Year in Review — Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology:

Breast Cancer

Tuesday, February 9, 2021
5:00 PM – 6:00 PM ET

Faculty

Harold J Burstein, MD, PhD
Lisa Carey, MD

Moderator

Neil Love, MD

RESEARCH TO PRACTICE
2021
YEAR IN REVIEW

YiR Breast Cancer Faculty

Harold J Burstein, MD, PhD
Institute Physician, Dana-Farber Cancer Institute
Professor of Medicine, Harvard Medical School
Boston, Massachusetts

Lisa Carey, MD
Richardson and Marilyn Jacobs Preyer Distinguished Professor for Breast Cancer Research
Deputy Director of Clinical Sciences
Lineberger Comprehensive Cancer Center
University of North Carolina
Chapel Hill, North Carolina

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2021
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Commercial Support

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Dr Love — Disclosures

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Dr Burstein — Disclosures

No relevant conflicts of interest to disclose.

Dr Carey — Disclosures

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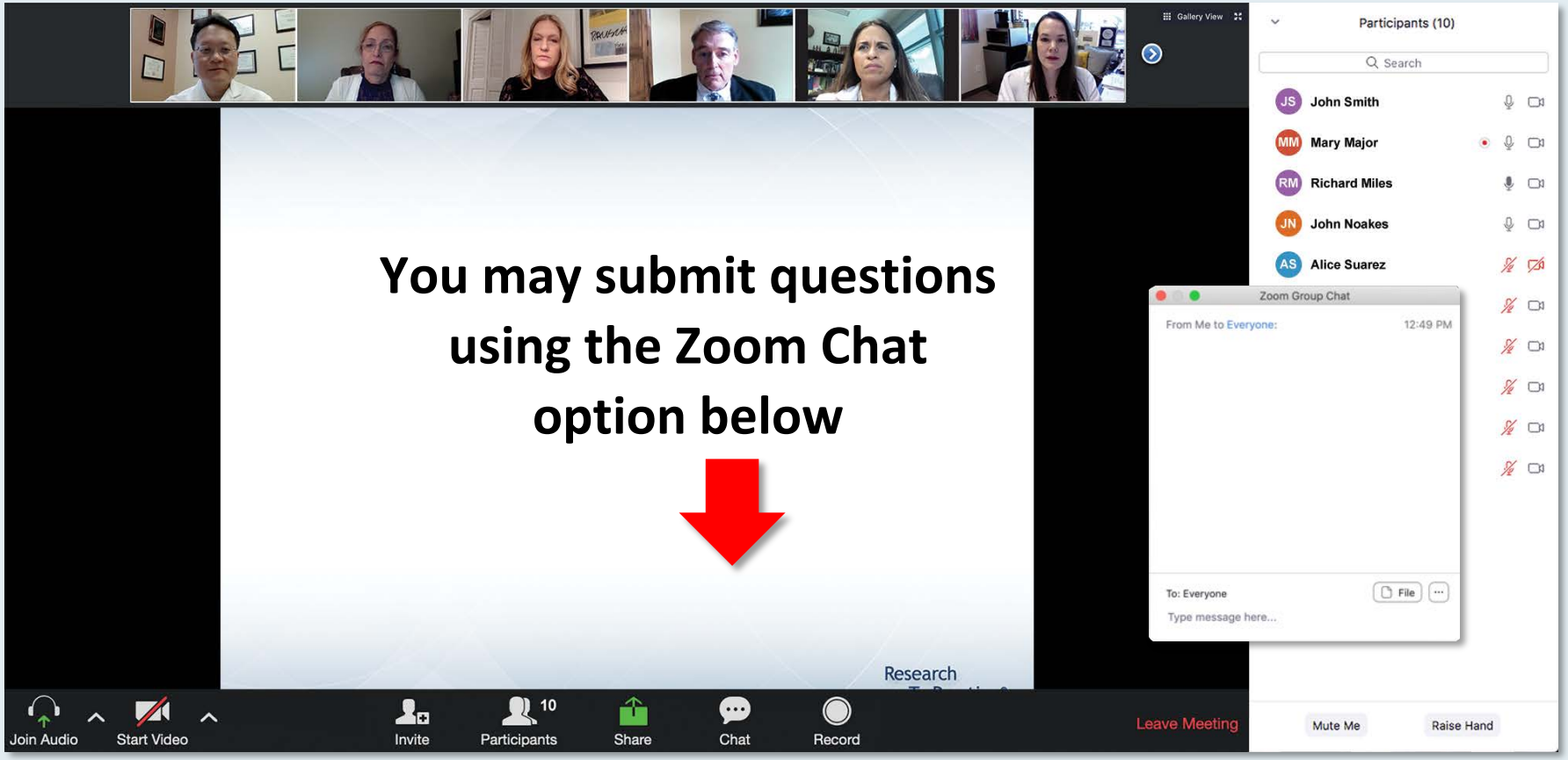
We Encourage Clinicians in Practice to Submit Questions



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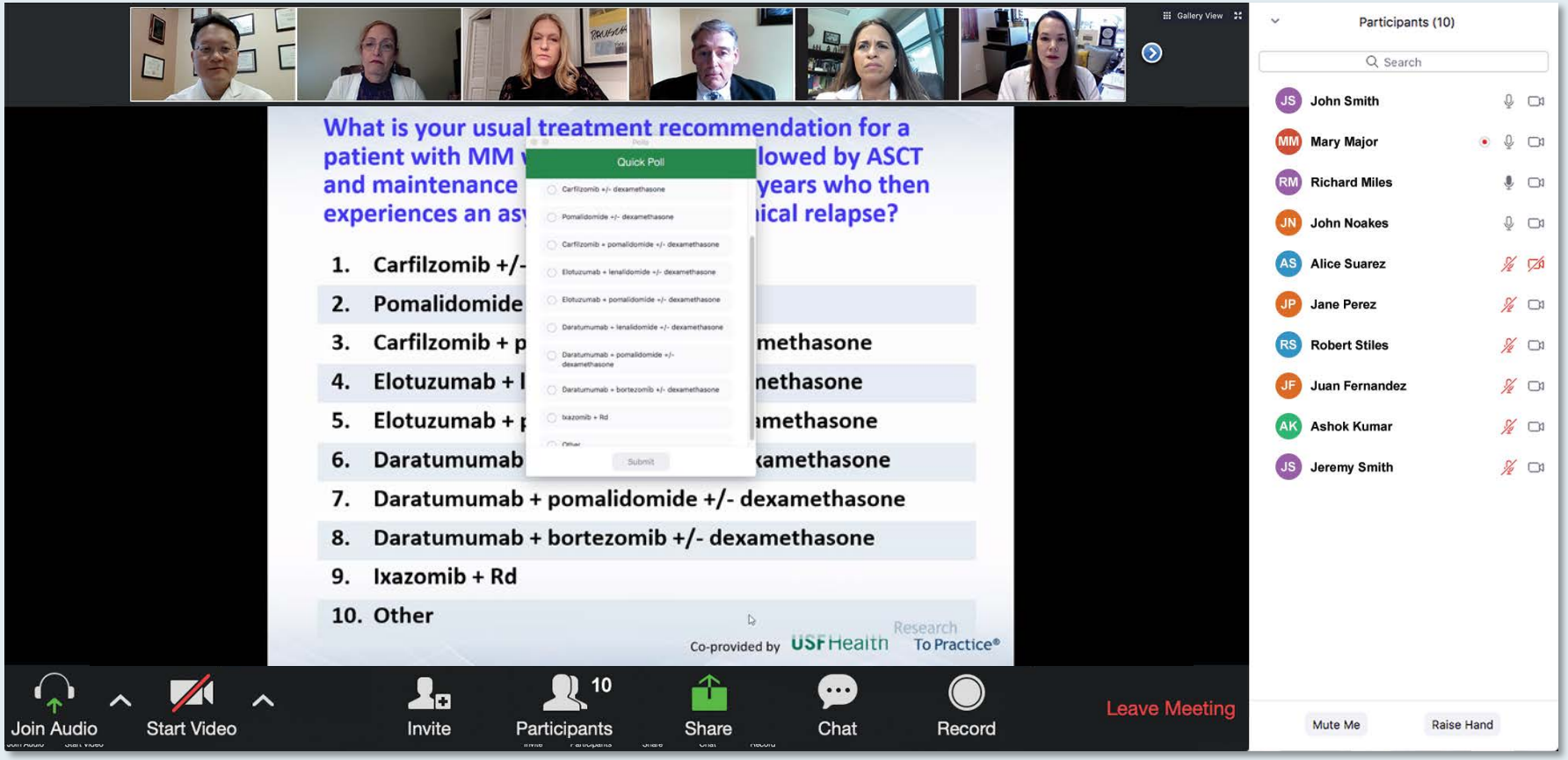

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ONCOLOGY TODAY

WITH DR NEIL LOVE

The Role of PARP Inhibition in the Management of Breast Cancer

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Recent Advances in Hematologic Oncology: A 4-Part Live Webinar Series Reviewing Key Data and Presentations from the 62nd ASH Annual Meeting

Part 3 — Multiple Myeloma

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Edward A Stadtmauer, MD

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RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Colorectal Cancer (Part 3 of a 3-Part Series)

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Kristen K Ciombor, MD, MSCI
Eric Van Cutsem, MD, PhD

Moderator

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RTP RESEARCH TO PRACTICE


A 65-year-old woman with ER-positive, HER2-negative, node-negative breast cancer has developed multiple minimally symptomatic bone metastases 2 years after starting adjuvant anastrozole. Which endocrine-based treatment would you most likely recommend?
Fulvestrant
Tamoxifen
Other hormone inhibitor
Palbociclib + fulvestrant
Palbociclib + letrozole
Ribociclib + fulvestrant
Ribociclib + letrozole
Abemaciclib + fulvestrant
Abemaciclib + letrozole
Other

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

A Daylong Clinical Summit Hosted in Partnership with North Carolina Oncology Association (NCOA) and South Carolina Oncology Society (SCOS)

Saturday, February 13, 2021

8:30 AM – 4:30 PM ET

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Robert Dreicer, MD, MS
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Alexander Perl, MD
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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

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RTP RESEARCH TO PRACTICE

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

RESEARCH TO PRACTICE 2021 YEAR IN REVIEW


Prognosis by RS Group
TAILORx: Impact of Clinical Risk (CR) on Prognosis by RS Group

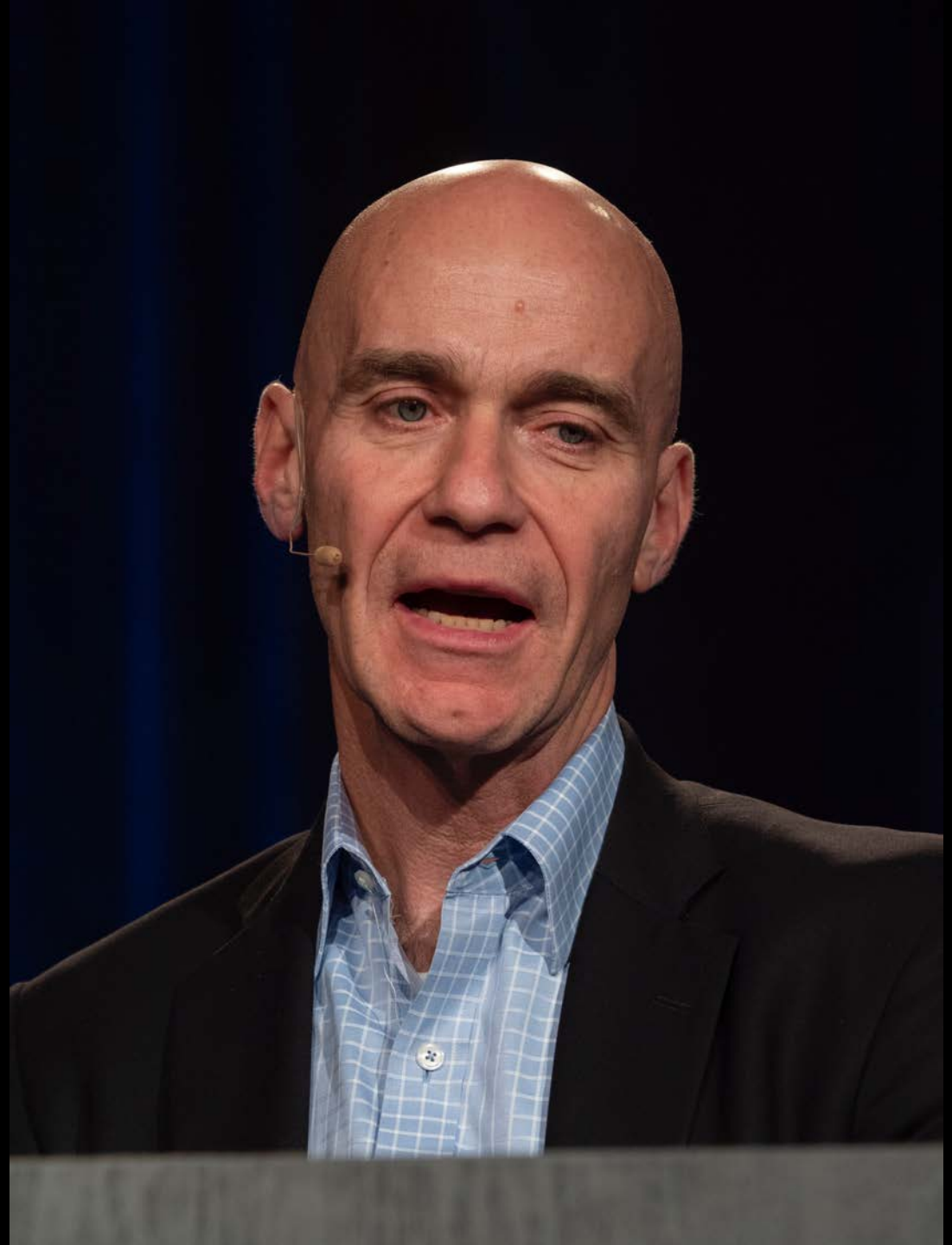

Gene Expression Assays in Breast Cancer
Unsupervised analysis
Breast cancer is heterogeneous
Distinct subtypes
Prognosis varies by subtype (PAM50)
Supervised analysis
Several other prognostic assays (21-gene, 70-gene, others)
Lack of concordance in prognostic classification
Luminal A
Luminal B
ERBB2+
Basal
Normal
C
D
E
F
G
Sorlie et al PNAS 2003; 100(14): 8418-8423
Bartlett JM et al. J Natl Cancer Inst. 2016;108(9)


