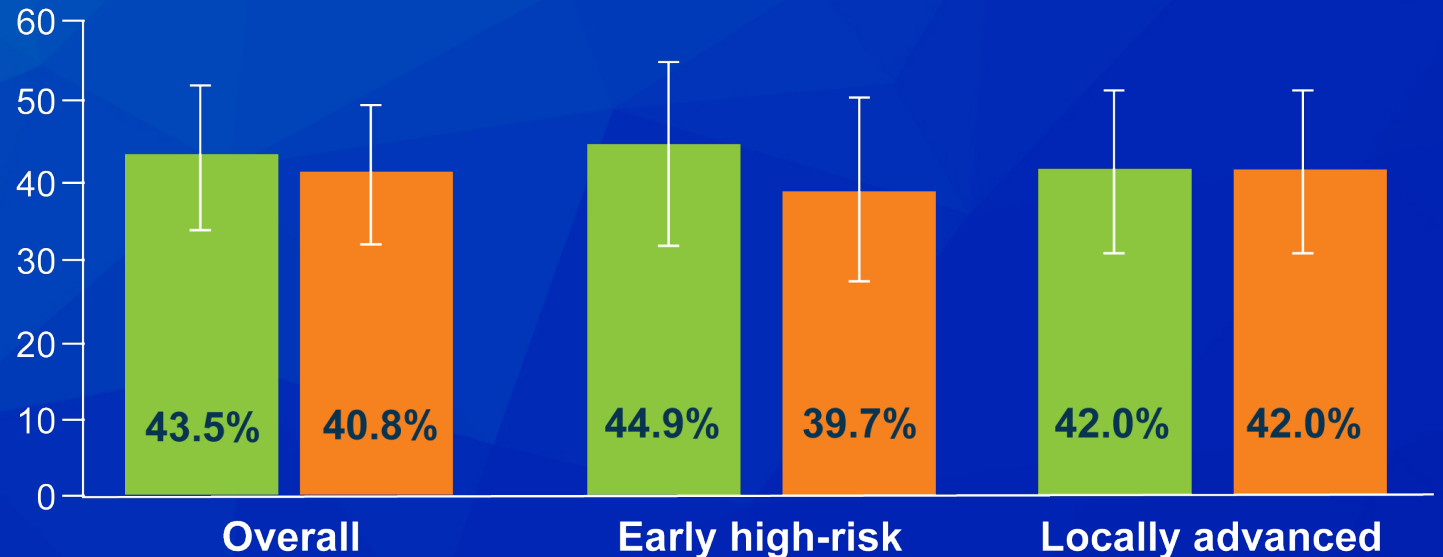


Clinical overall response

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

Clinical complete response

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



Editorial — Dr Krop

Results from the first-line metastatic setting (IMpassion130) and neoadjuvant setting (I-SPY) that demonstrate benefit from the addition of immune checkpoint inhibitors to chemotherapy in triple-negative breast cancer (TNBC) have created excitement about the use of this approach to meaningfully improve long-term outcomes in early stage TNBC. Recent data from the phase 3 KEYNOTE-522 study, evaluating the addition of 1 year of pembrolizumab to neoadjuvant carboplatin/paclitaxel/AC, demonstrated that adding pembro led to a significant increase in pCR and a strong trend toward improvement in EFS (in an interim analysis). In contrast, the smaller randomized phase 3 NeoTRIPaPDL1 study, which evaluated the addition of neoadjuvant atezolizumab to 8 cycles of carboplatin/paclitaxel, showed no improvement in pCR with the addition of the checkpoint inhibitor. Interestingly, in both studies, PD-L1 positivity was associated with higher rates of pCR but did not predict benefit of the checkpoint inhibitor.

Editorial — Dr Krop (continued)

Why the checkpoint inhibitor was beneficial in KEYNOTE-522 and not NeoTRIPaPDL1 is not clear. It is possible that differences in the 2 trial designs may have played a role: KEYNOTE-522 used a PD-1 inhibitor and included AC in the neoadjuvant regimen; NeoTRIPaPDL1 used a PD-L1 inhibitor and delayed the AC until the adjuvant setting. Additional follow-up of both studies will, hopefully, clarify the long-term benefit of checkpoint inhibitors in this setting. If there is a definitive benefit seen, it will still be important to identify patients most likely to benefit, since the checkpoint inhibitors are associated with potentially serious toxicity, which not infrequently can be permanent.

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 Cancer¹

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 Cancer²

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

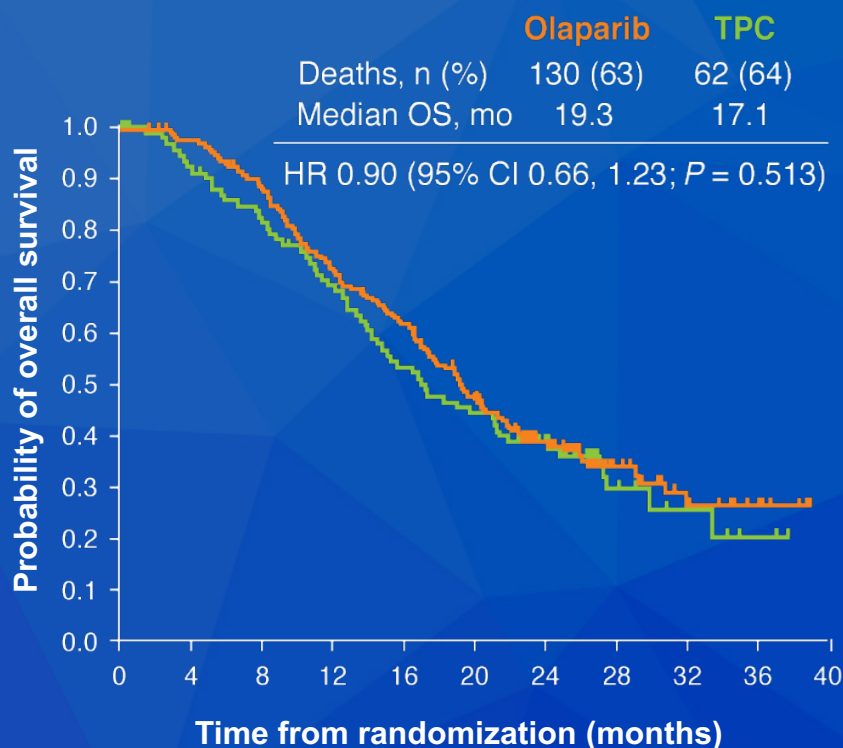
² Robson M et al.
San Antonio Breast Cancer Symposium 2019;Abstract PD4-03.



