Oncology Grand Rounds

New Agents and Strategies in Breast Cancer

Tuesday, May 26, 2020

5:00 PM – 6:30 PM ET

Faculty

Virginia Kaklamani, MD, DSc

Marissa Marti, APRN, AGNP-C, AOCNP

Joyce O'Shaughnessy, MD

Daniel G Pizana, MSN-FNP, OCN

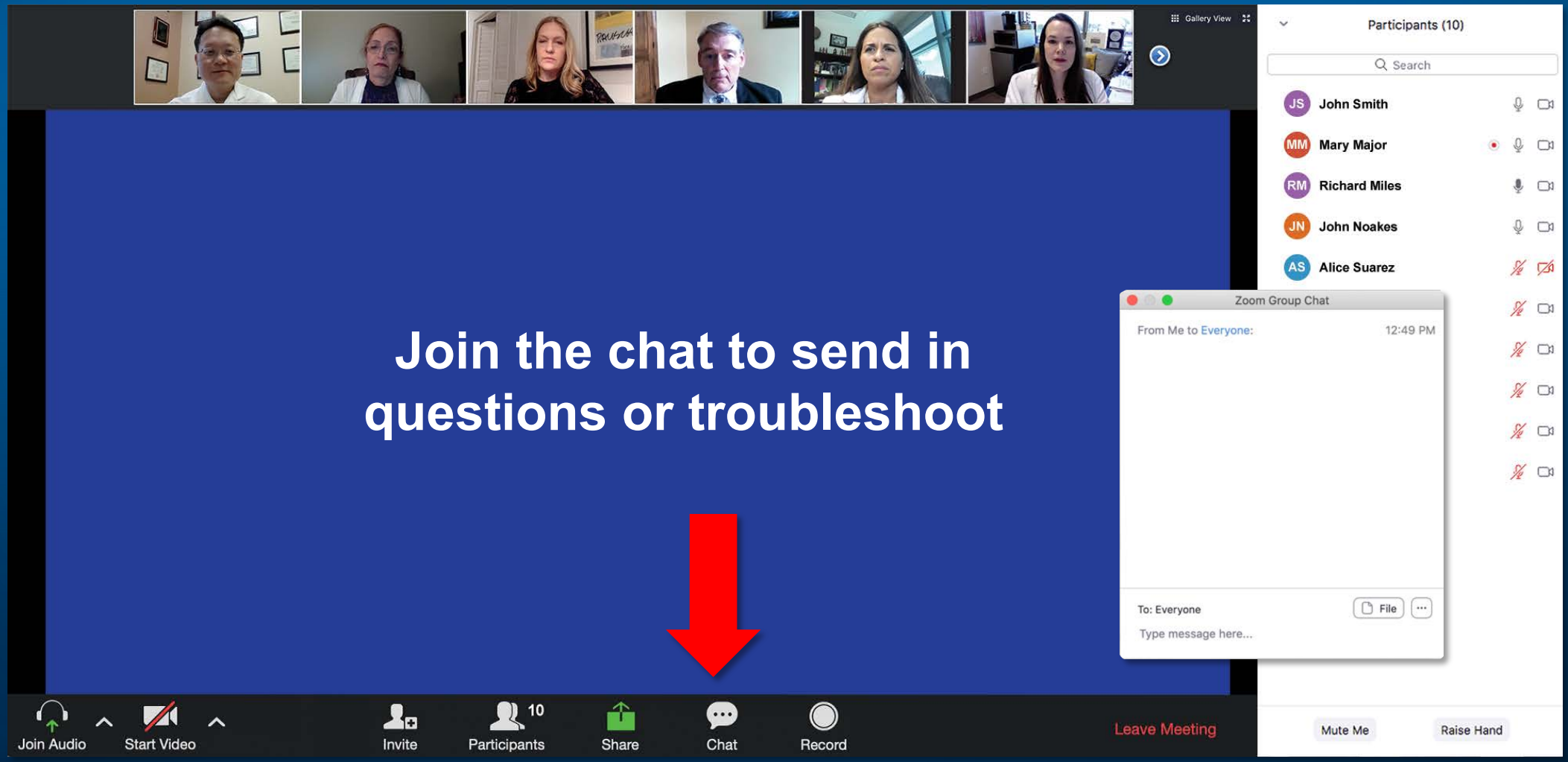
Moderator

Neil Love, MD

Research To Practice®

Familiarizing yourself with the Zoom interface

How to participate in the chat



RTP Live Webinar Nursing Series

May 26th	**Breast Cancer** 5:00 PM – 6:30 PM
May 28th	**Gastrointestinal Cancers** 5:00 PM – 6:30 PM
June 2nd	**Hodgkin and Non-Hodgkin Lymphomas** 5:00 PM – 6:30 PM
June 4th	**Chronic Lymphocytic Leukemia** 5:00 PM – 6:30 PM
June 9th	**Gynecologic Cancers** 5:00 PM – 6:30 PM
June 11th	**Metastatic Lung Cancer** 5:00 PM – 6:30 PM
June 16th	**Locally Advanced Non-Small Cell Lung Cancer** 5:00 PM – 6:30 PM
June 18th	**Urothelial Bladder Carcinoma** 5:00 PM – 6:30 PM
June 23rd	**Chimeric Antigen Receptor T-Cell Therapy** 5:00 PM – 6:30 PM
June 25th	**PARP Inhibition in the Management of Common Cancers** 5:00 PM – 6:30 PM
June 30th	**Prostate Cancer** 5:00 PM – 6:30 PM

Oncology Grand Rounds
Gastrointestinal Cancers

Nurse and Physician Investigators Discuss New Agents, Novel Therapies and Actual Cases from Practice

Thursday, May 28, 2020

Faculty

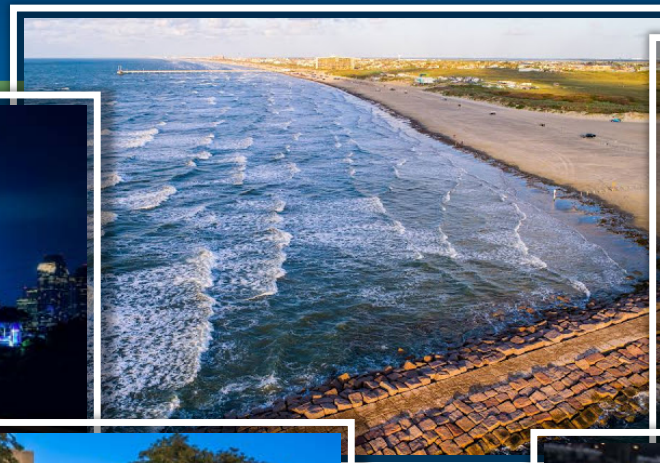
Melony Avella-Howell, NP
Wells A Messersmith, MD
Philip A Philip, MD, PhD, FRCP
Tammy Triglianos, RN, MS, ANP-BC, AOCNP

Moderator

Neil Love, MD

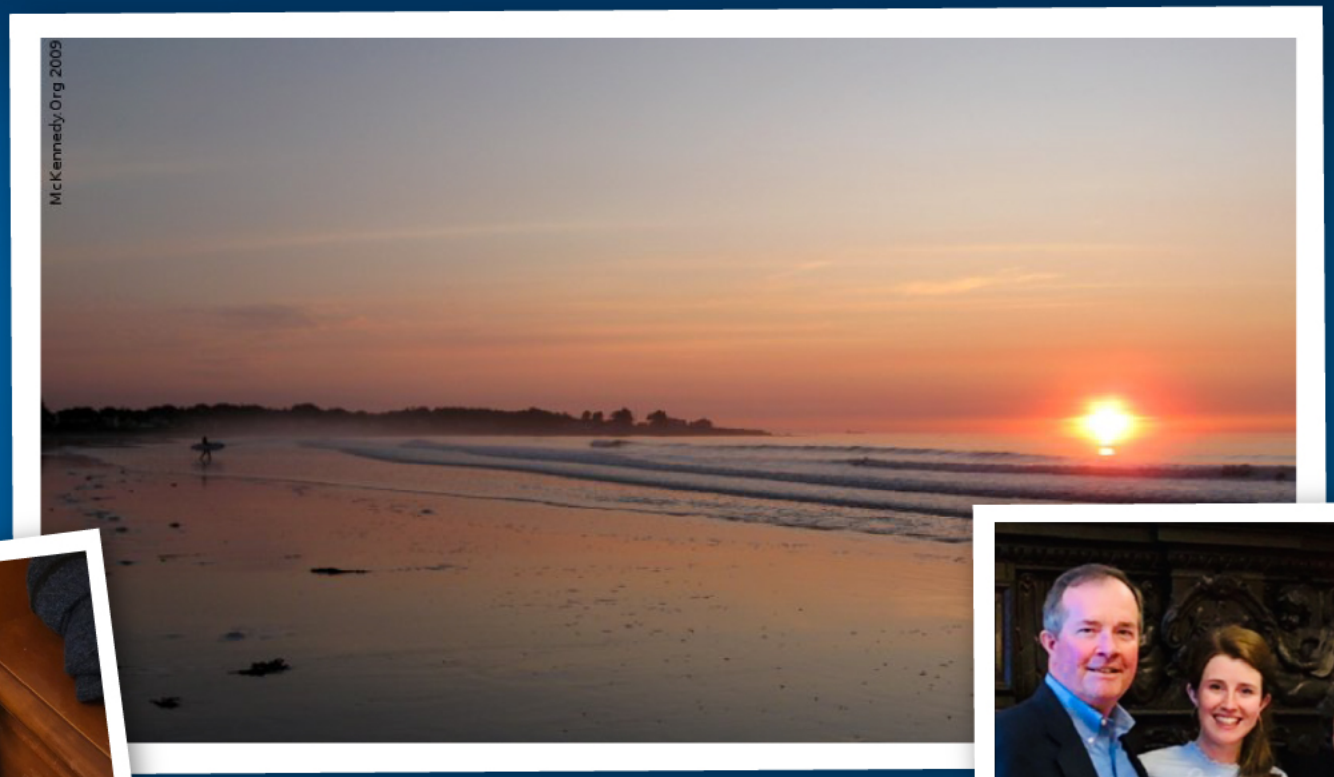
Research To Practice®

All Things Texas



Virginia Kaklamani, MD, DSc
The University of Texas
MD Anderson Cancer Center
San Antonio, Texas

Joyce O'Shaughnessy, MD
Baylor University Medical Center
Dallas, Texas



Marissa Marti, APRN, AGNP-C, AOCNP
Texas Oncology-Baylor Charles A Sammons Cancer Center
Dallas, Texas

Daniel G Pizana, MSN-FNP, OCN
UT Health San Antonio Mays Cancer Center
Breast Oncology Clinic
San Antonio, Texas

Oncology Grand Rounds

Nurse and Physician Investigators Discuss New Agents, Novel Therapies and Actual Cases from Practice

Part 5: Breast Cancer



Faculty

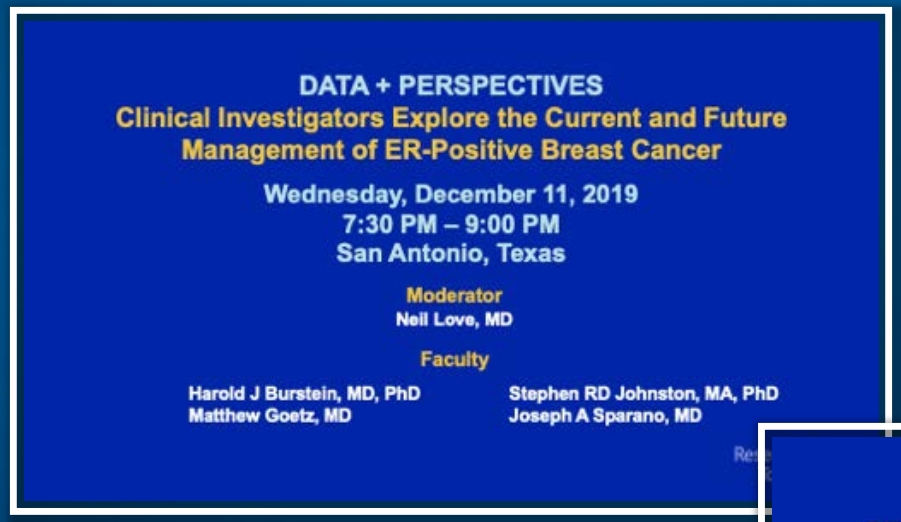
Jamie Carroll, APRN, MSN, CNP
Erika Hamilton, MD
Elizabeth O'Reilly, RN, NP, MSN, MPH
Hope S Rugo, MD

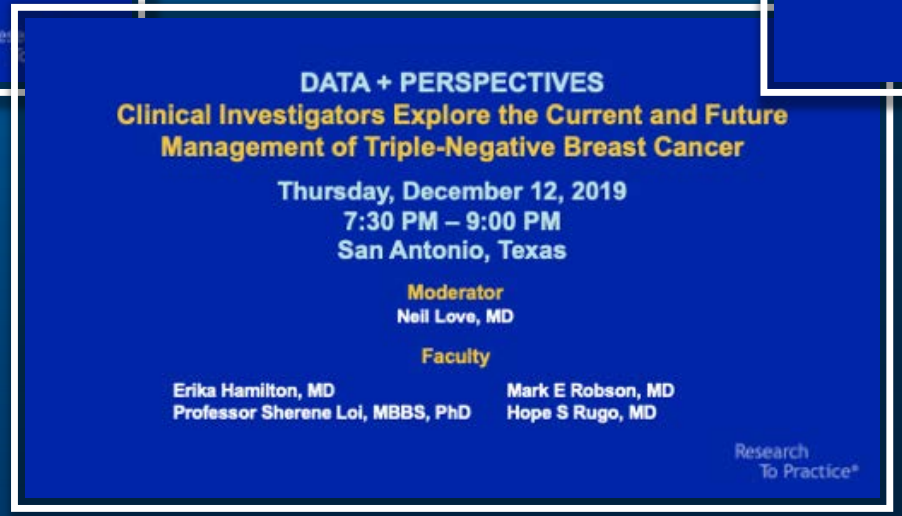
Thursday, April 11, 2019

6:00 PM – 8:00 PM

Anaheim Marriott
Anaheim, California

Research To Practice's 2019 San Antonio Breast Cancer Symposia





Agenda

Module 1: Management of HER2-Positive Breast Cancer

- Neoadjuvant, adjuvant treatment of localized disease
- New agents, regimens in metastatic disease