Case Presentation: Dr Carey
• 85 yo otherwise healthy retired teacher from NC mountains ~ 2.5h away. Transportation issues.
• Clinical T3N1 IDC right breast; ER40%, P
without peau d'orange, > 2cm axillary L
• Nab-paclitaxel denied, Rx dose-
complicated


7/2019
11/2019


Prevalence of BRCA mutations
BRCA1 1 in 300
BRCA2 1 in 800
Certain ethnic groups have higher prevalence:
Ashkenazi Jews 1 in 40
SARAH CANNON
Development of breast cancer in women
12%
General Population
72%
BRCA1 Mutation
69%
BRCA2 Mutation
20 years after the
breast cancer diagnosis
40%
Women with BRCA1 mutation that will have contralateral BC
26%
Women with BRCA2 mutation that will have contralateral BC


KEYNOTE 522: NEOADJUVANT CHEMO + PEMBROLIZUMAB IN TNBC
Addition of pembrolizumab to neoadjuvant chemo led to statistically significant improvement in pCR of 13.6%
Benefit with pembrolizumab was independent of PD-L1 status
SARAH CANNON
KEYNOTE 522: NEOADJUVANT CHEMO + PEMBROLIZUMAB IN TNBC
SARAH CANNON




Gemcitabine
Capecitabine
Vinorelbine
Eribulin
Other


HIGHER IMMUNOGENICITY IN PRIMARY TUMORS COMPARED TO METASTATIC
Potential Biomarkers of Immune Response
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CASE PRESENTATION: DR HAMILTON

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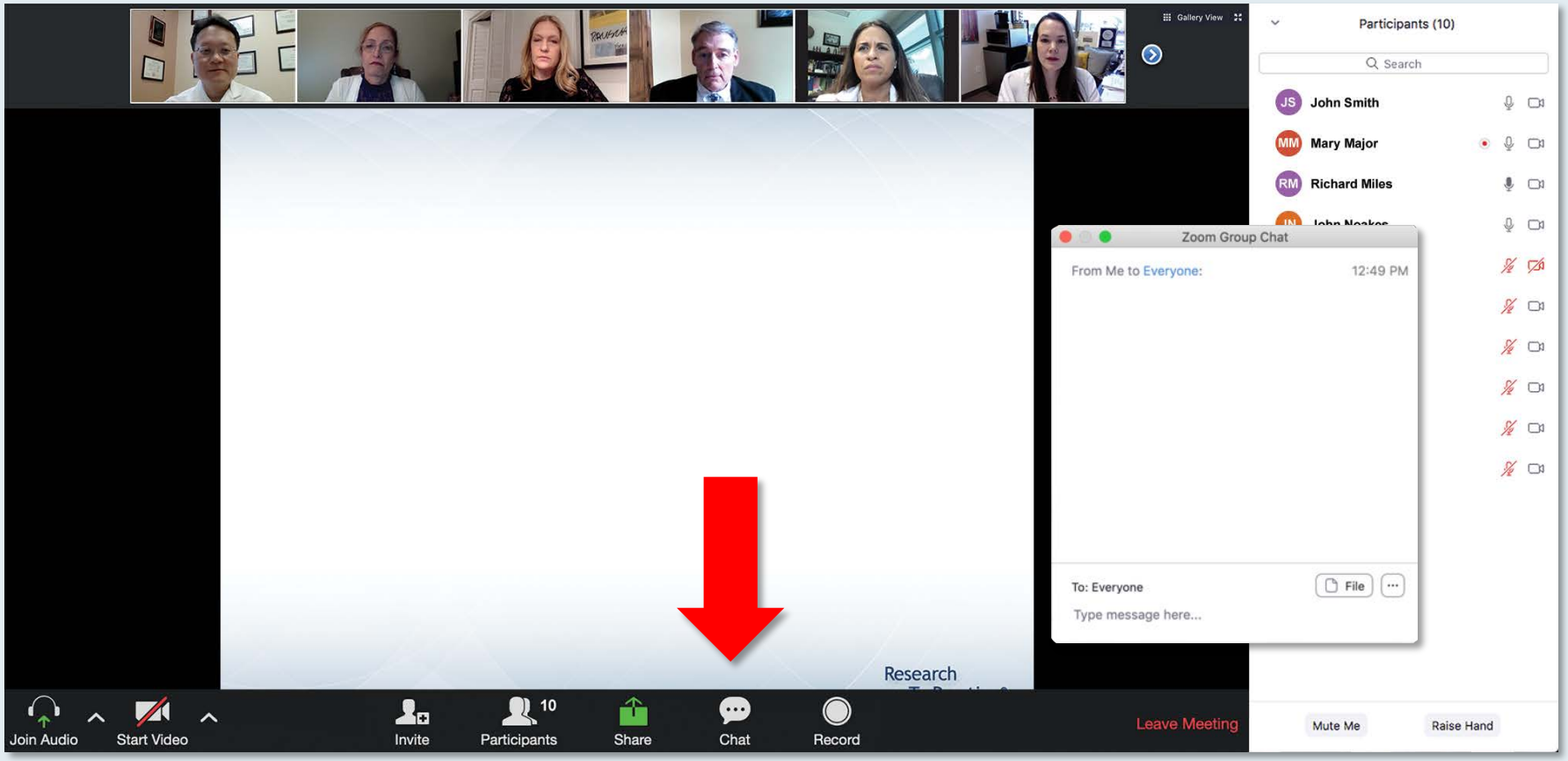

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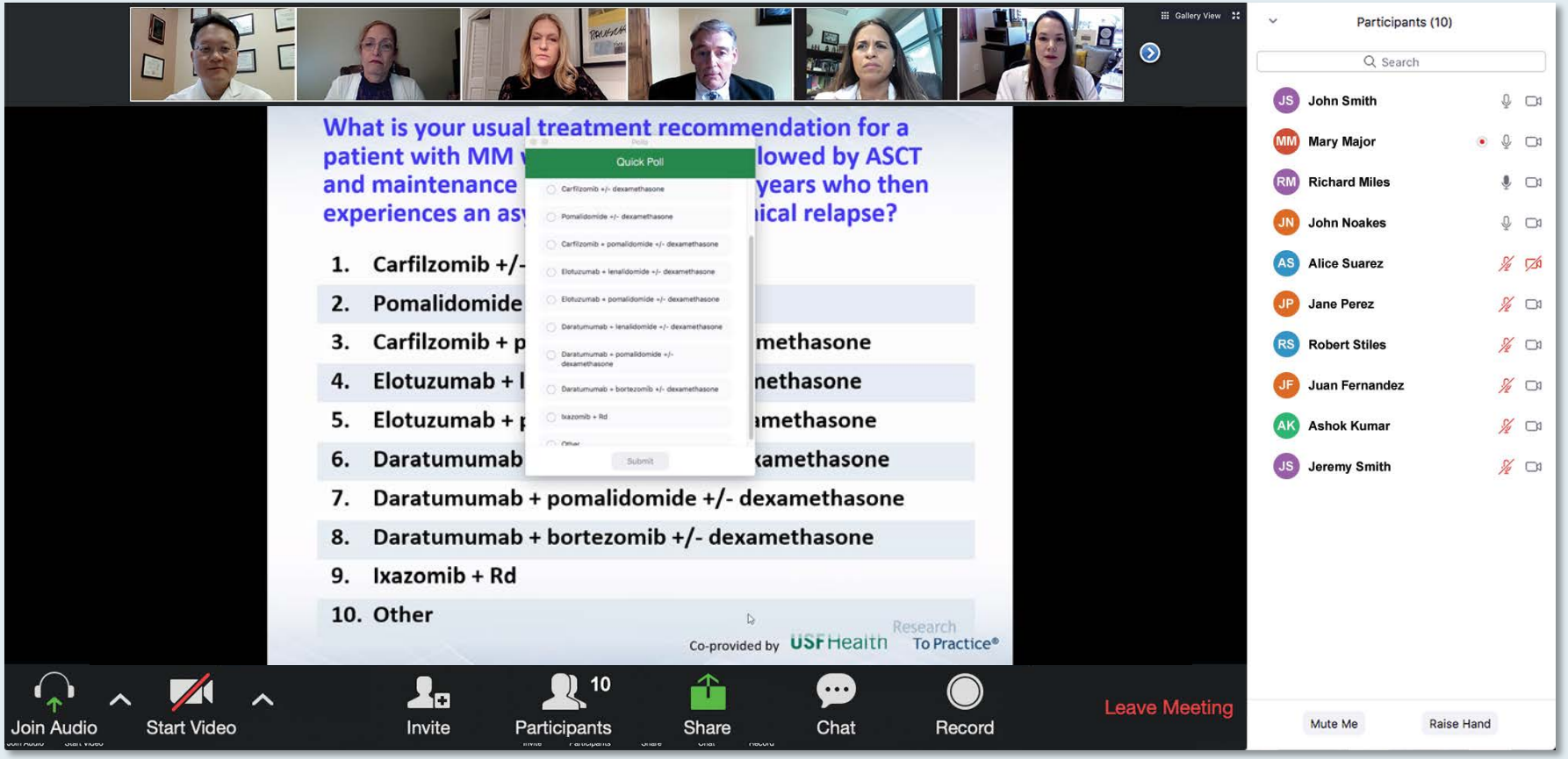

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Agenda

ER-Positive, HER2-Negative Breast Cancer

- Module 1: CDK4/6 inhibitors
- Module 2: PI3K inhibitors
- Module 3: Genomic assays

HER2-Positive Breast Cancer

- Module 4: Early-stage disease; neoadjuvant therapy
- Module 5: Metastatic disease

Triple-Negative Breast Cancer

- Module 6: Immunotherapy for advanced disease
- Module 7: Immunotherapy in the neoadjuvant setting
- Module 8: PARP inhibition
- Module 9: Sacituzumab govitecan

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Module 9: Sacituzumab govitecan

A 52-year-old premenopausal woman presents with an 8-cm breast mass with skin changes. ER = 35%, PR = 10%, HER2-negative Grade I IDC. What would be your most likely initial approach?

1. Genomic assay, consider endocrine therapy (ET) only
2. Chemotherapy
3. Surgery

A 52-year-old premenopausal woman presents with an 8-cm breast mass with skin changes. ER = 35%, PR = 10%, HER2-negative Grade I IDC. The patient receives neoadjuvant dose-dense AC for 8 cm of residual cancer. In addition to radiation therapy and ET, which of the following, if any, would you include in the patient's postoperative management?

1. Capecitabine
2. Abemaciclib
3. Both capecitabine and abemaciclib
4. Other

Dear Neil,

I need your help regarding a difficult breast cancer case

52 yrs old pre-menopausal woman presented with inflammatory BC like left breast ca. No discrete mass but skin changes+.
Stage IIIb (cT4dcN1cM0), grade 1 invasive ductal carcinoma
ER 35% positive, PR 10% positive and HER-2/neu negative
On MRI: Suspicious enhancement measures 9 X4 X 3 cm. FNA of the lymph node is positive for metastatic disease

s/p NACT with DD AC-weekly paclitaxel
Genetic testing : negative

1/5/2021: S/p left mastectomy + axillary node dissection
8.1 cm, grade 2 residual IDC
Minimal therapeutic effect in the tumor bed
10 out of 15 LN + for micrometastatic disease largest measuring 8 mm. 1 lymph node had evidence of therapy effect
No extranodal extension
Surgical margins negative
Repeat ER 95% positive, PR <1%, HER-2/neu negative

I did mammaprint and blueprint from surgical specimen: Low risk, Luminal type

Question:

1. Role of adjuvant capecitabine?
2. She will receive adjuvant PMRT
3. Role of Abemaciclib with AI + OFS in adjuvant setting
4. Any other suggestions?

Thank you so much for your help.