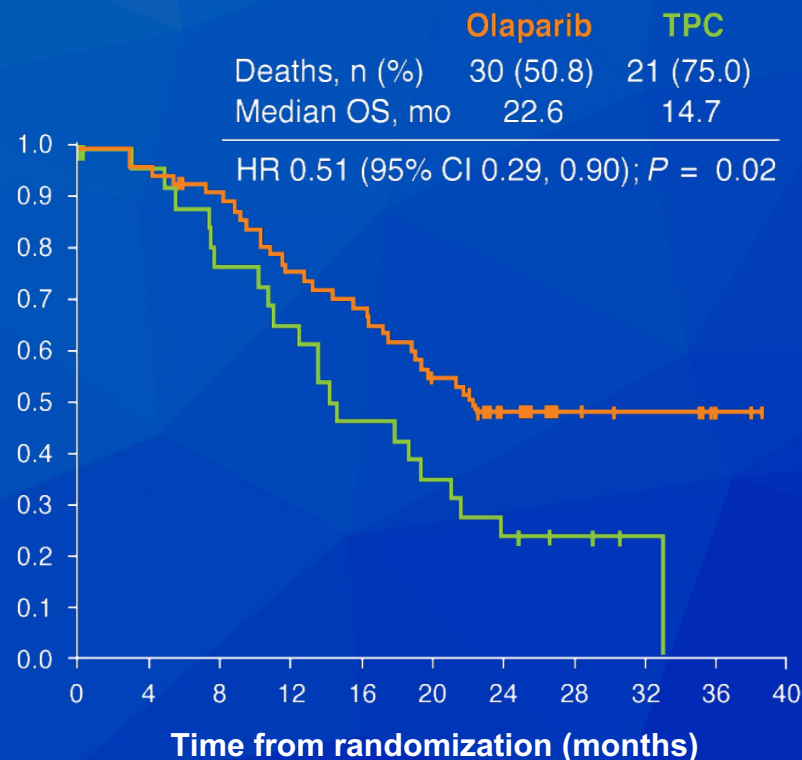
OlympiAD: Final OS Results

Overall Survival

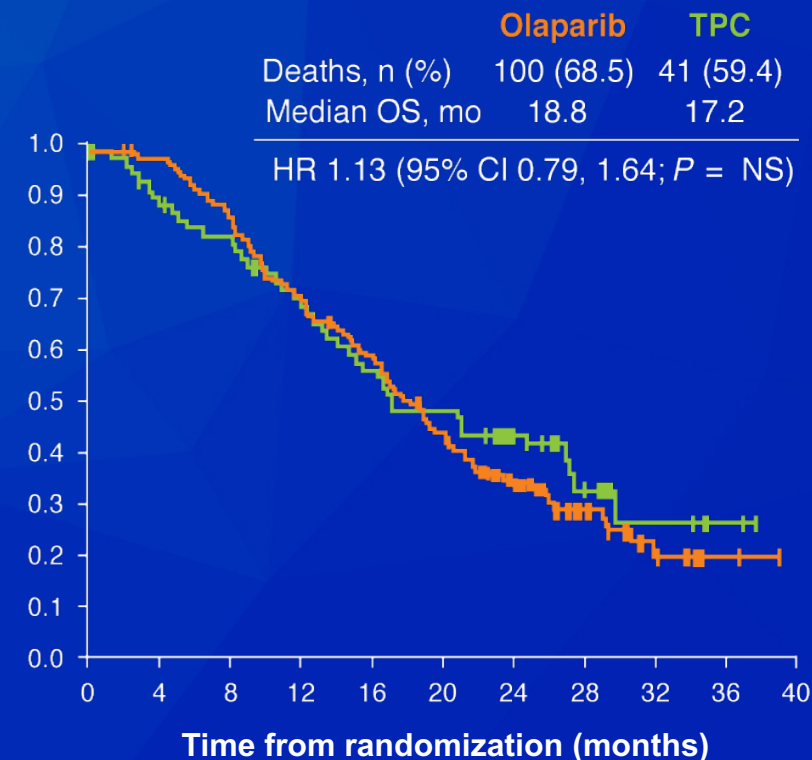
Full Population (n = 205, 97)



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



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



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)