Module 2: Anti-PD-1/PD-L1 Antibodies, Novel Agents in Triple-Negative Breast Cancer (TNBC)

- Metastatic TNBC: Atezolizumab/*nab* paclitaxel, pembrolizumab/chemotherapy
- Neoadjuvant pembrolizumab/chemotherapy in localized TNBC
- Recent FDA approval of sacituzumab govitecan

Module 3: Genomic Testing and PARP Inhibitors

- Germline and somatic mutation testing
- Indications for and selection of available PARP inhibitors (olaparib, talazoparib)

Module 4: CDK4/6 and PI3 Kinase Inhibitors in ER-Positive Disease

- Current role of CDK4/6 inhibitors for pre- and postmenopausal women
- Alpelisib/fulvestrant (PIK3CA mutation)

Module 5: Management of Breast Cancer in the Era of COVID-19

Module 1: Management of HER2-Positive Breast Cancer

- **Neoadjuvant, Adjuvant Treatment of Localized Disease**
  - Pertuzumab and neratinib for patients with higher-risk disease
  - T-DM1 as adjuvant and postneoadjuvant therapy
- **New Agents, Regimens in Metastatic Disease**
  - Neratinib/capecitabine, tucatinib, trastuzumab deruxtecan

A 60-year-old woman presents with a palpable 2.5-cm breast mass that on biopsy is diagnosed as an ER-negative, HER2-positive infiltrating ductal carcinoma (IDC). Biopsy of a small axillary lymph node is positive. In general, the most common next step in this situation is…

a. Surgery to remove the primary tumor and axillary dissection followed by systemic therapy

b. Neoadjuvant systemic therapy followed by surgery

c. Either a or b

d. Neither a nor b

e. I don’t know

A patient with a HER2-positive IDC responds to neoadjuvant chemotherapy and trastuzumab/pertuzumab, but at surgery residual disease is detected. In general, the most common next treatment is…

a. Trastuzumab

b. Trastuzumab/pertuzumab

c. T-DM1

d. Any of the above

e. I don’t know

The toxicity associated with pertuzumab most likely to affect patient quality of life is…

a. Hand-foot syndrome

b. Peripheral neuropathy

c. Diarrhea

d. I don’t know

Patients who receive postadjuvant neratinib after chemotherapy/anti-HER2 therapy for HER2-positive localized breast cancer have a significant reduction in the risk of recurrence if the tumor is…

a. ER-positive

b. ER-negative

c. Both a and b

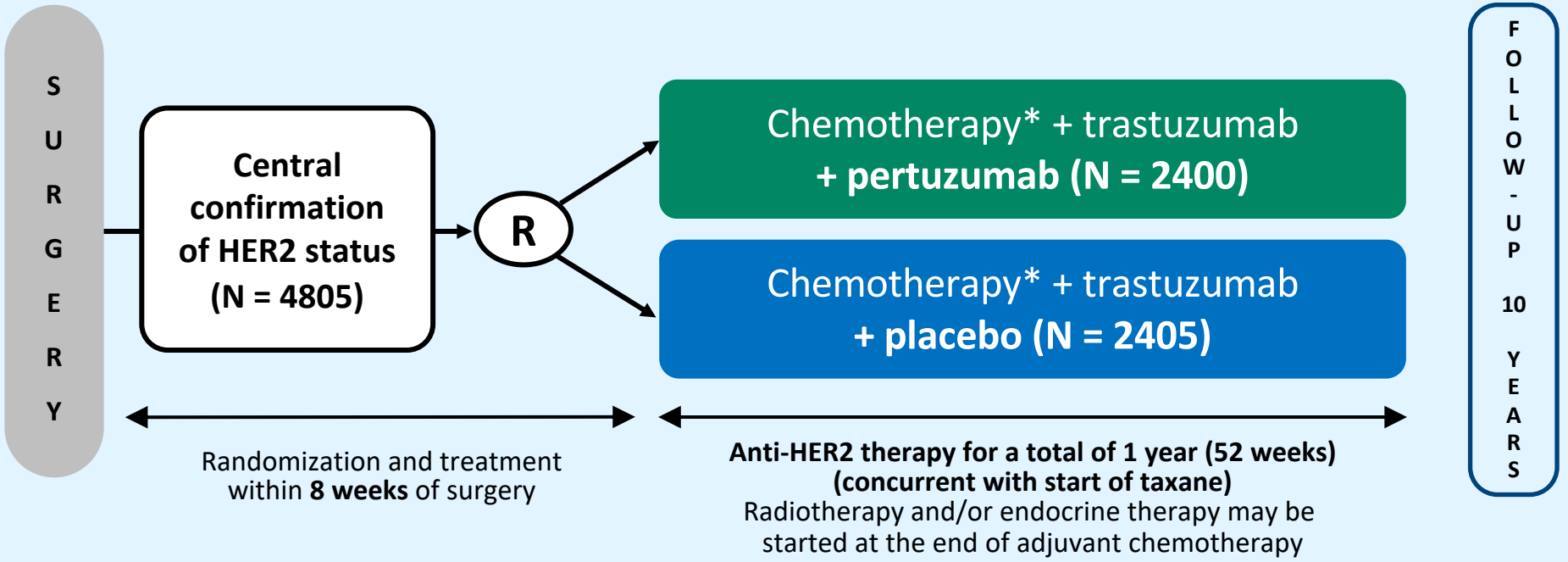
d. Neither a nor b

e. I don’t know

The most common side effect/toxicity of neratinib is…

a. Hand-foot syndrome
b. Diarrhea
c. Cytopenias
d. I don’t know

APHINITY: A Phase III adjuvant study investigating the benefit of pertuzumab when added to trastuzumab + chemotherapy



* Standard anthracycline or non-anthracycline (TCH) regimens were allowed: 3–4 x FEC (or FAC) → 3–4 x TH; 4 x AC (or EC) → 4 x TH; 6 x TCH

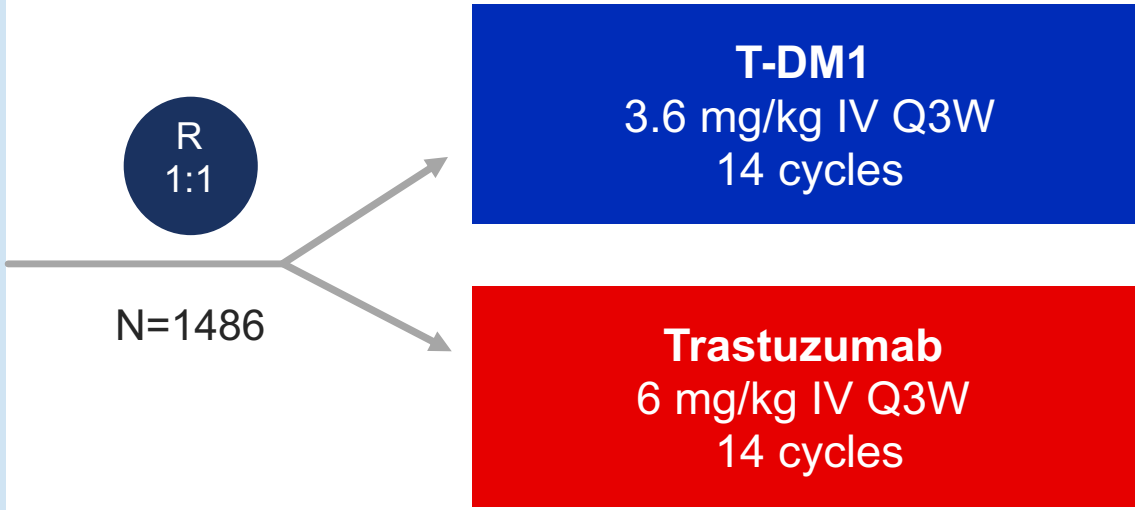
- **Primary endpoint:** IDFS (APHINITY definition differs from STEEP definition)
- **Secondary endpoint:** IDFS with 2nd primary non-breast primary cancers included, DFS, OS, RFI, DRFI, safety, and HRQoL
- **Stratification factors:** nodal status, HR status, chemotherapy regimen, geographic region, Protocol version (A vs. B)
- **Clinical cut off date (CCOD)** at the time of primary analysis was 19 Dec 2016, median follow up of 45.4 months

DFS, disease-free survival; DRFI, distant relapse-free interval; HR, hormone receptor; HRQoL, health-related quality of life; IDFS, invasive disease-free survival; OS, overall survival; RFI, relapse-free interval

Adapted from von Minckwitz et al. N Engl J Med 2017
www.clinicaltrials.gov/ct2/show/NCT01358877

KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



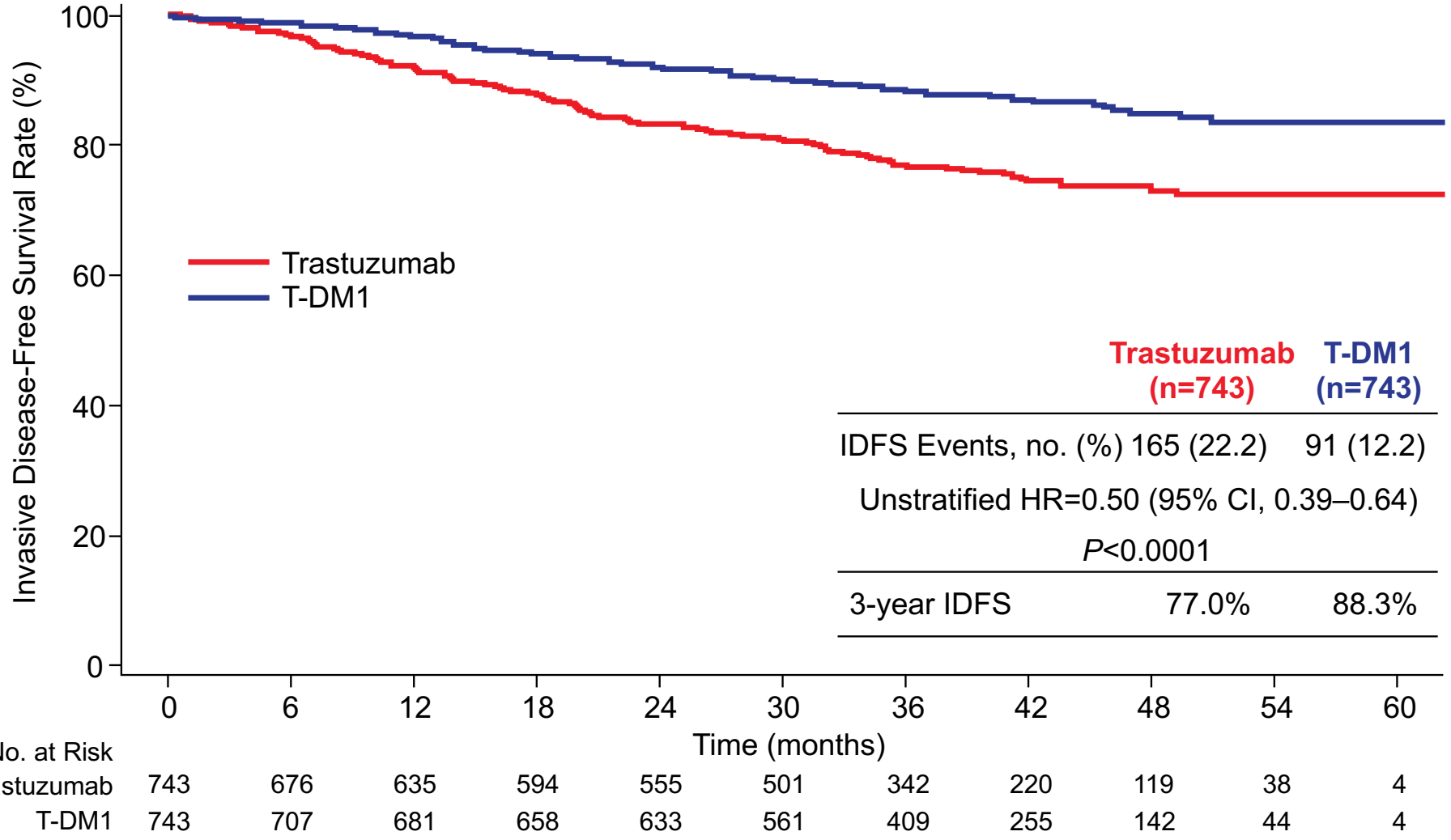
Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:

- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Geyer CE et al. SABCS 2018;Abstract GS1-10.

Invasive Disease-Free Survival



	Trastuzumab (n=743)	T-DM1 (n=743)
IDFS Events, no. (%)	165 (22.2)	91 (12.2)
Unstratified HR=0.50 (95% CI, 0.39–0.64)		
P<0.0001		
3-year IDFS	77.0%	88.3%

Geyer CE et al. SABCS 2018;Abstract GS1-10.

Safety Overview

	Trastuzumab n=720	T-DM1 n=740
Number of patients with at least one, n (%)		
Grade ≥3 AEs	111 (15.4)	190 (25.7)
Serious AEs	58 (8.1)	94 (12.7)
AE leading to treatment discontinuation	15 (2.1)	133 (18.0)
AE with fatal outcome^	0	1 (0.1)

^Fatal AE was intracranial hemorrhage diagnosed after a fall with platelet count of 55,000.

Geyer CE et al. SABCS 2018;Abstract GS1-10.