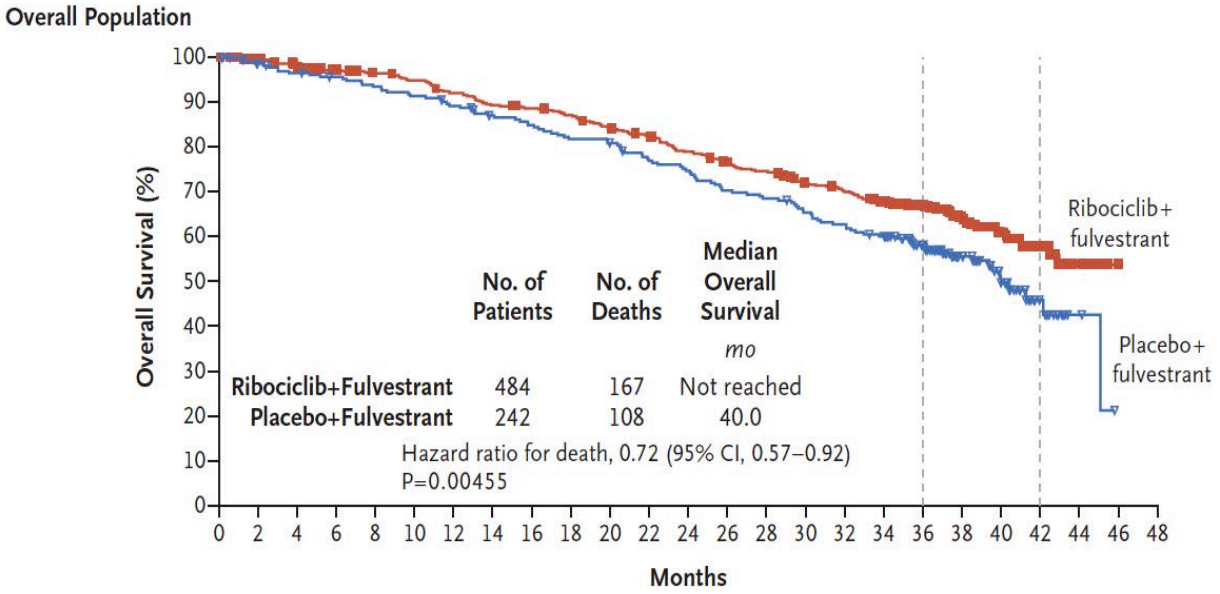
Best regards

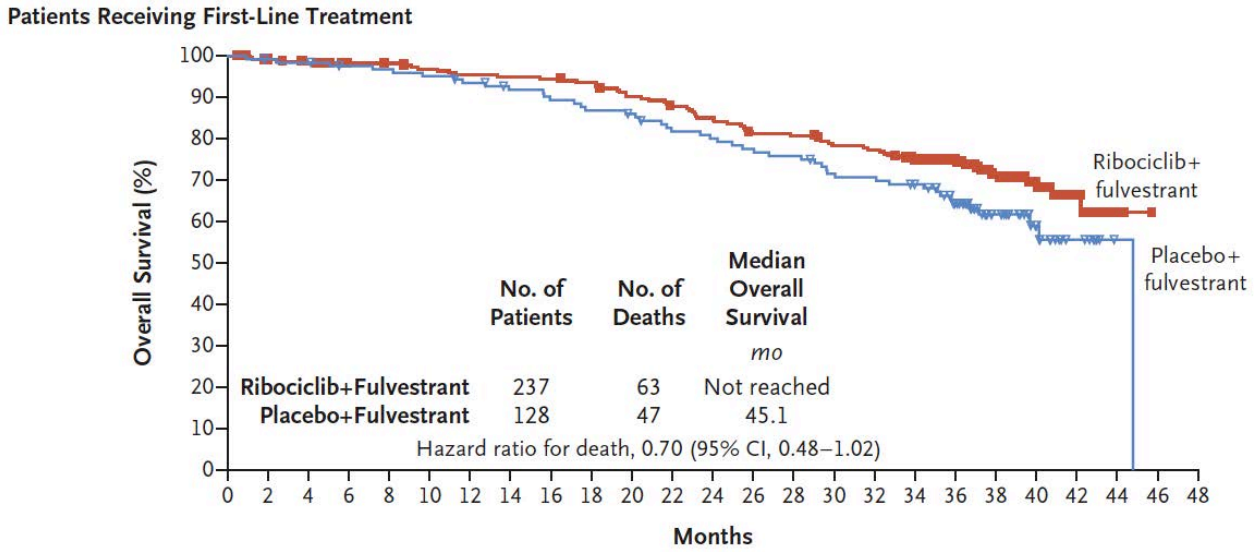
Ranju Gupta, MD
Attending Physician
Co-Director Cardio-Oncology Program
LVPG- Hematology Oncology Associates
Lehigh Valley Health Network, Muhlenberg Pa

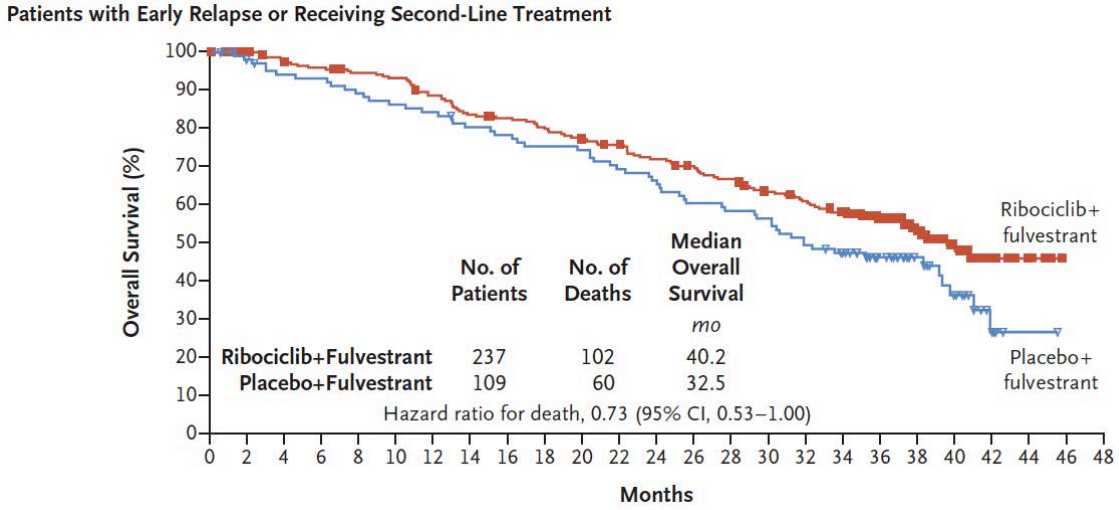
Module 1: CDK4/6 inhibitors for ER-positive breast cancer

- **Key Relevant Data Sets**
  - MONALEESA-3: Overall survival with ribociclib + fulvestrant for metastatic breast cancer
  - monarchE: Adjuvant abemaciclib + ET for high-risk early breast cancer
  - PALLAS: Adjuvant palbociclib +/- ET for early breast cancer
  - PENELOPE-B: Palbociclib + ET for early breast cancer with high relapse risk after neoadjuvant chemotherapy

Overall Survival in the Overall Population and According to Line of Treatment for Advanced Disease: MONALEESA-3.



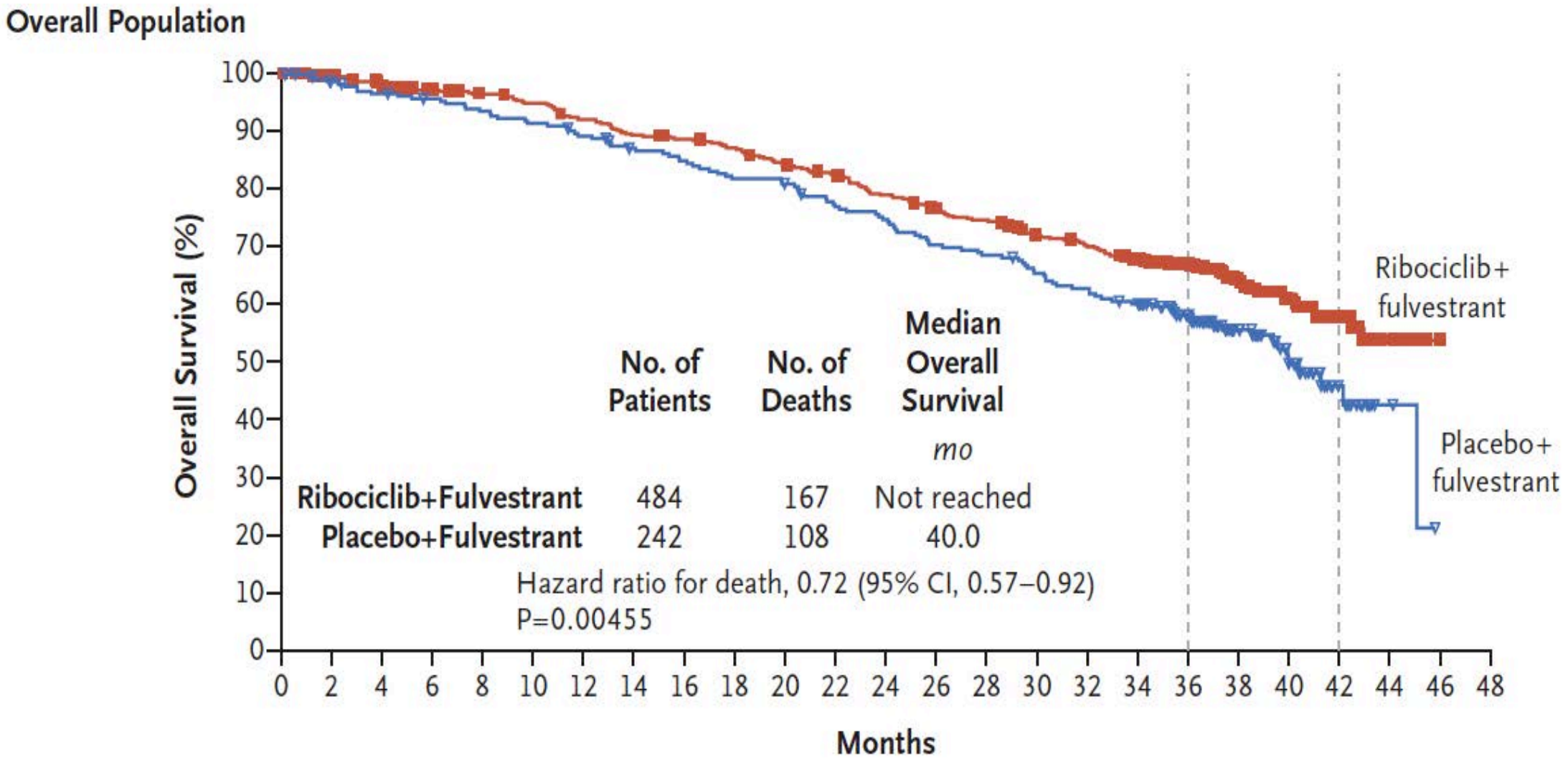




DJ Slamon et al. N Engl J Med 2020;382:514-524.

Courtesy of Harold J Burstein, MD, PhD

Overall Survival in the Overall Population: MONALEESA-3.



DJ Slamon et al. N Engl J Med 2020;382:514-524.

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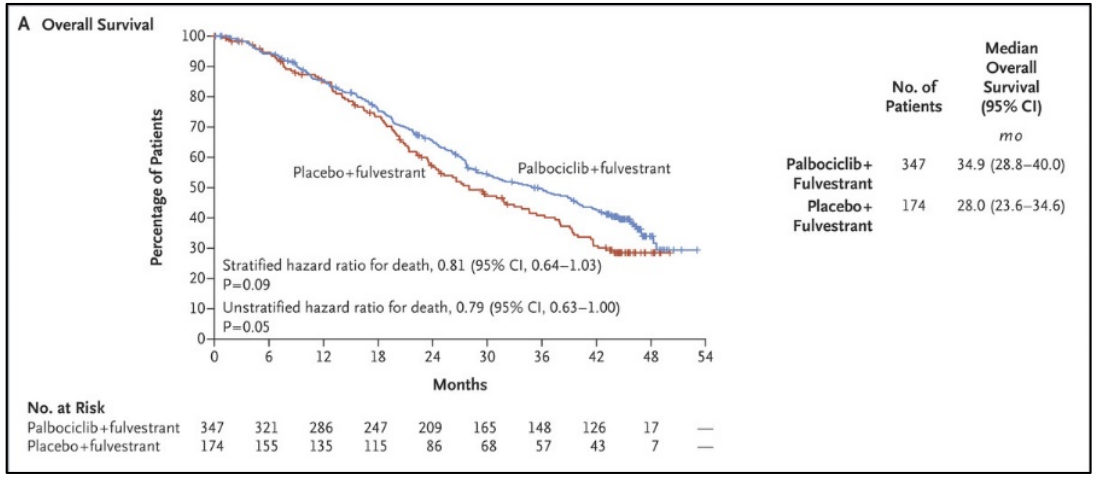
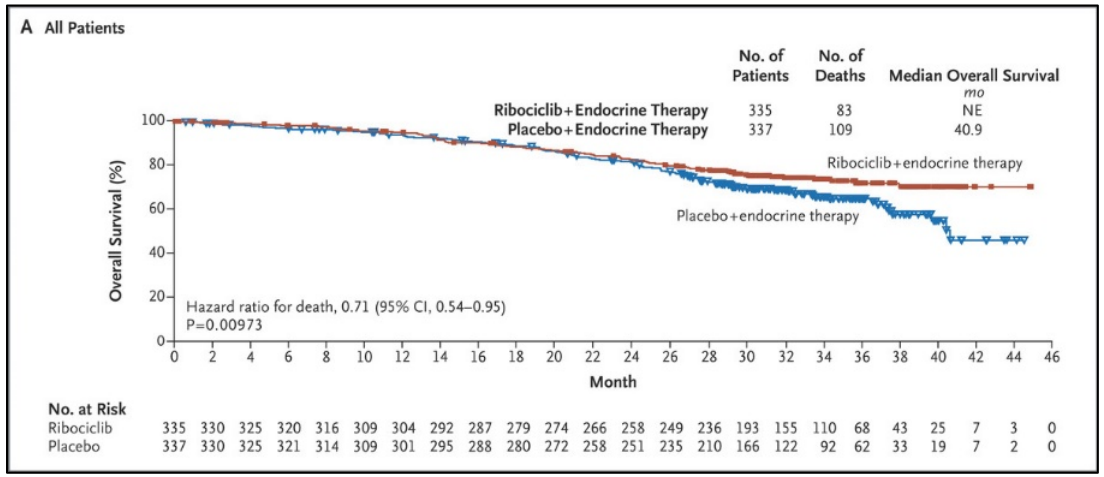
Overall Survival with CDK4/6i

Palbociclib



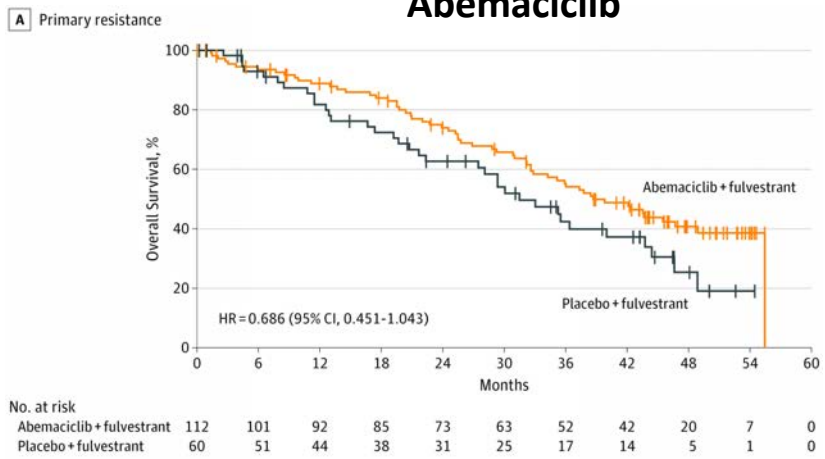
NC Turner et al. N Engl J Med 2018;379:1926-1936.

Ribociclib



S Im et al. N Engl J Med 2019;381:307-316.

