VISITING PROFESSORS
Investigator Perspectives on Recently Approved and Emerging Strategies in the Management of Breast Cancer

An Interactive Grand Rounds Series

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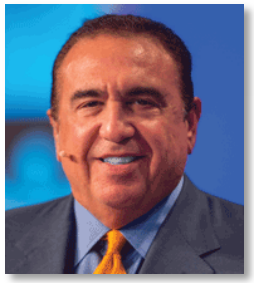

Project Chair
Neil Love, MD
Research To Practice
Miami, Florida

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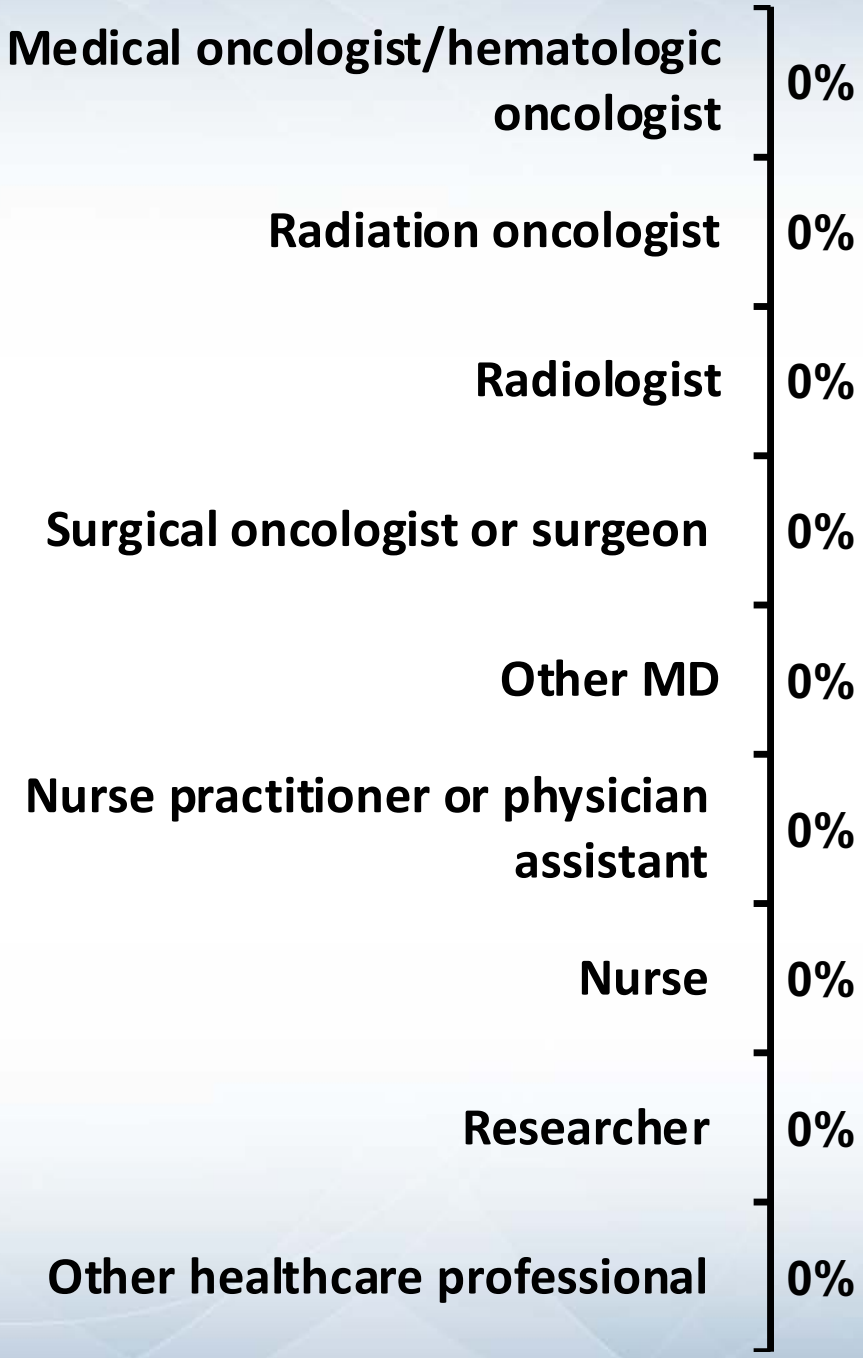
Which of the following best represents your clinical background?

1. Medical oncologist/hematologic oncologist
2. Radiation oncologist
3. Radiologist
4. Surgical oncologist or surgeon
5. Other MD
6. Nurse practitioner or physician assistant
7. Nurse
8. Researcher
9. Other healthcare professional



Investigator Perspectives on Recently Approved and Emerging Strategies in the Management of Breast Cancer

Module 1: Chemotherapy with Immunotherapy as First-Line Treatment for Metastatic Triple-Negative Breast Cancer (TNBC)

- IMpassion130 trial: Atezolizumab/*nab* paclitaxel for untreated advanced TNBC

Module 2: T-DM1 for Residual HER2-Positive Disease After Neoadjuvant Therapy

- KATHERINE trial: T-DM1 for residual invasive HER2-positive breast cancer

Module 3: PARP Inhibitors in Metastatic Breast Cancer

- Somatic and germline BRCA testing
- Olaparib and talazoparib for HER2-negative metastatic breast cancer with germline BRCA mutation (OlympiAD, EMBRACA trials)

Module 4: PI3 Kinase Inhibitors in Hormone Receptor-Positive Metastatic Disease

- SOLAR-1 trial: Alpelisib/fulvestrant for HR-positive advanced disease with PIK3CA mutation

Module 5: Novel HER2-Directed Investigational Approaches

- Tucatinib, margetuximab and trastuzumab deruxtecan

Do you generally evaluate PD-L1 status for your patients with metastatic triple-negative breast cancer? Which assay do you generally use?

	Evaluate PD-L1?	Assay
 HAROLD J BURSTEIN, MD, PHD	Yes, at initial diagnosis of metastatic disease	In-house testing
 CHARLES E GEYER, MD	Yes, at initial diagnosis of metastatic disease	SP142 Assay
 ERIKA HAMILTON, MD	Yes, at initial diagnosis of metastatic disease	SP142 Assay
 SARA A HURVITZ, MD	Yes, at initial diagnosis of metastatic disease	SP142 Assay
 RITA NANDA, MD	Yes, at initial diagnosis of metastatic disease	SP142 Assay
 JOYCE O'SHAUGHNESSY, MD	Yes, at initial diagnosis of metastatic disease	SP142 Assay
 HOPE S RUGO, MD	Yes, at initial diagnosis of metastatic disease	SP142 Assay
 SARAH M TOLANEY, MD, MPH	Yes, at initial diagnosis of metastatic disease	SP142 Assay

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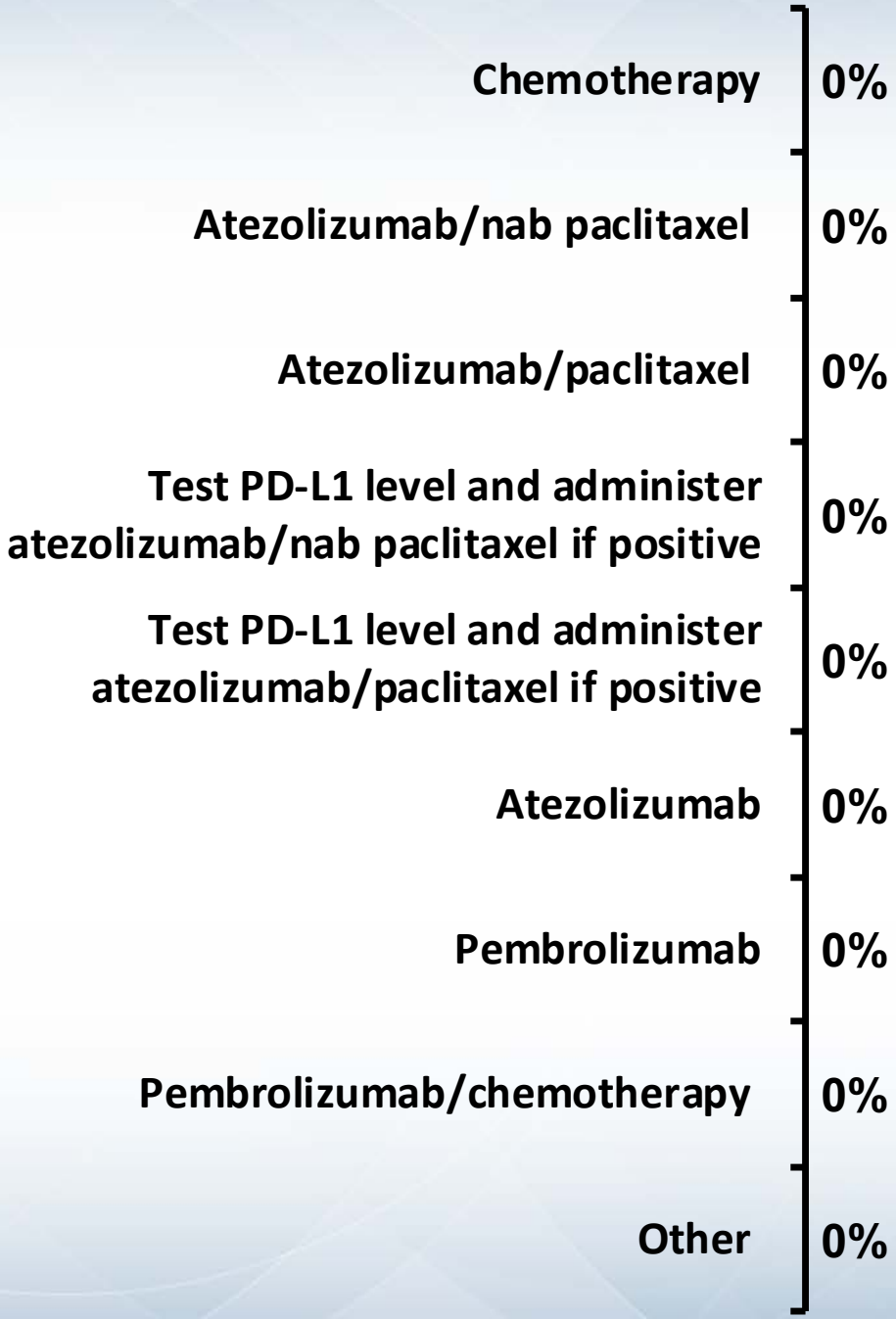
A 60-year-old woman presents with de novo metastatic triple-negative breast cancer (BRCA wild type). Which first-line treatment would you generally recommend?

1. Chemotherapy
2. Atezolizumab/*nab* paclitaxel
3. Atezolizumab/paclitaxel
4. Test PD-L1 level and administer atezolizumab/*nab* paclitaxel if positive
5. Test PD-L1 level and administer atezolizumab/paclitaxel if positive
6. Atezolizumab
7. Pembrolizumab
8. Pembrolizumab/chemotherapy
9. Other



Which first-line treatment would you generally recommend for a woman who presents with de novo metastatic triple-negative breast cancer (BRCA wild type)?

	60 yo	78 yo
 HAROLD J BURSTEIN, MD, PHD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 CHARLES E GEYER, MD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 ERIKA HAMILTON, MD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 SARA A HURVITZ, MD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 RITA NANDA, MD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 JOYCE O'SHAUGHNESSY, MD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 HOPE S RUGO, MD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 SARAH M TOLANEY, MD, MPH	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive

Atezo/*nab*-P = atezolizumab/*nab* paclitaxel

Faculty responses unchanged for pts with diabetes and Grade 1 PN, except for a 78-year-old, Dr Geyer would administer pembro/chemo + CMF, Dr Hurvitz would administer atezo/gem or cape and Dr Tolaney would consider atezo/cape

Which first-line treatment would you generally recommend for a woman who received an adjuvant anthracycline/taxane regimen and presents 1 year later with metastatic triple-negative breast cancer (BRCA wild type)?

	60 yo	78 yo
 HAROLD J BURSTEIN, MD, PHD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 CHARLES E GEYER, MD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 ERIKA HAMILTON, MD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 SARA A HURVITZ, MD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 RITA NANDA, MD	Test PD-L1; atezo/paclitaxel if positive	Test PD-L1; atezo/*nab*-P if positive
 JOYCE O'SHAUGHNESSY, MD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 HOPE S RUGO, MD	Test PD-L1; atezo/*nab*-P if positive	Test PD-L1; atezo/*nab*-P if positive
 SARAH M TOLANEY, MD, MPH	Test PD-L1; atezo/carbo or pembro/eribulin if positive	Test PD-L1; atezo/carbo or pembro/eribulin if positive

Atezo/*nab*-P = atezolizumab/*nab* paclitaxel; carbo = carboplatin; pembro = pembrolizumab

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FDA Approval of Atezolizumab for PD-L1-Positive Unresectable Advanced TNBC

Press Release – March 8, 2019

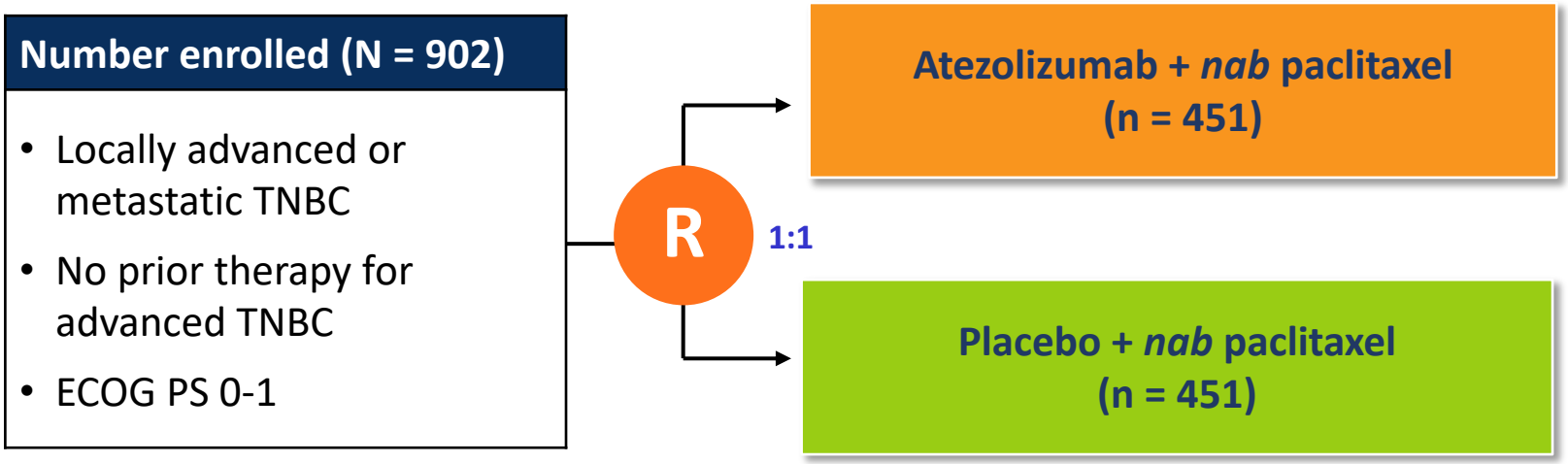
"On March 8, 2019, the Food and Drug Administration granted accelerated approval to atezolizumab in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test.

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/InformationOnDrugs/ApprovedDrugs/ucm633065.htm.