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 Geyer and Krop

HER2-Positive Breast Cancer

Triple-Negative Breast Cancer

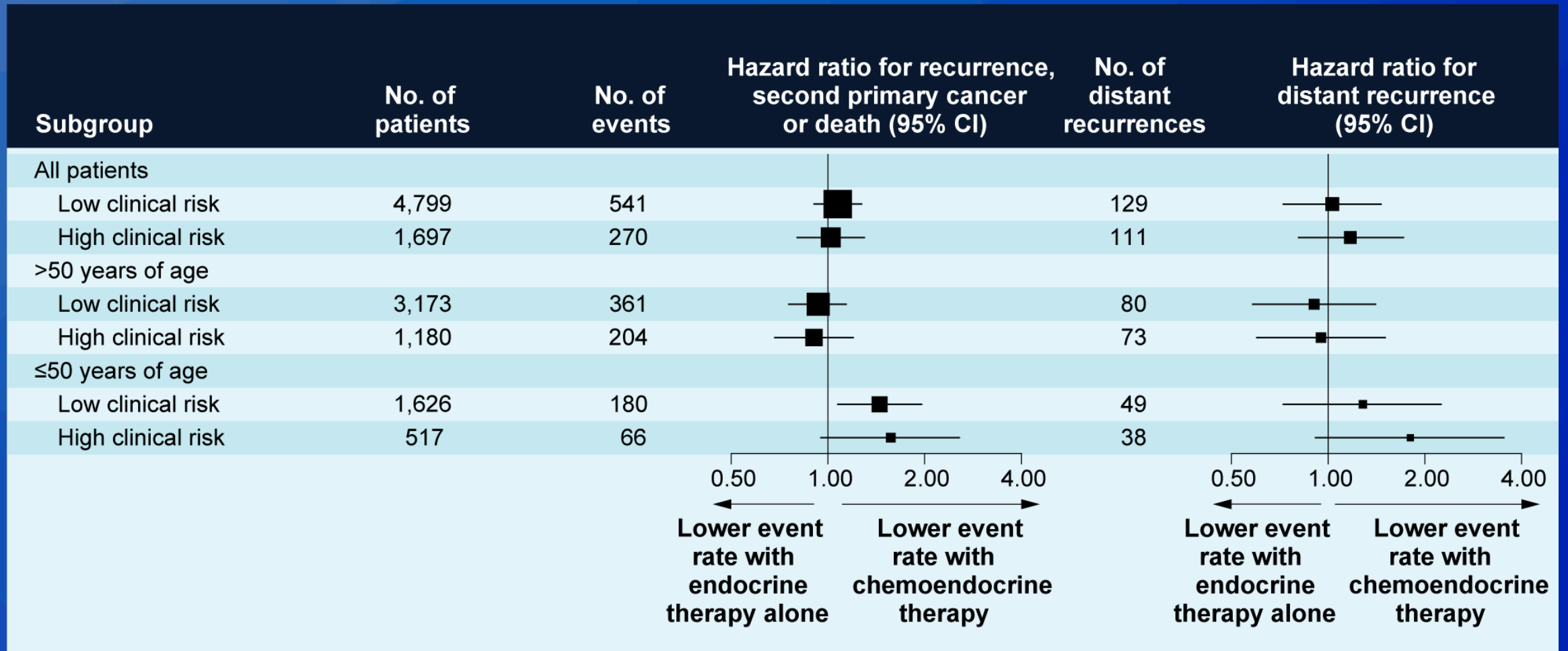
ER-Positive Breast Cancer

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

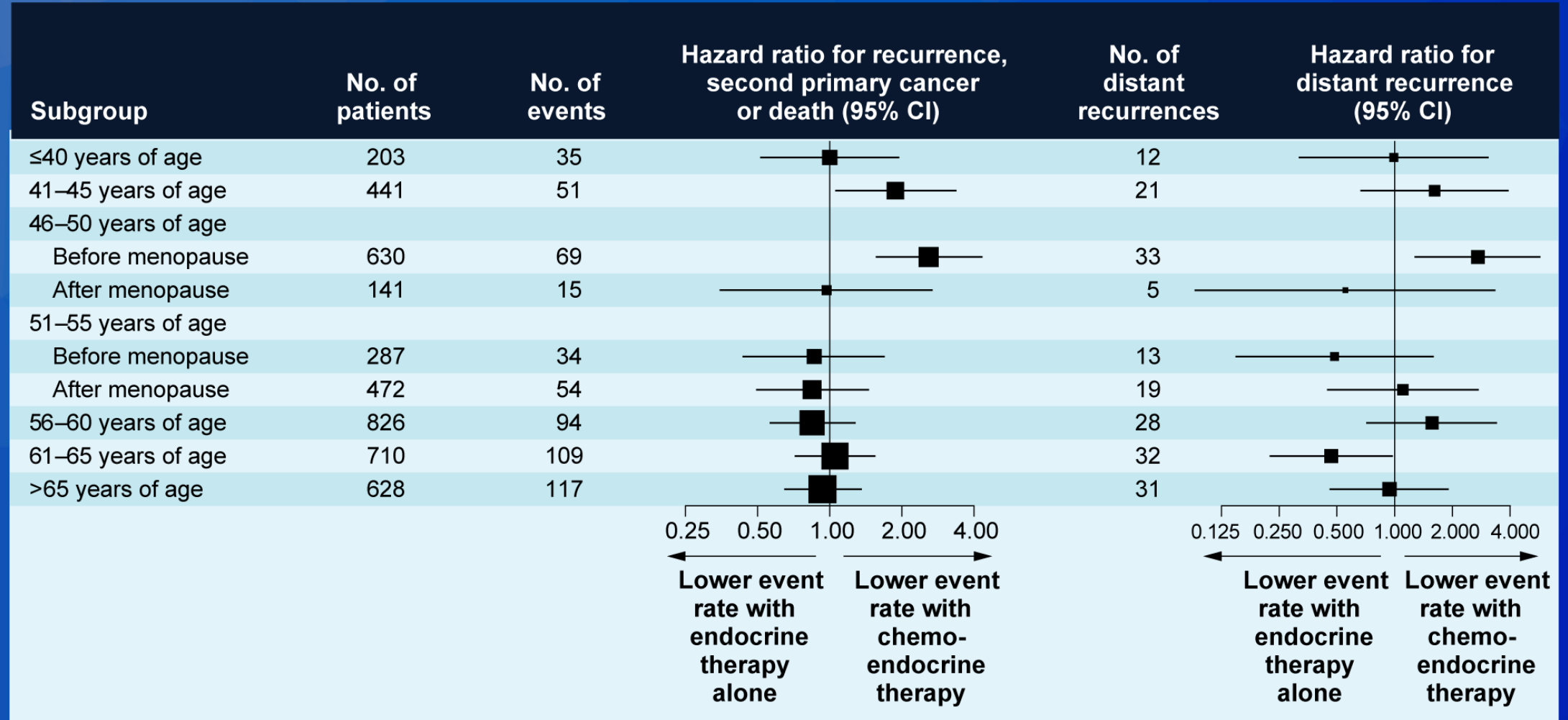
Sparano JA et al.
N Engl J Med 2019;380(25):2395-405.



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



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



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, $p = 0.046$).

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.