Abemaciclib

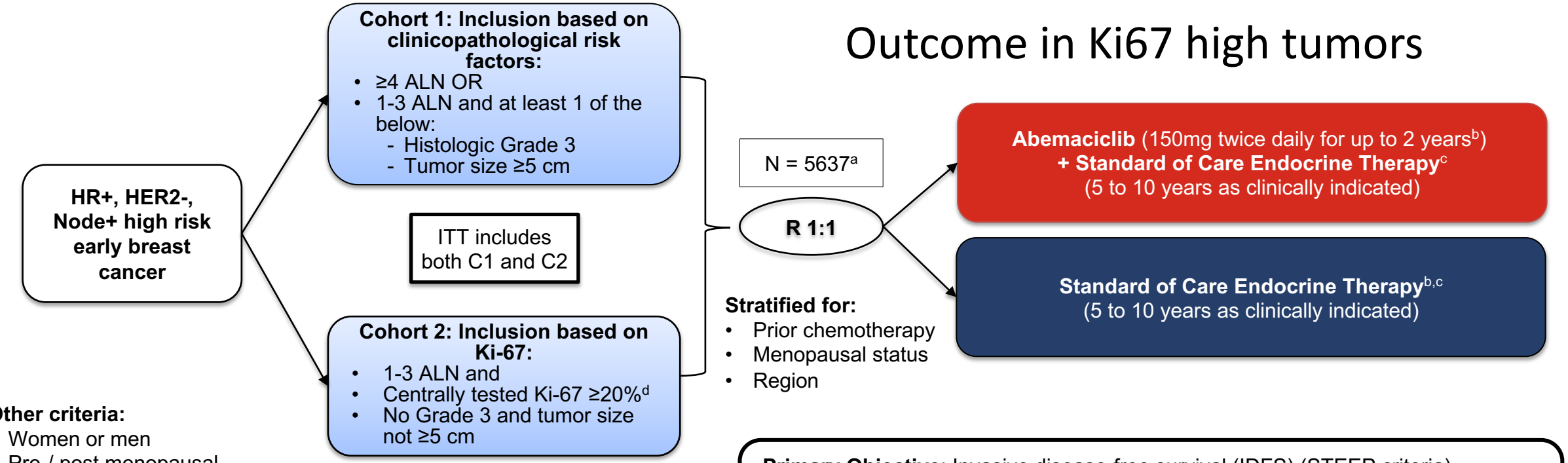


Sledge GW et al. JAMA Oncol 2020;6:116-124.

Courtesy of Harold J Burstein, MD, PhD

monarchE Study Design

New★
Additional 3.6-month F/up
67 additional IDFS events
Outcome in Ki67 high tumors



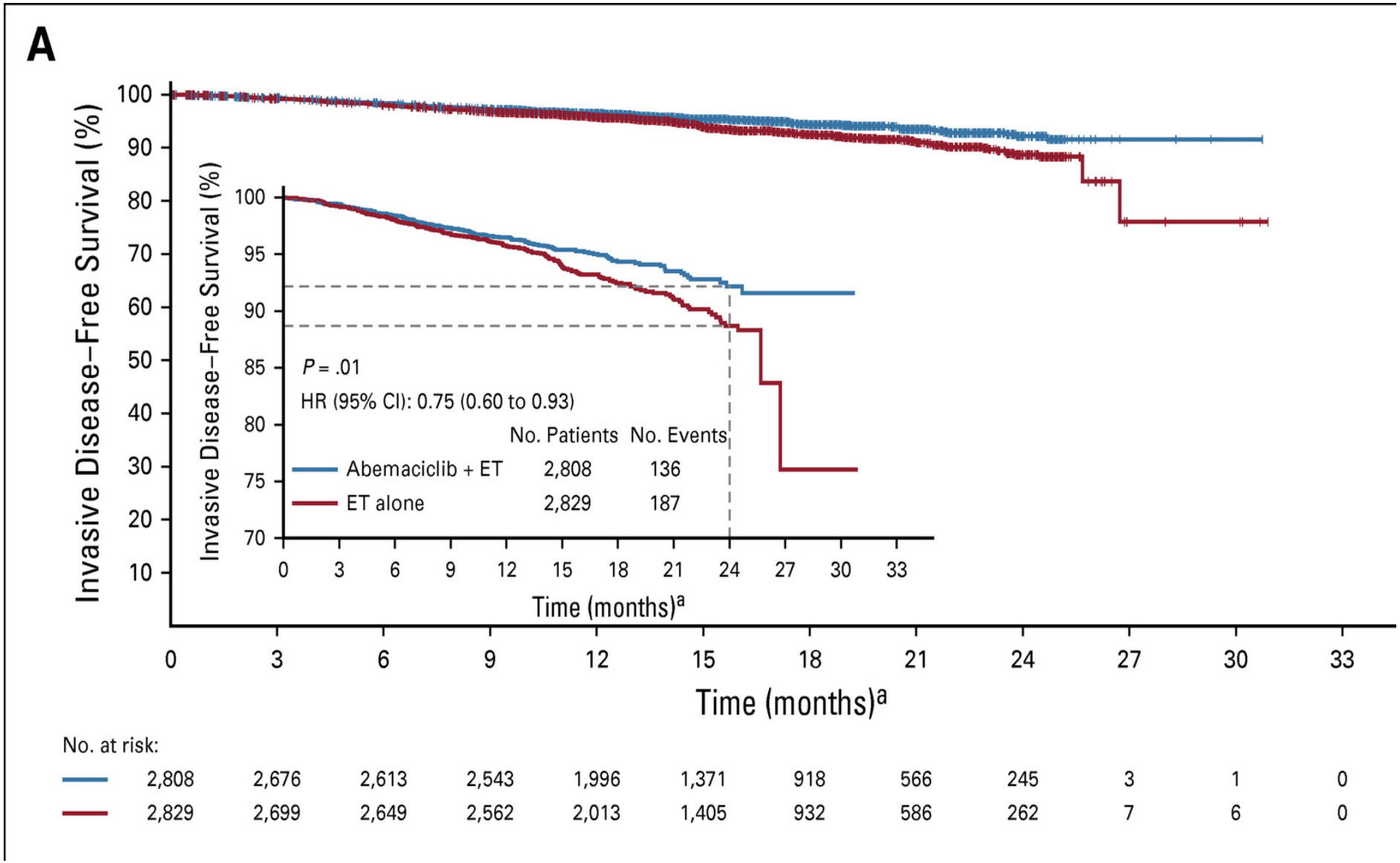
Other criteria:
- Women or men
- Pre-/ post menopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No distant metastasis
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Primary Objective: Invasive disease-free survival (IDFS) (STEEP criteria)
Key Secondary Objectives: IDFS in Ki-67 high (≥20%) population, Distant relapse-free survival (DRFS), Overall survival, Safety, Patient reported outcomes, and Pharmacokinetics

[a]Recruitment from July 2017 to August 2019; [b]Treatment period = first 2 years on study treatment after randomization; [c]Endocrine therapy of physician's choice [e.g. aromatase inhibitors, tamoxifen, LHRH agonist]; [d]Ki-67 expression assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry Assay by Dako/Agilent
Abbreviations: ALN, positive axillary lymph nodes; R, randomized

Courtesy of Harold J Burstein, MD, PhD

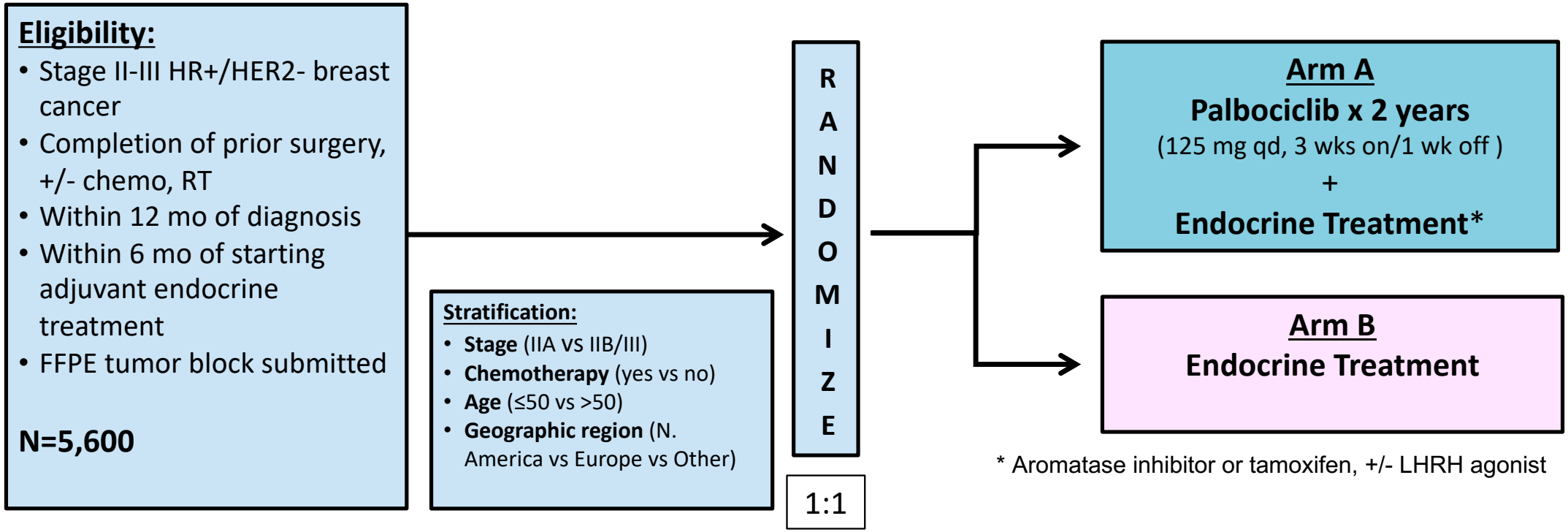
monarchE: Disease-free Survival



Johnston SRD et al. *J Clin Oncol* 2020;38(34):3987-98.

Courtesy of Harold J Burstein, MD, PhD

PALLAS: Phase III open-label study of palbociclib and adjuvant endocrine therapy



Primary Endpoint: invasive Disease-Free Survival (iDFS)

PALLAS
ABCSG 42 / AFT-05 / BIG 14-03

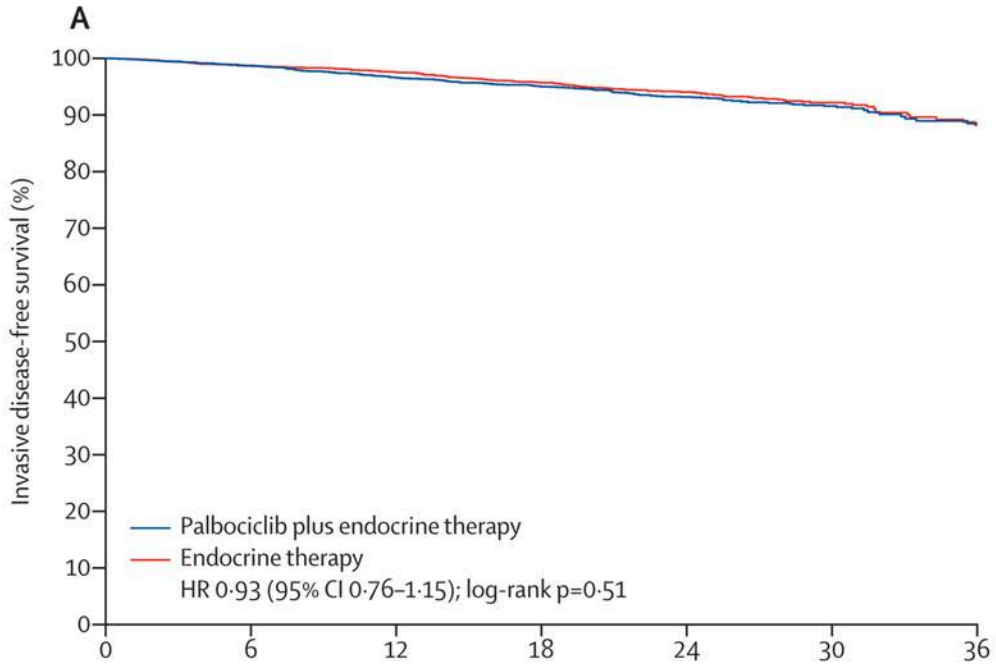
Sponsored by AFT and ABCSG, in cooperation with PrECOG, BIG, GBG, NSABP, and supported by Pfizer.

ABCSG ALLIANCE FOUNDATION TRIALS, LLC BIG Pfizer Oncology

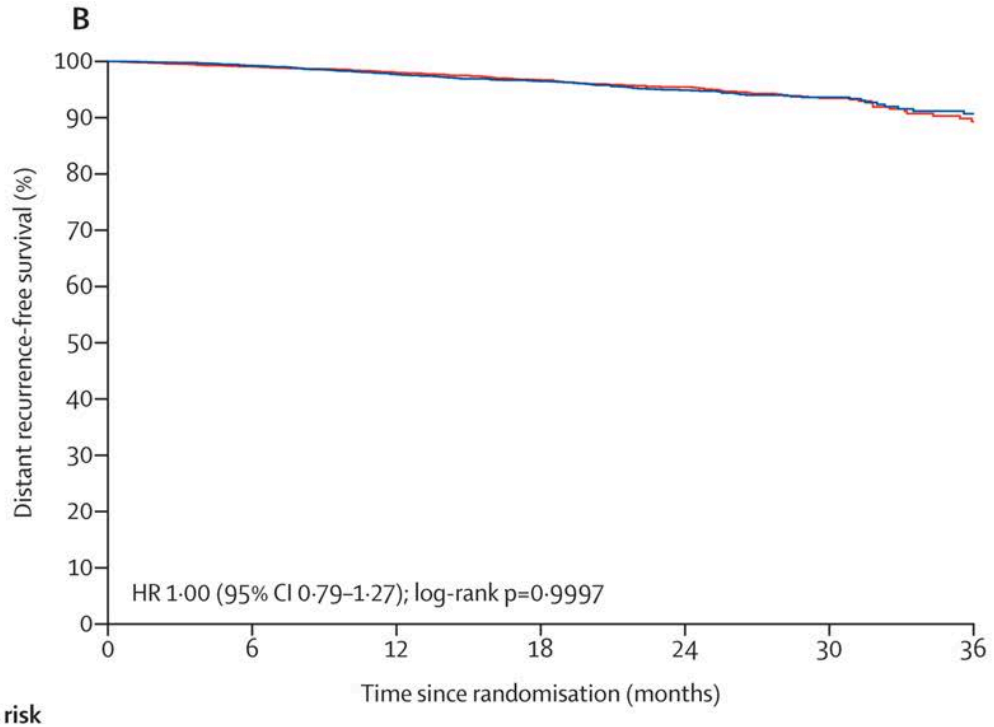
Courtesy of Harold J Burstein, MD, PhD

Mayer et al. ESMO 2020;Abstract LBA12.