IMpassion130: A Phase III Study of Atezolizumab in Combination with *Nab* Paclitaxel for Untreated Advanced TNBC



Stratification factors: Prior (curative setting) taxane use (yes vs no); liver metastases (yes vs no); PD-L1 IC status (positive [≥1%] vs negative [<1%])

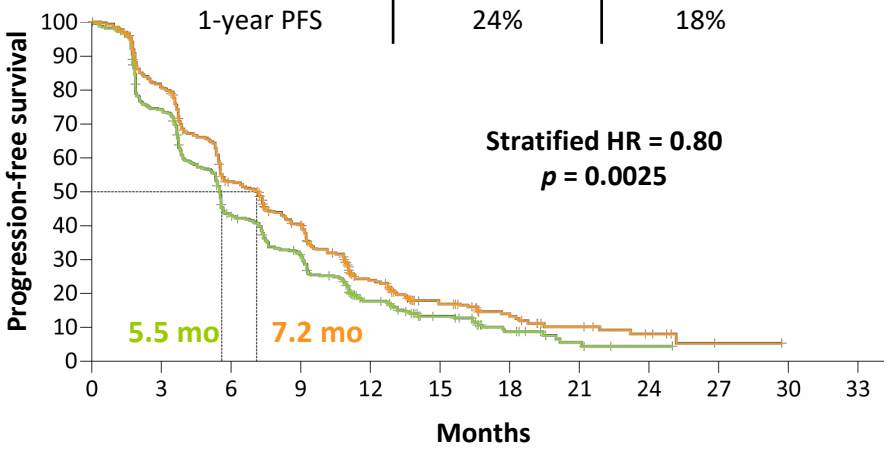
Primary endpoints: PFS and OS in ITT and in PD-L1-positive population

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

IMpassion130: PFS Results

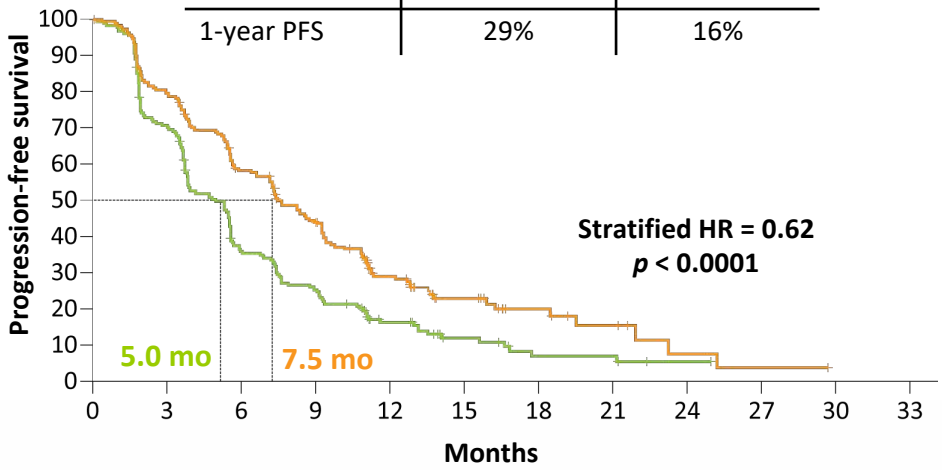
Primary PFS analysis: ITT population

	Atezo + *nab*-P (n = 451)	Plac + *nab*-P (n = 451)
PFS events, n	358	378
1-year PFS	24%	18%



Primary PFS analysis: PD-L1+ population

	Atezo + *nab*-P (n = 185)	Plac + *nab*-P (n = 184)
PFS events, n	138	157
1-year PFS	29%	16%

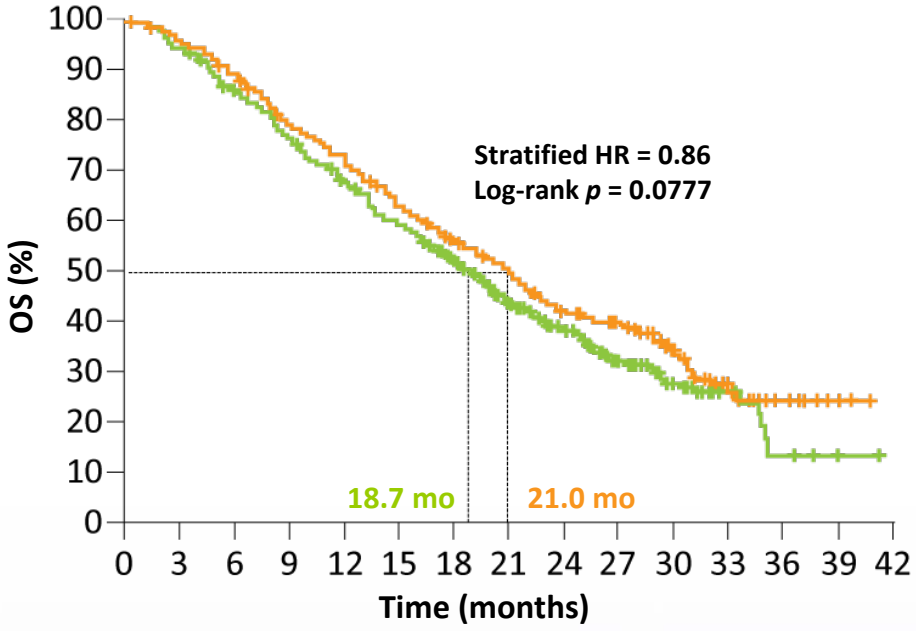


Schmid P et al. *N Engl J Med* 2018;379(22):2108-21; Schmid P et al. *Proc ESMO* 2018;Abstract LBA1_PR.

IMpassion130: Updated OS Results

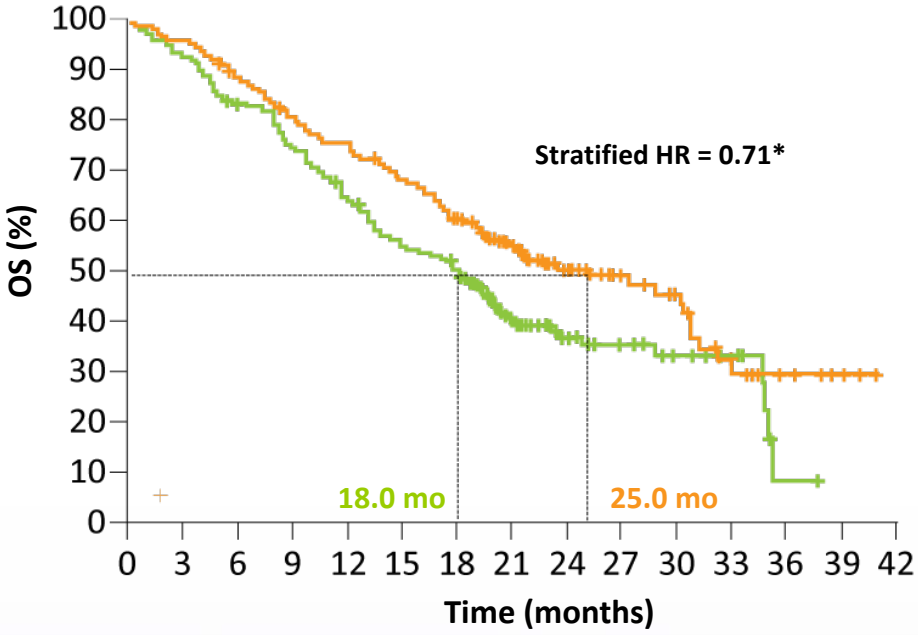
Updated OS analysis: ITT population

	Atezo + *nab*-P (n = 451)	Plac + *nab*-P (n = 451)
24-month OS rate	42%	39%



Updated OS analysis: PD-L1+ population

	Atezo + *nab*-P (n = 185)	Plac + *nab*-P (n = 184)
24-month OS rate	51%	37%



* Not formally tested because of prespecified hierarchical analysis plan

Schmid P et al. ASCO 2019;Abstract 1003.

IMpassion130: Key Adverse Events of Special Interest Suggestive of Immune-Related Etiology

All-grade AEs	Atezolizumab + *nab*-P (n = 452)	Placebo + *nab*-P (n = 438)
Hepatitis	15%	14%
Hypothyroidism	17%	4%
Hyperthyroidism	4%	1%
Pneumonitis	3%	<1%
Colitis	1%	1%
Rash	34%	26%

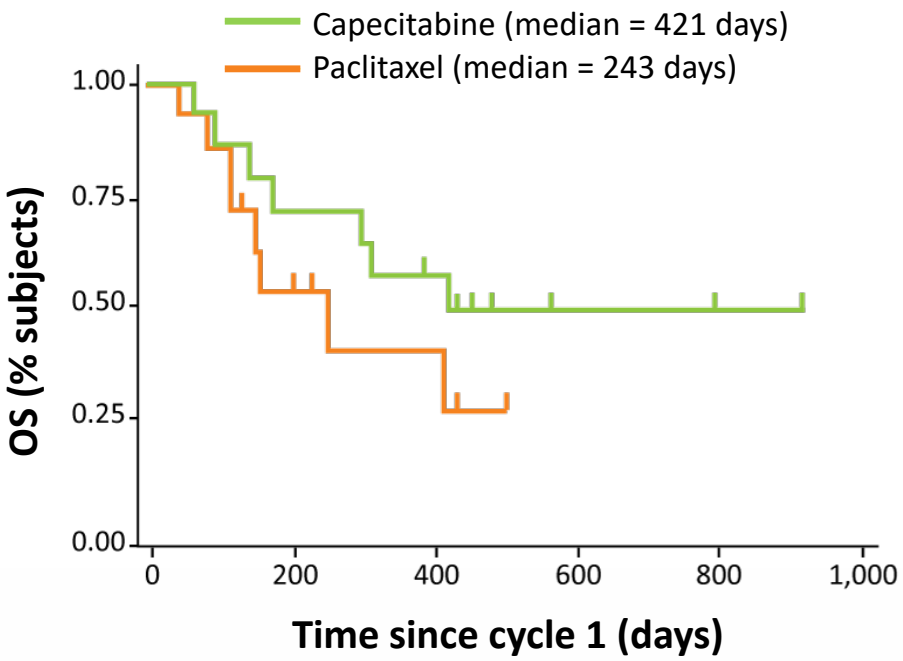
- 1 Grade 5 AE of special interest per arm (both related to hepatitis or hepatic failure)
- All hypothyroidism AEs of special interest were Grade 1-2; none led to discontinuation
- Pneumonitis was infrequent with only 1 Grade 3-4 event in the Atezo + *nab*-P arm

Schmid P et al. *Proc ESMO* 2018;Abstract 2056.

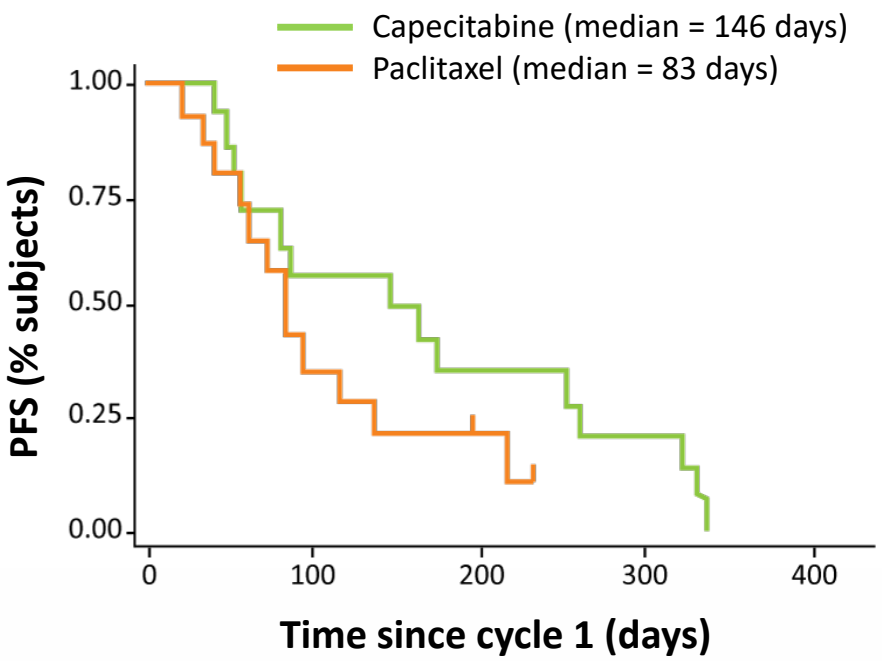
First- or Second-Line Pembrolizumab with Paclitaxel or Capecitabine for mTNBC

- Week 12 ORR (primary efficacy endpoint): 43% (capecitabine) and 23% (paclitaxel)

OS estimate by arm (n = 29)



PFS estimate by arm (n = 29)



- Common toxicities associated with capecitabine included hand-foot syndrome (86%), diarrhea (92%) and fatigue (57%), manageable with dose reduction
- Common toxicities associated with paclitaxel included fatigue (50%), nausea (43%) and neuropathy (43%)

Page DB et al. ASCO 2019;Abstract 1015.

Select Ongoing Phase III Trials of Immune Checkpoint Inhibitor-Based Therapies for TNBC

Trial	N	Entry criteria (TNBC)	Randomization
KEYNOTE-355 (NCT02819518)	882	Previously untreated, locally recurrent inoperable or metastatic	• Pembrolizumab + chemotherapy • Placebo + chemotherapy
IMpassion131 (NCT03125902)	600	Previously untreated, inoperable locally advanced or metastatic	• Atezolizumab + paclitaxel • Placebo + paclitaxel
IMpassion132 (NCT03371017)	350	Early-relapsing recurrent (inoperable locally advanced or metastatic)	• Atezolizumab + chemotherapy • Placebo + chemotherapy
KEYSTONE (NCT03777579)	375	Previously untreated, metastatic	• JS001 + *nab* paclitaxel • Placebo + *nab* paclitaxel

www.clinicaltrials.gov. Accessed August 2019.

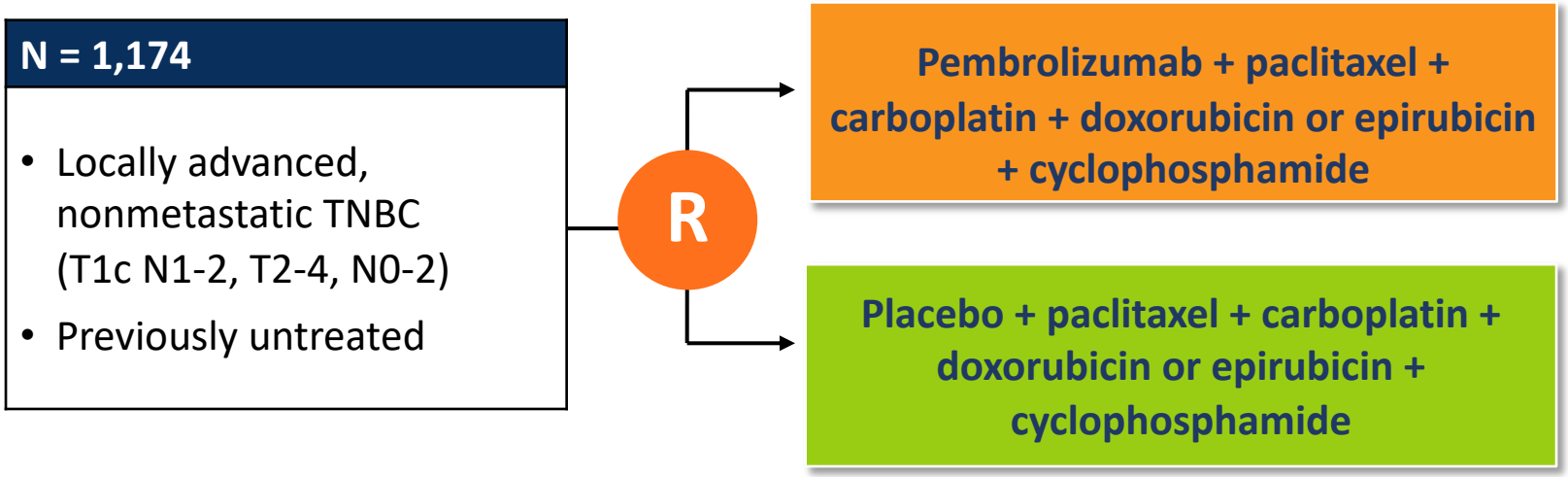
Select Ongoing Phase III Trials of Immune Checkpoint Inhibitor-Based Therapies in Earlier Lines of Therapy

Trial	N	Entry criteria	Randomization
NSABP-B-59/GBG-96-GeparDouze (NCT03281954)	1,520	(Neo)adjuvant, early-stage TNBC	• Atezolizumab + chemotherapy → atezolizumab • Placebo + chemotherapy → placebo
KEYNOTE-756 (NCT03725059)	1,140	(Neo)adjuvant, high-risk, early-stage ER-positive, HER2-negative BC	• Pembrolizumab + chemotherapy → pembrolizumab + ET • Placebo + chemotherapy → placebo + ET
IMpassion050 (NCT03726879)	224	(Neo)adjuvant, early-stage HER2-positive BC	• Atezolizumab + ddAC → paclitaxel/trastuzumab/pertuzumab • Placebo + ddAC → paclitaxel/trastuzumab/pertuzumab
A-Brave (NCT02926196)	335	(Neo)adjuvant, high-risk TNBC	• Avelumab • Observation
IMpassion030 (NCT03498716)	2,300	Adjuvant, operable TNBC	• Atezolizumab + chemotherapy • Chemotherapy
IMpassion031 (NCT03197935)	324	Neoadjuvant, early-stage TNBC	• Atezolizumab + chemotherapy • Placebo + chemotherapy

ET = endocrine therapy; dd = dose-dense

www.clinicaltrials.gov. Accessed August 2019.