Study Design: ATEMPT Trial

Key Eligibility Criteria

- Stage 1 HER2+ breast cancer
  - HER2 centrally tested (ASCO CAP 2013 guidelines)
- N0 or N1mic
- Left Ventricular EF ≥ 50%
- No prior invasive breast cancer
- ≤90 days from last surgery

N = 497

R 3:1

3

1

N = 383

T-DM1

3.6 mg/kg IV q3 wks x 17

N = 114

TH

Paclitaxel 80 mg/m^2 IV + Trastuzumab 2 mg/kg IV wkly x12 → Trastuzumab 6 mg/kg every 3 wks x13

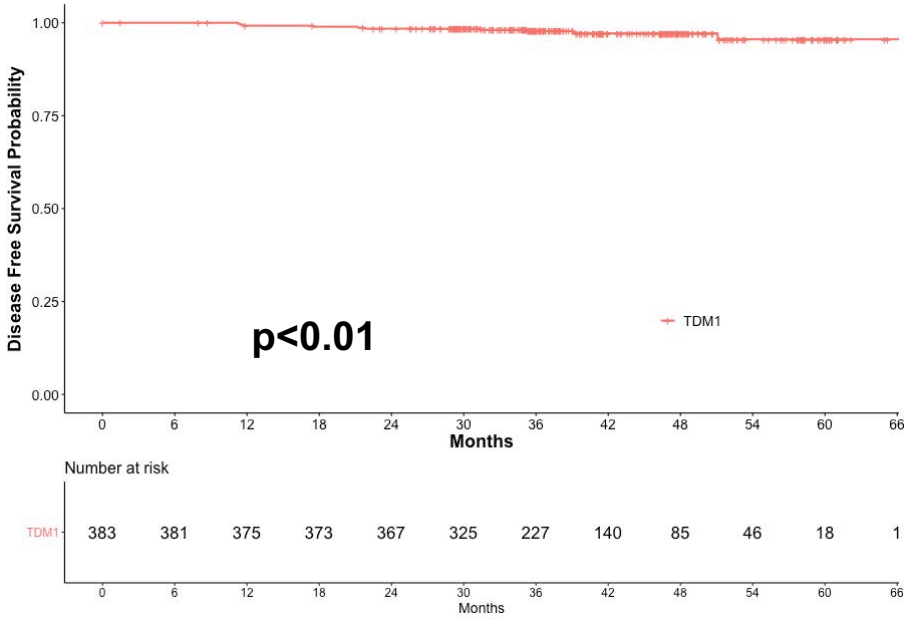
Stratification factors:

- Age (<55, ≥55)
- Planned radiation (Yes/No)
- Planned hormonal therapy (Yes/No)

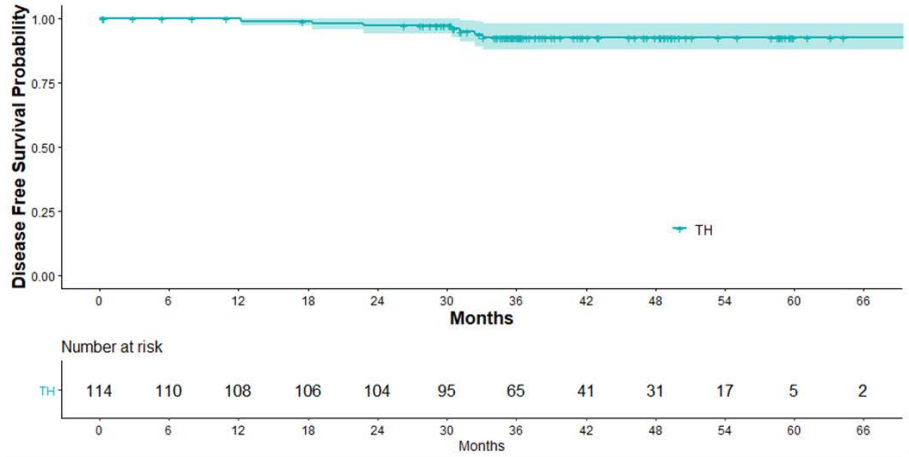
Radiation and endocrine therapy could be initiated after 12 weeks on study therapy

Tolaney SM et al. SABCS 2019;Abstract GS1-05.

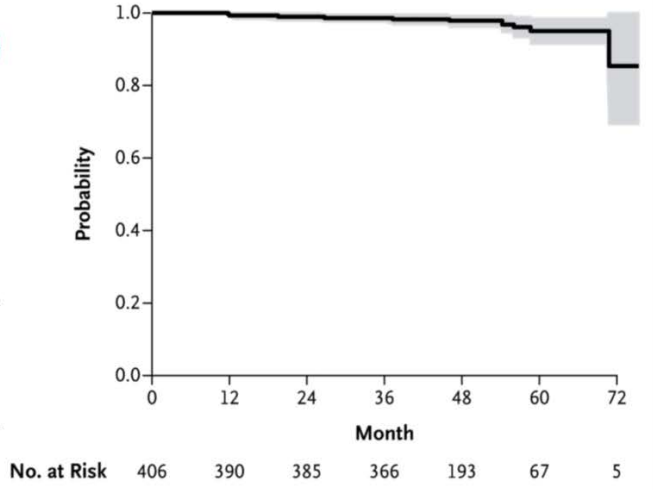
Disease-Free Survival: T-DM1



Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
T-DM1	383	10	97.7%	96.2-99.3%



Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
TH	114	7	92.8%	87.8-98.1%



Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
TH	406	12	98.7%	97.6-99.8%

Tolaney SM et al. SABCS 2019;Abstract GS1-05.

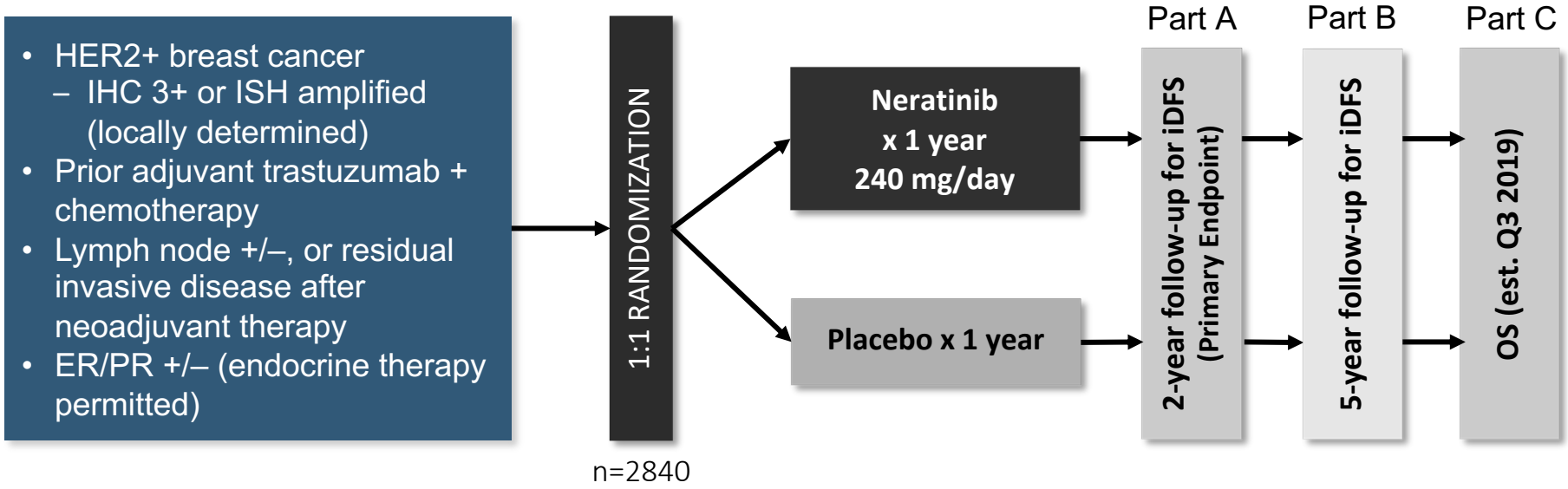
Clinically Relevant Toxicity

Clinically Relevant Toxicity	T-DM1 (n = 383) N (%)	TH (n = 114) N (%)
Grade ≥3 non-hematologic toxicity	37 (10%)	13 (11%)
Grade ≥2 neurotoxicity	42 (11%)	26 (23%)
Grade ≥4 hematologic toxicity	4 (1%)	0 (0%)
Febrile neutropenia	0 (0%)	2 (2%)
Any toxicity requiring dose delay	106 (28%)	30 (26%)
Any toxicity requiring early discontinuation	67 (17%)	7 (6%)
Total	176 (46%)	53 (46%)

Tolaney SM et al. SABCS 2019;Abstract GS1-05.

p=0.91

ExteNET: Study Design



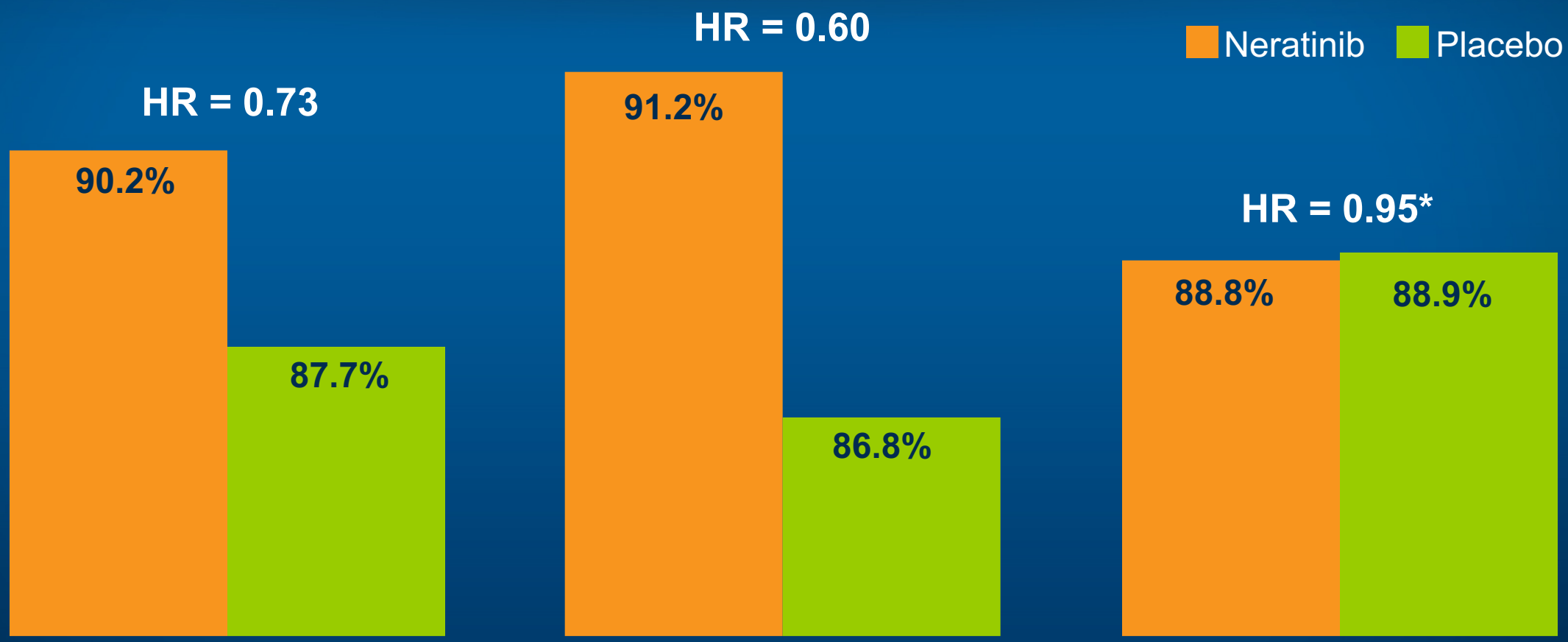
Primary endpoint:	invasive disease-free survival (iDFS)
Secondary endpoints:	DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, OS, safety
Other analyses:	biomarkers, health outcome assessment (FACT-B, EQ-5D)
Stratified by:	nodes 0, 1–3 *vs.* 4+, ER/PR status, concurrent *vs.* sequential trastuzumab

Follow-up for overall survival is ongoing (estimated: Q3 2019)

CNS=central nervous system; DCIS=ductal carcinoma in situ; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=in situ hybridization; PR=progesterone receptor; OS=overall survival.

Martin et al. Lancet Oncol. 2017;18(12):1688-1700. NCT00878709

ExteNET: Five-Year Invasive Disease-Free Survival by Patient Population

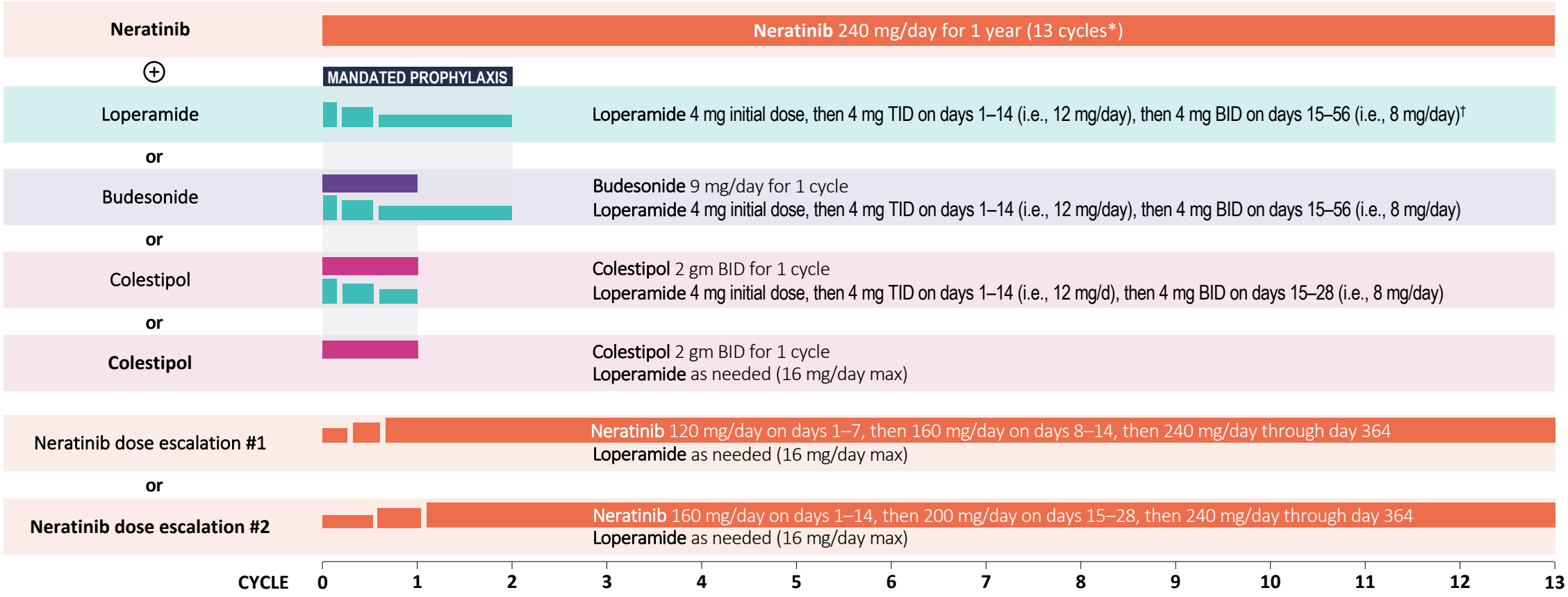


* Not statistically significant

Martin M et al. *Lancet Oncol* 2017;18(12):1688-700; Martin M et al. ESMO 2017;Abstract 149O.