PALLAS



Number at risk (number censored)							
Palbociclib plus endocrine therapy	2883 (0)	2684 (163)	2563 (253)	1946 (827)	1257 (1488)	583 (2145)	163 (2554)
Endocrine therapy	2877 (0)	1649 (192)	2535 (250)	1953 (796)	1275 (1444)	574 (2131)	172 (2524)



Number at risk (number censored)							
Palbociclib plus endocrine therapy	2883 (0)	2692 (165)	2573 (256)	1956 (843)	1270 (1508)	588 (2172)	163 (2586)
Endocrine therapy	2877 (0)	1662 (195)	2554 (261)	1976 (811)	1288 (1473)	579 (2171)	175 (2567)

Mayer EL et al. Lancet Oncol 2021

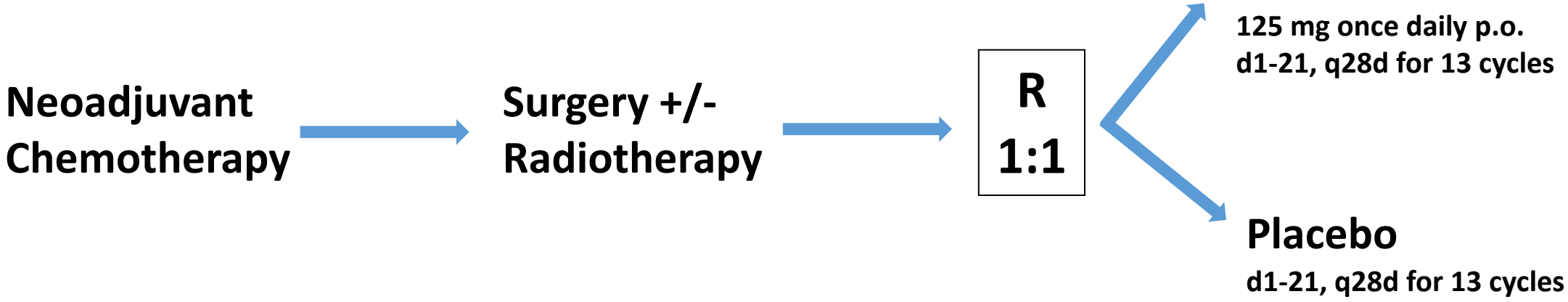
Courtesy of Harold J Burstein, MD, PhD

PENELOPE-B: Study Design

N=1250
- HR+/HER2- breast cancer
- no pCR after NACT
- CPS-EG score ≥3 or ≥2 with ypN+

Primary Endpoint: iDFS

Stratification factors
- Nodal status: ypN 0-1 vs ypN2-3
- Age: ≤50 vs >50 yrs
- Ki-67: >15% vs ≤ 15%
- Region: Asian vs non Asian
- CPS-EG Score: ≥3 vs 2 and ypN+



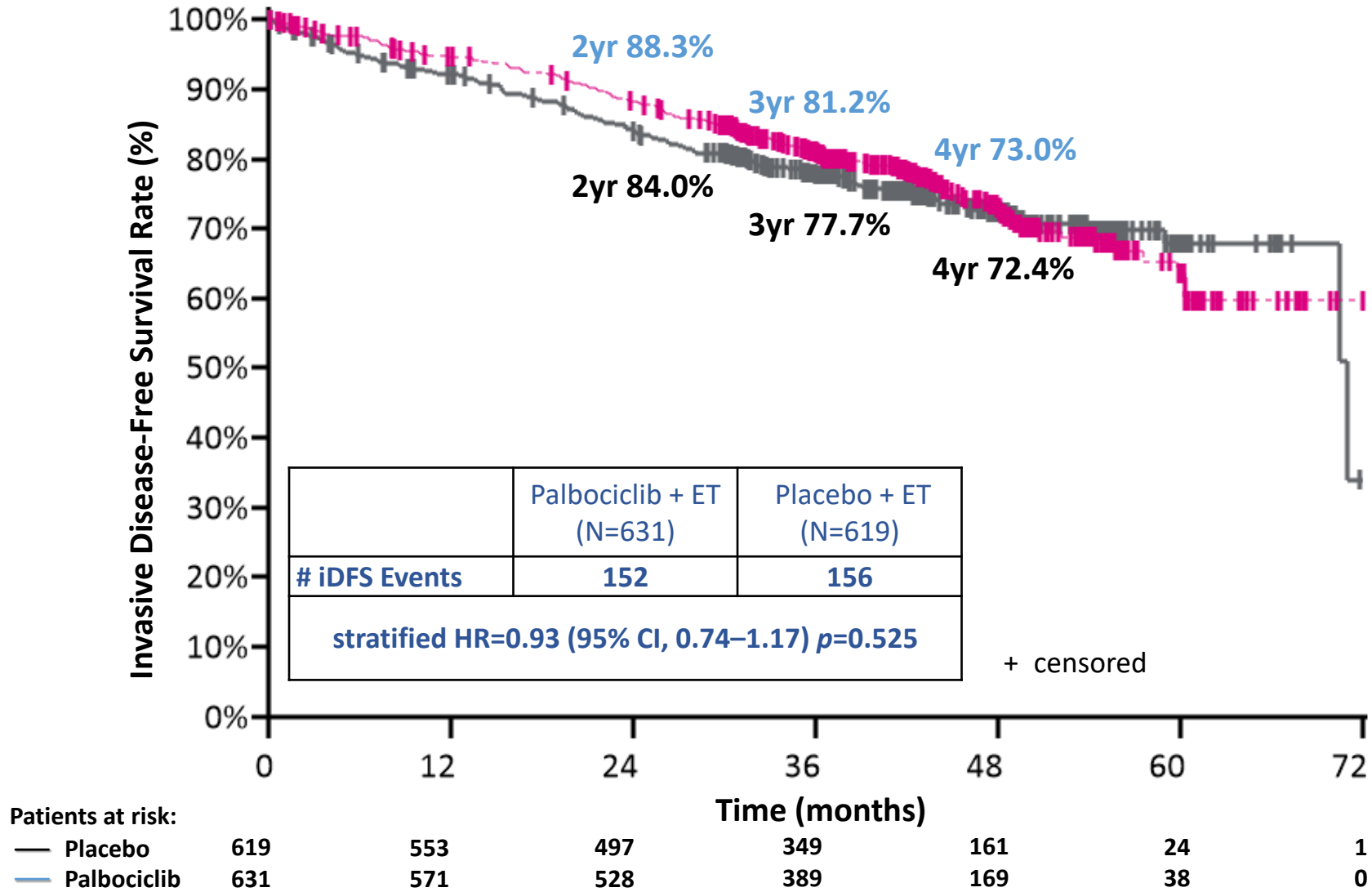
All patients will receive concomitantly endocrine therapy according to local standards

Penelope-B: ClinicalTrials.gov NCT01864746

Loibl S et al. SABCS 2020;Abstract GS1-02.

Courtesy of Harold J Burstein, MD, PhD

PENELOPE-B: Primary Endpoint iDFS



	Palbociclib + ET (N=631)	Placebo + ET (N=619)
# iDFS Events	152	156
stratified HR=0.93 (95% CI, 0.74–1.17) *p*=0.525		

Median Follow-Up
42.8 Months

* Weighted log-rank test based on the CHW method, taking into account the adaptive sample size re-estimation and group-sequential nature of the design

Courtesy of Harold J Burstein, MD, PhD

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- **Module 2: PI3K inhibitors**
- Module 3: Genomic assays

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Triple-Negative Breast Cancer

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- Module 8: PARP inhibition
- Module 9: Sacituzumab govitecan

A patient who presents with ER-positive, HER2-negative mBC with liver and bone metastases that is stable on palbociclib/letrozole is found on imaging to have asymptomatic disease progression. Genomic testing reveals a PIK3CA mutation. What would you recommend?

1. Continue palbociclib/letrozole
2. Continue palbociclib and switch ET
3. Continue ET and switch CDK4/6 inhibitor
4. Switch to everolimus with ET
5. Switch to alpelisib/fulvestrant
6. Other

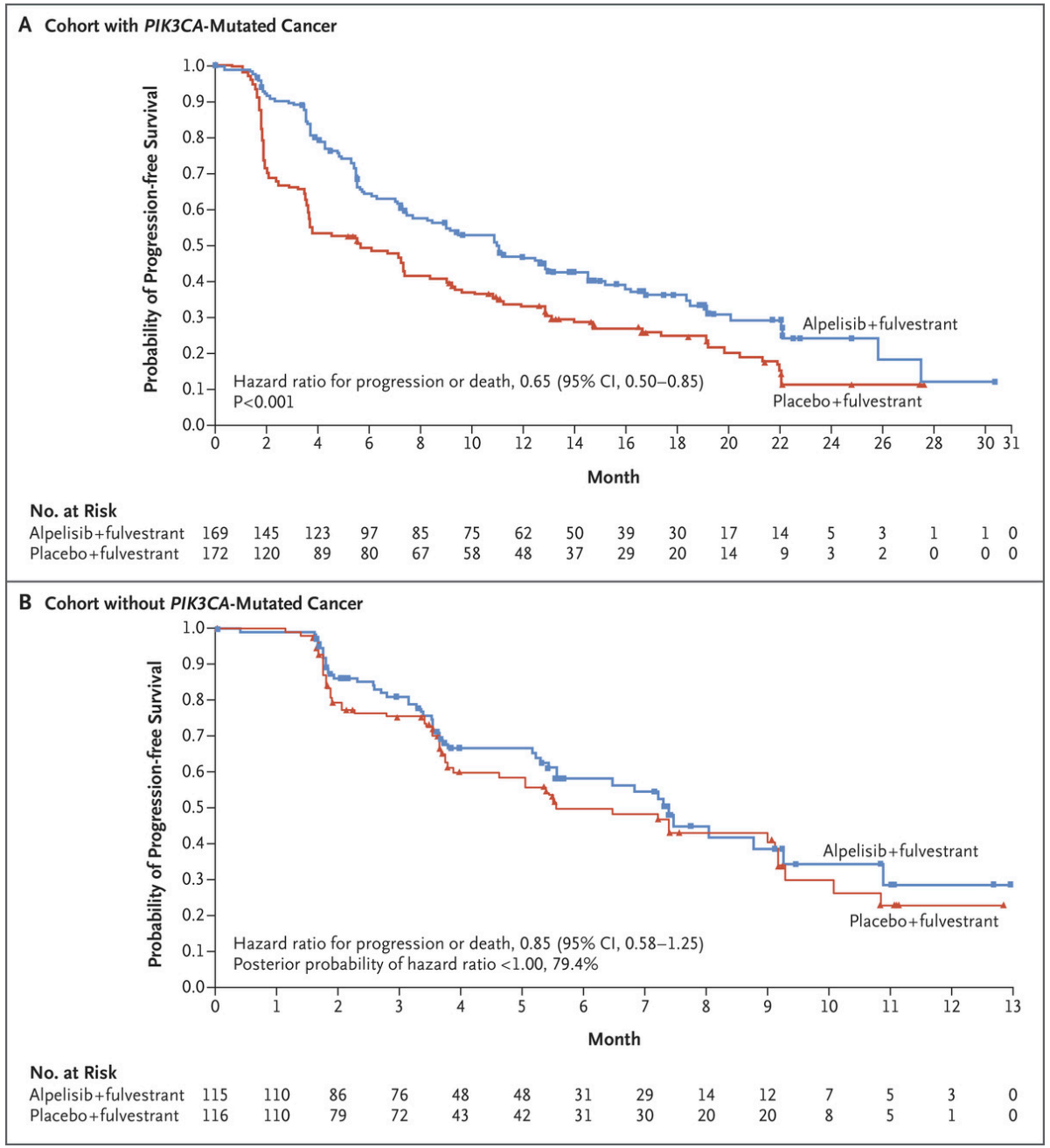
A patient with ER-positive mBC experiences asymptomatic disease progression on palbociclib/letrozole. Genomic testing reveals a PIK3CA mutation. Her baseline fasting glucose is 130 mg/dL and hemoglobin A1c = 6.5%. Would you recommend alpelisib/fulvestrant for this patient?