KEYNOTE-522: A Phase III Trial of Neoadjuvant Chemotherapy with Pembrolizumab or Placebo followed by Adjuvant Pembrolizumab or Placebo in TNBC



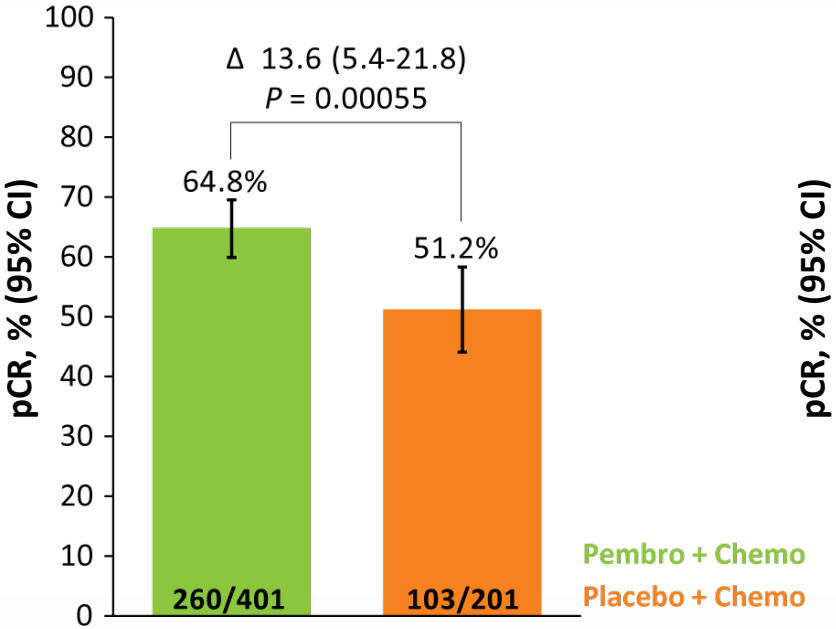
Stratification factors: Tumor nodal status (positive or negative), size (T1/T2 vs T3/T4) and carboplatin choice (q3wk vs qwk)

Primary endpoints: pCR rate and event-free survival

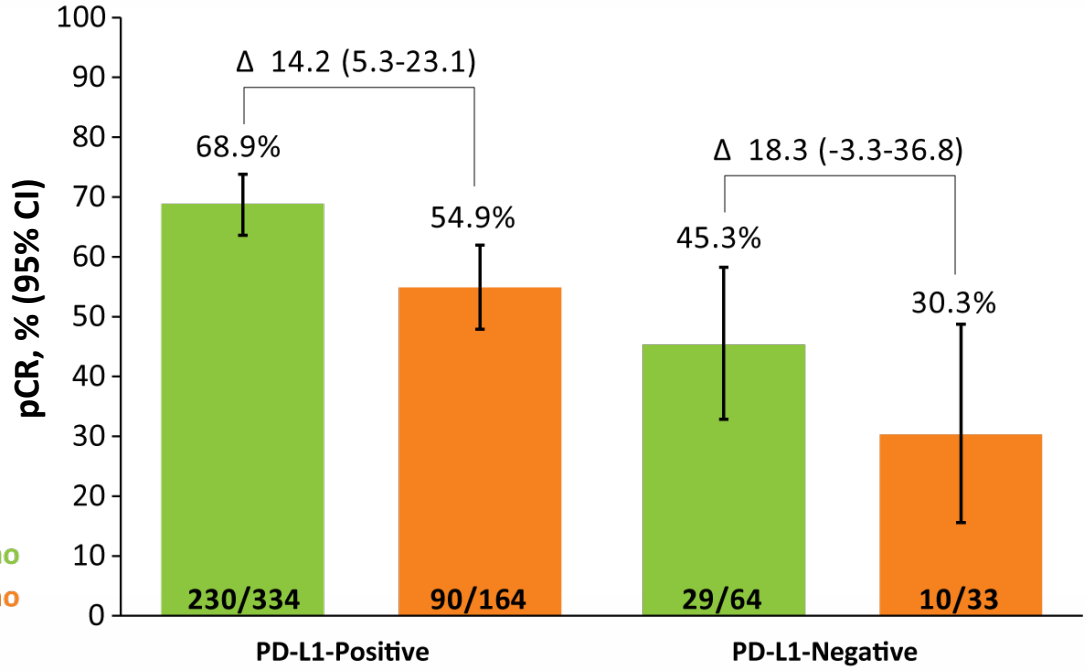
Schmid P et al. *Proc ESMO* 2017;Abstract 233TiP; *Proc ASCO* 2018;Abstract TPS602. www.clinicaltrials.gov (NCT03036488)

KEYNOTE-522: Pathologic Complete Response at First Interim Analysis*

Primary Endpoint: ypT0/Tis ypN0



By PD-L1 Status: ypT0/Tis ypN0



* Primary pCR analysis to test primary hypothesis of pCR based on prespecified first 602 subjects (pre-calculated *p*-value boundary for significance of 0.003)

At this early timepoint, a favorable trend is apparent for event-free survival with pembrolizumab (HR 0.63)

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

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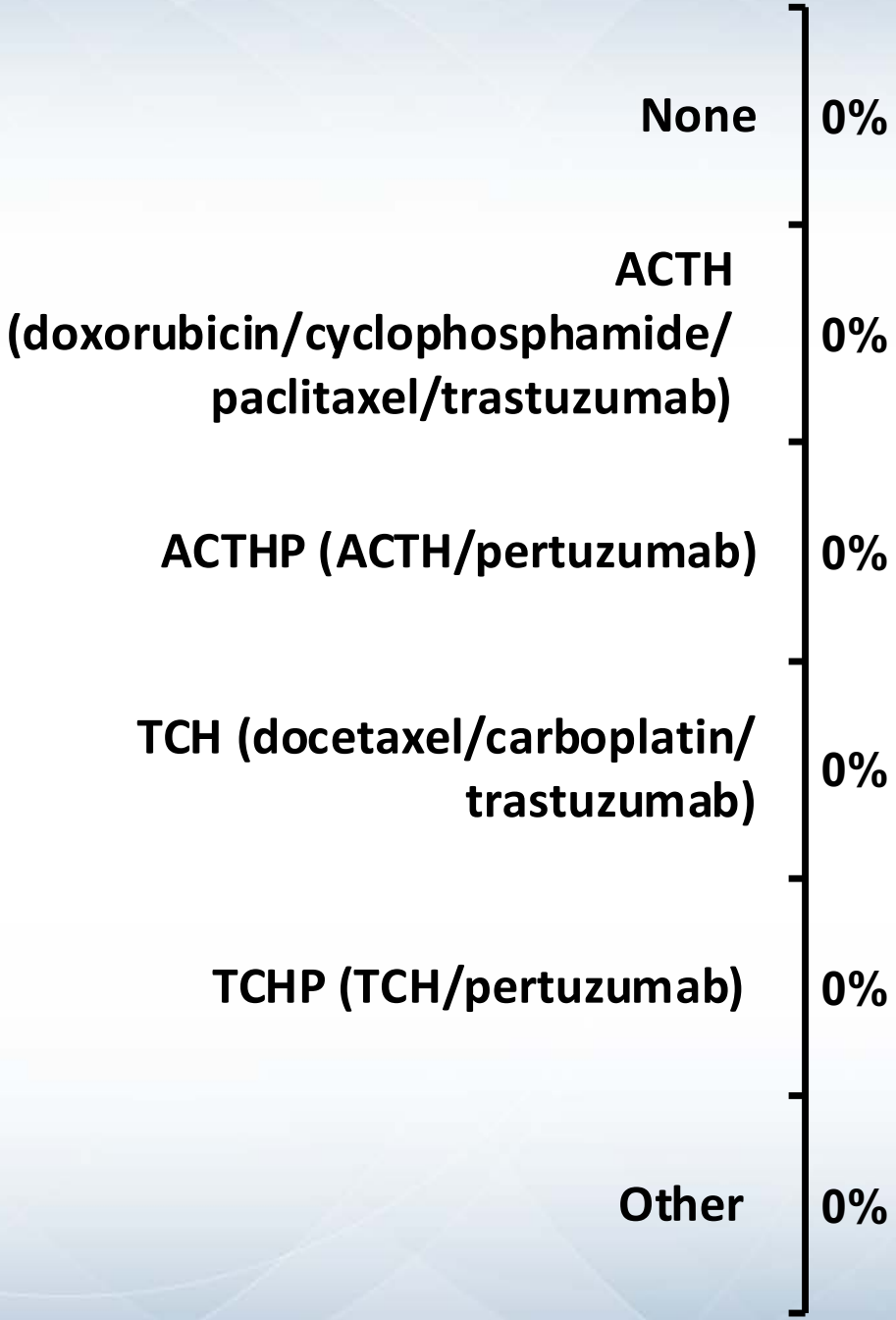
- SOLAR-1 trial: Alpelisib/fulvestrant for HR-positive advanced disease with PIK3CA mutation

Module 5: Novel HER2-Directed Investigational Approaches

- Tucatinib, margetuximab and trastuzumab deruxtecan

Which neoadjuvant systemic therapy, if any, do you generally recommend for a patient with a 1.4-cm, ER-negative, HER2-positive IDC with 3 axillary nodes that are positive on biopsy?

1. None
2. ACTH (doxorubicin/cyclophosphamide/paclitaxel/trastuzumab)
3. ACTHP (ACTH/pertuzumab)
4. TCH (docetaxel/carboplatin/trastuzumab)
5. TCHP (TCH/pertuzumab)
6. Other



Which neoadjuvant systemic therapy, if any, do you generally recommend for a patient with an ER-negative, HER2-positive IDC with the following tumor size and nodal status?

	1.4-cm, N-	1.4-cm, N3+	2.4-cm, N-	3.4-cm, N-
 HAROLD J BURSTEIN, MD, PHD	None	TCHP	TCHP	TCHP
 CHARLES E GEYER, MD	THP	ACTHP or TCHP	ACTHP or TCHP	ACTHP or TCHP
 ERIKA HAMILTON, MD	TCH	TCHP	TCHP	TCHP
 SARA A HURVITZ, MD	TCH	TCHP	TCHP	TCHP
 RITA NANDA, MD	None	THP-AC	THP-AC	THP-AC
 JOYCE O'SHAUGHNESSY, MD	TCH	TCHP	TCHP	TCHP
 HOPE S RUGO, MD	THP*	TCHP or ACTHP	TCHP	TCHP
 SARAH M TOLANEY, MD, MPH	None	TCHP	TCHP	TCHP

THP = docetaxel/trastuzumab/pertuzumab

* If pCR continue HP alone after surgery

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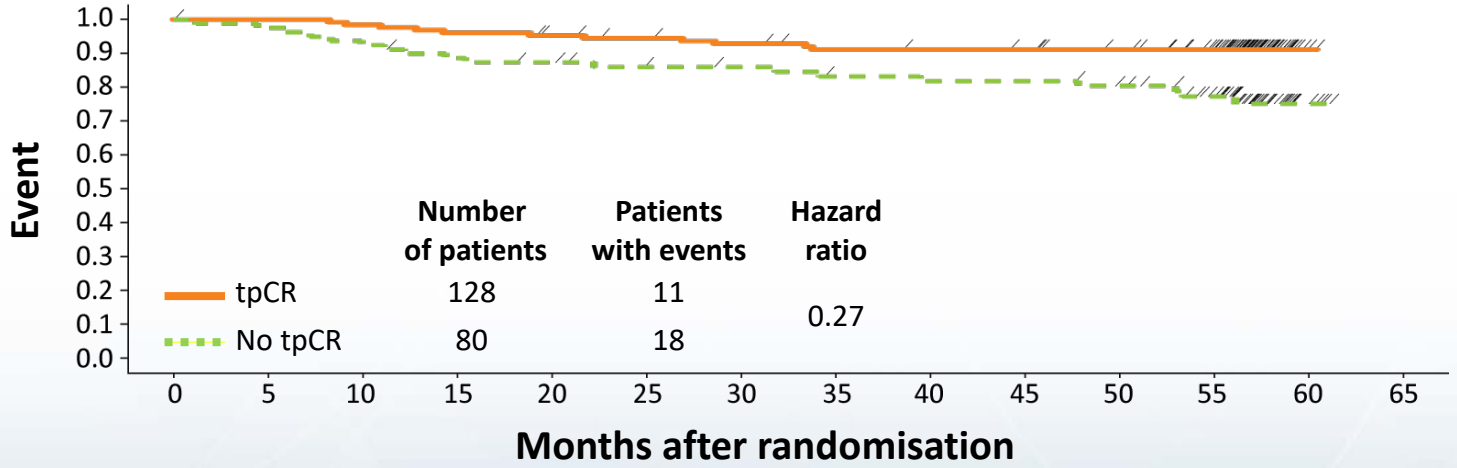
Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer

Scheeweiss A et al. *Eur J Cancer* 2018;89:27-35.

Outcomes with the Use of Anthracycline- and Nonanthracycline-Based NST and Prognosis for Patients Who Experience a Total Pathologic CR (tpCR) Compared to Those Who Do Not

	T + P + FEC + D	FEC → T + P + D	T + P + D + C
3-year DFS (n = 69, 67, 72)	87%	88%	90%
3-year PFS (n = 73, 75, 77)	89%	89%	87%
3-year OS (n = 73, 75, 77)	94%	94%	93%
Any grade left ventricular systolic dysfunction* (n = 72, 75, 76)	2.8%	4%	5.4%
LVEF declines ≥10% from baseline to <50% (n = 72, 75, 76)	11.1%	16%	11.8%

DFS for patients with and without tpCR across treatment groups



T = trastuzumab; P = pertuzumab; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; D = docetaxel; C = carboplatin

* During post-treatment follow-up

Schneeweiss A et al. *Eur J Cancer* 2018;89:27-35.

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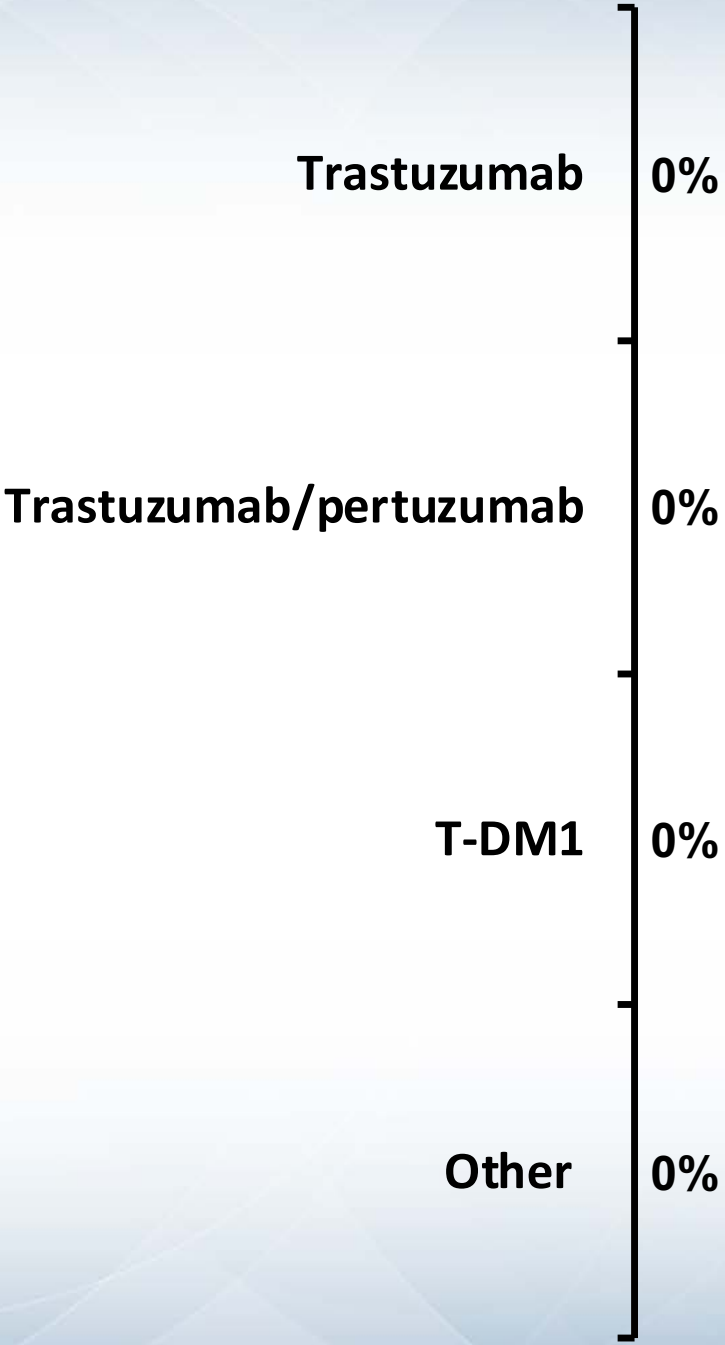
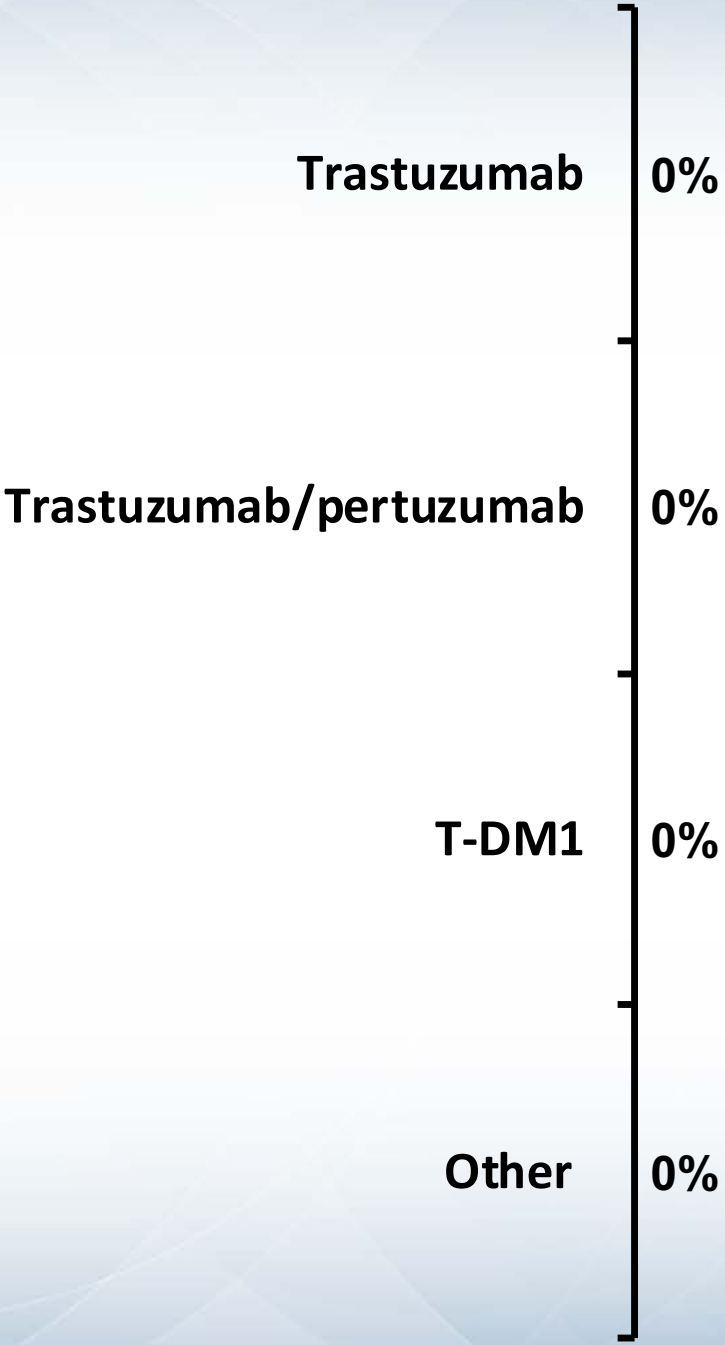
A 65-year-old woman presents with a 3.4-cm, ER-negative, HER2-positive IDC with biopsy-proven positive axillary nodes, receives neoadjuvant TCHP and at surgery is found to have significant residual disease in the breast and axilla. Which adjuvant anti-HER2 therapy would you generally recommend?