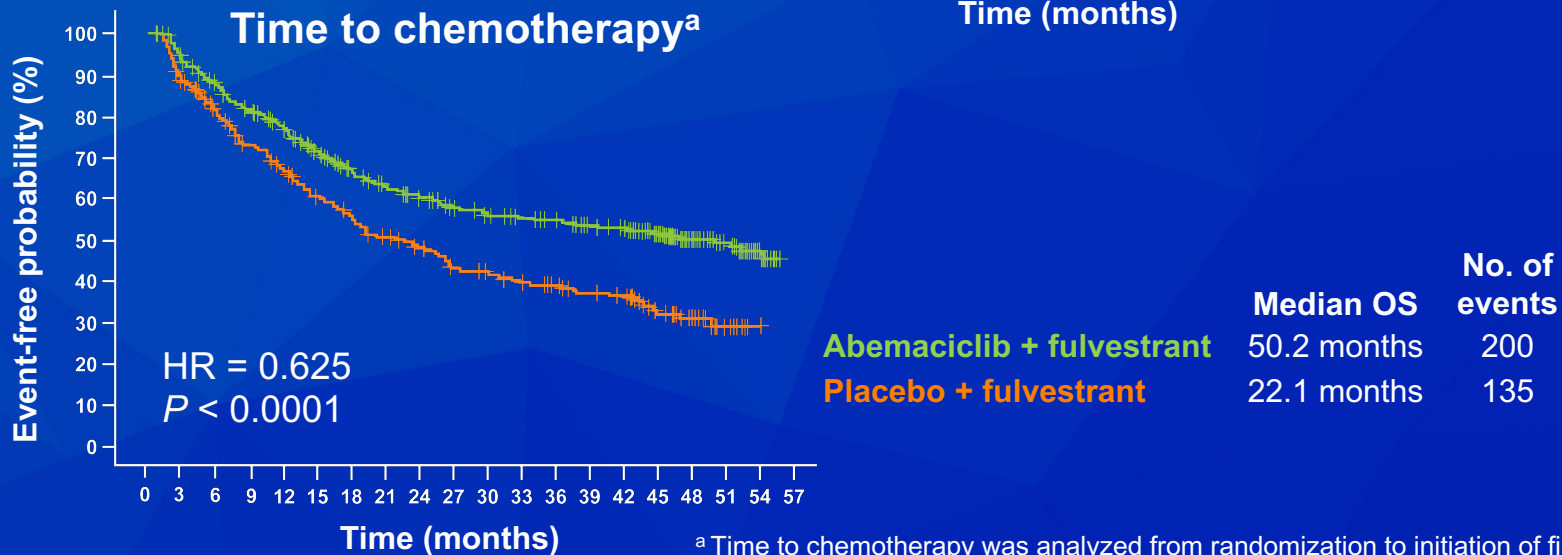
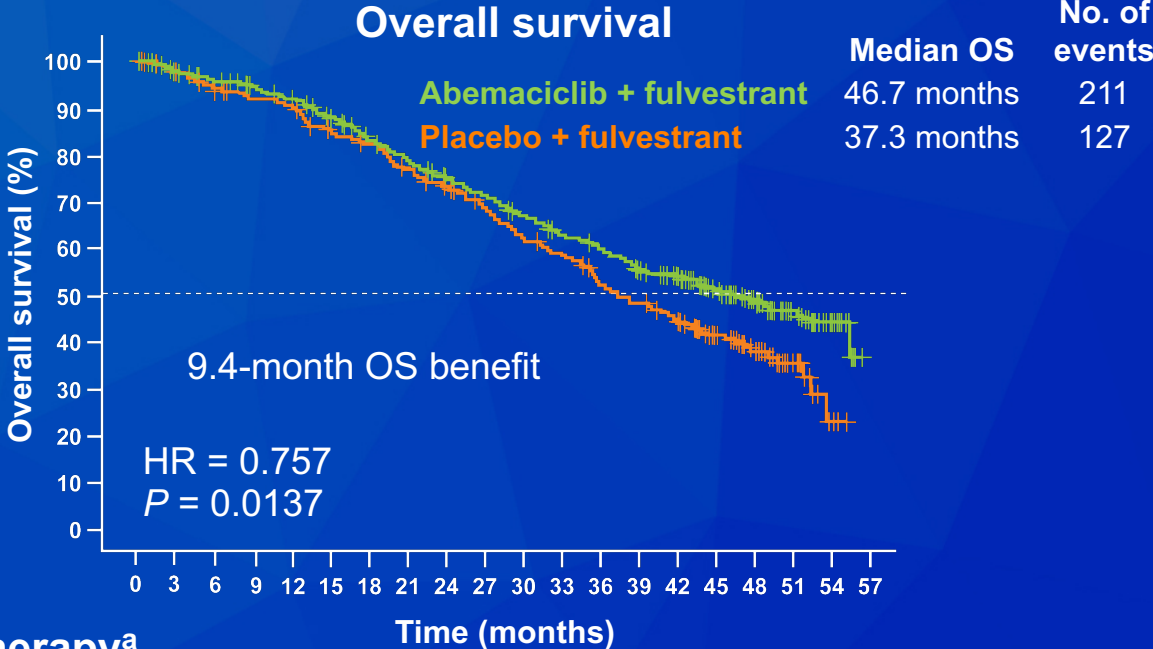
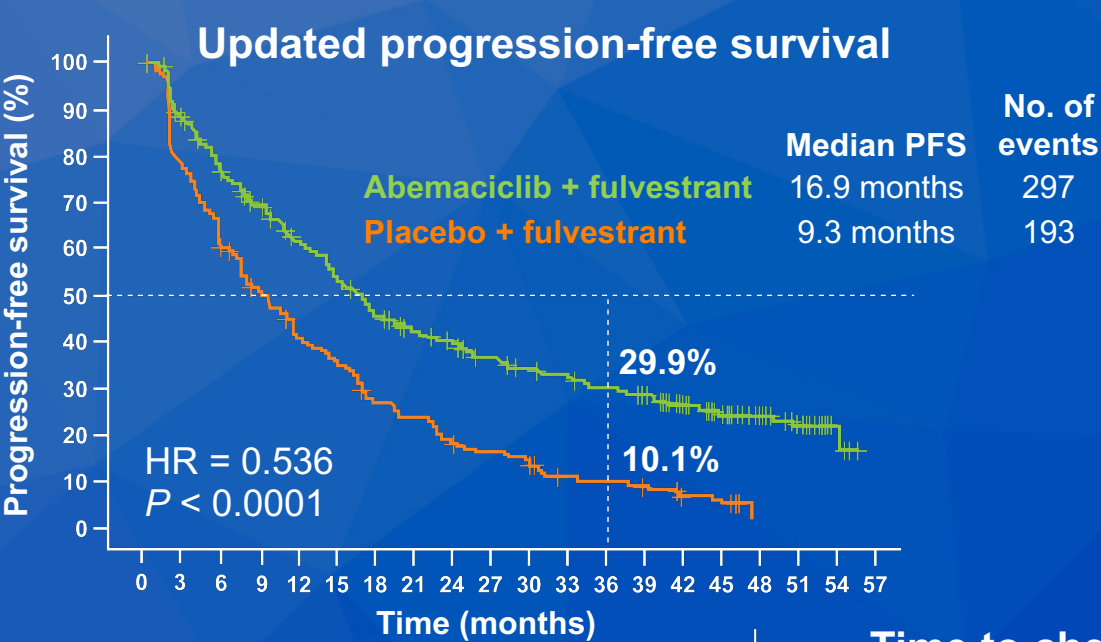
MONARCH 2: Overall Survival of Abemaciclib plus Fulvestrant in Patients with HR+, HER2- Advanced Breast Cancer

Sledge GW et al.