1. No
2. Yes, with standard-dose alpelisib
3. Yes, with reduced-dose alpelisib

Module 2: PI3K inhibitors for ER-positive metastatic breast cancer (mBC)

- **Key Relevant Data Sets**
  - SOLAR-1: Overall survival results with alpelisib + fulvestrant for mBC
  - BYLieve: Alpelisib + fulvestrant for mBC previously treated with CDK4/6 inhibitor + aromatase inhibitor

SOLAR-1

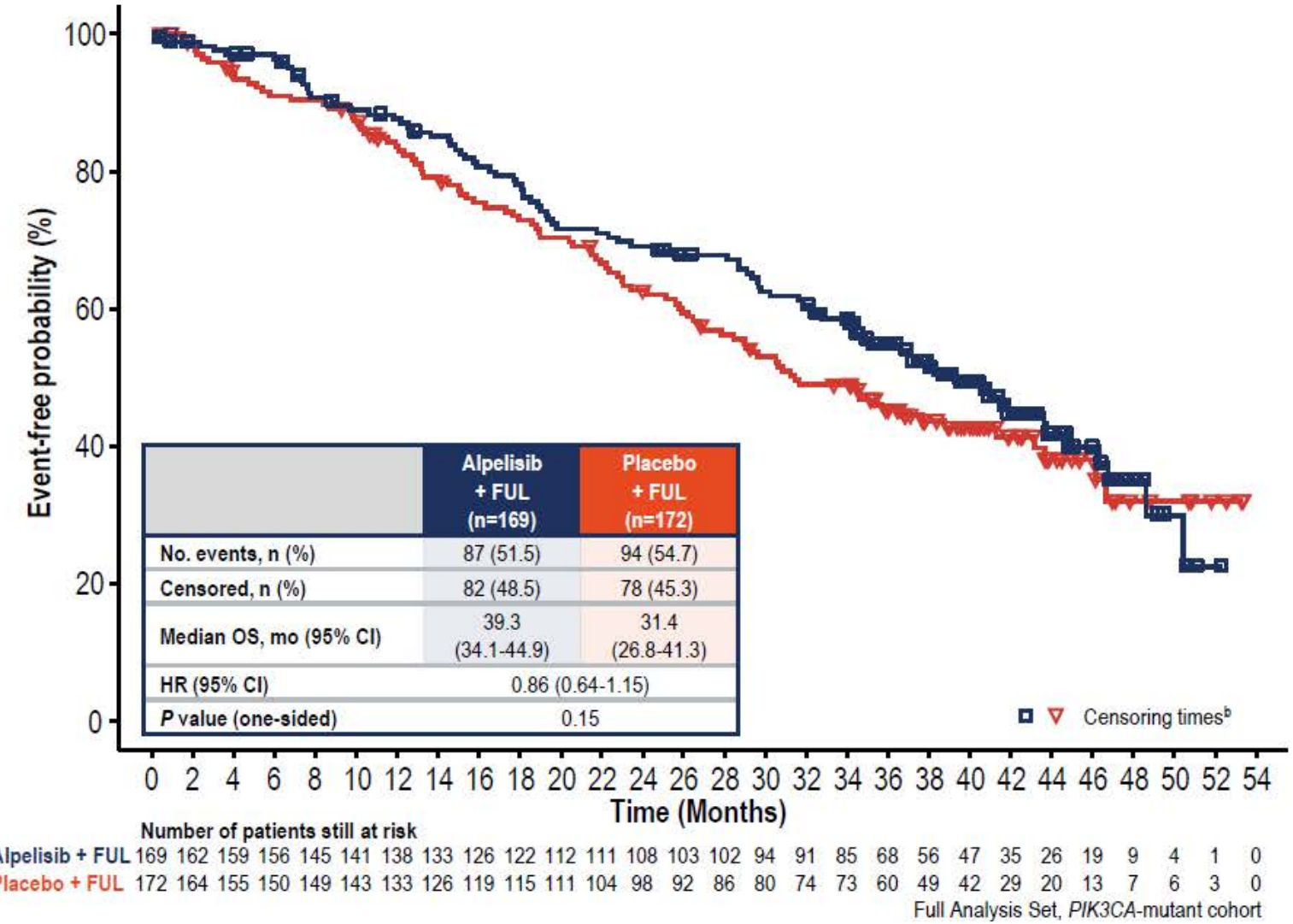


F André et al. N Engl J Med 2019;380:1929-1940.

Courtesy of Harold J Burstein, MD, PhD

SOLAR-1: OS in Patients in PIK3CA-mutant Cohort[a]

- mOS was prolonged by 7.9 mo for patients in the alpelisib + fulvestrant arm
- Final OS analysis in the *PIK3CA*-mutant cohort did not cross the prespecified O'Brien-Fleming efficacy boundary (1-sided $P \leq 0.0161$)



	Alpelisib + FUL (n=169)	Placebo + FUL (n=172)
No. events, n (%)	87 (51.5)	94 (54.7)
Censored, n (%)	82 (48.5)	78 (45.3)
Median OS, mo (95% CI)	39.3 (34.1-44.9)	31.4 (26.8-41.3)
HR (95% CI)	0.86 (0.64-1.15)	
P value (one-sided)	0.15	

[a] Between randomisation to OS event or censoring, median time was 30.8 mo.
[b] Date of censoring is defined as the last contact date for OS.

Andre F et al. ESMO 2020;Abstract LBA18.

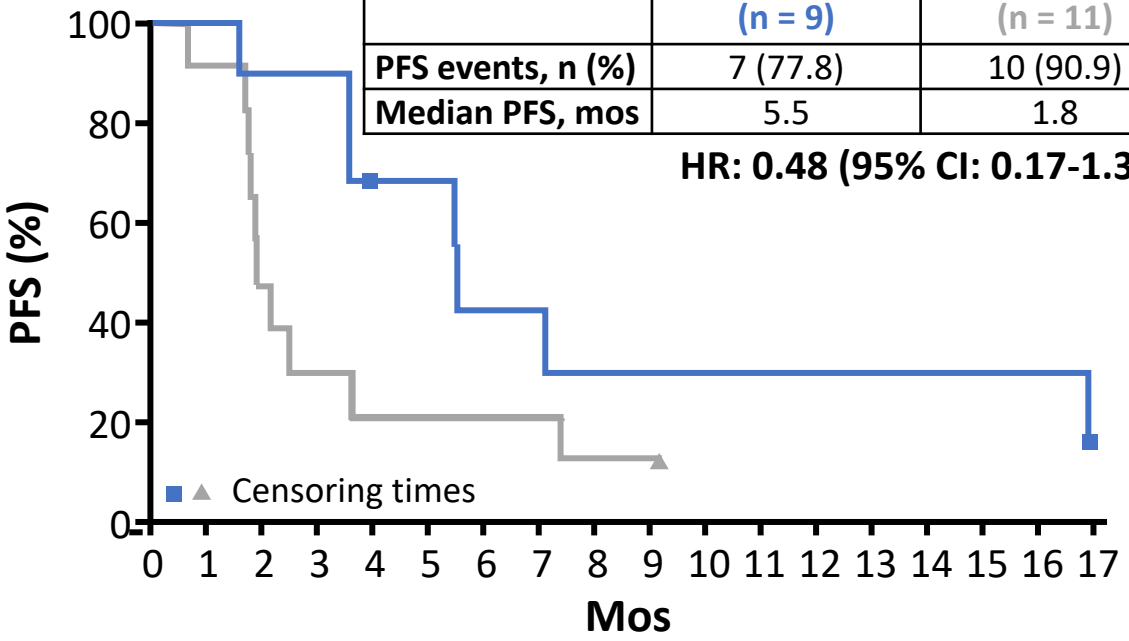
Courtesy of Harold J Burstein, MD, PhD

SOLAR-1: PFS by Prior CDK4/6 Exposure in PIK3CA-Mutant Cohort

With Prior CDK4/6 Inhibitor Therapy

	Alpelisib + FULV (n = 9)	Placebo + FULV (n = 11)
PFS events, n (%)	7 (77.8)	10 (90.9)
Median PFS, mos	5.5	1.8

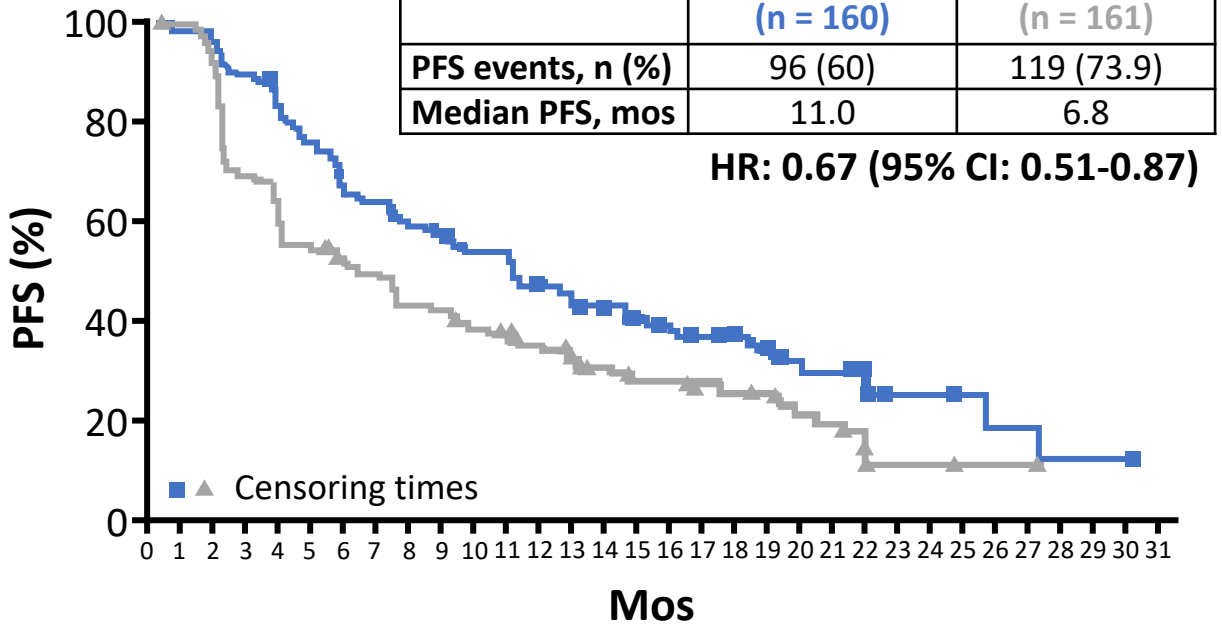
HR: 0.48 (95% CI: 0.17-1.36)



Without Prior CDK4/6 Inhibitor Therapy

	Alpelisib + FULV (n = 160)	Placebo + FULV (n = 161)
PFS events, n (%)	96 (60)	119 (73.9)
Median PFS, mos	11.0	6.8

HR: 0.67 (95% CI: 0.51-0.87)



- Randomization was stratified by prior treatment with any CDK4/6 inhibitor, but the number of patients enrolled who had received prior CDK4/6 inhibitor therapy was small
- Benefit with alpelisib observed regardless of prior CDK4/6 inhibitor therapy

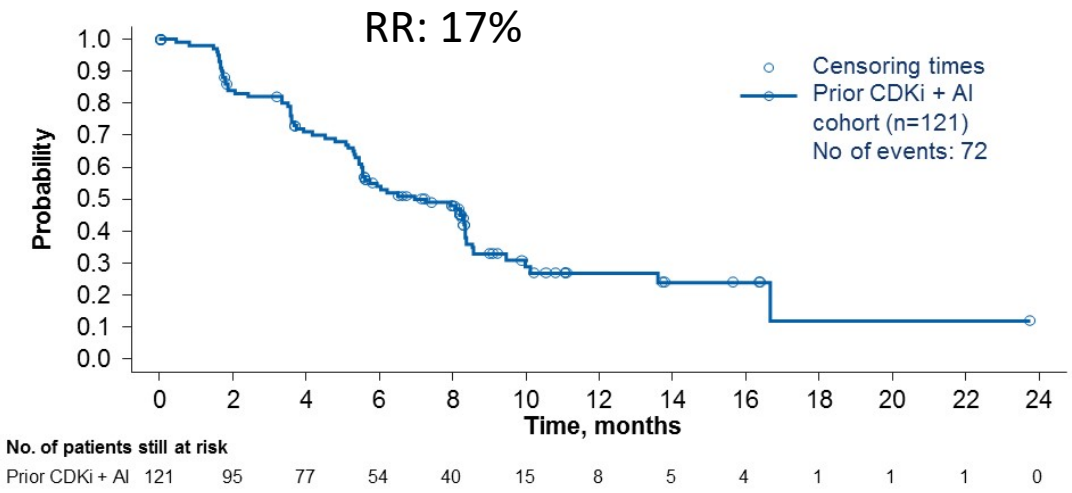
Juric. SABCS 2018. Abstr GS3-08.

Courtesy of Harold J Burstein, MD, PhD

BYLieve Trial Efficacy: Primary Endpoint and PFS Results

BYLieve
Alpelisib (BYL719) In patients with PIK3CA mutant, HR+, HER2- adVanced brEast cancer

Endpoint	Prior CDKi + AI (Cohort A) (n=121)
Primary endpoint: Patients who were alive without disease progression at 6 mo	**50.4%** (n=61; 95% CI, 41.2-59.6)
Secondary endpoint: Median PFS	**7.3 mo** [n=72 (59.5%) with event]; 95% CI, 5.6-8.3)



The primary endpoint for the prior CDKi + AI cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months

- In SOLAR-1, 44.4% of patients in the *PIK3CA*-mutant cohort with prior CDKi treated with alpelisib plus fulvestrant were alive without disease progression at 6 months

AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; CI, confidence interval; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

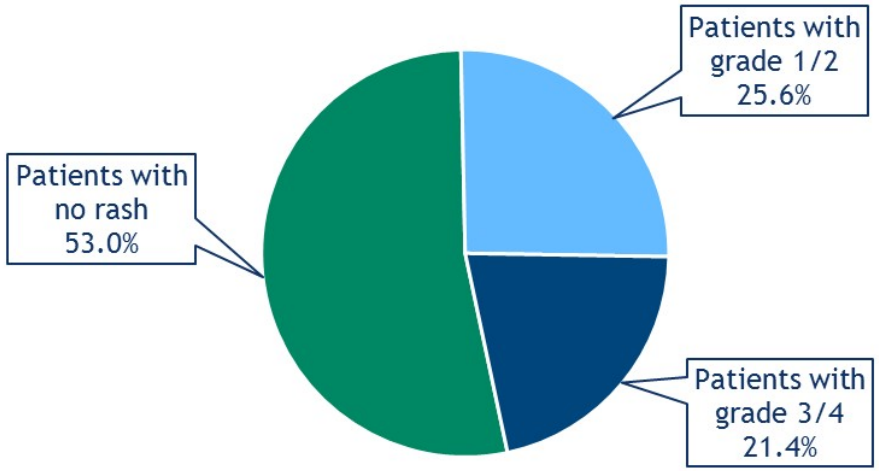
Presented By Hope Rugo at TBD

Courtesy of Harold J Burstein, MD, PhD

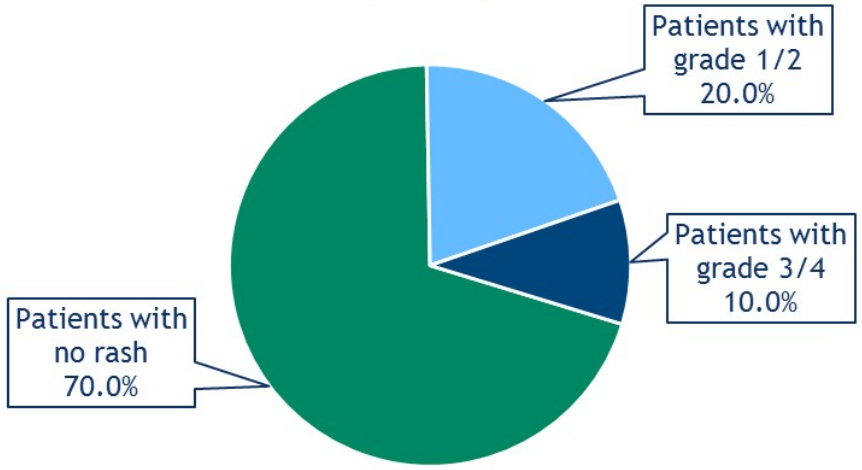
Incidence of Rash in Patients With/Without Prophylactic Antihistamines

BYLieve
Alpelisib (BYL719) In patients with PIK3CA mutant, HR+, HER2- adVanced brEast cancer

Patients who did not receive antihistamines or received antihistamines after rash (n=117)



Patients who received antihistamines before rash or had no event (n=10)



Presented By Hope Rugo at TBD

Courtesy of Harold J Burstein, MD, PhD

Agenda

ER-Positive, HER2-Negative Breast Cancer

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- Module 2: PI3K inhibitors
- **Module 3: Genomic assays**

HER2-Positive Breast Cancer

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Triple-Negative Breast Cancer

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A premenopausal woman presents with 2 Grade II, ER/PR-positive, HER2-negative 2.1-cm IDC with 2 positive sentinel lymph nodes. Would you order a genomic assay for this patient?