1. **Trastuzumab**
2. **Trastuzumab/pertuzumab**
3. **T-DM1**
4. **Other**



A 65-year-old woman presents with a 3.4-cm, ER-negative, HER2-positive IDC with biopsy-proven positive axillary nodes, receives neoadjuvant TCHP and at surgery is found to have a pathologic complete response. Which adjuvant anti-HER2 therapy would you generally recommend?

1. **Trastuzumab**
2. **Trastuzumab/pertuzumab**
3. **T-DM1**
4. **Other**



Which adjuvant anti-HER2 therapy would you generally recommend for a 65-year-old woman with a 3.4-cm, ER-negative, HER2-positive IDC with biopsy-proven positive axillary nodes who receives neoadjuvant TCHP and at surgery is found to have the following disease status in the breast and axilla?

	Significant residual disease	Pathologic complete response
 HAROLD J BURSTEIN, MD, PHD	T-DM1	Trastuzumab/pertuzumab
 CHARLES E GEYER, MD	T-DM1	Trastuzumab/pertuzumab
 ERIKA HAMILTON, MD	T-DM1	Trastuzumab/pertuzumab
 SARA A HURVITZ, MD	T-DM1	Trastuzumab/pertuzumab
 RITA NANDA, MD	T-DM1	Trastuzumab/pertuzumab
 JOYCE O'SHAUGHNESSY, MD	T-DM1	Trastuzumab/pertuzumab
 HOPE S RUGO, MD	T-DM1	Trastuzumab/pertuzumab
 SARAH M TOLANEY, MD, MPH	T-DM1	Trastuzumab/pertuzumab

TCHP = docetaxel/carboplatin/trastuzumab/pertuzumab

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FDA Approval of T-DM1 for HER2-Positive Early Breast Cancer

Press Release – May 3, 2019

"On 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.

Patients should be selected based on an FDA-approved companion diagnostic for ado-trastuzumab emtansine. FDA also approved both the… PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody assay and the INFORM HER2 Dual ISH DNA Probe Cocktail assay as companion diagnostic devices for selecting patients.

Approval was based on KATHERINE (NCT01772472), a randomized, multicenter, open-label trial of 1486 patients with HER2-positive EBC."

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

KATHERINE Phase III Study Design

Eligibility (N = 1,486)

- HER2-positive early breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum 6 cycles of chemotherapy with a minimum 9 weeks of taxane-based treatment
  - Minimum 9 weeks of trastuzumab
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

R

T-DM1 (n = 743)
3.6 mg/kg IV q3wk
14 cycles

Trastuzumab (n = 743)
6 mg/kg IV q3wk
14 cycles

Radiation and endocrine therapy per protocol and local guidelines

Primary endpoint: Invasive disease-free survival

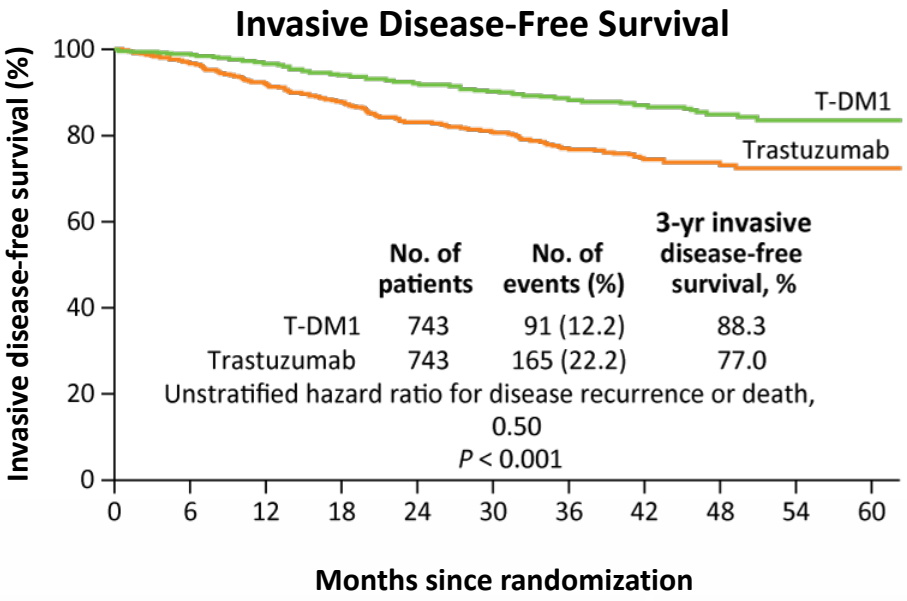
Geyer CE Jr et al. San Antonio Breast Cancer Symposium 2018;Abstract GS1-10;
von Minckwitz G et al. *N Engl J Med* 2019;380(7):617-28.

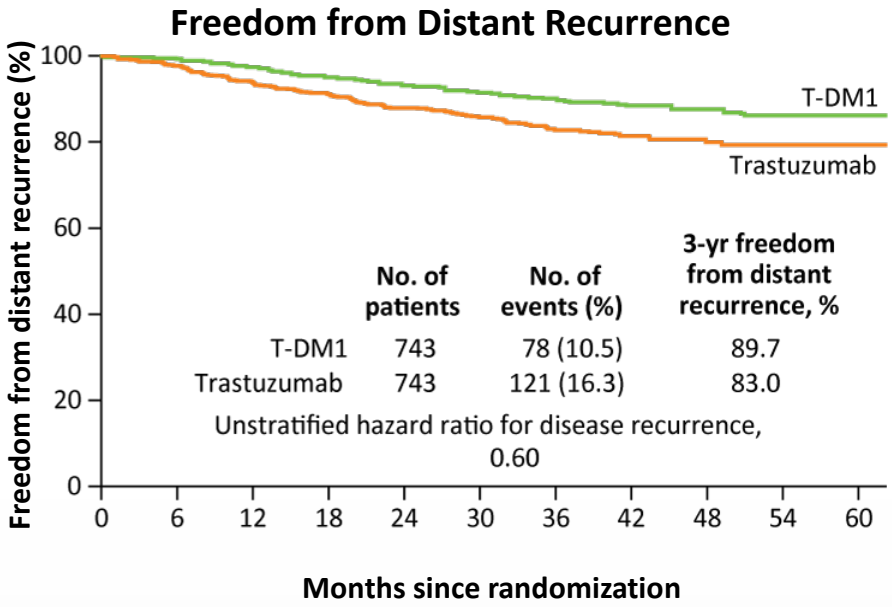
KATHERINE: Patient Demographics and Clinical Characteristics at Baseline

	Trastuzumab group (n = 743)	T-DM1 group (n = 743)
Median age (range)	49 (23-80)	49 (24-79)
Clinical stage at presentation		
Inoperable BC	25.6%	24.9%
Operable BC	74.4%	75.1%
Hormone receptor status		
ER/PR-negative or status unknown	27.3%	28.1%
ER/PR-positive	72.7%	71.9%
Previous treatment with anthracyclines	75.9%	77.9%
Neoadjuvant HER2-targeted therapy		
Trastuzumab alone	80.2%	80.8%
Trastuzumab and pertuzumab	18.7%	17.9%
Trastuzumab and other HER2-targeted therapy	1.1%	1.3%

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

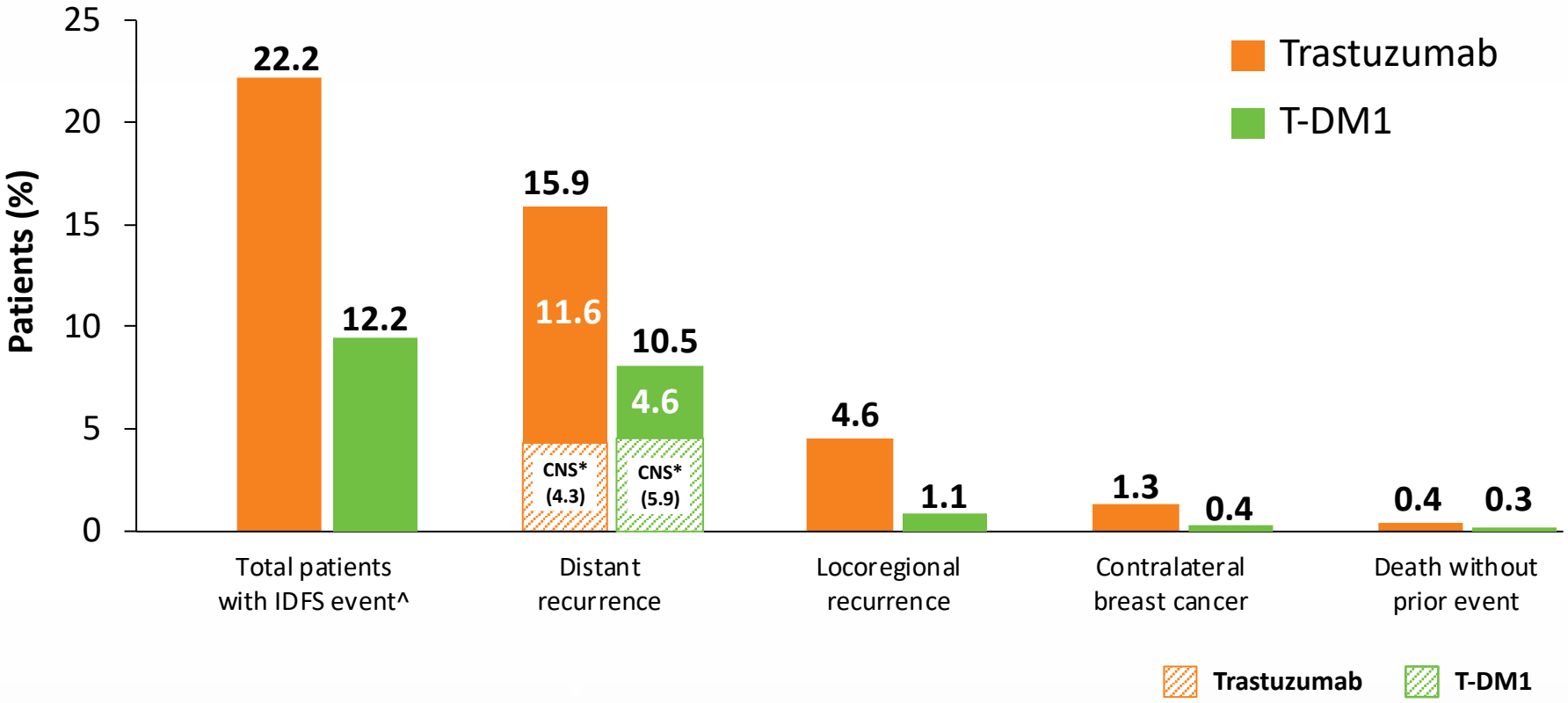
KATHERINE: Invasive DFS and Freedom from Distant Recurrence





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

KATHERINE: First Invasive DFS Events

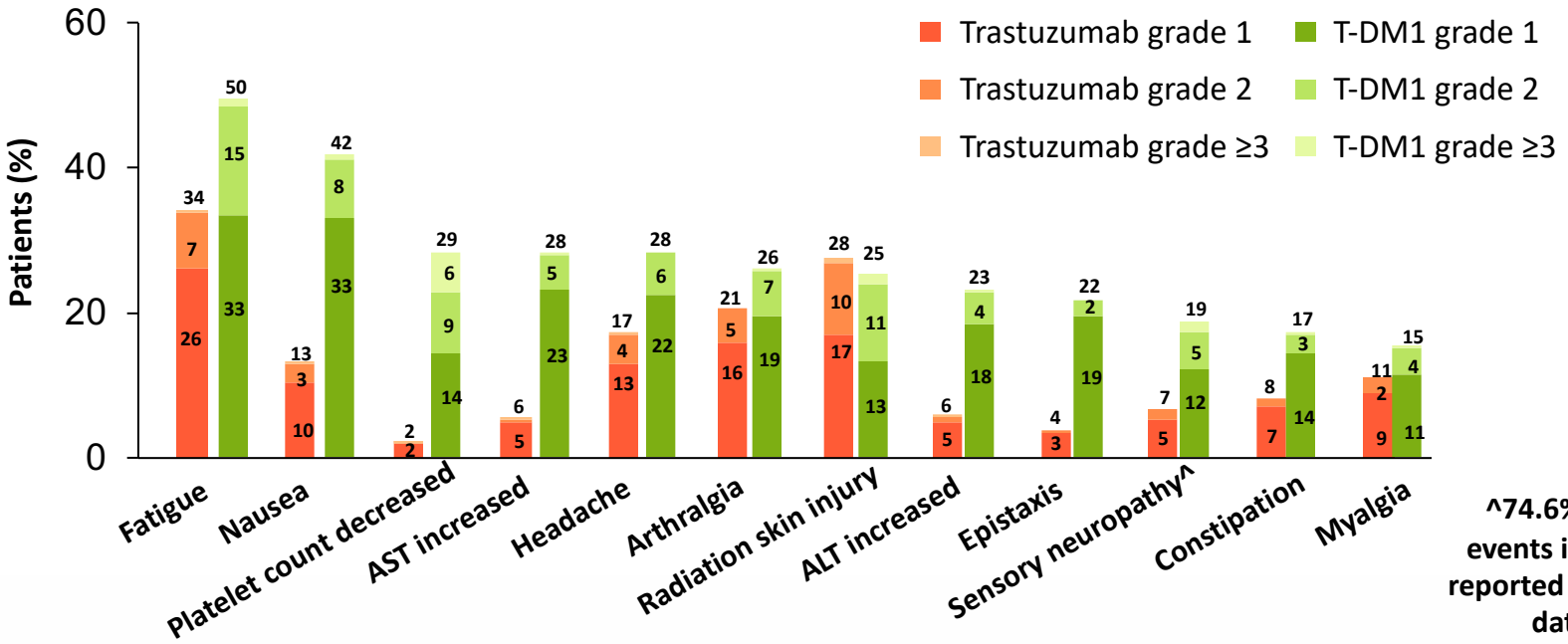


^Patients who experience additional IDFS event(s) within 61 days of their first IDFS event are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Death without prior event.

*CNS metastases as component of distant recurrence (isolated or with other sites).

Geyer CE Jr et al. San Antonio Breast Cancer Symposium 2018;Abstract GS1-10.

KATHERINE: All-Grade AEs with ≥15% Incidence in Either Arm



^74.6% (103/138) events in T-DM1 arm reported as resolved by data cutoff

2% (trastuzumab) vs 18% (T-DM1) discontinued due to adverse events

Geyer CE et al. San Antonio Breast Cancer Symposium 2018;Abstract GS1-10.

Investigator Perspectives on Recently Approved and Emerging Strategies in the Management of Breast Cancer

Module 1: Chemotherapy with Immunotherapy as First-Line Treatment for Metastatic Triple-Negative Breast Cancer (TNBC)

- IMpassion130 trial: Atezolizumab/*nab* paclitaxel for untreated advanced TNBC

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- Somatic and germline BRCA testing
- Olaparib and talazoparib for HER2-negative metastatic breast cancer with germline BRCA mutation (OlympiAD, EMBRACA trials)

Module 4: PI3 Kinase Inhibitors in Hormone Receptor-Positive Metastatic Disease

- SOLAR-1 trial: Alpelisib/fulvestrant for HR-positive advanced disease with PIK3CA mutation

Module 5: Novel HER2-Directed Investigational Approaches

- Tucatinib, margetuximab and trastuzumab deruxtecan

In general, at what point, if any, would you order BRCA testing for a 65-year-old woman who presents with mTNBC or metastatic ER-positive, HER2-negative breast cancer and no relevant family history?