CONTROL Study Schema

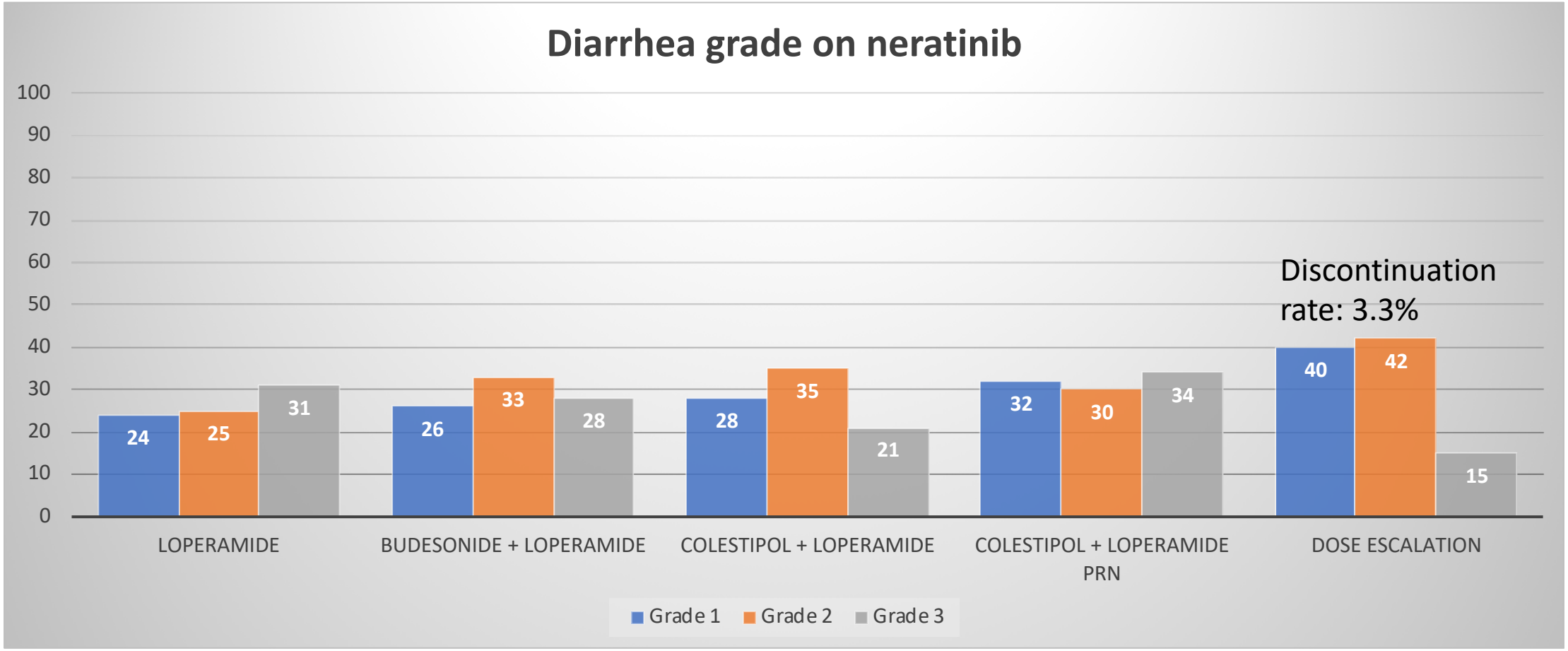
- Prophylactic study to prevent and manage neratinib-associated diarrhea
  - Stage I-IIIc HER2+ disease; prior therapy allowed: endocrine therapy, **pertuzumab, and T-DM1**



*One cycle=28 days. †Under the original protocol, subjects received loperamide 4 mg initial dose, 2 mg every 4 hours days 1–3, and 2 mg every 6 to 8 hours days 4–56 (n=28) before the "standard" loperamide regimen of 4 mg initial dose, 4 mg TID for 14 days and 4 mg BID days 14–56 was introduced (n=109). All subjects received loperamide as needed (16 mg/day max) after completion of mandated loperamide prophylaxis.

Barcenas et al. ASCO 2019 #548.

CONTROL Trial



Barcenas CH et al. ASCO 2019

56-year-old woman (from the practice of Mr Pizana)

- 11/2018: Presents with left breast pain and nipple inversion → Mammography
- Pathology (lymph node): Grade 3, triple-positive (ER: >95%, PR: 75%, HER2: 2+) IDC, with lobular features, positive lymph node
- 3/28/2019: Completed neoadjuvant TCHP x 6
  - Gr 1 fatigue, diarrhea, nausea/vomiting
  - Lost to follow-up, noncompliance
- 8/02/2019: Left mastectomy, ALND, tissue expander
  - 1.2-cm, pT2c pN3a, Nodes 15+ with residual disease
- 9/26/2019: Switched to T-DM1, initiated anastrozole
- 11/2019: RT
- Currently, on cycle 11 of T-DM1
- Plan to initiate neratinib after completion of T-DM1

43-year-old woman (from the practice of Mr Pizana)

- 5/2018: Right, Grade 3, ER-positive (90%), PR-positive (2%), HER2-positive IDC
  - Lumpectomy (pT2pN0)
  - AC x 4 → weekly paclitaxel and trastuzumab → RT → tamoxifen
- 11/2019: Neratinib
  - Initial diarrhea controlled with loperamide and budesonide
- Currently, remains on neratinib and doing well

Module 1: Management of HER2-Positive Breast Cancer

- **Neoadjuvant, Adjuvant Treatment of Localized Disease**
  - Pertuzumab and neratinib for patients with higher-risk disease
  - T-DM1 as adjuvant and postneoadjuvant therapy
- **New Agents, Regimens in Metastatic Disease**
  - Neratinib/capecitabine, tucatinib, trastuzumab deruxtecan

The recently approved agent tucatinib is classified as which type of anti-HER2 agent?

a. Monoclonal antibody

b. Antibody-drug conjugate

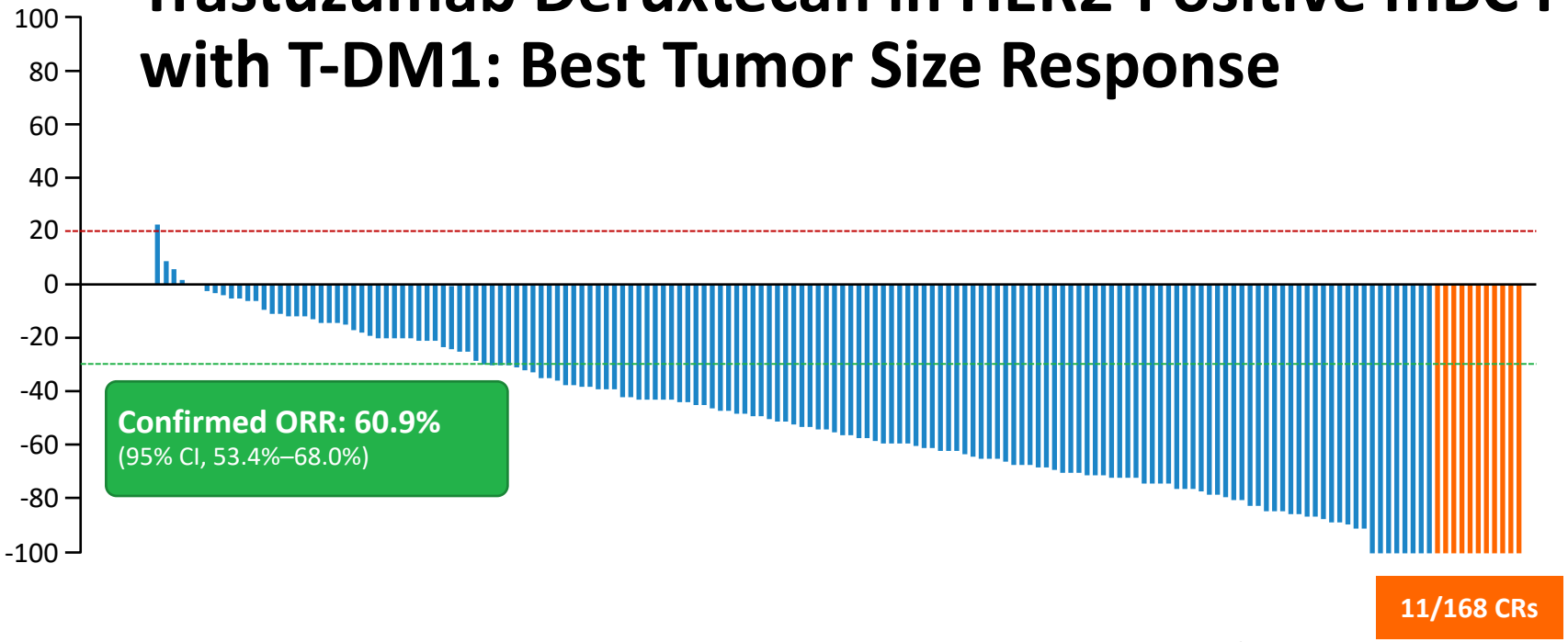
c. Small molecule tyrosine kinase inhibitor

d. I don’t know

Trastuzumab deruxtecan carries a black box warning for…

a. QT interval prolongation
b. Interstitial lung disease
c. Cardiovascular events
d. I don’t know

Trastuzumab Deruxtecan in HER2-Positive mBC Previously Treated with T-DM1: Best Tumor Size Response



Patients who received T-DXd 5.4 mg/kg (N=184)

Preferred Term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial lung disease	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**

Median time from the first infusion of T-DXd to onset of ILD was 27.6 weeks (range, 6-76 weeks)

Krop IE et al. SABCS 2019;Abstract GS1-03.

HER2CLIMB Trial Design

Key Eligibility Criteria

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

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
(21-day cycle)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

Placebo + Trastuzumab + Capecitabine
(21-day cycle)

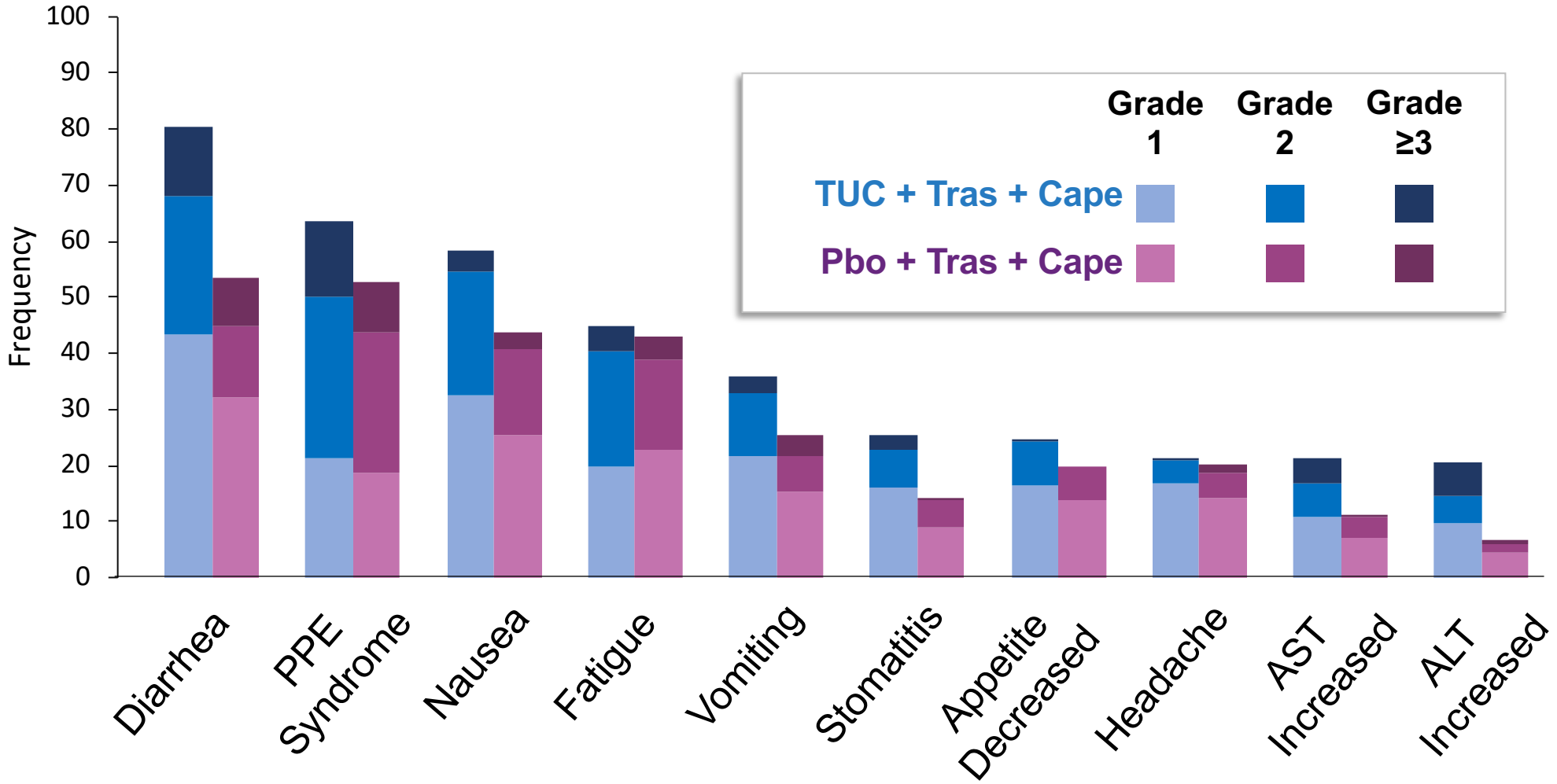
Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

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

https://clinicaltrials.gov/ct2/show/NCT02614794

Murthy R et al. SABCS 2019;Abstract GS1-01.