1. No
2. Yes, the 21-gene assay
3. Yes, the 70-gene signature
4. Yes, Prosigna® PAM50
5. Yes, Breast Cancer Index
6. Yes, other

Module 3: Genomic assays

- **Key Relevant Data Set**
  - RxPONDER (SWOG-S1007): ET +/- chemotherapy for patients with Recurrence Score® <25 and 1-3 positive nodes
  - ADAPT HR-positive/HER2-negative trial

RxPONDER Schema

Key Entry Criteria

- Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- breast cancer with 1*-3 LN+ without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy**
- Axillary staging by SLNB or ALND

REGISTRATION

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by
Endocrine Therapy Recommended

RANDOMIZATION

N = 5,000 pts

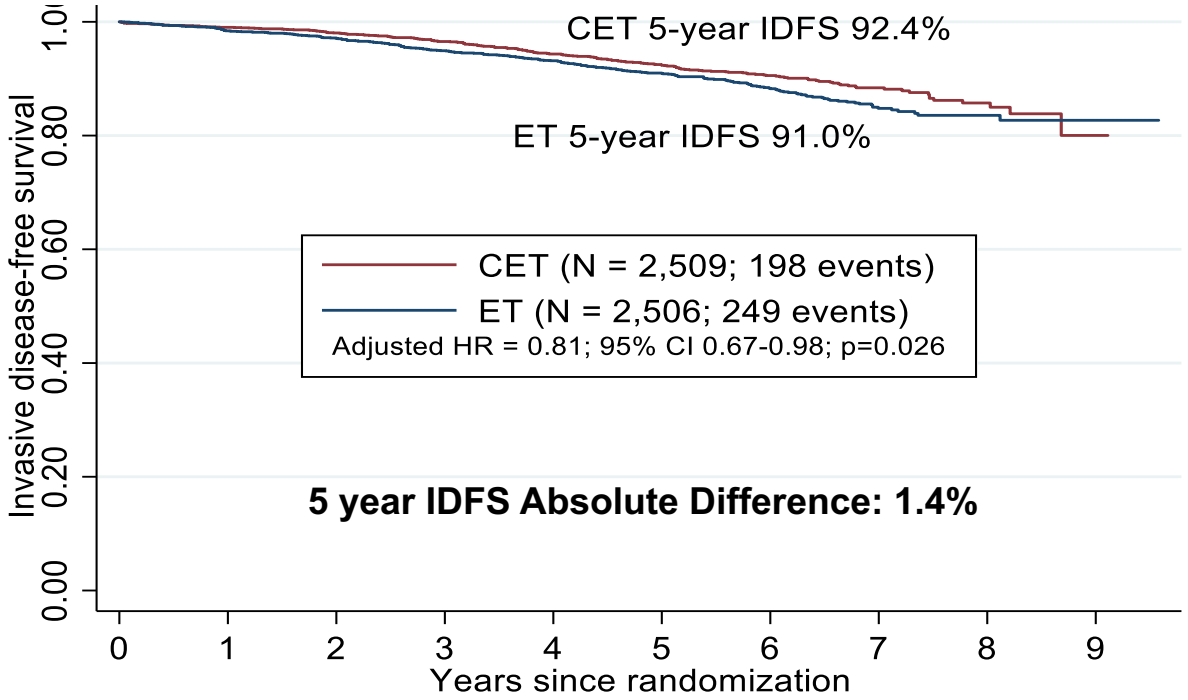
Arm 1:
Chemotherapy Followed by
Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

Stratification Factors
Recurrence Score: 0-13 vs.14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.
** Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.
ALND = Axillary Lymph Node Dissection, SLNB = Sentinel Lymph Node Biopsy

RxPONDER: IDFS in Overall Population by Treatment Arm



Number at risk

CET	2509	2277	2104	1893	1648	1397	857	403	122	4
ET	2506	2327	2161	1910	1696	1404	846	397	135	11

CET = Chemotherapy + Endocrine Therapy; ET = Endocrine Therapy Alone

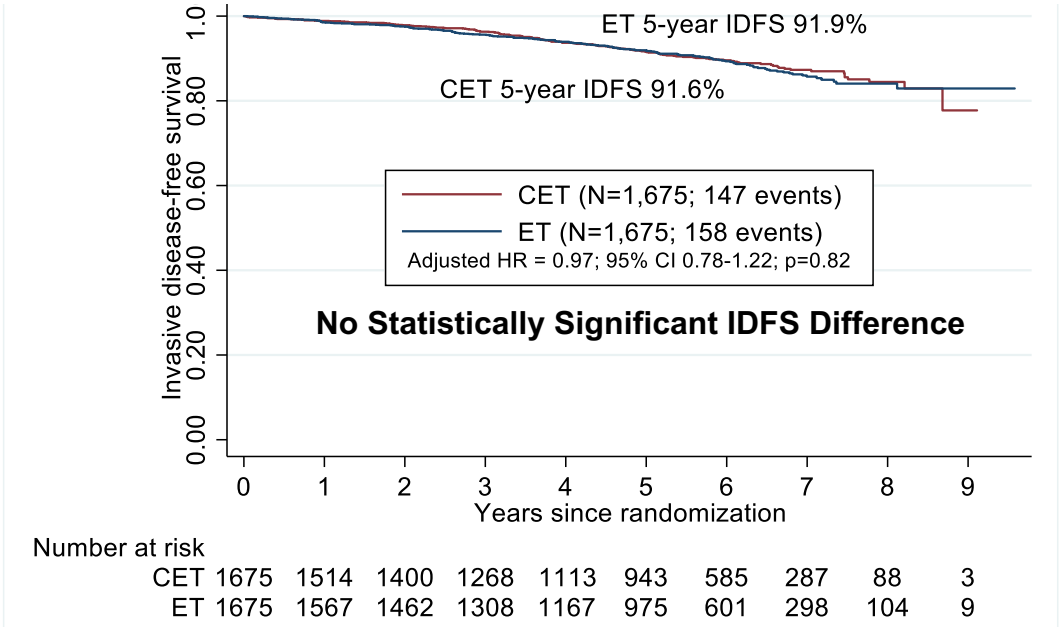
447 observed IDFS events (54% of expected at final analysis) at a median follow-up of 5.1 years

Kalinsky K et al. SABCS 2020;Abstract GS3-00.

Courtesy of Harold J Burstein, MD, PhD

RxPONDER: IDFS Stratified by Menopausal Status

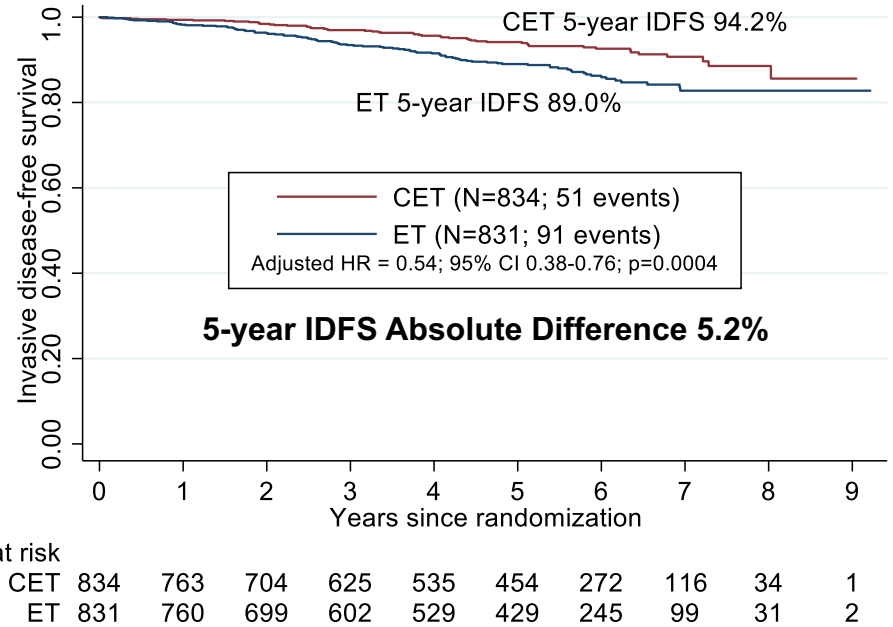
Postmenopausal



IDFS Event	CET	ET	Total (%)
Distant	39	44	83 (27%)
Local-Regional	10	14	24 (8%)
Contralateral	10	9	19 (6%)
Non-Breast Primary	44	47	91 (30%)
Recurrence Not Classified	9	7	16 (5%)
Death not due to Recurrence or Second Primary	35	37	72 (24%)

Absolute Difference in Distant Recurrence as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

Premenopausal



IDFS Event	CET	ET	Total (%)
Distant	26	50	76 (54%)
Local-Regional	8	17	25 (18%)
Contralateral	4	8	12 (8%)
Non-Breast Primary	10	10	20 (14%)
Recurrence Not Classified	1	1	2 (1%)
Death not due to Recurrence or Second Primary	2	5	7 (5%)

Absolute Difference in Distant Recurrence as 1st site: 2.9% (3.1% CET vs. 6.0% ET)

Courtesy of Harold J Burstein, MD, PhD

Kalinsky K et al. SABCS 2020.

Endocrine Therapy Alone in Patients with Intermediate or High-Risk Luminal Early Breast Cancer (0-3 lymph nodes), Recurrence Score <26 and Ki67 Response After Preoperative Endocrine Therapy: First Efficacy Results from the ADAPT HR+/HER2- Trial

Harbeck N et al.

SABCS 2020;Abstract GS4-04.

Agenda

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HER2-Positive Breast Cancer

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- Module 5: Metastatic disease

Triple-Negative Breast Cancer

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A 65-year-old woman presents with a 1.3-cm, ER-positive, HER2-positive IDC with 2 positive sentinel nodes. Regulatory and reimbursement issues aside, what adjuvant anti-HER2 therapy would you recommend?

1. Trastuzumab
2. Trastuzumab/pertuzumab
3. T-DM1
4. Trastuzumab → neratinib
5. Trastuzumab/pertuzumab → neratinib
6. T-DM1 → neratinib
7. Other

RTP RESEARCH TO PRACTICE

Module 4: Early-stage HER2-positive breast cancer; neoadjuvant therapy

- **Key Relevant Data Sets**
  - ExteNET: Final efficacy results with neratinib
  - CONTROL: Improved tolerability of neratinib

ExteNET

Background: Final efficacy analysis of a trial that was the basis for approval of neratinib for extended adjuvant therapy in HER2-positive BrCa.

Methods: Placebo-controlled phase III trial of neratinib for 1 year in stage I-IIIC HER2+ BrCa after completion of 1 year of trastuzumab-based therapy.