	Triple-negative	ER-positive, HER2-negative
 HAROLD J BURSTEIN, MD, PHD	Immediately	Immediately
 CHARLES E GEYER, MD	Immediately	I would not order BRCA testing for this patient
 ERIKA HAMILTON, MD	Immediately	Immediately
 SARA A HURVITZ, MD	Immediately	Immediately
 RITA NANDA, MD	Immediately	Immediately
 JOYCE O'SHAUGHNESSY, MD	Immediately	Immediately
 HOPE S RUGO, MD	Immediately	I would not order BRCA testing for this patient
 SARAH M TOLANEY, MD, MPH	Immediately	Immediately

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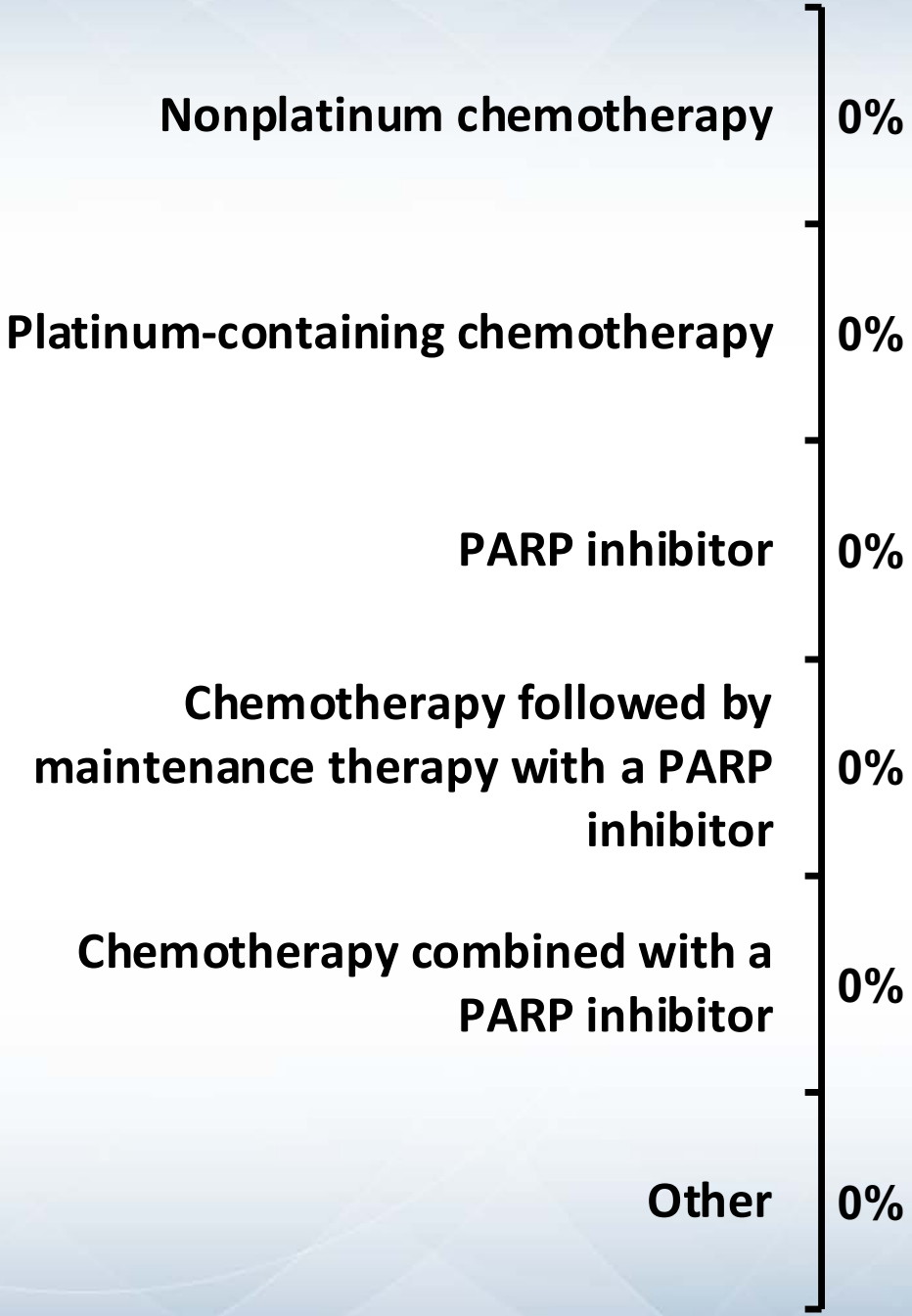
In general, what would be your preferred treatment approach for a 60-year-old patient with a germline BRCA mutation and de novo metastatic triple-negative breast cancer that is PD-L1-negative?

1. Nonplatinum chemotherapy
2. Platinum-containing chemotherapy
3. PARP inhibitor
4. Chemotherapy followed by maintenance therapy with a PARP inhibitor
5. Chemotherapy combined with a PARP inhibitor
6. Other



In general, what would be your preferred treatment approach for a 60-year-old patient with a germline BRCA mutation and de novo metastatic triple-negative breast cancer that is …

	PD-L1-negative	PD-L1-positive
 HAROLD J BURSTEIN, MD, PHD	Olaparib	Atezo/*nab*-P
 CHARLES E GEYER, MD	Carbo/pac/pembro	Atezo/*nab*-P + carbo (cycle 2)
 ERIKA HAMILTON, MD	Talazoparib or olaparib	Atezo/*nab*-P
 SARA A HURVITZ, MD	Talazoparib	Atezo/*nab*-P
 RITA NANDA, MD	Talazoparib or olaparib	Atezo/*nab*-P
 JOYCE O'SHAUGHNESSY, MD	Olaparib	Atezo/*nab*-P
 HOPE S RUGO, MD	Platinum-based chemo → maintenance therapy with a PARP inhibitor (agnostic)	Atezo/*nab*-P → atezo, PARP at progression or potentially as maintenance
 SARAH M TOLANEY, MD, MPH	Olaparib	Atezo/*nab*-P

Atezo/*nab*-P = atezolizumab/*nab* paclitaxel

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Pivotal Phase III Trials Supporting the FDA Approvals of Olaparib and Talazoparib for mBC with a Germline BRCA Mutation

Trial	Eligibility	Randomization	Primary endpoint
OlympiAD[1] (n = 302)	• HER2-negative mBC – ER+ and/or PR+ or TNBC • Deleterious or suspected deleterious gBRCA mutation • Prior anthracycline and taxane • ≤2 prior chemotherapy lines in metastatic setting	• Olaparib • Physician's choice – Capecitabine – Eribulin – Vinorelbine	• PFS by blinded independent central review
EMBRACA[2] (n = 431)	• HER2-negative locally advanced or metastatic BC • Germline BRCA1 or BRCA2 mutation • ≤3 prior cytotoxic chemotherapy regimens • Prior treatment with a taxane and/or anthracycline unless medically contraindicated	• Talazoparib • Physician's choice – Capecitabine – Eribulin – Gemcitabine – Vinorelbine	• PFS by blinded independent central review

[1] Robson M et al. *N Engl J Med* 2017;377(6):523-33. [2] Litton JK et al. San Antonio Breast Cancer Symposium 2017;Abstract GS6-07; www.clinicaltrials.gov. Accessed August 2019.

OlympiAD and EMBRACA: Efficacy Summary

	OlympiAD [1,2]	EMBRACA [3-5]
HR (PFS)	0.58	0.54
HR (PFS) ER/PR-positive	0.82	0.47
HR (PFS) TNBC	0.43	0.60
HR (OS)	0.90	0.76
ORR	59.9% (vs 28.8% TPC)	67.6% (vs 27.2% TPC)

TPC = treatment of physician choice

Cross-trial comparisons are challenging in terms of determining the relative efficacy and tolerability of treatments

[1] Robson M et al. *N Engl J Med* 2017;377(6):523-33. [2] Robson M et al. *Ann Oncol* 2019;30(4):558-66. [3] Litton JK et al. *N Engl J Med* 2018;379(8):753-63. [4] Litton JK et al. San Antonio Breast Cancer Symposium 2017;Abstract GS6-07. [5] Rugo HS et al. ASCO 2018;Abstract 1069.

OlympiAD and EMBRACA: Adverse Event and Quality of Life Summary

	OlympiAD [1,2]	EMBRACA [3,4]
Deterioration in health-related QoL	0.44 (0.25-0.77)	0.38 (0.26-0.56)
Serious AEs Grade ≥3	36.6% (vs 50.5% TPC)	25.5% (v. 25.4% TPC)
Anemia Grade ≥3	16.1%	39.2%
Neutropenia Grade ≥3	9.3%	20.9%
Thrombocytopenia Grade ≥3	2.4%	14.7%
MDS/AML	0	0
Nausea (any grade)	58.0%	48.6%
Alopecia (any grade)	3.4%	25.2%
Dose modification/reduction due to AE	25.4% (vs 30.8% TPC)	66% (vs 60% TPC)
Treatment discontinuation due to AE	4.9% (vs 7.7% TPC)	5.9% (vs 8.7% TPC)

Cross-trial comparisons are challenging in terms of determining the relative efficacy and tolerability of treatments

[1] Robson M et al. *N Engl J Med* 2017;377(6):523-33. [2] Robson M et al. *Ann Oncol* 2019;30(4):558-66. [3] Litton JK et al. *N Engl J Med* 2018;379(8):753-63. [4] Litton JK et al. San Antonio Breast Cancer Symposium 2017;Abstract GS6-07.

Next Steps in PARP Inhibition

- In combination with conventional cytotoxics
- In combination with immune checkpoint inhibitors
  - Niraparib + pembrolizumab (Phase I/II TOPACIO trial)
  - Olaparib +/- durvalumab (Phase II DORA trial)
- In combination with targeted agents
- In early-stage disease
  - Adjuvant olaparib (Phase III OlympiA trial)
  - Neoadjuvant talazoparib (Phase II trial NCT03499353)
- Other genes, somatic mutations
  - Olaparib for mBC with germline or somatic mutations (Phase III trial NCT03286842)
  - Rucaparib for mBC with high loss of heterozygosity/HRD (Phase II RUBY trial)

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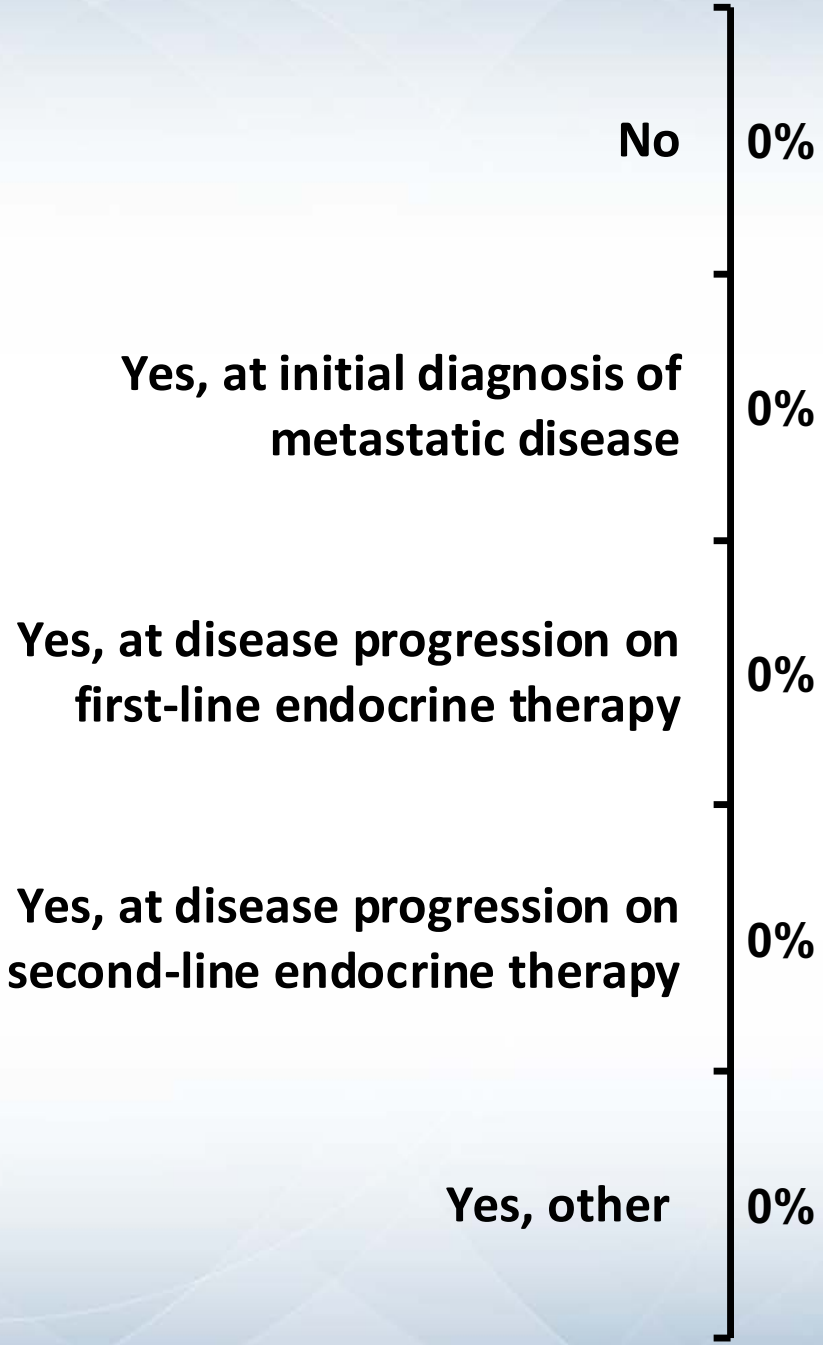
Do you generally test for PIK3CA mutations in your patients with metastatic ER-positive, HER2-negative breast cancer?

1. No
2. Yes, at initial diagnosis of metastatic disease
3. Yes, at disease progression on first-line endocrine therapy
4. Yes, at disease progression on second-line endocrine therapy
5. Yes, other



Do you generally test for PIK3CA mutations in your patients with metastatic ER-positive, HER2-negative breast cancer? Which assay do you generally use?

	Test for PIK3CA?	Assay
 HAROLD J BURSTEIN, MD, PHD	Yes, at initial diagnosis of metastatic disease	Next-generation sequencing
 CHARLES E GEYER, MD	Yes, at disease progression on first-line endocrine therapy	Companion diagnostic test (therascreen® PIK3CA RGQ PCR Kit) or NGS
 ERIKA HAMILTON, MD	Yes, at disease progression on first-line endocrine therapy	Next-generation sequencing
 SARA A HURVITZ, MD	Yes, at disease progression on first-line endocrine therapy	Next-generation sequencing
 RITA NANDA, MD	Yes, at initial diagnosis of metastatic disease	Next-generation sequencing
 JOYCE O'SHAUGHNESSY, MD	Yes, at initial diagnosis of metastatic disease	Next-generation sequencing
 HOPE S RUGO, MD	Yes, at disease progression on first-line endocrine therapy	Next-generation sequencing
 SARAH M TOLANEY, MD, MPH	Yes, at initial diagnosis of metastatic disease	Next-generation sequencing

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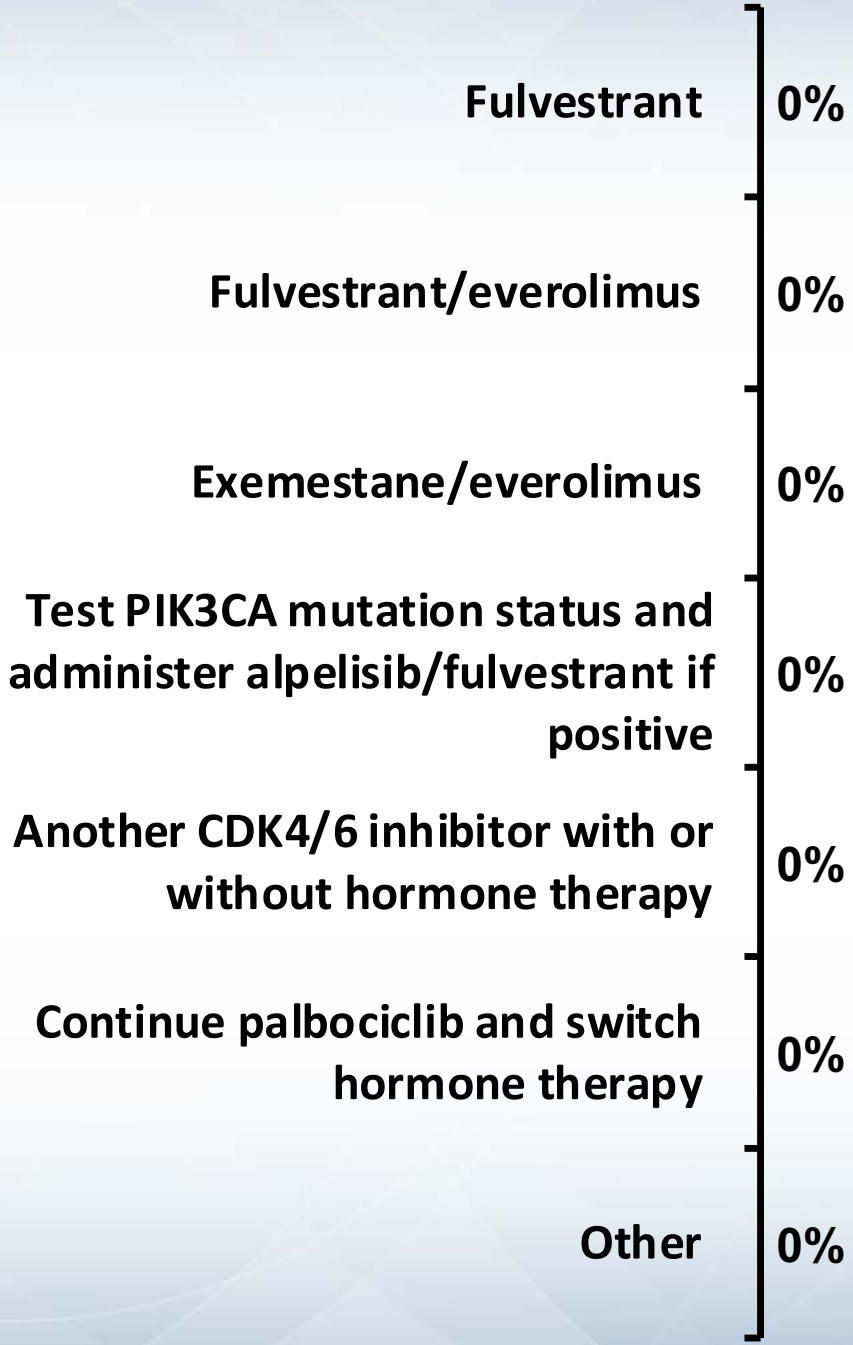
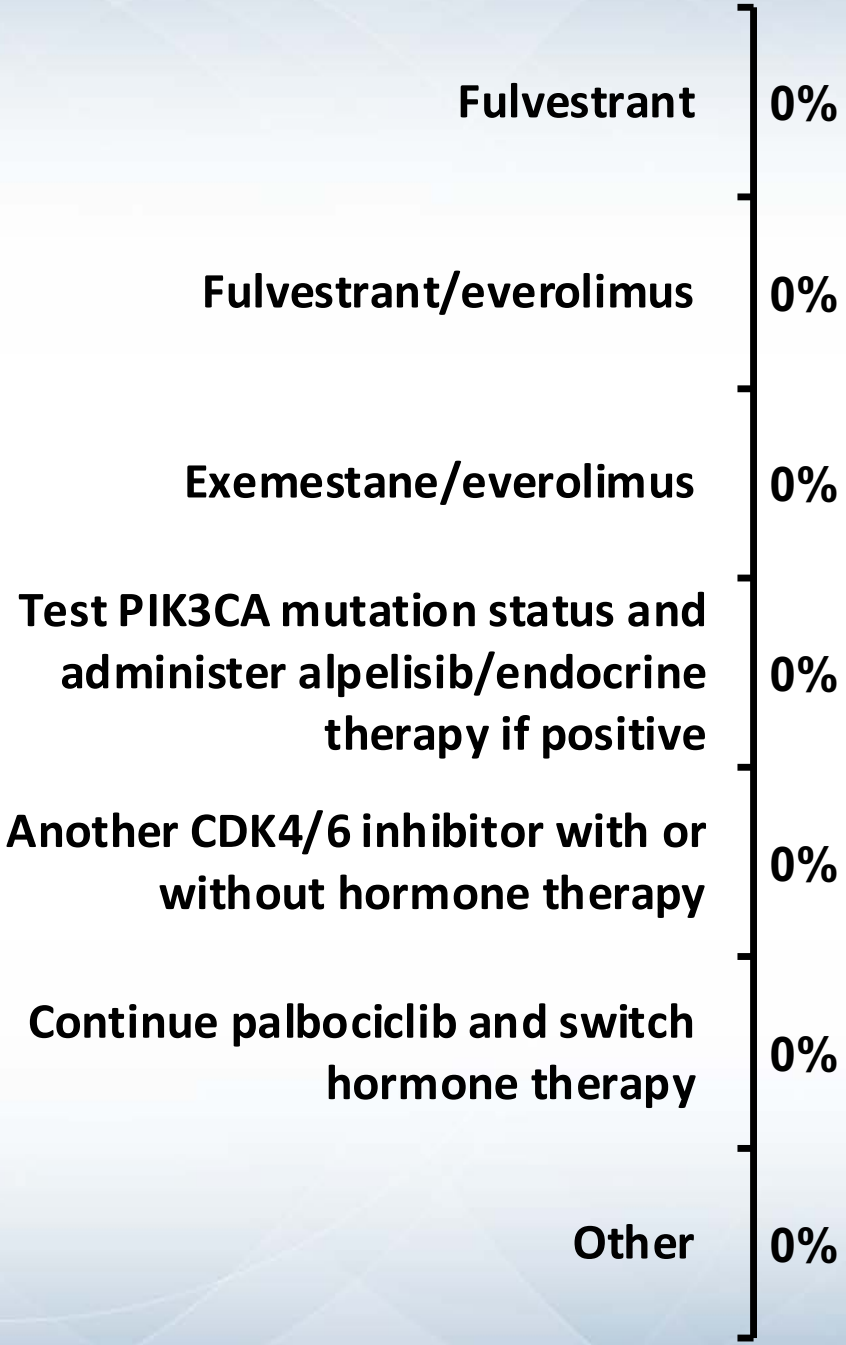
A patient who is receiving palbociclib/letrozole for ER-positive, HER2-negative metastatic breast cancer experiences disease progression. Which endocrine-based treatment would you most likely recommend next?