Most Common Adverse Events (≥20% in the Tucatinib Arm)



PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

Murthy R et al. SABCS 2019;Abstract GS1-01.

75-year-old woman (from the practice of Dr Kaklamani)

- Presents with ER-negative, HER2-positive mBC, with a breast mass and liver metastases
- Paclitaxel, trastuzumab and pertuzumab x 2 years → PD
- T-DM1
  - Not tolerated due to low blood counts
- Capecitabine/lapatinib
  - Capecitabine discontinued due to tolerability issues
  - Lapatinib continued x 8 cycles → PD
- Tucatinib/trastuzumab
- Currently on treatment and doing well

40-year-old woman (from the practice of Dr O'Shaughnessy)

- Stage III ER/PR-negative, HER2-positive breast cancer
- Neoadjuvant TCHP (pCR in breast and axilla)
- Currently, S/P SRS for brain met, but still with multiple, small untreated brain mets
- Tucatinib + trastuzumab (tolerating well)
- Initiating lower-dose capecitabine and will increase dose as tolerated

34-year-old woman (from the practice of Dr Kaklamani)

- Presents with a 3.5-cm, ER-negative, HER2-positive mass in left breast
- Neoadjuvant TCHP and atezolizumab on a clinical trial
  - 2-cm residual disease after completion of neoadjuant therapy
- T-DM1 x 14 cycles
  - Remained disease free x 6 months → liver metastases
- Trastuzumab deruxtecan
  - Currently receiving her third cycle

55-year-old woman (from the practice of Dr O'Shaughnessy)

- ER/PR-negative, HER2-positive breast cancer
- Neoadjuvant TCHP → mastectomy (residual disease) → T-DM1 + RT
- Recurrence in left axilla, with multiple 1-2 cm nodules (ER-neg, HER2+)
- Capecitabine/trastuzumab (no response)
- Ibrutinib/trastuzumab on trial (no response)
- Axillary disease grew into a confluent flat mass across anterior axilla and ventral surface of her upper arm
- Trastuzumab deruxtecan
  - After 1 cycle: Major response
  - After 2 cycles: Axillary mass no longer palpable
  - Tolerating therapy well, mild nausea for 2-3 days after each infusion

Module 2: Anti-PD-1/PD-L1 Antibodies, Novel Agents in Triple-Negative Breast Cancer (TNBC)

- Metastatic TNBC: Atezolizumab/*nab* paclitaxel, pembrolizumab/chemotherapy
- Neoadjuvant pembrolizumab/chemotherapy in localized TNBC
- Recent FDA approval of sacituzumab govitecan

The anti-PD-L1 antibody atezolizumab is currently FDA approved in combination with *nab* paclitaxel as first-line treatment for…

a. All patients with metastatic breast cancer

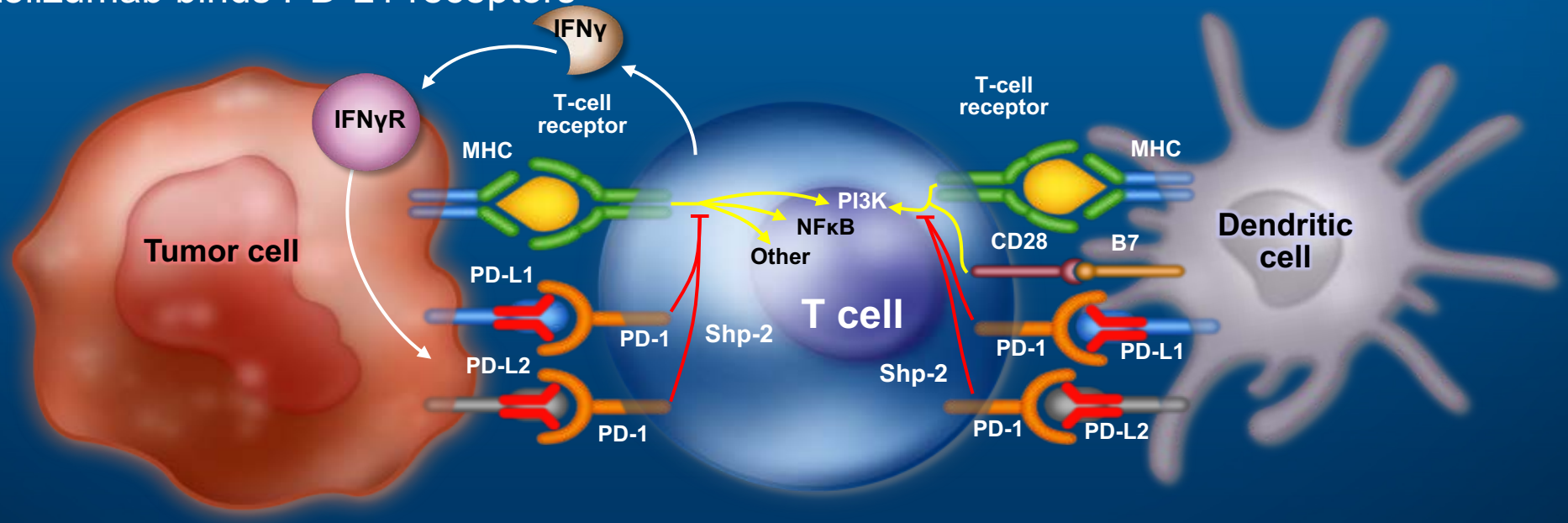
b. Metastatic triple-negative breast cancer

c. Metastatic PD-L1-positive triple-negative breast cancer

d. I don’t know

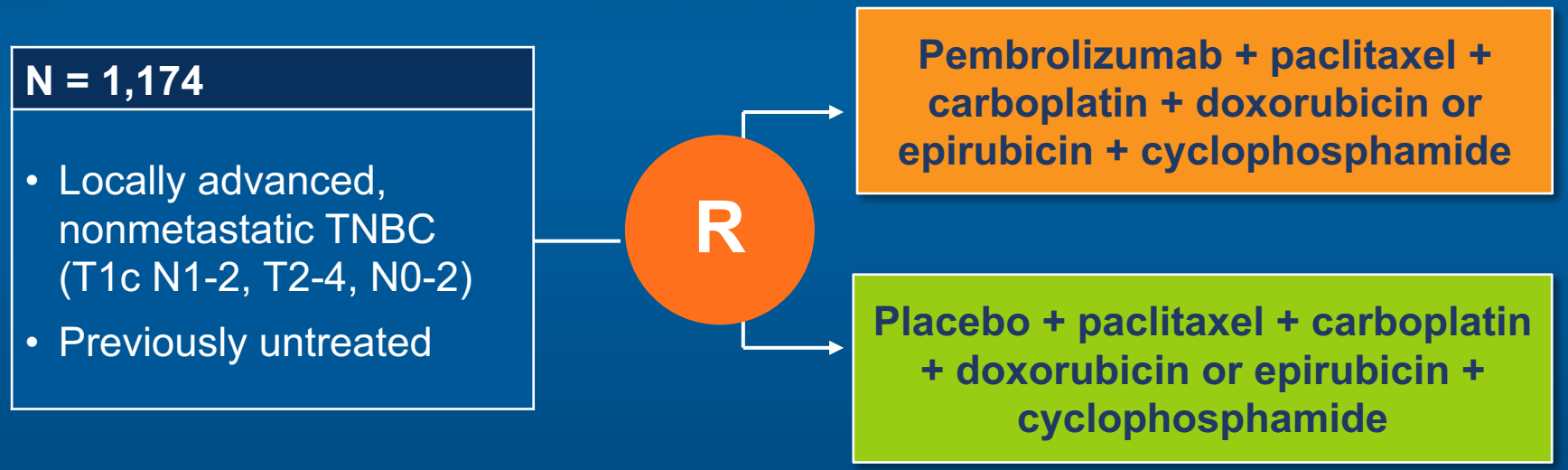
Anti-PD-1/PD-L1 Antibodies: Mechanism of Action

- PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function
- 3 approved drugs:
  - Nivolumab/pembrolizumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function
  - Atezolizumab binds PD-L1 receptors



Nivolumab/pembrolizumab: PD-1 receptor blocking Ab
Atezolizumab: PD-L1 receptor blocking Ab

KEYNOTE-522: A Phase III Trial of Neoadjuvant Chemotherapy with Pembrolizumab or Placebo Followed by Adjuvant Pembrolizumab or Placebo for 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. San Antonio Breast Cancer Symposium 2019;Abstract GS3-03; Schmid P et al. ASCO 2018;Abstract TPS602. www.clinicaltrials.gov (NCT03036488).

IMpassion130 Study Design

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + *nab*-P arm:

Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ ***nab*-paclitaxel** 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

Plac + *nab*-P arm:

Placebo IV
- On days 1 and 15 of 28-day cycle

+ ***nab*-paclitaxel** 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

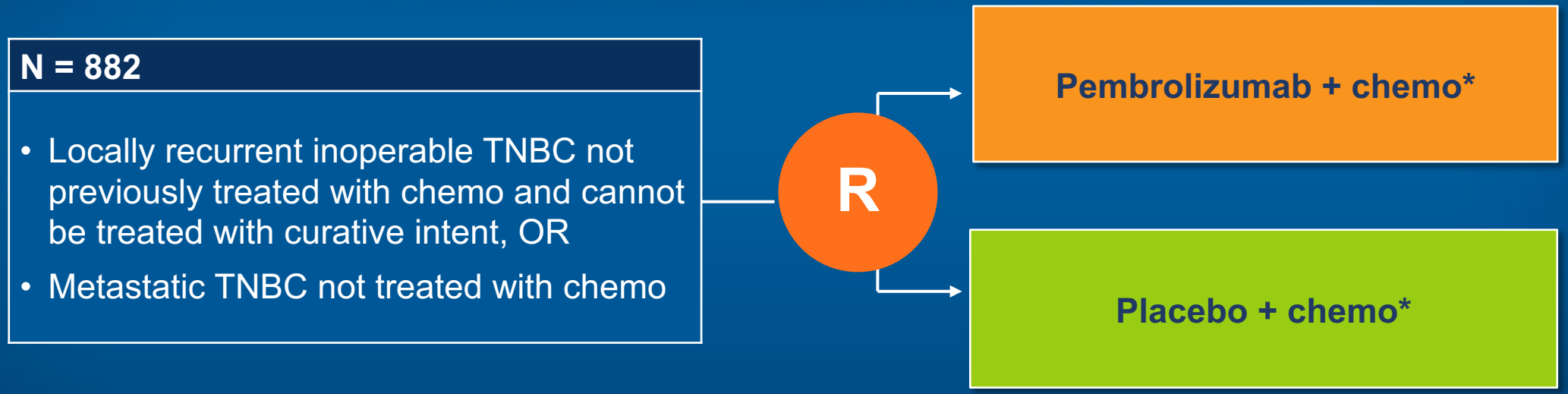
RECIST v1.1
PD or toxicity

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

Schmid P, et al. NEJM 2018, Schmid and Rugo et al, Lancet Oncol 2020

KEYNOTE-355: A Phase III Study of Chemotherapy +/- Pembrolizumab



Primary endpoints: Progression-free and overall survival

- In Part 1, individual chemo regimens combined with pembrolizumab were evaluated.
- In Part 2, participants receive 1 of 3 chemo regimens: *nab* paclitaxel, paclitaxel or gemcitabine/carboplatin.

Cortes J et al. ASCO 2020;Abstract 1000. www.clinicaltrials.gov. Accessed May 24, 2020.

FDA Grants Accelerated Approval to Sacituzumab Govitecan for Metastatic TNBC

Press Release – April 22, 2020

"The Food and Drug Administration granted accelerated approval to sacituzumab govitecan-hziy for adult patients with metastatic triple-negative breast cancer who received at least two prior therapies for metastatic disease.

Efficacy was demonstrated in IMMU-132-01 (NCT 01631552), a multicenter, single-arm trial enrolling 108 patients with metastatic triple negative breast cancer (mTNBC) who received at least two prior treatments for metastatic disease. Patients received sacituzumab govitecan-hziy 10 mg/kg intravenously on days 1 and 8 every 21 days. Tumor imaging was obtained every 8 weeks, and patients were treated until disease progression or intolerance to therapy.