Proc ESMO 2019;Abstract LBA6.



MONARCH 2: Survival Analysis and Time to Treatment with Chemotherapy



^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

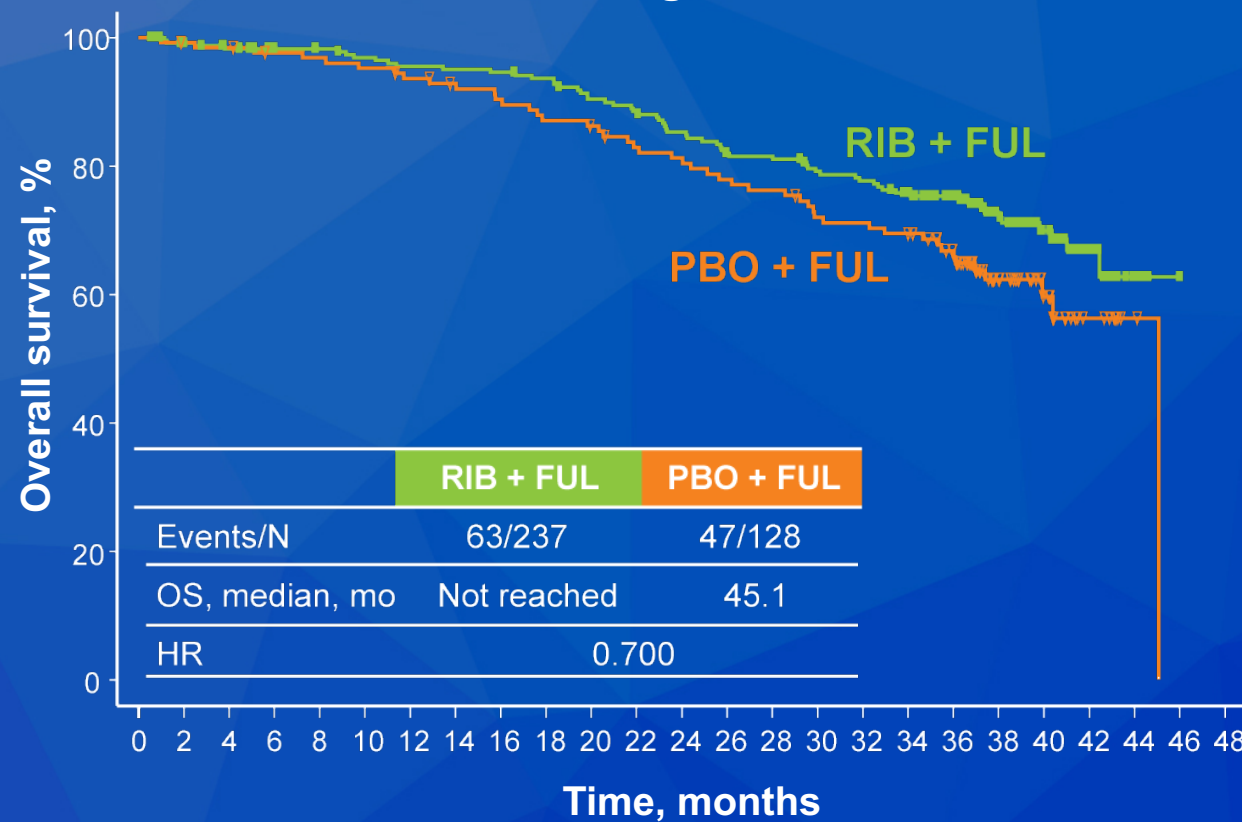
Slamon DJ et al.

N Engl J Med 2019;[Epub ahead of print].