1. Fulvestrant
2. Fulvestrant/everolimus
3. Exemestane/everolimus
4. Test PIK3CA mutation status and administer alpelisib/fulvestrant if positive
5. Another CDK4/6 inhibitor with or without hormone therapy
6. Continue palbociclib and switch hormone therapy
7. Other



A patient who developed metastatic disease after adjuvant anastrozole for ER-positive, HER2-negative breast cancer is receiving palbociclib/fulvestrant and experiences disease progression. Which endocrine-based treatment would you most likely recommend next?

1. Fulvestrant
2. Fulvestrant/everolimus
3. Exemestane/everolimus
4. Test PIK3CA mutation status and administer alpelisib/endocrine therapy if positive
5. Another CDK4/6 inhibitor with or without hormone therapy
6. Continue palbociclib and switch hormone therapy
7. Other



Which endocrine-based treatment would you most likely recommend for a patient with ER-positive, HER2-negative metastatic disease who experiences disease progression while receiving …

	Palbociclib/letrozole	Palbociclib/fulvestrant after adjuvant anastrozole
 HAROLD J BURSTEIN, MD, PHD	Test PIK3CA mutation status; alpelisib/fulvestrant if positive	Test PIK3CA mutation status; alpelisib/ET if positive
 CHARLES E GEYER, MD	Test PIK3CA mutation status; alpelisib/fulvestrant if positive	Test PIK3CA mutation status; alpelisib/ET if positive
 ERIKA HAMILTON, MD	Test PIK3CA mutation status; alpelisib/fulvestrant if positive	Test PIK3CA mutation status; alpelisib/ET if positive
 SARA A HURVITZ, MD	Test PIK3CA mutation status; alpelisib/fulvestrant if positive	Test PIK3CA mutation status; alpelisib/ET if positive
 RITA NANDA, MD	Test PIK3CA mutation status; alpelisib/fulvestrant if positive	Test PIK3CA mutation status; alpelisib/ET if positive
 JOYCE O'SHAUGHNESSY, MD	Test PIK3CA mutation status; alpelisib/fulvestrant if positive	Test PIK3CA mutation status; alpelisib/ET if positive
 HOPE S RUGO, MD	Test PIK3CA mutation status; alpelisib/fulvestrant if positive	Test PIK3CA mutation status; alpelisib/ET if positive
 SARAH M TOLANEY, MD, MPH	Test PIK3CA mutation status; alpelisib/fulvestrant if positive	Test PIK3CA mutation status; alpelisib/ET if positive

ET = endocrine therapy

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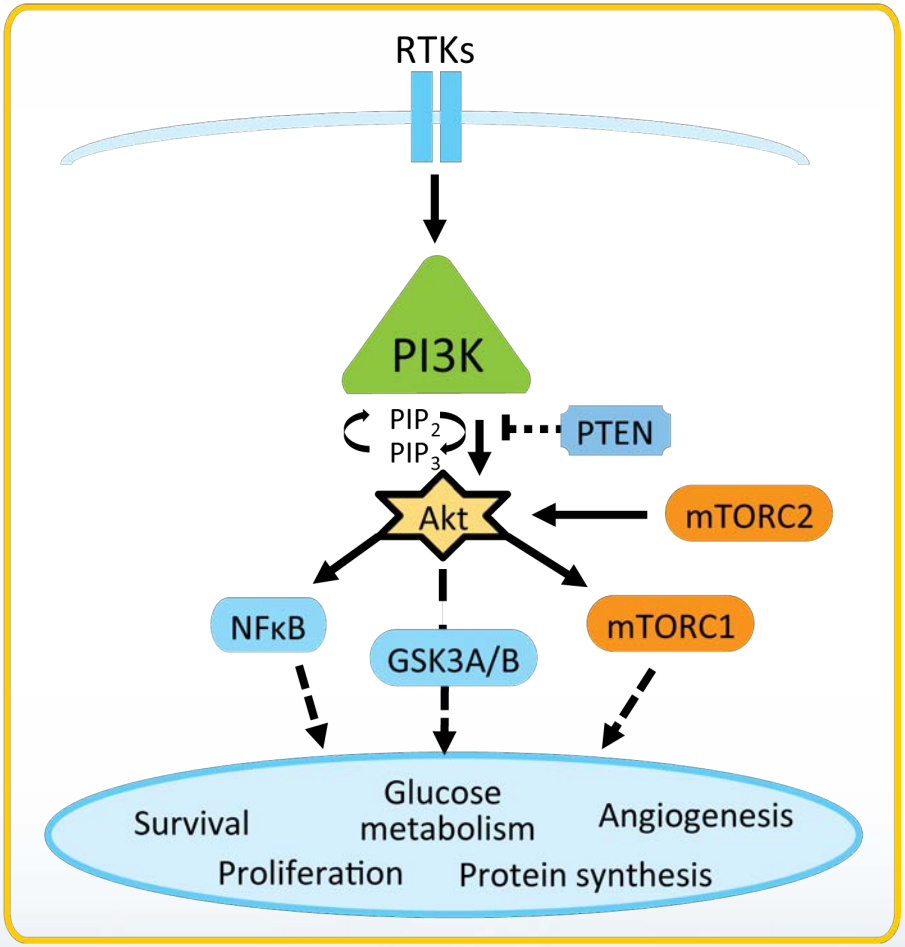
PI3K Inhibitors: Mechanism of Action



- PI3K is involved in the activation of Akt.
- Hyperactivation of the PI3K pathway is implicated in malignant transformation, cancer progression and endocrine therapy resistance.
- PIK3CA encodes the alpha isoform of the PI3K catalytic subunit.
- Around 40% of patients with HR+, HER- BC present with an activating PIK3CA tumor mutation.
- Alpelisib is a specific inhibitor of the PI3K alpha isoform.

André F et al. *Proc ESMO* 2018;Abstract LBA3_PR.

FDA Approval of First PI3K Inhibitor for Breast Cancer

Press Release – May 24, 2019

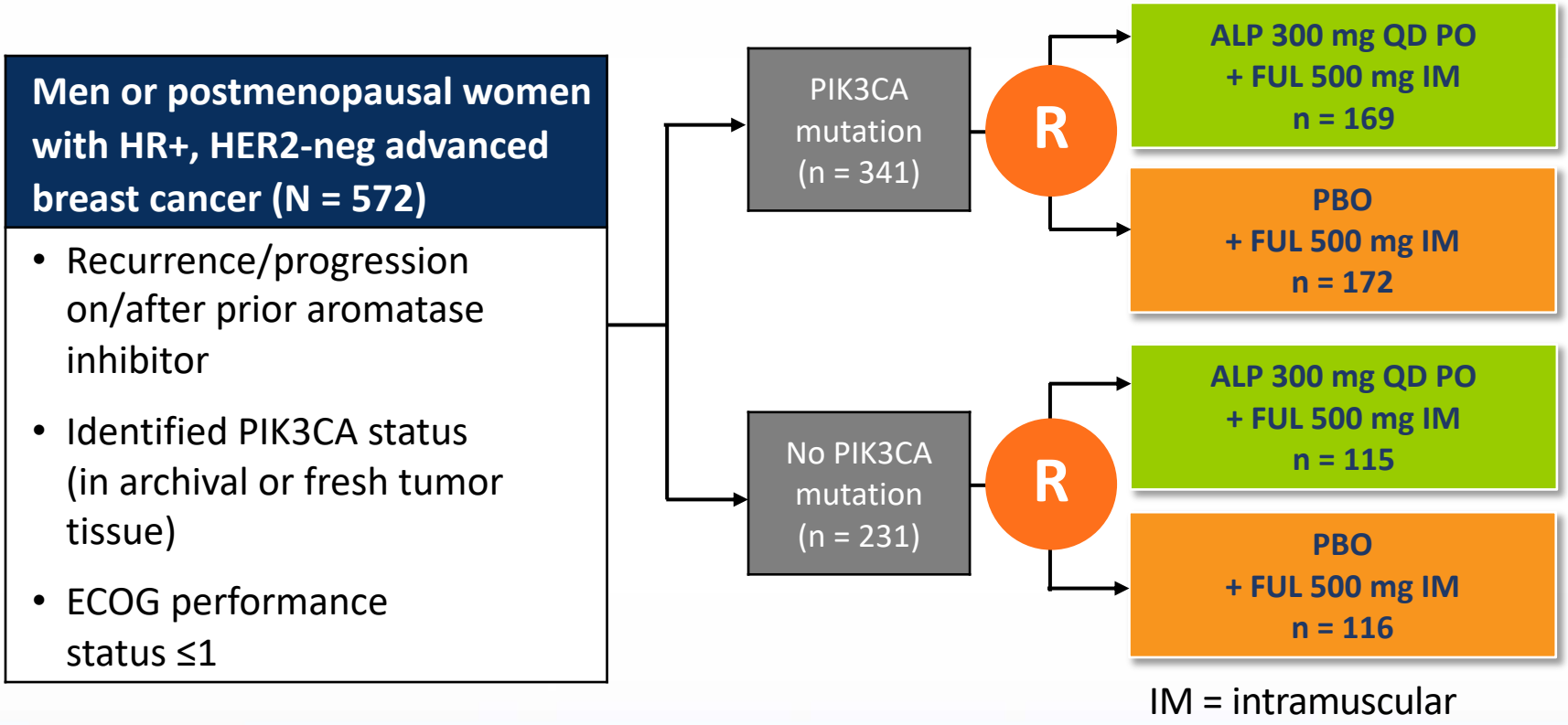
"The Food and Drug Administration approved alpelisib tablets, to be used in combination with the FDA-approved endocrine therapy fulvestrant, to treat postmenopausal women, and men, with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer (as detected by an FDA-approved test) following progression on or after an endocrine-based regimen.

Approval was based on data from the Phase III SOLAR-1 trial, a randomized trial of 572 postmenopausal women and men with HR-positive, HER2-negative, advanced or metastatic breast cancer whose cancer had progressed while on or after receiving an aromatase inhibitor.

The FDA also approved the companion diagnostic test, therascreen PIK3CA RGQ PCR Kit, to detect the PIK3CA mutation in a tissue and/or a liquid biopsy. Patients who are negative by the therascreen test using the liquid biopsy should undergo tumor biopsy for PIK3CA mutation testing."

https://www.fda.gov/news-events/press-announcements/fda-approves-first-pi3k-inhibitor-breast-cancer

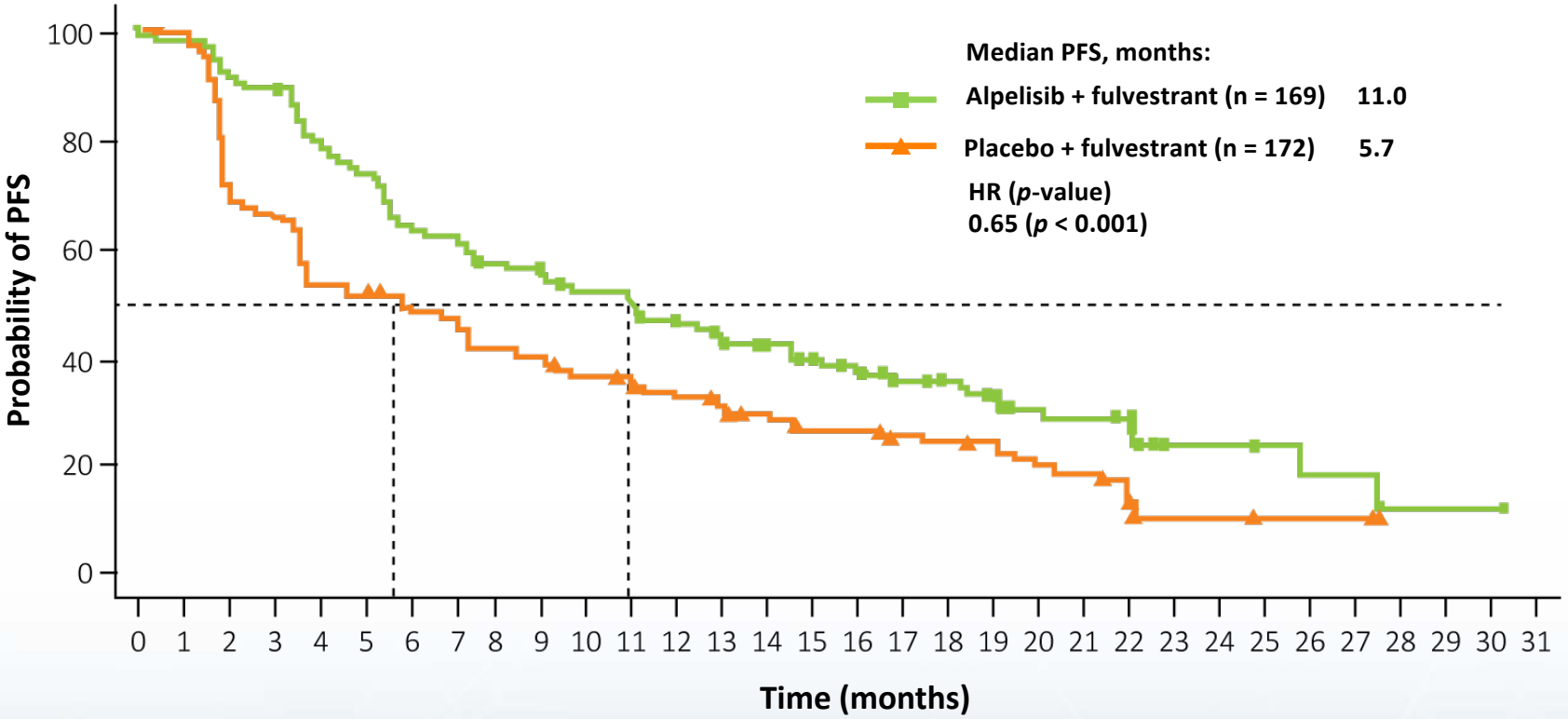
SOLAR-1 Phase III Study Design



Primary endpoint: Locally assessed PFS in PIK3CA mutation cohort

André F et al. *Proc ESMO* 2018;Abstract LBA3_PR.