The primary efficacy outcome measures were investigator assessed overall response rate (ORR) using RECIST 1.1 and response duration. The ORR was 33.3%. The median response duration was 7.7 months."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer

67-year-old woman with triple-negative mBC (from the practice of Ms Marti)

- 6/2018: 5-cm, ER-positive, PR-negative, HER2-positive mixed metaplastic and IDC, with LVI
- Neoadjuvant TCHP (no response, PD) → surgery
- Pathology: Grade 3, ER (1-4%), PR-negative, HER2 IHC1+ metaplastic carcinoma, N-negative
- Postmastectomy RT → adjuvant dose-dense AC → capecitabine x 6 mos → adj anastrozole
- 7/2019 New lung nodules, brain mets
- Repeat testing (mastectomy tissue): TNBC, PD-L1 1%
- 10/2019: *Nab* paclitaxel/atezolizumab → atezolizumab alone after 6 mos
  - Minimal side effects; fatigue and hypothyroidism resolved with low-dose levothyroxine
- 2/2020 Brain MRI: Response to SRS
- 4/2020 Chest CT: Negative

Module 3: Genomic Testing and PARP Inhibitors

- Germline and somatic mutation testing
- Indications for and selection of available PARP inhibitors (olaparib, talazoparib)

A germline mutation is found in every cell in the body and a somatic mutation is found in the tumor.

a. Agree

b. Disagree

c. I don’t know

The PARP inhibitors olaparib and talazoparib are FDA approved for patients with metastatic breast cancer and a germline BRCA mutation…

a. As maintenance therapy after platinum chemotherapy

b. As monotherapy

c. Both a and b

d. I don’t know

A higher proportion of TNBC patients have BRCA mutations than HR+ patients…[1,2]

The majority of TNBC are BRCA1m and HR+ tumours are BRCA2m [1,2]

TNBC patients

~17%

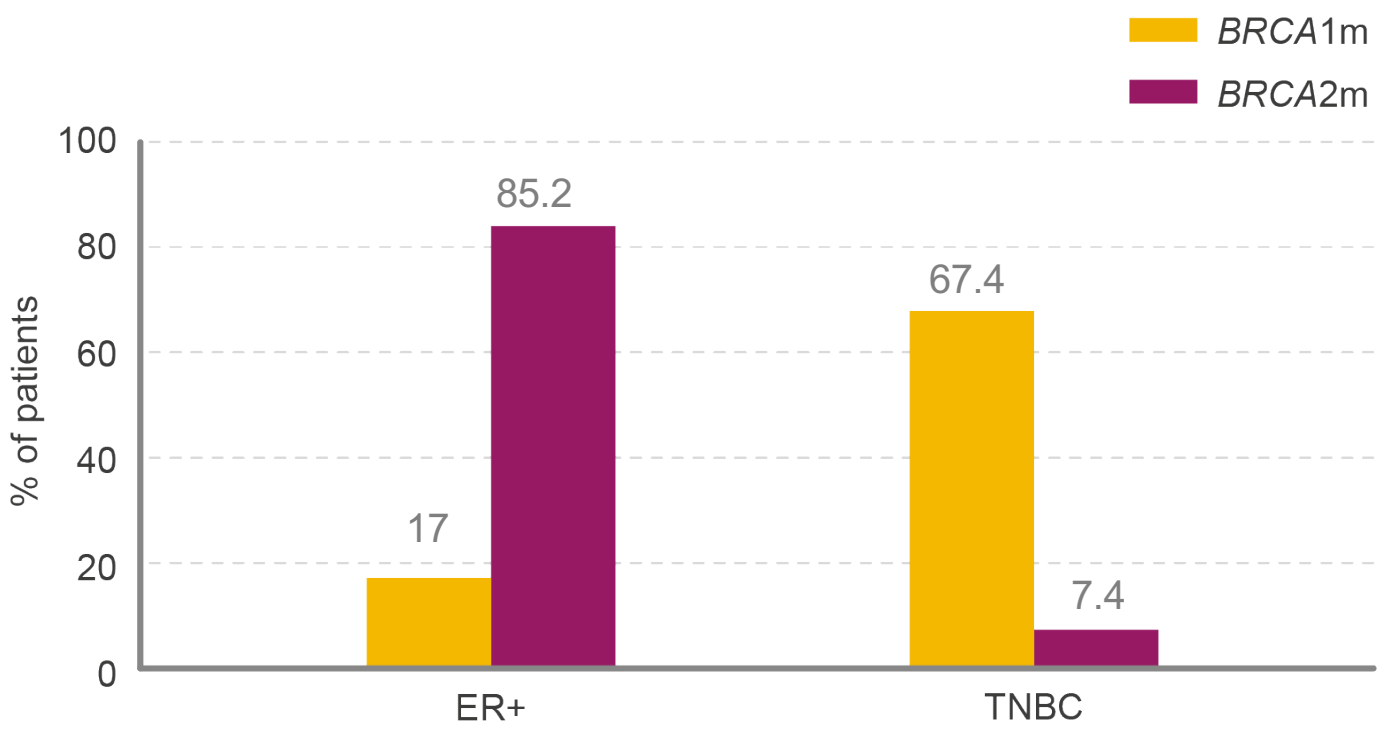
have *BRCA* mutations

HR+ patients

~6%

have *BRCA* mutations

Hormone receptor status in BC patients by *BRCA* status

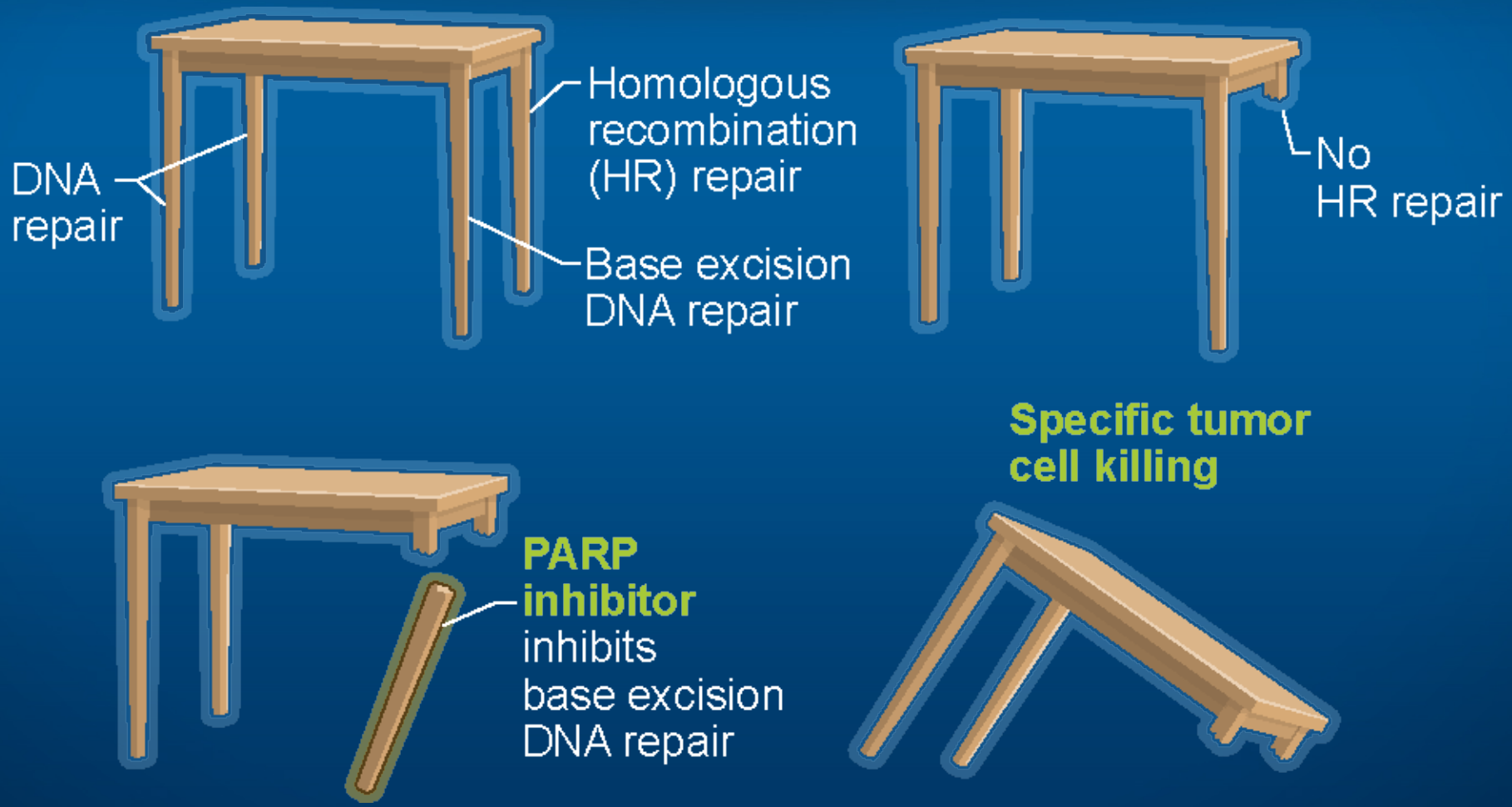


Note that these calculations are based on very small patient populations.
Detailed analysis of *BRCA*m prevalence, age of onset and survival outcomes are currently lacking for breast cancer subtypes.

*BRCA*m=*BRCA* mutation; TNBC=triple negative breast cancer; HR+=hormone receptor positive; ER+=oestrogen receptor positive

1. Winter et al. Ann Oncol. 2016 Aug; 27(8): 1532–1538; 2. Aleskandarany M, et al. Breast Cancer Res Treat. 2015;150:81-90

Mechanism of Cell Death from Synthetic Lethality Induced by PARP Inhibition



Courtesy of Jenny C Chang, MD

Common Side Effects of PARP Inhibitors Olaparib and Talazoparib

Hematologic

- Anemia
- Neutropenia
- Thrombocytopenia (more with talazoparib)

Grade ≥3 in 10% to 40% of patients

Nonhematologic

- Nausea
- Vomiting
- Fatigue

Mostly Grade 1 or 2

Litton JK et al. *N Engl J Med* 2018;379(8):753-63.
Robson M et al. *N Engl J Med* 2017;377(6):523-33.

Phase III trials of PARP inhibitors in gBRCA HER2-negative metastatic breast cancer patients

OlympiAD[1]

gBRCAm HER2- mBC

≤2 prior chemotherapy lines for mBC

Previous treatment with anthracycline and taxane in either the (neo)adjuvant or metastatic setting

Randomise 2:1

Olaparib
300mg *po* bid

Treatment of Physician's Choice (TPC)

Primary endpoint
PFS (BICR)

EMBRACA[2]

gBRCAm HER2- LABC or ABC

≤3 prior lines of chemotherapy

Previous treatment with a taxane, an anthracycline, or both, unless this treatment was contraindicated

Randomise 2:1

Talazoparib
1mg *po* qd

Treatment of Physician's Choice (TPC)

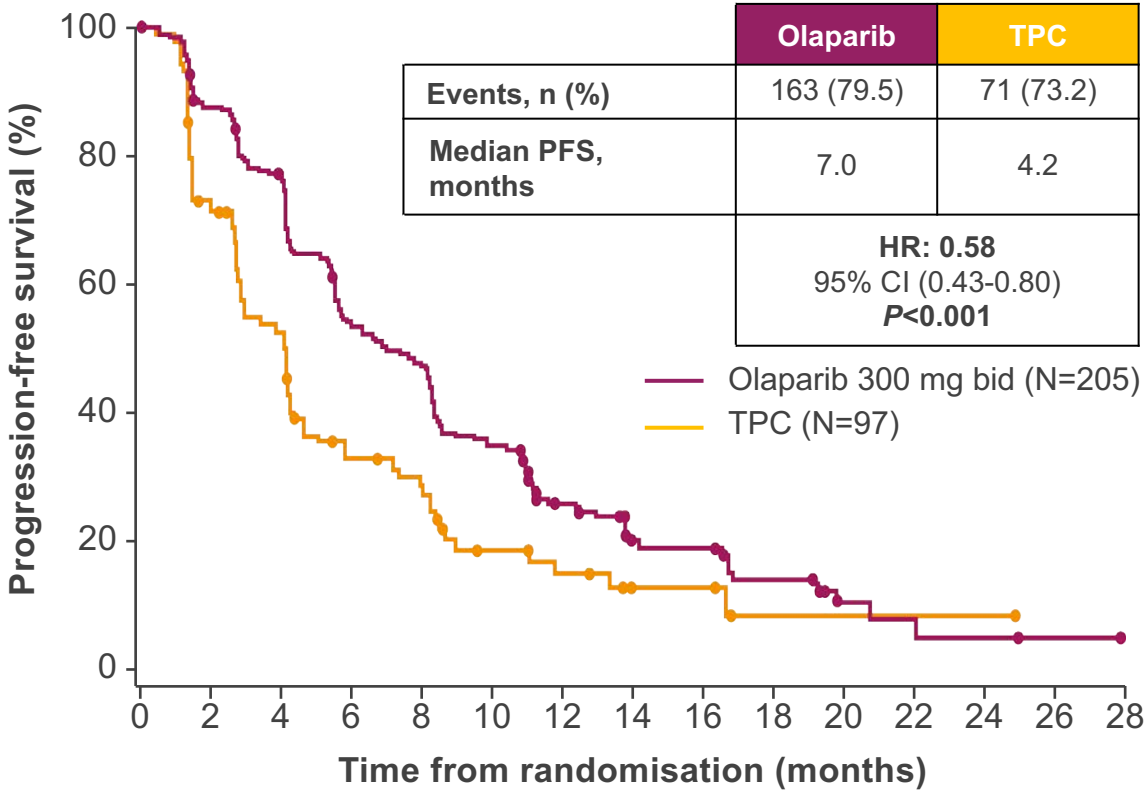
Primary endpoint
PFS (BICR)

1. Robson et al. N Engl J Med 2017; 377:523-533;
2. Litton J et al. N Engl J Med 2018; 379:753-763

Phase III trials of PARP inhibitors in gBRCA HER2-negative metastatic breast cancer patients

Olaparib and talazoparib both improve PFS in gBRCA mBC patients vs chemotherapy of physician's choice

OlympiAD: Olaparib PFS[1,2]