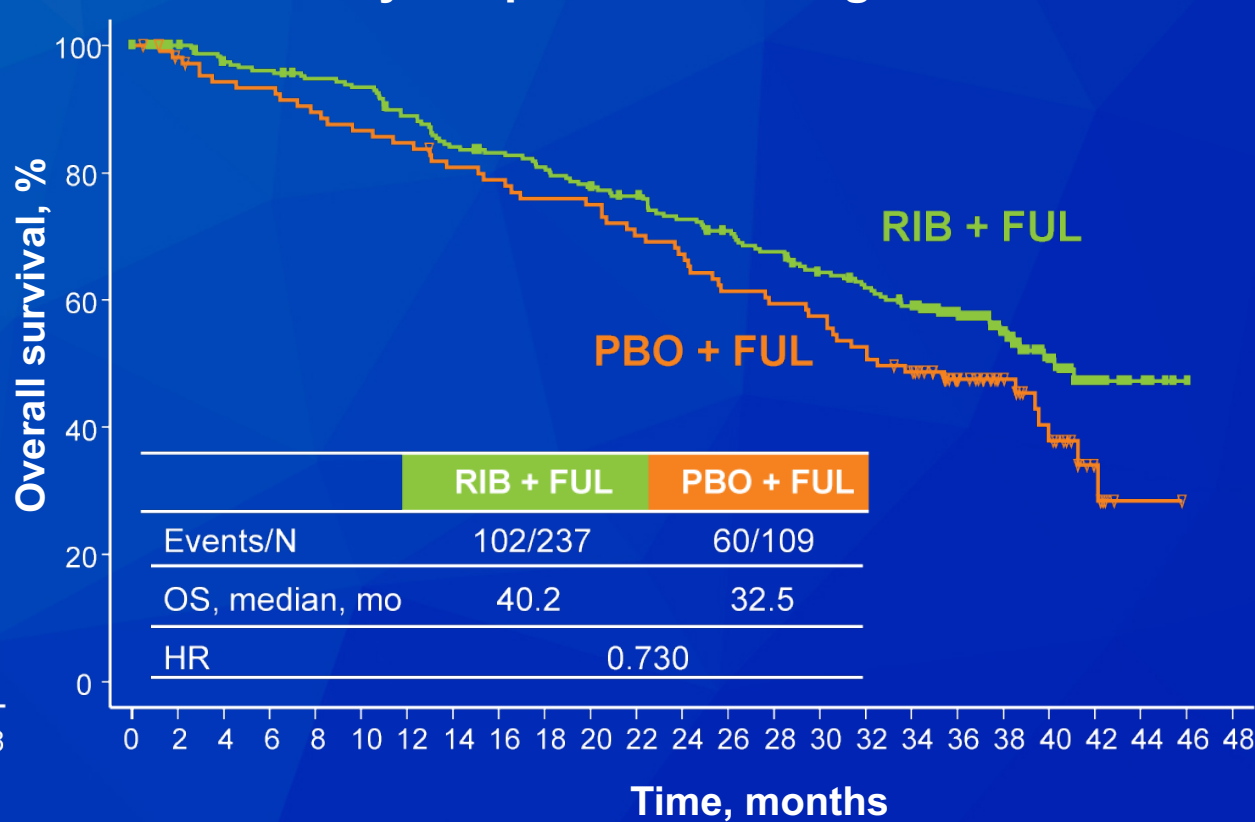


MONALEESA-3: Overall Survival Results

Pts receiving first-line tx



Pts with early relapse or receiving second-line tx



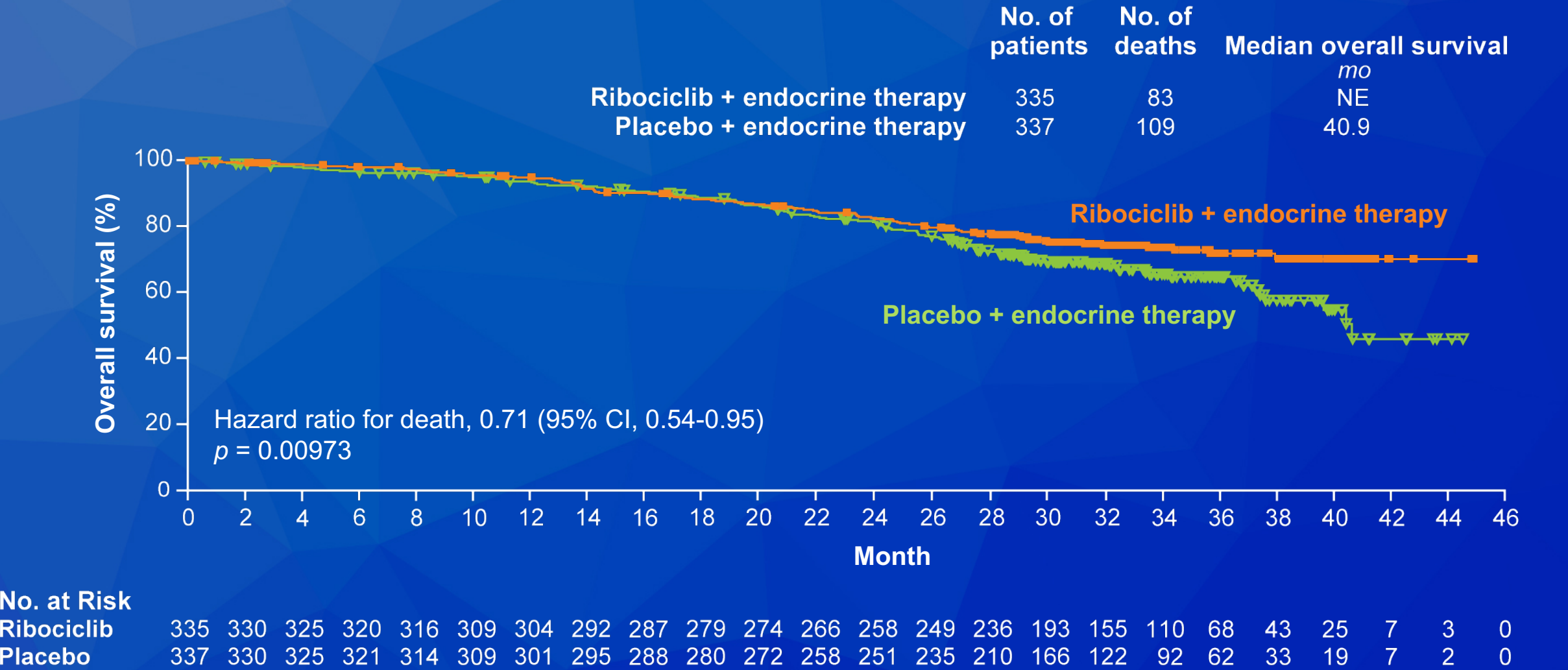
Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer

Im SA et al.

N Engl J Med 2019;381(4):307-16.