SOLAR-1: Alpelisib/Fulvestrant for Advanced Breast Cancer After Prior AI – PFS Results for Patients with PIK3CA Mutation



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

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SOLAR-1: Select Adverse Events

AEs ≥20% in either arm, n (%)	Alpelisib + fulvestrant N = 284		Placebo + fulvestrant N = 287	
	All	Grade ≥3	All	Grade ≥3
Any adverse event	282 (99.3)	216 (76.1)	264 (92.0)	102 (35.5)
Hyperglycemia	181 (63.7)	104 (36.6)	28 (9.8)	2 (0.7)
Diarrhea	164 (57.7)	19 (6.7)	45 (15.7)	1 (0.3)
Nausea	127 (44.7)	7 (2.5)	64 (22.3)	1 (0.3)
Decreased appetite	101 (35.6)	2 (0.7)	30 (10.5)	1 (0.3)
Rash	101 (35.6)	28 (9.9)	17 (5.9)	1 (0.3)
Vomiting	77 (27.1)	2 (0.7)	28 (9.8)	1 (0.3)
Decreased weight	76 (26.8)	11 (3.9)	6 (2.1)	0
Stomatitis	70 (24.6)	7 (2.5)	18 (6.3)	0
Fatigue	69 (24.3)	10 (3.5)	49 (17.1)	3 (1.0)
Asthenia	58 (20.4)	5 (1.8)	37 (12.9)	0

Management of hyperglycemia:
Early detection: day 8 visit, metformin if glycemia (or Hb1c) above normal level
Exclude diabetic patients

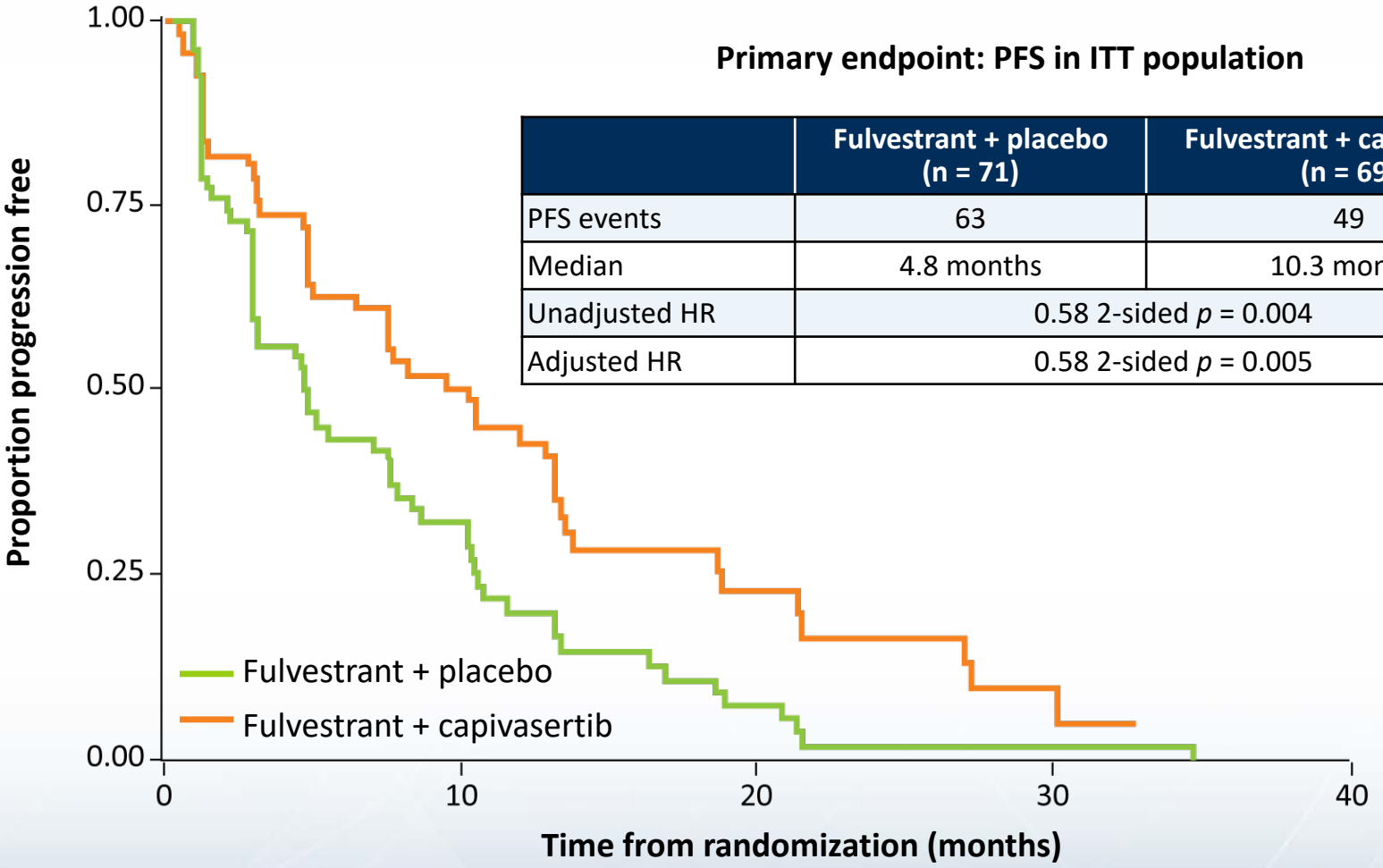
Management of rash:
Topical steroids, antihistamine (prophylaxis ++)

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

FAKTION: A Phase II Trial of the Novel AKT Inhibitor Capivasertib (AZD5363) with Fulvestrant for ER-Positive, HER2-Negative Locally Advanced or Metastatic BC After Relapse or Progression on an AI

Primary endpoint: PFS in ITT population

	Fulvestrant + placebo (n = 71)	Fulvestrant + capivasertib (n = 69)
PFS events	63	49
Median	4.8 months	10.3 months
Unadjusted HR	0.58 2-sided *p* = 0.004	
Adjusted HR	0.58 2-sided *p* = 0.005	



Jones RH et al. ASCO 2019;Abstract 1005.

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FAKTION: Select Adverse Events

AEs in >10% of study population, n (%)	Capivasertib + fulvestrant N = 69		Placebo + fulvestrant N = 71	
	All	Grade 3-5	All	Grade 3-5
Any adverse event	69 (100)	40 (58)	67 (94)	21 (30)
Diarrhea	56 (81)	10 (14)	25 (35)	3 (4)
Rash	35 (51)	14 (20)	13 (18)	0
Hyperglycemia	29 (42)	3 (4)	11 (16)	0
Vomiting	27 (39)	2 (3)	15 (21)	0
Nausea	38 (55)	0	36 (51)	0
Infections (composite term)*	26 (38)	4 (6)	13 (18)	2 (3)
Oral mucositis	10 (14)	0	5 (7)	0
Fatigue	40 (58)	1 (1)	41 (58)	3 (4)
Dizziness	7 (10)	0	1 (1)	0
Back pain	17 (25)	0	11 (16)	0

* Preferred terms falling under the Systems Organ Classification: infections and infestations

Jones RH et al. ASCO 2019;Abstract 1005.

Select Ongoing Trials Targeting the PI3K/AKT or mTOR Pathway in ER-Positive mBC

Trial	Phase	n	Randomization
IPATunity130	II/III	450	• Ipatasertib + paclitaxel • Ipatasertib + placebo
MORPHEUS*	Ib/II	111	• Ipatasertib + atezolizumab • Ipatasertib + atezolizumab + fulvestrant • Fulvestrant (active comparator)
plasmaMATCH*	II	1,150	• Capivasertib + fulvestrant • Capivasertib
NCT02684032	Ib	148	• Gedatolisib + palbociclib + fulvestrant • Gedatolisib + palbociclib + letrozole • Letrozole or fulvestrant

* Umbrella/basket study; only arms targeting PI3K/AKT mTOR pathway reflected

www.clinicaltrials.gov. Accessed August 2019.

Investigator Perspectives on Recently Approved and Emerging Strategies in the Management of Breast Cancer

Module 1: Chemotherapy with Immunotherapy as First-Line Treatment for Metastatic Triple-Negative Breast Cancer (TNBC)

- IMpassion130 trial: Atezolizumab/*nab* paclitaxel for untreated advanced TNBC

Module 2: T-DM1 for Residual HER2-Positive Disease After Neoadjuvant Therapy

- KATHERINE trial: T-DM1 for residual invasive HER2-positive breast cancer

Module 3: PARP Inhibitors in Metastatic Breast Cancer

- Somatic and germline BRCA testing
- Olaparib and talazoparib for HER2-negative metastatic breast cancer with germline BRCA mutation (OlympiAD, EMBRACA trials)

Module 4: PI3 Kinase Inhibitors in Hormone Receptor-Positive Metastatic Disease

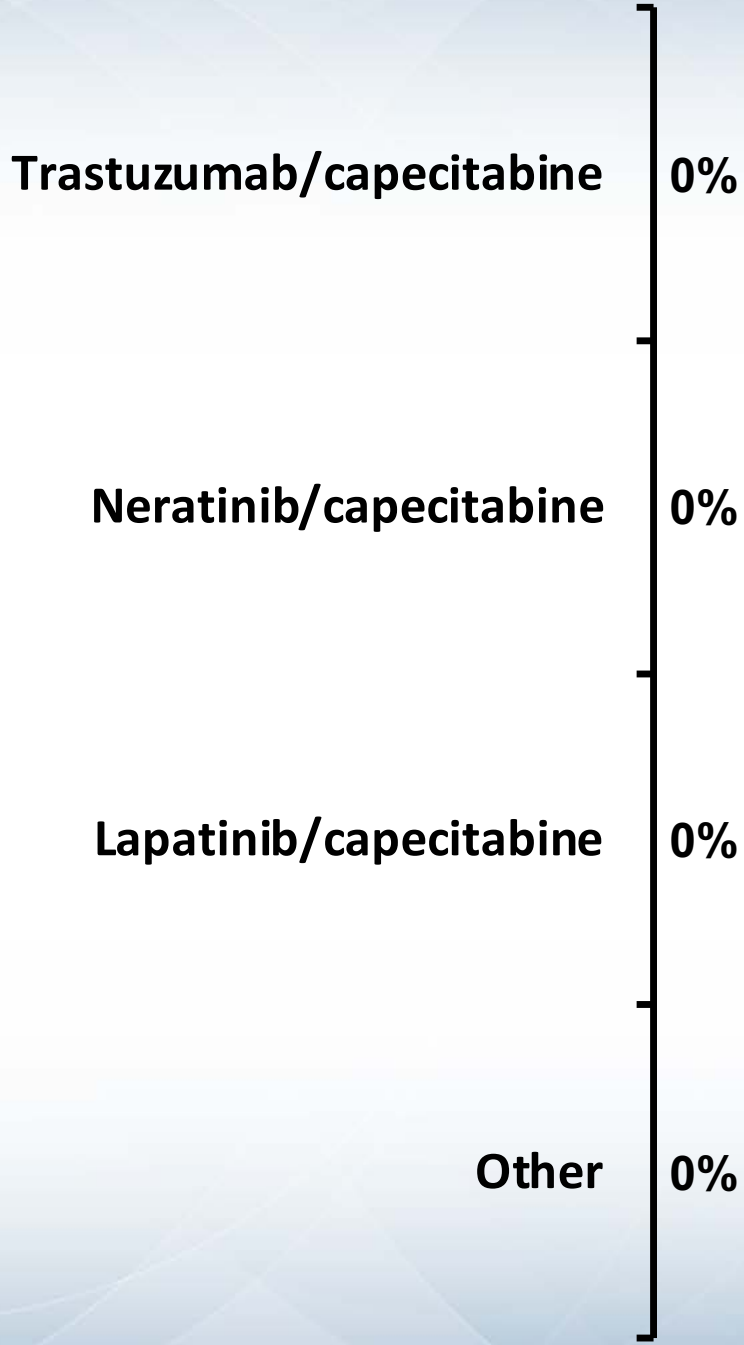
- SOLAR-1 trial: Alpelisib/fulvestrant for HR-positive advanced disease with PIK3CA mutation

Module 5: Novel HER2-Directed Investigational Approaches

- Tucatinib, margetuximab and trastuzumab deruxtecan

Regulatory and reimbursement issues aside, which treatment would you most likely recommend for a patient with HER2-positive metastatic breast cancer who has received chemotherapy/trastuzumab/pertuzumab followed by T-DM1 and has experienced disease progression?

1. **Trastuzumab/capecitabine**
2. **Neratinib/capecitabine**
3. **Lapatinib/capecitabine**
4. **Other**



Regulatory and reimbursement issues aside, which treatment would you most likely recommend next for a patient with HER2-positive metastatic breast cancer who has experienced disease progression on first-line chemotherapy/trastuzumab/pertuzumab and second-line T-DM1?

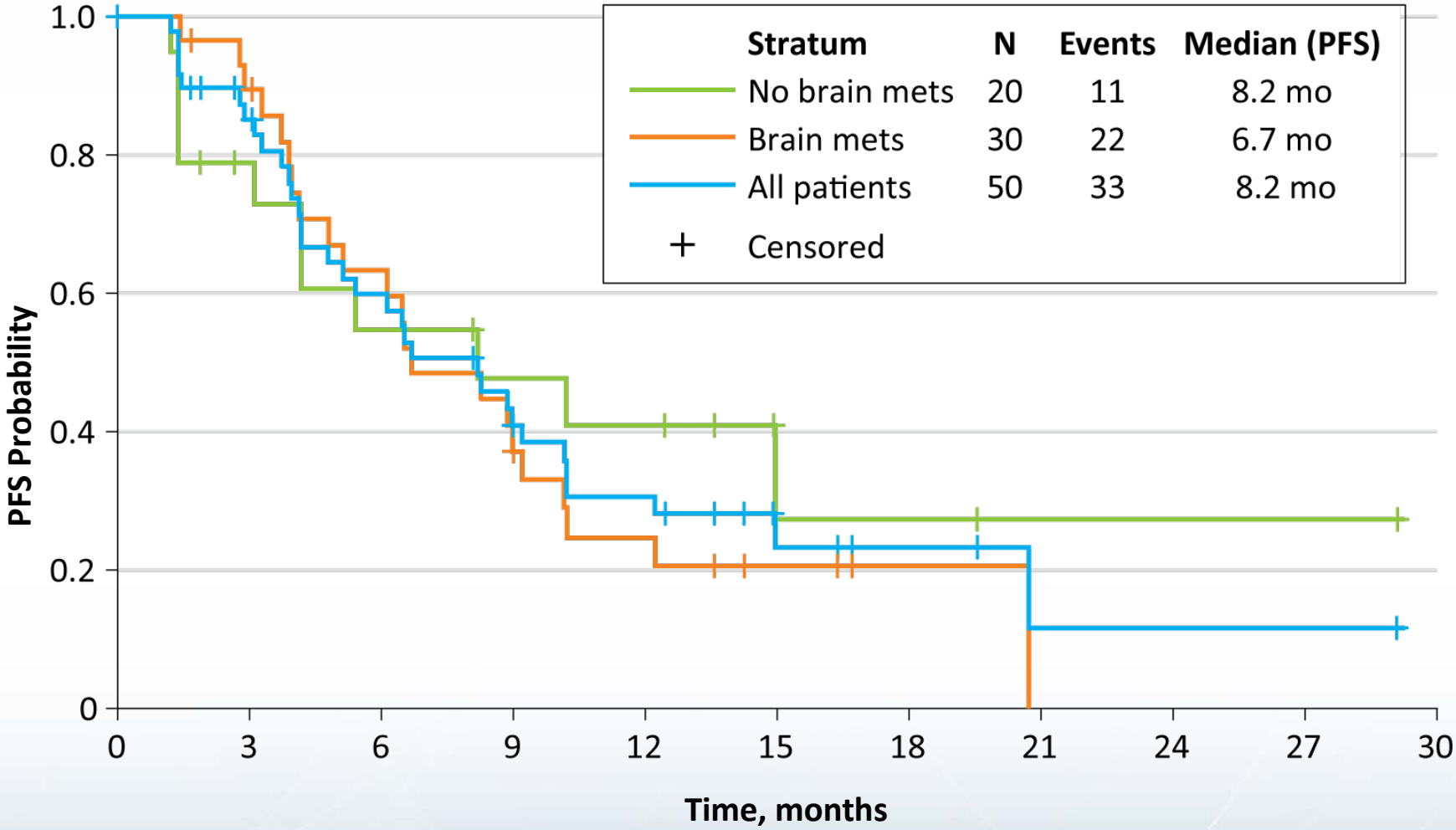
	Progressive disease	Progressive disease + brain mets
 HAROLD J BURSTEIN, MD, PHD	Trastuzumab/capecitabine	Neratinib/capecitabine
 CHARLES E GEYER, MD	Neratinib/capecitabine	Neratinib/capecitabine
 ERIKA HAMILTON, MD	Lapatinib/capecitabine	Neratinib/capecitabine
 SARA A HURVITZ, MD	Neratinib/capecitabine	Neratinib/capecitabine
 RITA NANDA, MD	Trastuzumab/capecitabine	Neratinib/capecitabine
 JOYCE O'SHAUGHNESSY, MD	Trastuzumab/capecitabine	Neratinib/capecitabine
 HOPE S RUGO, MD	Trastuzumab/capecitabine	Neratinib/capecitabine
 SARAH M TOLANEY, MD, MPH	Trastuzumab/capecitabine	Neratinib/capecitabine

Mechanisms of Action of Investigational HER2-Targeted Agents

Agent	Mechanism of action	Defining features
Tucatinib[1]	Selective small molecular tyrosine kinase inhibitor	Potent selective inhibitor of HER2 but not EGFR, resulting in decreased potential for EGFR-related toxicities
Margetuximab[2]	Chimeric monoclonal antibody	Binds Fab region of HER2 but also Fc-engineered to activate and enhance immune responses compared to trastuzumab (binds Fab only)
Trastuzumab deruxtecan[3]	Antibody-drug conjugate	Humanized HER2 antibody with cleavable peptide-based linker and potent topoisomerase I inhibitor (exatecan derivative) payload

[1] Tolaney S. ASCO 2018. Metastatic Breast Cancer Poster Discussion Session Discussant;
[2] Rugo H et al. ASCO 2019;Abstract 1000; [3] Modi S et al. ASCO 2019;Abstract TPS1102.

Tucatinib in Combination with T-DM1 for Advanced HER2-Positive mBC with and without Brain Metastases



Borges VF et al. *JAMA Oncol* 2018;4(9):1214-20.