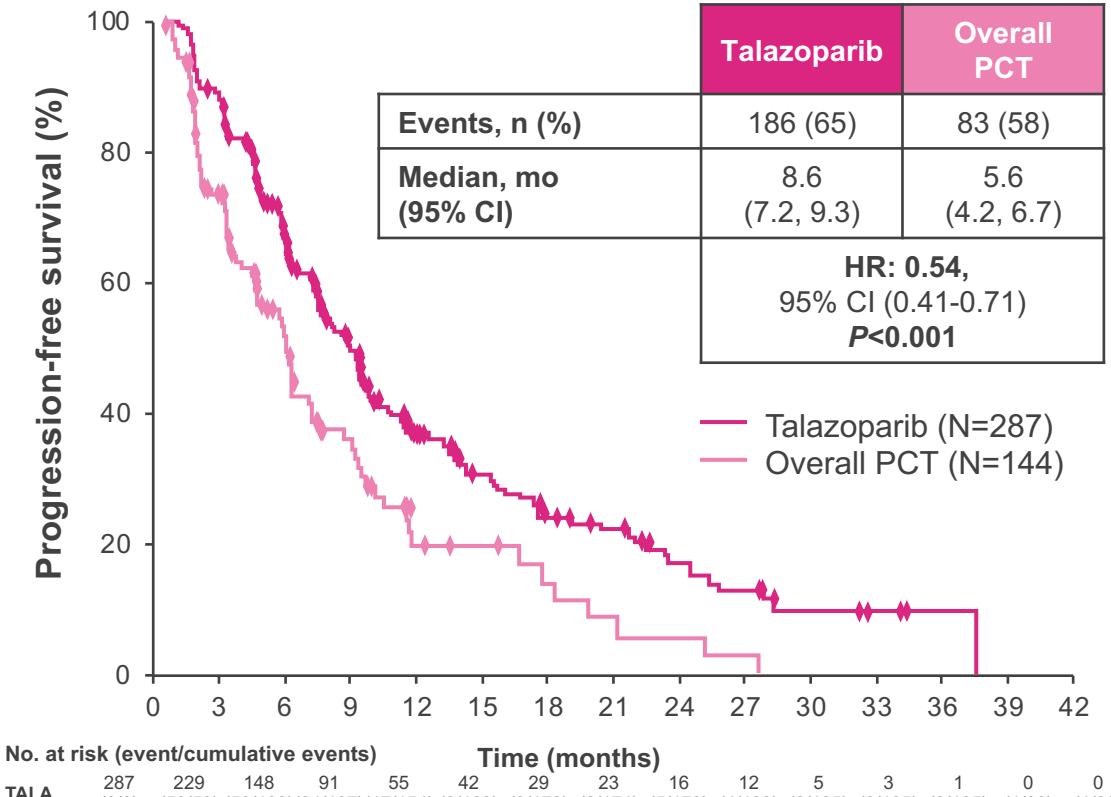


	Olaparib	TPC
Events, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
	HR: 0.58 95% CI (0.43-0.80) ***P*<0.001**	

Number at risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
TPC	97	88	83	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

EMBRACA: Talazoparib PFS[3]



	Talazoparib	Overall PCT
Events, n (%)	186 (65)	83 (58)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	HR: 0.54, 95% CI (0.41-0.71) ***P*<0.001**	

No. at risk (event/cumulative events)

TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/86)	0 (1/86)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

1. Robson M, et al. N Engl J Med. 2017;377:523-533; 2. Olaparib 150mg Film-Coated Tablets, SmPC. 2019; 3. Litton JK, et al. N Engl J Med. 2018;379:753-763 (supplementary appendix)

36-year-old woman with triple-negative mBC and a gBRCA mutation (from the practice of Ms Marti)

- 2013: cT3N3M0 TNBC while pregnant (Germline testing: gBRCA1 mutation)
- Preop cisplatin → bilateral mastectomy (MRD, 10+ LNs) → adjuvant TC → PMRT → BSO
- 2015: Nodal recurrence
- Gemcitabine/carboplatin (response) → PD in nodes → RT → capecitabine
- 4/2017: Recurrence (PD-L1: Negative in tumor and IC)
  - Brain MRI: 11-mm cerebellum mass with edema → SRS
- Clinical trial: PI3K/TORC1/2 inhibitor → PD (multiple, small lung mets) → *nab* paclitaxel/cisplatin
  - 12/2017 Restaging CT: CR of pulmonary mets and LNs
- 4/2018: Pembrolizumab → new rib lesion
- 12/2018: Discontinued pembrolizumab, initiated olaparib — rising TSH (thyroid replacement)
- Currently, on olaparib x 15 mos (+ zoledronic acid), with no PD or serious AEs, excellent PS

Module 4: CDK4/6 and PI3 Kinase Inhibitors in ER-Positive Disease

- Current role of CDK4/6 inhibitors for pre- and postmenopausal women
- Alpelisib/fulvestrant (PIK3CA mutation)

The mechanism of action of fulvestrant is essentially the same as that of tamoxifen, but fulvestrant is administered via intramuscular injection, whereas tamoxifen is administered orally.

a. Agree

b. Disagree

c. I don’t know

Therapy for premenopausal women with ER-positive metastatic breast cancer who undergo ovarian suppression or ablation is generally approached in the same manner as is therapy for postmenopausal patients.

a. Agree

b. Disagree

c. I don’t know

Which of the following toxicities is more common with palbociclib and ribociclib than with abemaciclib?

a. Gastrointestinal toxicity

b. Neutropenia

c. Anemia

d. Peripheral neuropathy

e. I don’t know

Which of the following toxicities is more common with abemaciclib than with palbociclib and ribociclib?

a. Gastrointestinal toxicity

b. Neutropenia

c. Anemia

d. Peripheral neuropathy

e. I don’t know

Which CDK4/6 inhibitor requires that an electrocardiogram be conducted prior to the initiation of treatment?

a. Palbociclib

b. Ribociclib

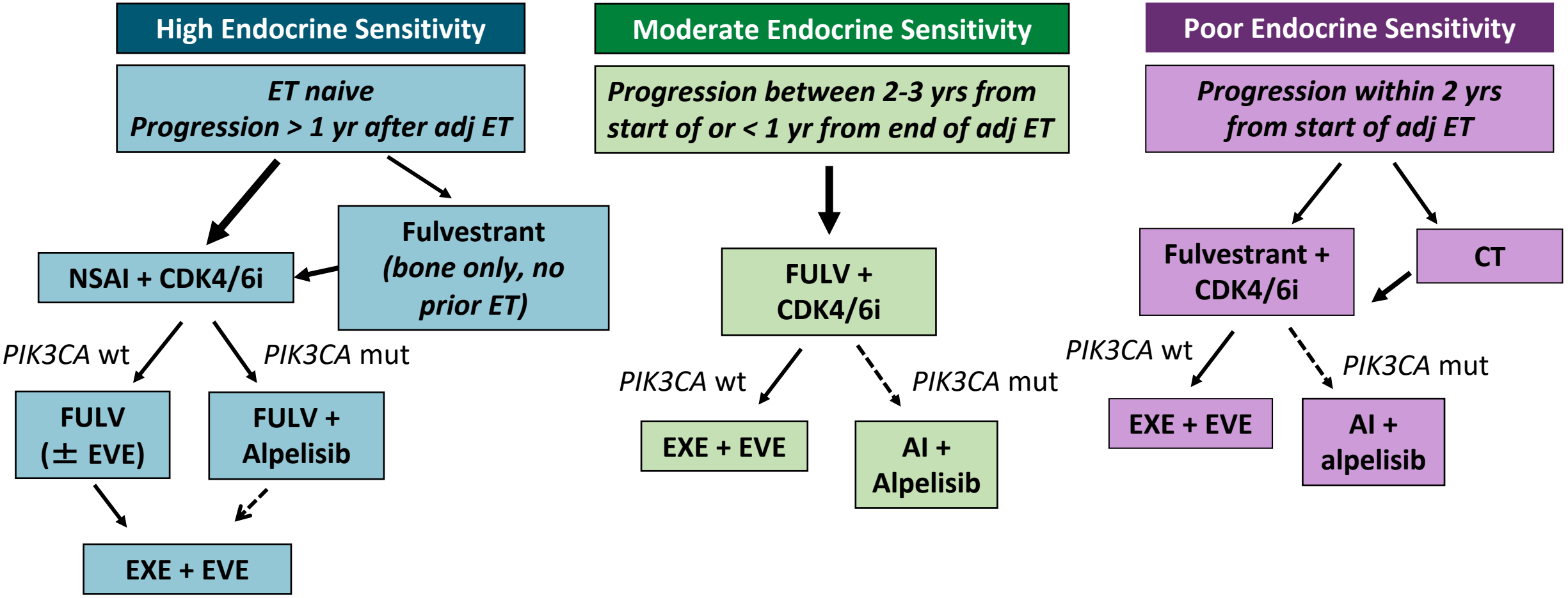
c. Abemaciclib

d. I don’t know

The PI3 kinase inhibitor alpelisib is used for patients with metastatic ER-positive, HER2-negative breast cancer with a…

a. PIK3CA germline mutation
b. PIK3CA somatic mutation
c. PIK3CA amplification
d. All of the above
e. I don’t know

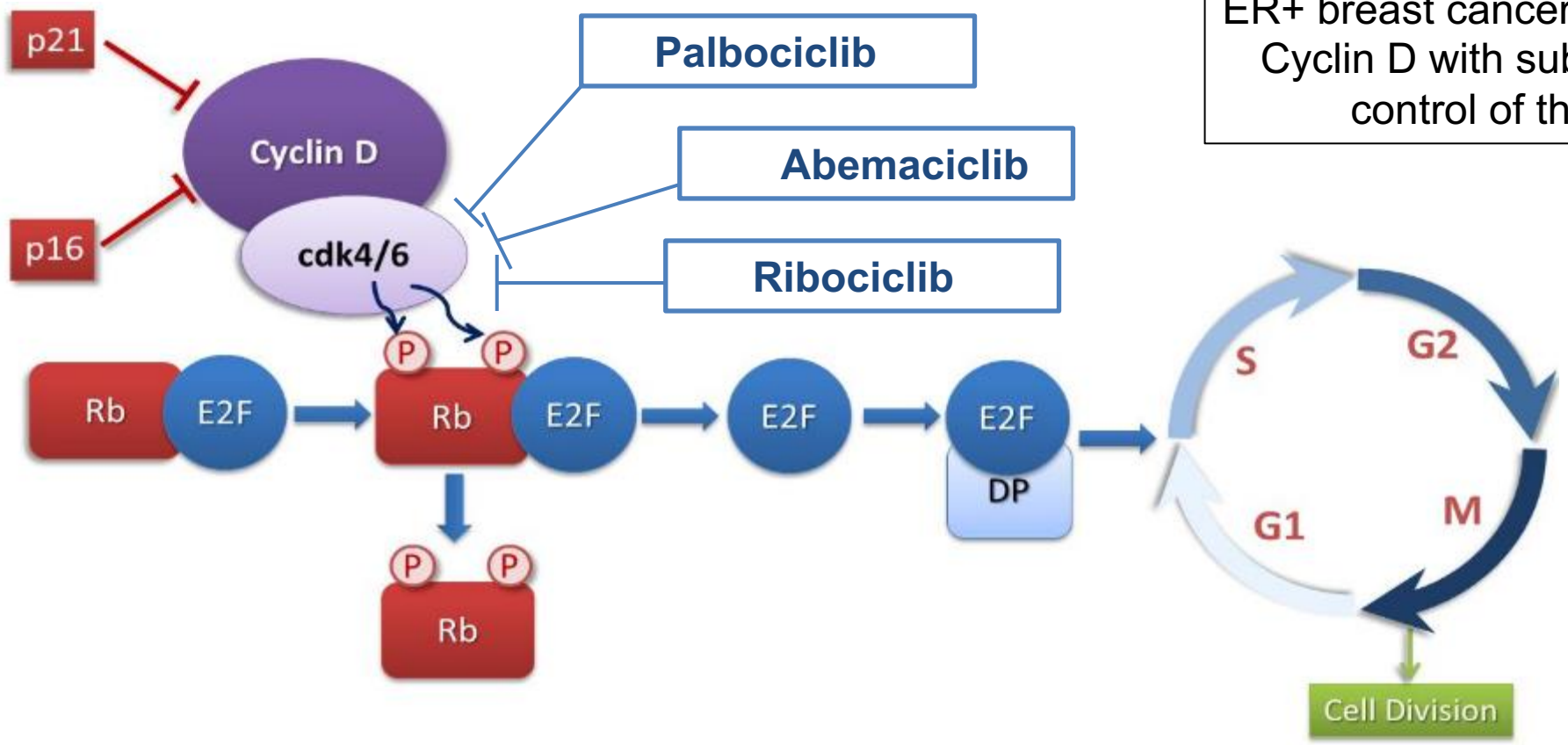
HR+/HER2- Advanced BC: Changing Paradigms



40% ER+ HER2- breast cancers harbor a PIK3CA mutation

CDK4/6 Regulates Cell Cycle Progression

ER+ breast cancer may overexpress Cyclin D with subsequent loss of control of the cell cycle



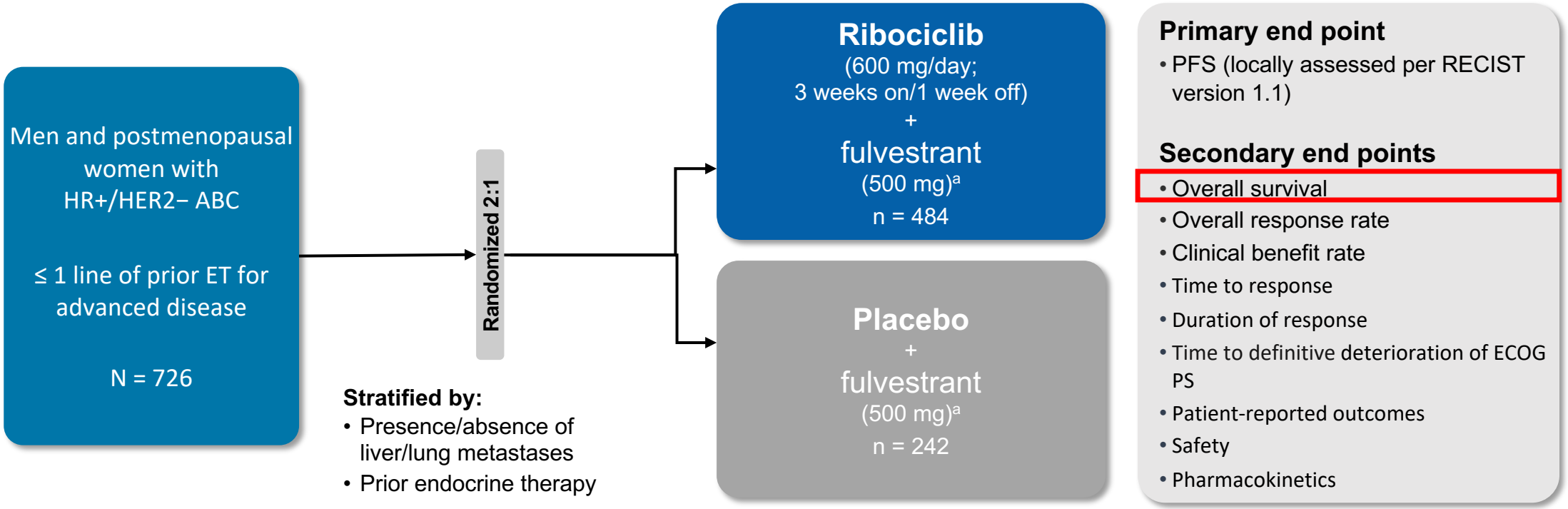
M, mitosis; Rb, retinoblastoma.
Adapted from Finn et al, 2016.