MONALEESA-7: Overall Survival Results



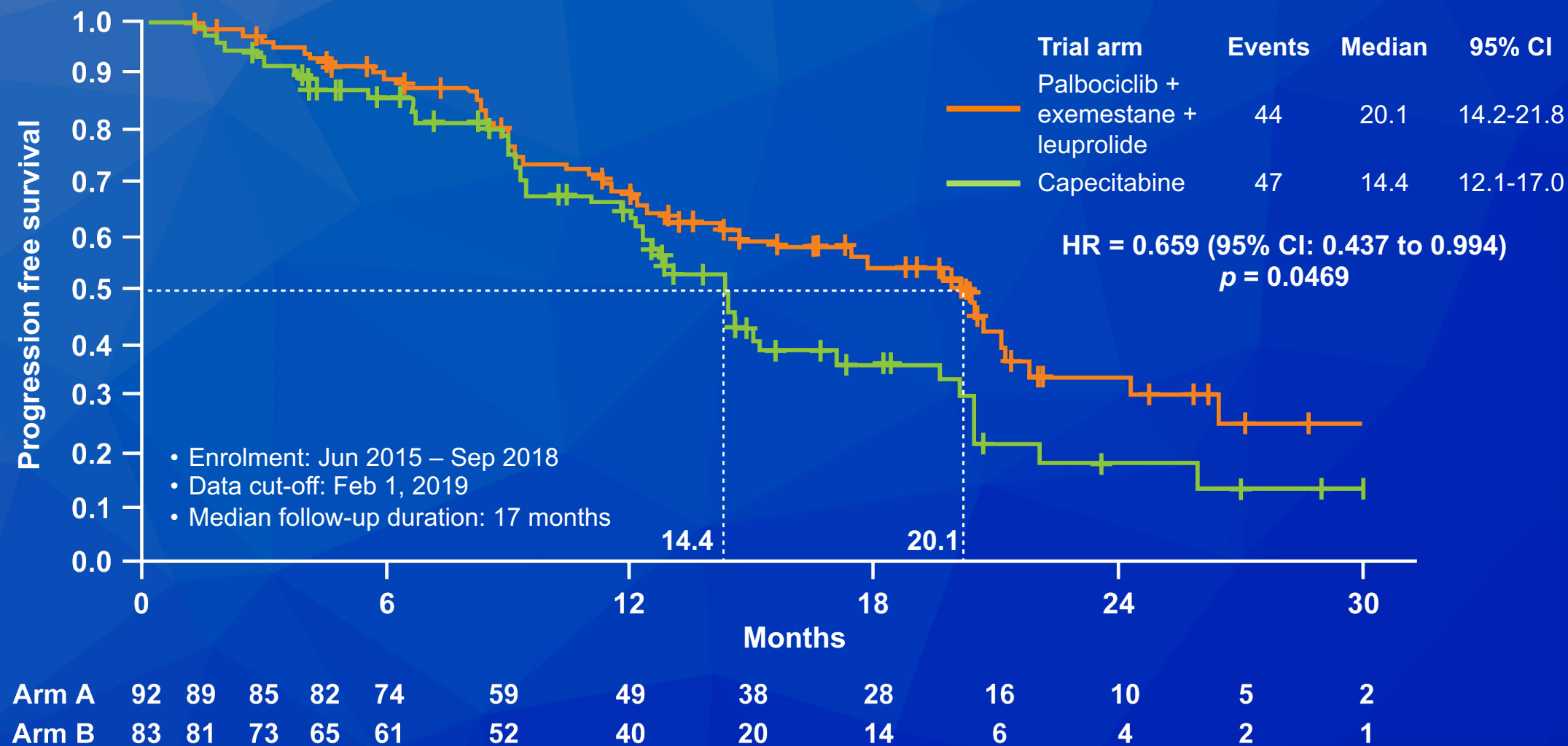
A Randomized Phase II Study of Palbociclib plus Exemestane with GNRH Agonist versus Capecitabine in Premenopausal Women with Hormone Receptor-Positive Metastatic Breast Cancer (KCSG-BR 15-10, NCT02592746)

Park YH et al.

Proc ASCO 2019;Abstract 1007.



KCSG-BR 15-10: Investigator-Assessed PFS



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

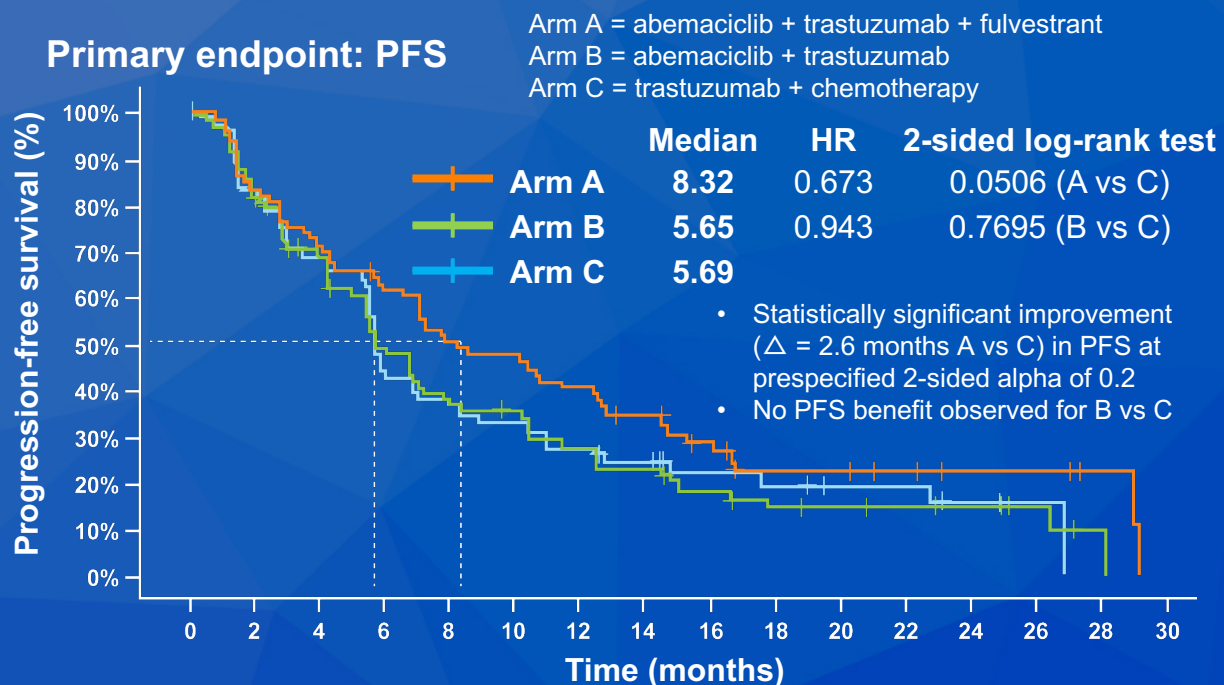
- Most frequent Grade ≥ 3 AEs with EXE+PAL, FUL+PAL and CAPE respectively were neutropenia (57.4%, 55.7% and 5.5%) with febrile neutropenia (1.3%, 0.7% and 1.4%), hand/foot syndrome (0%, 0% and 23.5%) and diarrhea (1.3%, 1.3% and 7.6%)

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.

monarchHER: Progression-Free Survival and Safety Summary

Primary endpoint: PFS



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)

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.”

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.”