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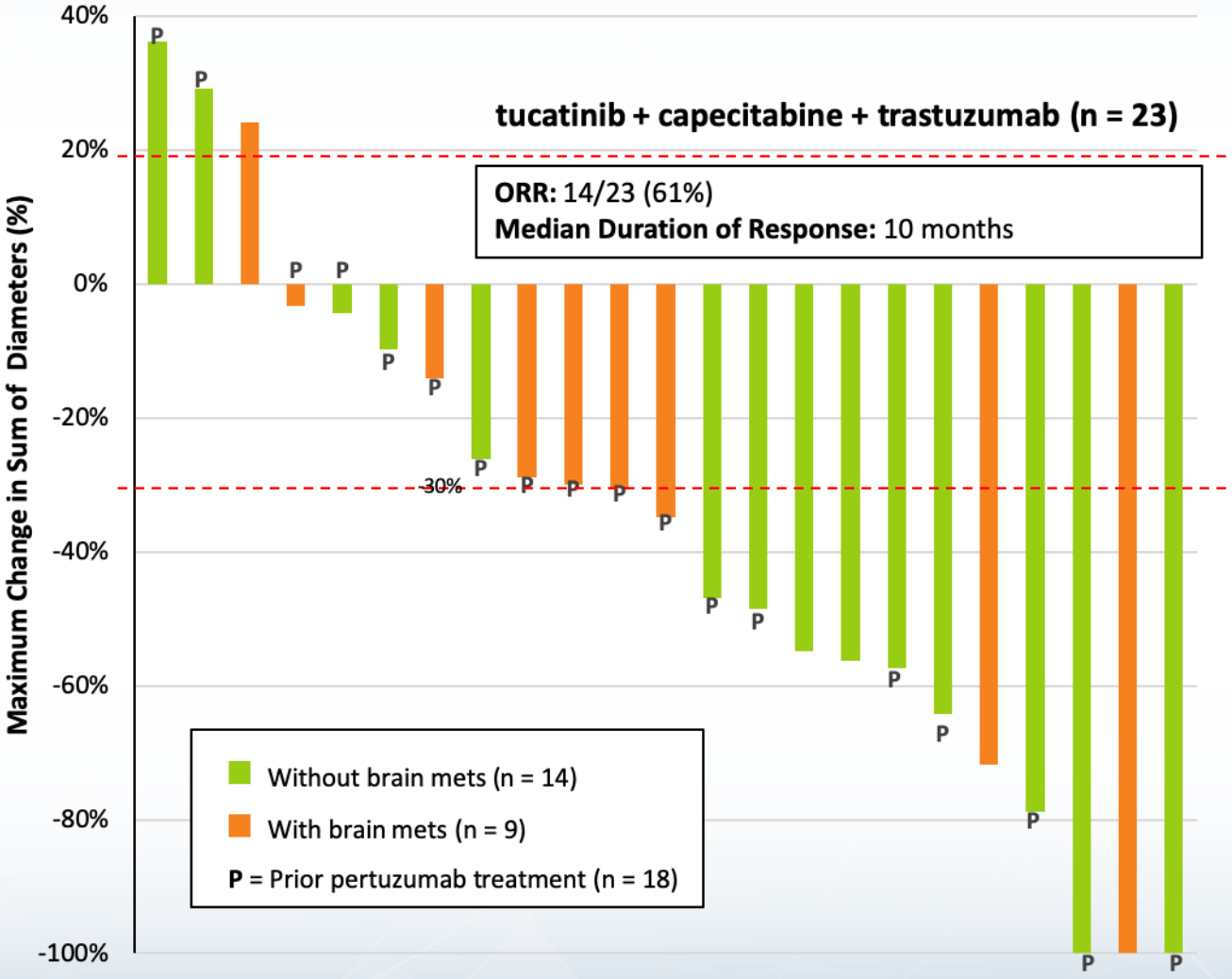
Tucatinib/Capecitabine/Trastuzumab for Advanced HER2-Positive mBC with and without Brain Metastases



Adverse events observed at recommended Phase II dose regardless of causality, grade, and treatment group:

- Diarrhea 67%
- Nausea 60%
- Hand-foot syndrome 44%
- Fatigue 38%
- Vomiting 38%

Hamilton E et al. SABCS 2016;Abstract P4-21-01; Murthy R et al. *Lancet Oncol* 2018;19:880-8.

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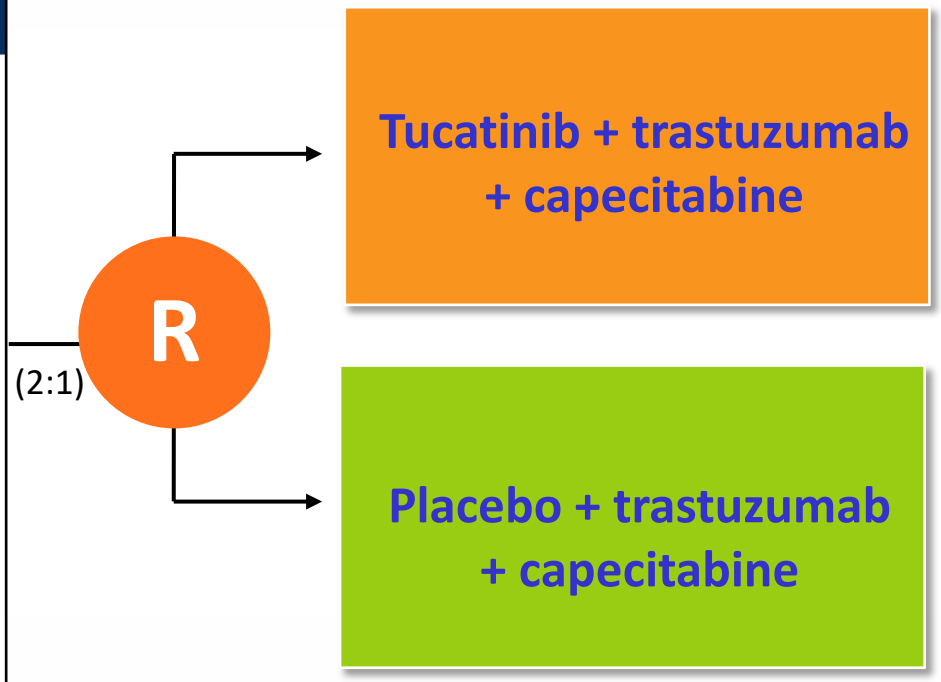
HER2CLIMB Phase II Trial Schema

Accrual: 612

Eligibility

- HER2-positive locally advanced or metastatic BC
- Prior trastuzumab, pertuzumab and T-DM1 required
- Active brain mets allowed (but not required)
- Measurable or evaluable disease
- No lapatinib in past 12 mo
- No prior investigational HER2 TKIs
- No prior capecitabine for mBC



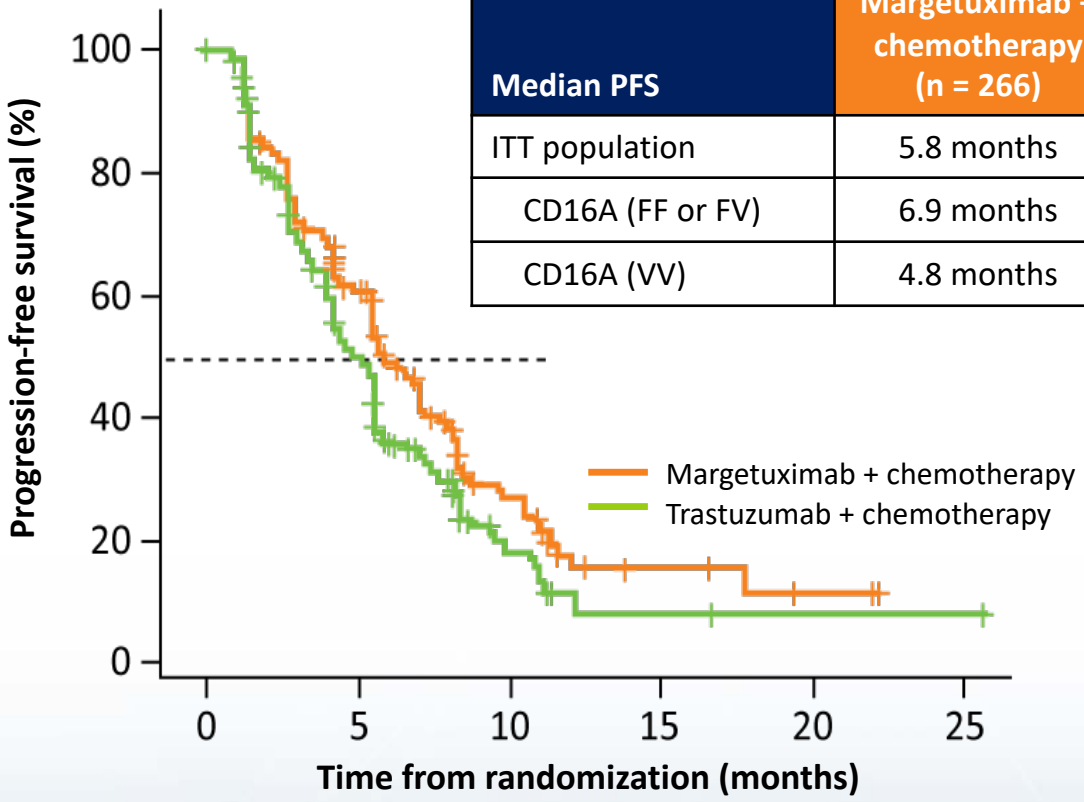
Primary endpoint: Progression-free survival by blinded independent central review (per RECIST 1.1)

www.clinicaltrials.gov. (NCT02614794) Accessed August 2019.

SOPHIA: Primary Analysis of a Phase III Trial of Margetuximab/Chemotherapy versus Trastuzumab/Chemotherapy for Previously Treated HER2-Positive mBC

Coprimary Endpoints: OS, PFS by Central Blinded Analysis
Exploratory Analysis: PFS by FcγR Genotypes

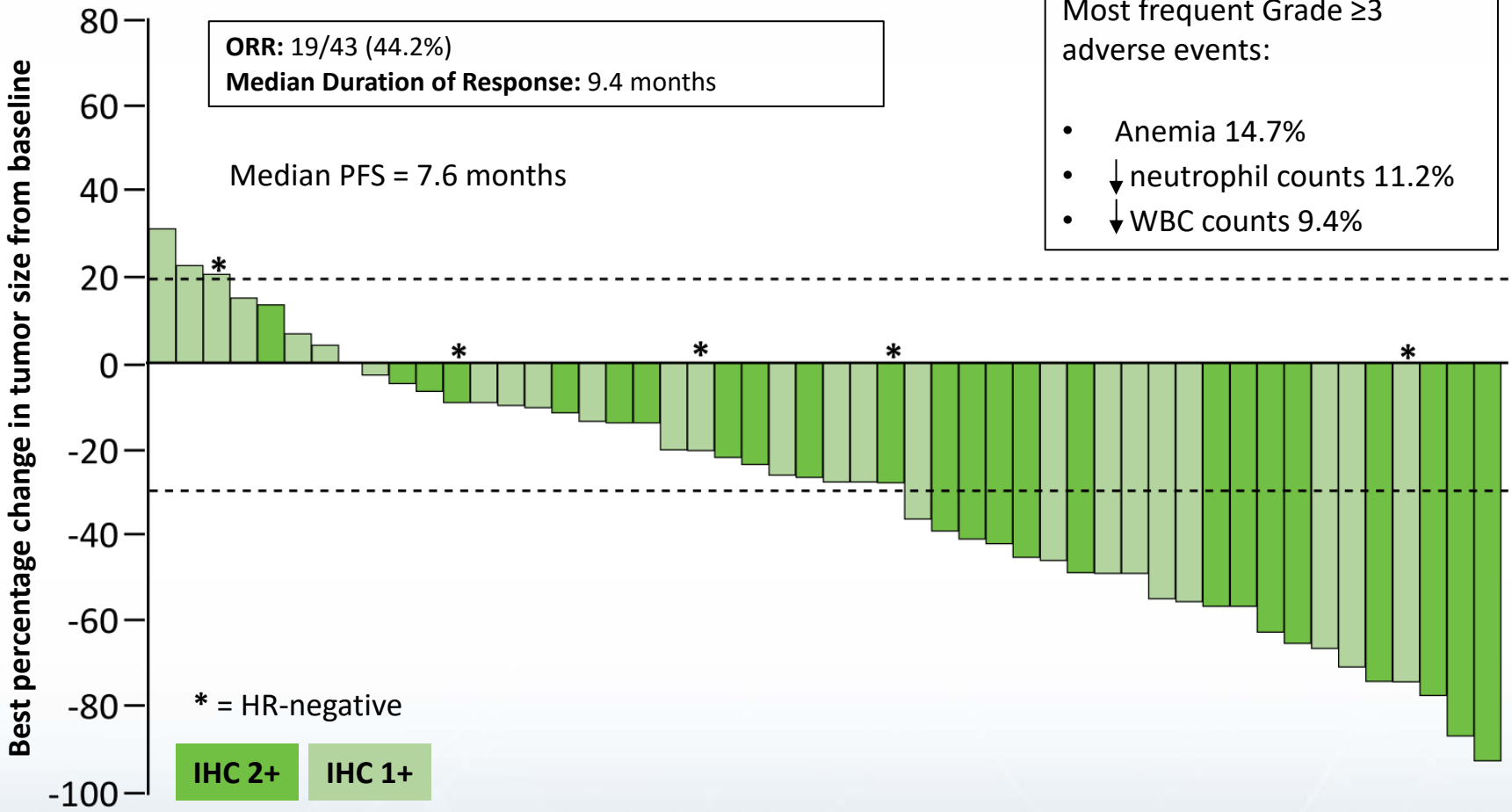
Median PFS	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)	HR (*p*-value)
ITT population	5.8 months	4.9 months	0.78 (0.044)
CD16A (FF or FV)	6.9 months	5.1 months	0.68 (0.005)
CD16A (VV)	4.8 months	5.6 months	1.78 (0.110)



- First interim OS analysis at time of PFS analysis (10/10/18) was immature

Rugo H et al. ASCO 2019;Abstract 1000.

Trastuzumab Deruxtecan for HER2 Low-Expressing Advanced BC



Modi S et al. SABCS 2018;Abstract P6-17-02; Modi S et al. ASCO 2019;Abstract TPS1102.

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Phase II DESTINY-Breast01 Trial Meets Its Primary Endpoint

Press Release – May 8, 2019

Positive top-line results were announced for the Phase II DESTINY-Breast01 trial of trastuzumab deruxtecan (DS-8201). The HER2-targeting antibody drug conjugate (ADC) was evaluated in patients with HER2-positive, unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine.

"The response rate in DESTINY-Breast01, as assessed by an independent review committee, confirms in a heavily-pretreated, global patient population the unprecedented clinical activity in the recently-published Phase I trial. The safety and tolerability profile of trastuzumab deruxtecan was also consistent with previous experience. These results are expected to support planned global regulatory submissions, including a Biologics License Application with the US Food and Drug Administration (FDA) anticipated in the second half of 2019."

https://www.astrazeneca.com/media-centre/press-releases/2019/trastuzumab-deruxtecan-demonstrated-clinically-meaningful-response-in-patients-with-refractory-her2-positive-metastatic-breast-cancer-a-population-with-high-unmet-need-08052019.html

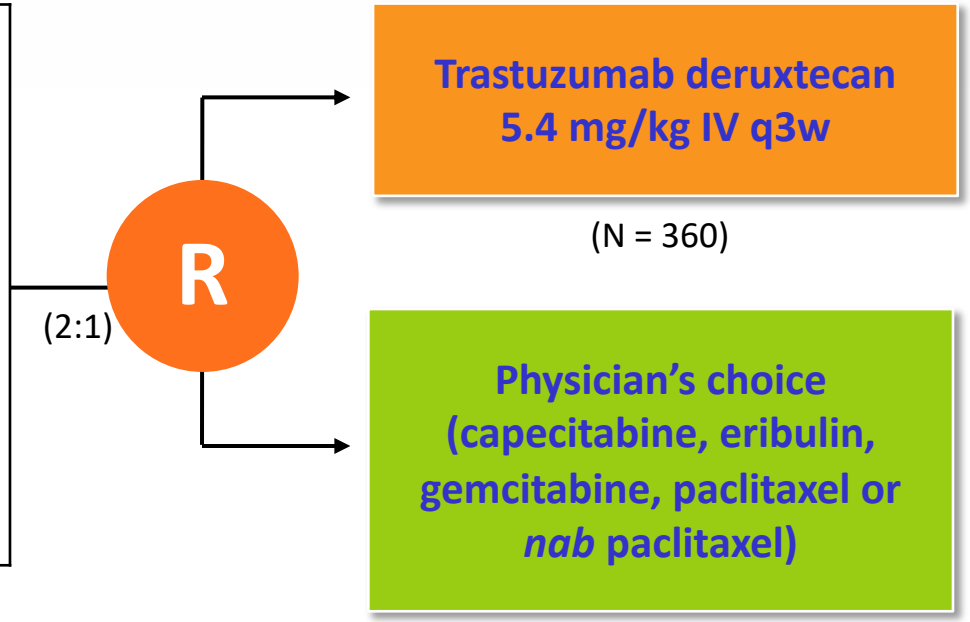
DESTINY-Breast04 Phase III Trial Schema

Target Accrual: 540

Unresectable and/or metastatic HER2-low BC (IHC 2+/ISH- or IHC 1+)

HER2 status is centrally confirmed and is based on ASCO-CAP 2018 guidelines using archival or fresh biopsy tissue samples

If archival tissue is not available, a fresh biopsy is required



Randomization is stratified by

- HER2 IHC status (HER2 IHC 1+ vs HER2 IHC 2+/ISH-)
- Number of prior lines of chemotherapy (1 vs 2)
- HR/CDK status (HR+ with prior CDK4/6 inhibitor treatment vs HR+ without prior CDK4/6 inhibitor treatment vs HR-)

Primary endpoint: Progression-free survival per modified RECIST v1.1 by blinded independent central review

Modi S et al. ASCO 2019;Abstract TPS1102.

Questions?

To view the slides please visit
www.ResearchToPractice.com/Meetings/Slides