Common Side Effects and Dosing of CDK4/6 Inhibitors

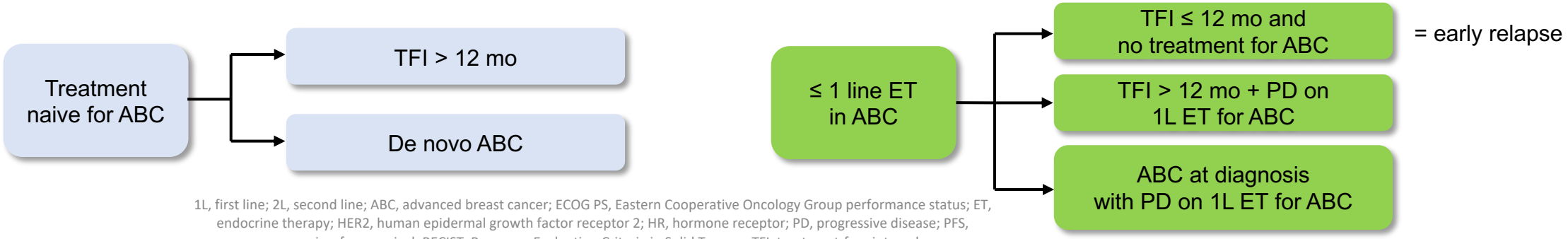
	Palbociclib		Abemaciclib		Ribociclib	
Dosing	125 mg qd 3 wk on, 1 wk off		200 mg BID continuously		600 mg qd 3 wk on, 1 wk off	
Common adverse events	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Neutropenia Thrombocytopenia	95% 76%	54% 19%	88% 42%	27% 2%	46% 37%	29% 10%
Diarrhea Nausea Vomiting	16% 23% 5%	0 0 0	90% 65% 35%	20% 5% 2%	22% 46% 25%	3% 2% 0

Barroso-Sousa R et al. *Breast Care* 2016;11:167-73.

MONALEESA-3 Study Design



Patient population definitions

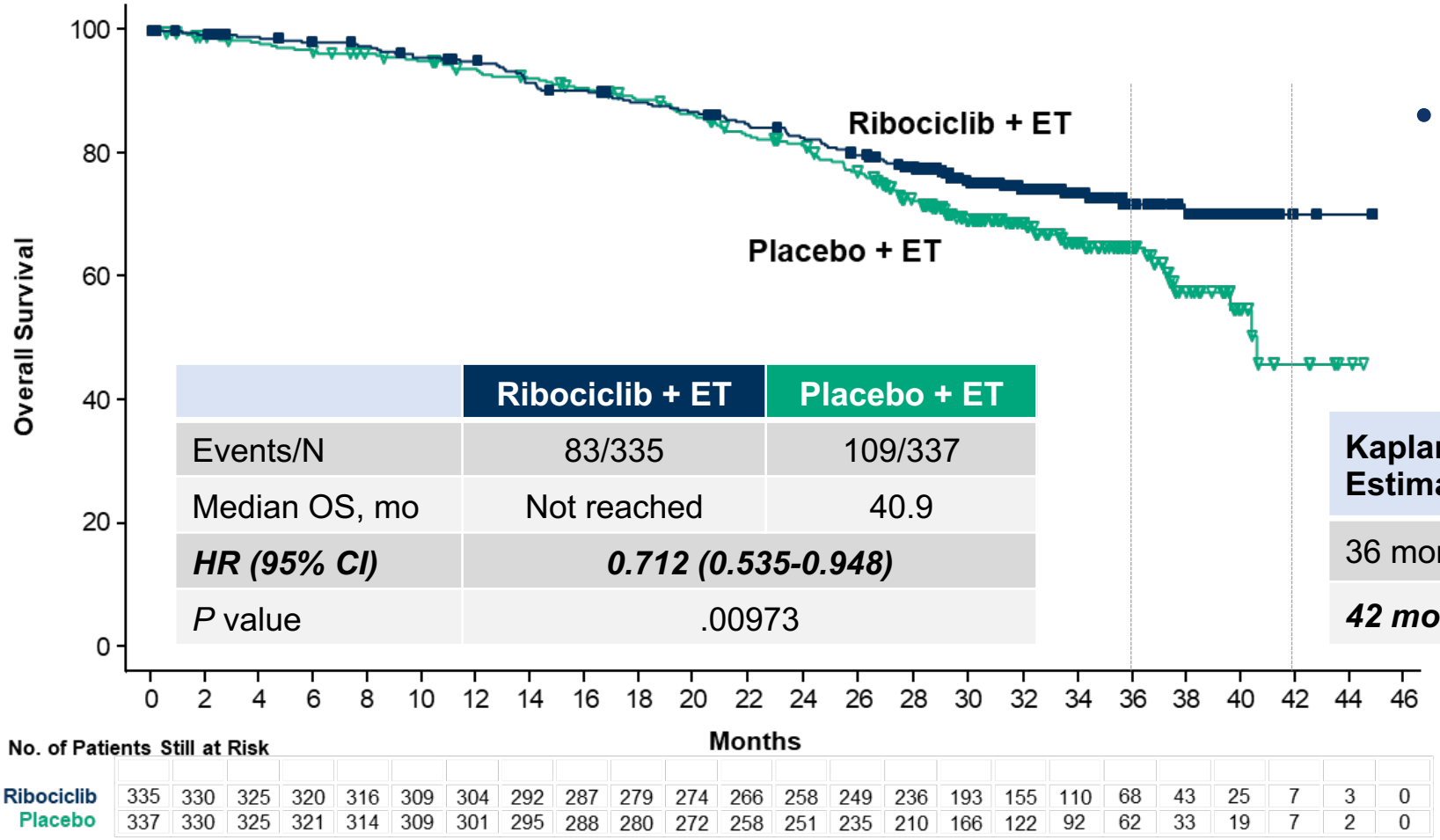


1L, first line; 2L, second line; ABC, advanced breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TFI, treatment-free interval.

[a] Fulvestrant 500 mg intramuscularly every 28 days plus an additional dose on Cycle 1, Day 15.

Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-247.

MONALEESA-7: Overall Survival – Premenopausal 1L mBC



	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	***0.712 (0.535-0.948)***	
P value	.00973	

- ≈ 29% relative reduction in risk of death
- The *P* value of 0.00973 crossed the prespecified boundary to claim superior efficacy

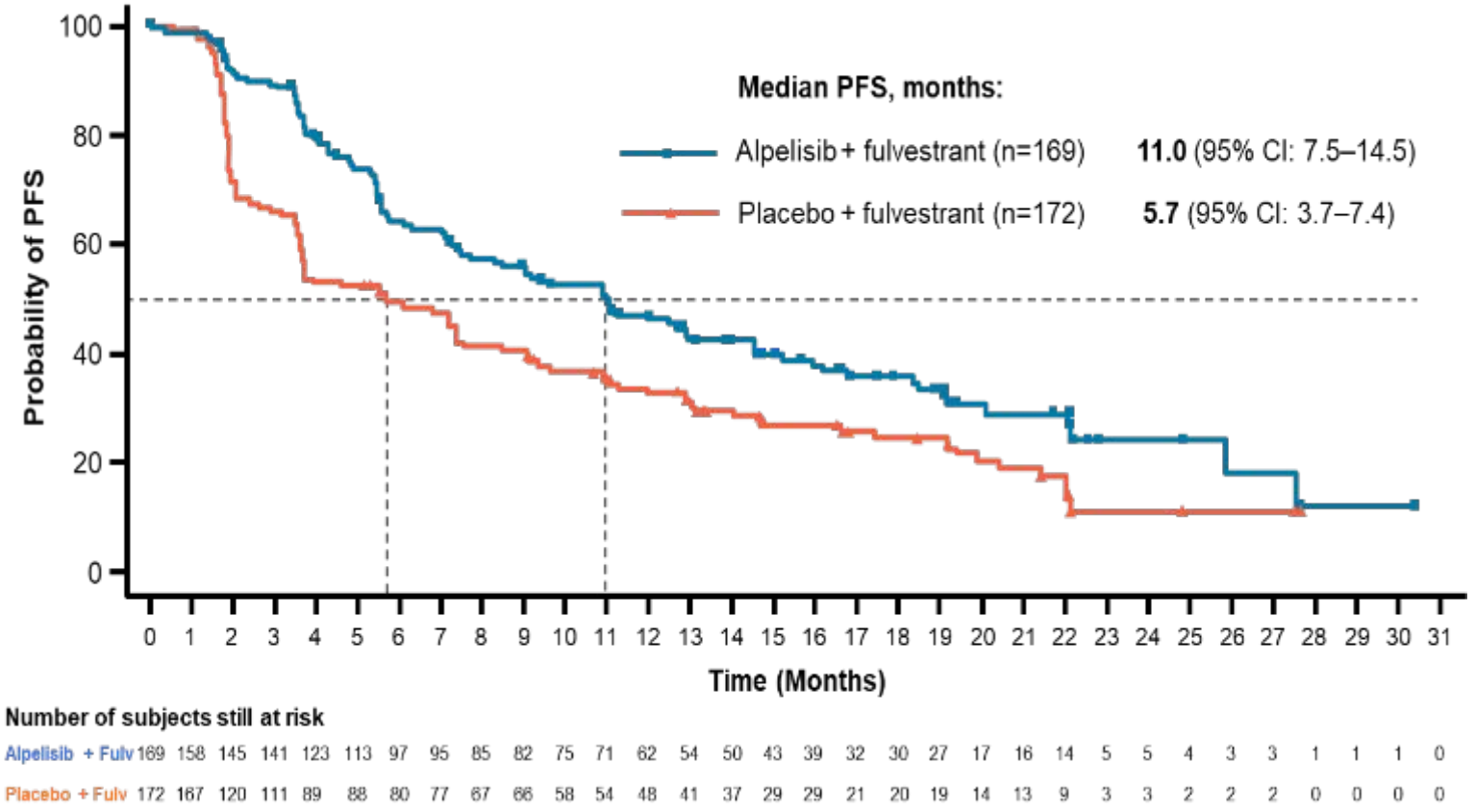
Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	71.9%	64.9%
42 months	***70.2%***	***46.0%***

Im SA, et al. NEJM 2019

SOLAR-1: Alpelisib Improved PFS in the *PIK3CA*-mutant Cohort[1,a]

Fulvestrant + Alpelisib or Placebo in ER+ HER2- mBC Patients Resistant to AI Therapy



Data cut-off: Jun 12, 2018	ALP + FUL (n = 169)	PBO + FUL (n = 172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
HR (95% CI)	0.65 (0.50-0.85)	
One-sided *P* value	0.00065	

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
At final PFS analysis, superiority was declared if one-sided, stratified log-rank test *P* value was ≤ 0.0199 (Haybittle–Peto boundary).
[a] Mutation status determined from tissue biopsy.
1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

58-year-old woman with ER-positive mBC (from the practice of Ms Marti)

- 10/2005: T1CpN1aM0, ER/PR-positive, HER2-negative IDC
  - BCS
  - Adjuvant AC x 4 → docetaxel/capecitabine x 4 → RT
  - Adjuvant tamoxifen x 4 yrs → anastrozole until metastatic disease
- 9/2014: ER-positive/PR-negative, HER2-negative pleural metastases
- Two lines of chemo, everolimus (x 1 month, not tolerated)
- 3rd-line: Letrozole/palbociclib x 6 mos → PD
- Fulvestrant/abemaciclib x 6 mos → PD
- Plasma testing: 2 PIK3CA mutations
- Fulvestrant/alpelisib x 10 mos
  - No serious AEs, but dose reduced from 300mg to 200mg daily due to 20 lbs weight loss

44-year-old woman with chronic cancer-related pain (from the practice of Mr Pizana)

- 8/2019: 4-cm, right, ER/PR-positive, HER2-negative breast cancer
- 9/2019 Staging scans: Bone and liver metastases
  - Liver biopsy: ER-positive, HER2-negative
- Zoledronic acid, letrozole/palbociclib
  - Myalgias, bone pain, Gr1 fatigue, decreased appetite
- PIK3CA testing: Positive
- 11/2019: Rash of unknown etiology: Palbociclib discontinued
- *Nab* paclitaxel x 2 cycles
- 2/26/2020: Transition to fulvestrant/alpelisib
  - Myalgias/arthralgias, Gr1 fatigue, oral mucositis, rash, Gr1 diarrhea
- 5/08/2020: Stable disease, plan to re-stage in 3 mos

Module 5: Management of Breast Cancer in the Era of COVID-19

Has the approach to primary surgery for patients with breast cancer changed at your institution during the COVID-19 pandemic?

a. Yes, quite a bit
b. Yes, but not very much
c. No
d. I don’t know

Has the approach to radiation therapy for patients with breast cancer changed at your institution during the COVID-19 pandemic?

a. Yes, quite a bit

b. Yes, but not very much

c. No

d. I don’t know

Do you believe that receiving an anti-PD-1/PD-L1 antibody makes a patient more susceptible to contracting COVID-19?

a. Yes

b. No

c. I don’t know

Do you believe that receiving an anti-PD-1/PD-L1 antibody increases a patient's risk of developing complications associated with COVID-19?

a. Yes

b. No

c. I don't know

Thank you for joining us!

CNE (NCPD) credit information will be emailed to each participant tomorrow morning.