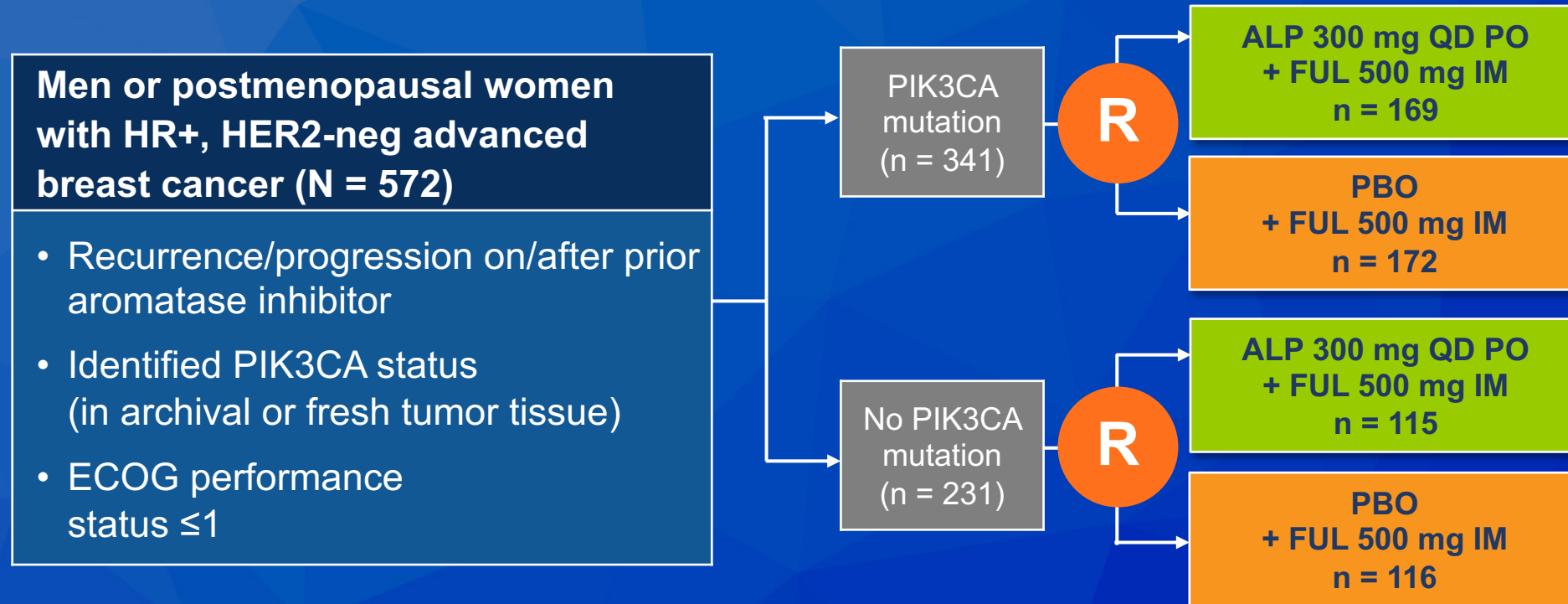
Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer

André F et al.

N Engl J Med 2019;380(20):1929-40.



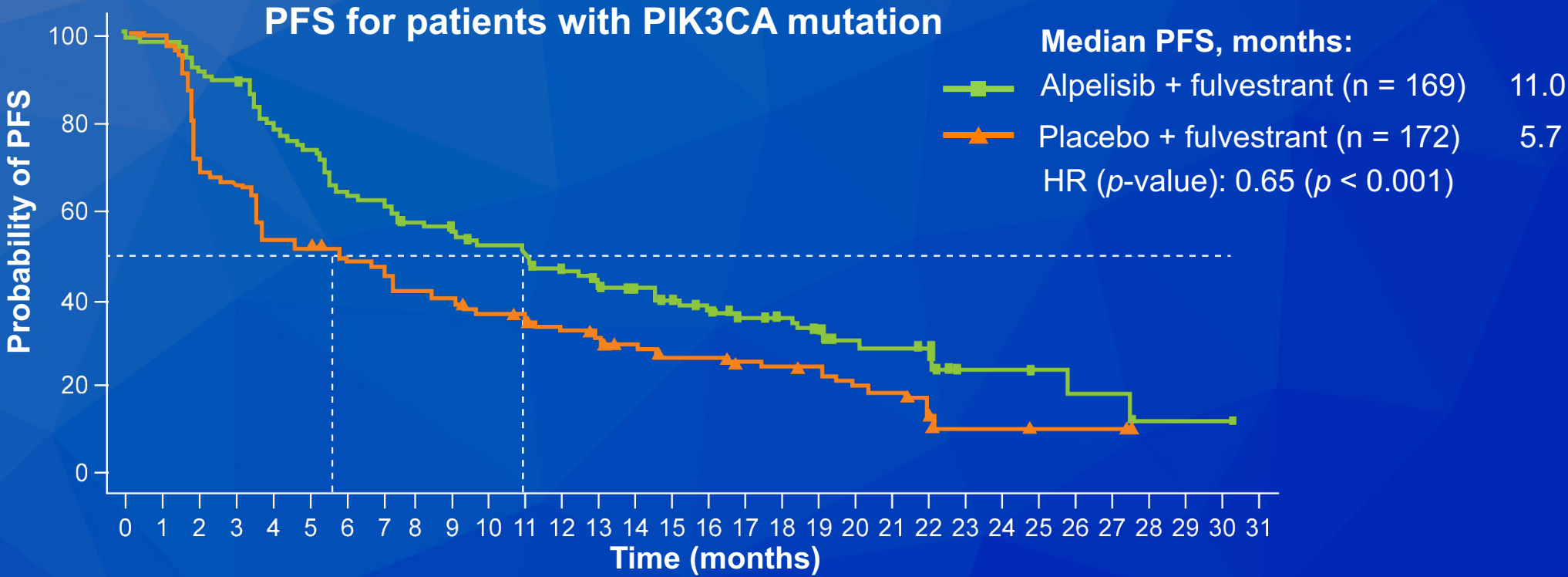
SOLAR-1 Phase III Study Design



IM = intramuscular

Primary endpoint: Locally assessed PFS in PIK3CA mutation cohort

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%

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.