Primary endpoint: iDFS

Findings, including exploratory:

	5y iDFS*	5y iDFS HR+*	5y DDFS	5y CNS relapse	8y OS
Neratinib	95.3%	90.8%	92.4%	0.7%	91.5%
Placebo	90.8%	85.7%	87.7%	2.1%	89.4%
Absolute Δ	4.5%	5.1%	4.7%	1.4%	2.1%

* starting within 1y of trastuzumab completion

Courtesy of Lisa Carey, MD

Chan A et al, Clin Breast Cancer, in press

CONTROL Trial

Background: Neratinib is approved for extended adjuvant therapy in HER2-positive BrCa

However, it is poorly tolerated – in ExteNET 17% discontinued, 40% had grade 3 diarrhea

Objective: Improve GI tolerability of neratinib

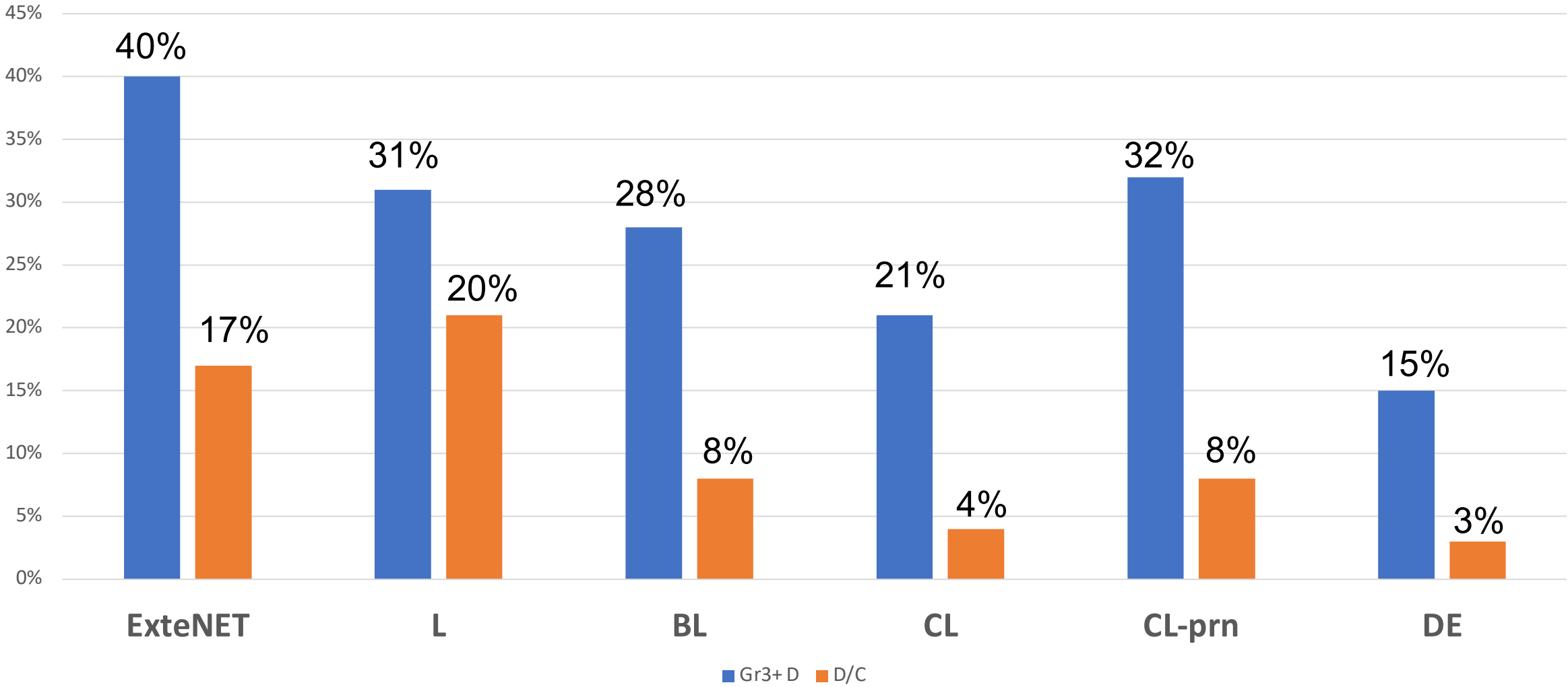
Methods: Sequential single arm interventions in adjuvantly treated patients

- Cohort 1 (n=137): Loperamide x 1-2m
- Cohort 2 (n=64): Budesonide + loperamide x 1m
- Cohort 3 (n=136 + 104): Colestipol + loperamide or prn loperamide x 1m
- Cohort 4 (n=60, ongoing): Dose escalation (120 mg/d x 1w, 160 mg/d x 1w)

Courtesy of Lisa Carey, MD

Barcenas CH et al, Ann Oncol 2020

CONTROL: Results



Courtesy of Lisa Carey, MD

Barcenas CH et al, Ann Oncol 2020

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A 65-year-old woman with ER-negative, HER2-positive mBC receives THP followed by T-DM1 on disease progression. She now presents with further progression but no evidence of CNS involvement. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

1. Continue T-DM1
2. Trastuzumab + chemotherapy
3. Trastuzumab + lapatinib
4. Neratinib + capecitabine
5. Tucatinib + trastuzumab/capecitabine
6. Trastuzumab deruxtecan
7. Margetuximab + chemotherapy
8. Other

A 65-year-old woman with ER-negative, HER2-positive mBC receives THP followed by T-DM1 on progression. She then presents with a single brain metastasis that is resected with no other evidence of progression. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

1. Continue T-DM1
2. Trastuzumab + chemotherapy
3. Trastuzumab + lapatinib
4. Neratinib + capecitabine
5. Tucatinib + trastuzumab/capecitabine
6. Trastuzumab deruxtecan
7. Margetuximab + chemotherapy
8. Other

Module 5: HER2-positive mBC

- **Key Relevant Data Sets**
  - HER2CLIMB: Tucatinib + trastuzumab + capecitabine – Survival results
  - HER2CLIMB: Intracranial efficacy and survival
  - DESTINY-Breast01: Trastuzumab deruxtecan
  - NALA: Neratinib + capecitabine vs lapatinib + capecitabine
  - SOPHIA: Margetuximab + chemotherapy vs trastuzumab + chemotherapy

HER2CLIMB

Background: Tucatinib, an irreversible small molecule HER2 inhibitor, showed promise in small trials of heavily pretreated HER2+ BrCa, including those with CNS metastases.

While we have many anti-HER2 agents, in the third-line+ setting patients have poor prognosis with a high degree of CNS involvement (~ 25% in NALA).

Objective: Test tucatinib in a population of pretreated metastatic HER2+ BrCa patients with preplanned cohort with CNS involvement.

Methods: Randomized (2:1) placebo-controlled phase II trial of tucatinib added to capecitabine + trastuzumab in heavily pretreated* patients with metastatic HER2+ BrCa with preplanned analysis of patients with brain metastases.

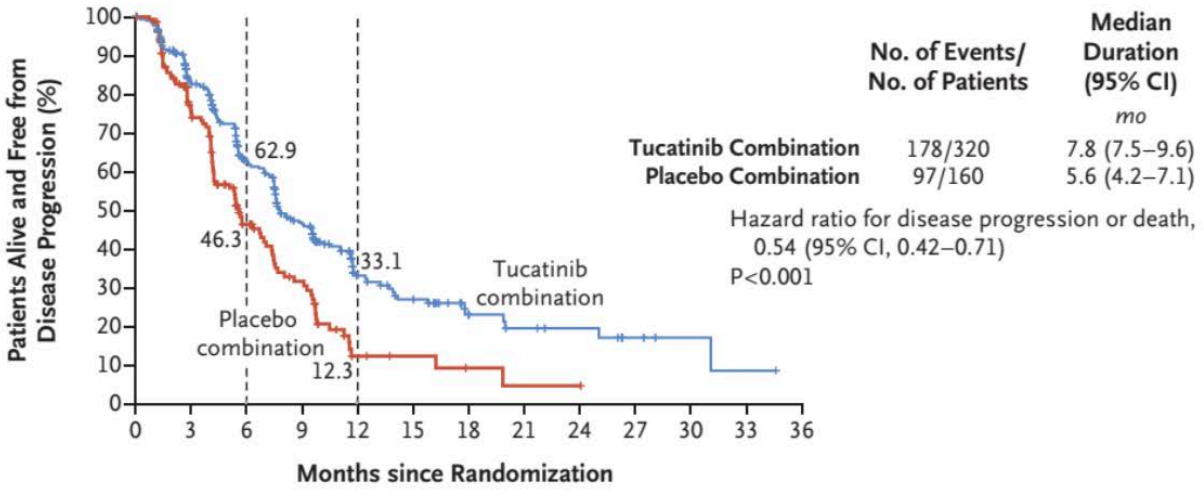
** Prior trastuzumab, pertuzumab, T-DM1 required. Median # prior lines for MBC = 3*

Courtesy of Lisa Carey, MD

Murthy R et al, NEJM 2020

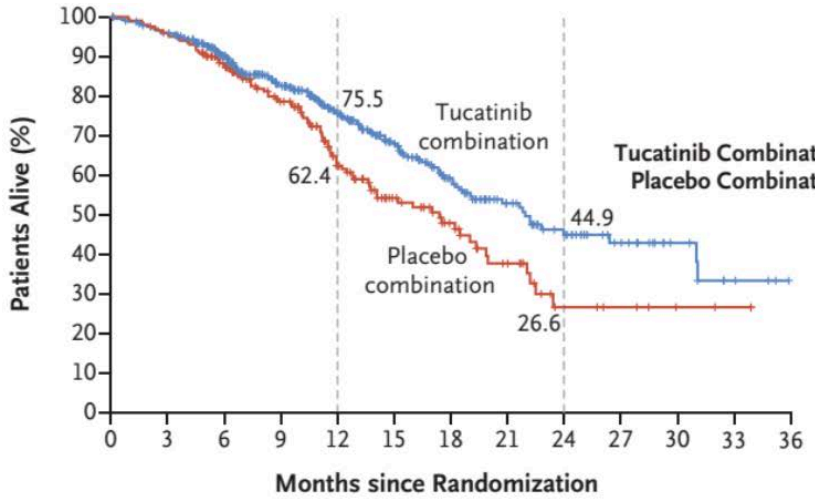
HER2CLIMB: Results

N=612 (48% with CNS mets). Event-driven reporting of primary endpoint (PFS) at 14m.



	No. of Events/ No. of Patients	Median Duration (95% CI) mo
Tucatinib Combination	178/320	7.8 (7.5–9.6)
Placebo Combination	97/160	5.6 (4.2–7.1)

Hazard ratio for disease progression or death, 0.54 (95% CI, 0.42–0.71)
P<0.001



	No. of Deaths/ No. of Patients	Median Duration (95% CI) mo
Tucatinib Combination	130/410	21.9 (18.3–31.0)
Placebo Combination	85/202	17.4 (13.6–19.9)

Hazard ratio for death, 0.66 (95% CI, 0.50–0.88)
P=0.005

- **All subgroups benefited essentially equally**.
- **Toxicity gr3+:** Diarrhea (13% vs 9%), PPE (13% vs 9%), LFT ↑ (~ 5% vs <1%). 6% discontinued drug.
- **Triggered *a priori* CNS cohort analysis**:

CNS cohort (n=291)	1y PFS	mPFS
Tucatinib	25%	7.6m
Placebo	0%	5.4m

Courtesy of Lisa Carey, MD

Murthy R et al, NEJM 2020

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

HER2CLIMB: CNS Cohort

- **HER2CLIMB allowed patients with CNS metastases, even active / progressing.**

- **291 / 612 (48%) in CNS cohort (198 tucatinib-treated, 93 placebo). Most had extracranial disease also.**
  - Stable BM after CNS Rx n=117
  - Progressive after CNS Rx n=108
  - New / untreated brain mets n=66

  } **"Active" BM**

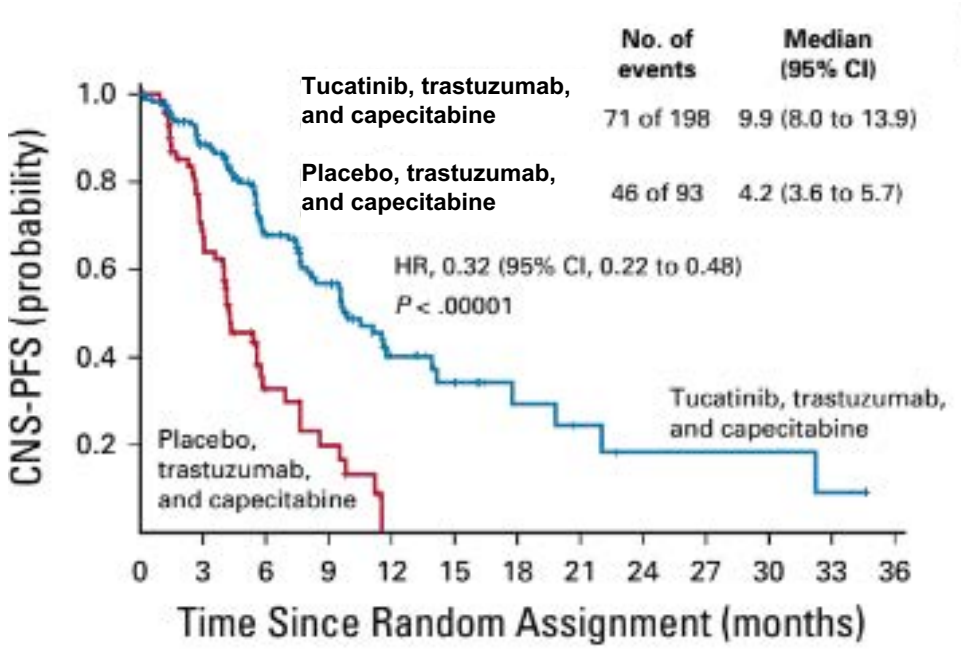
- **CNS-PFS secondary endpoint of parent trial**

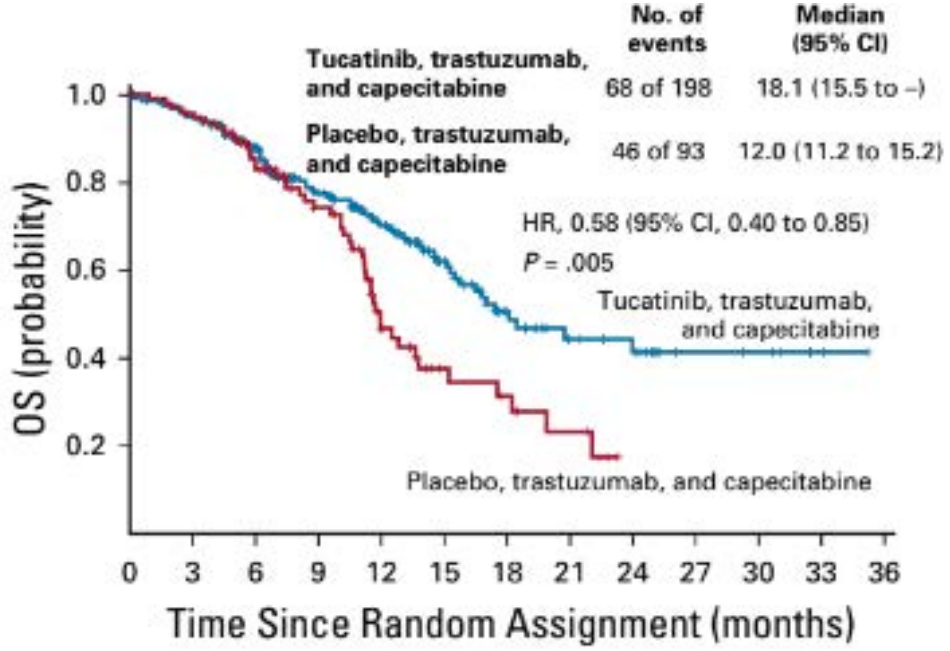
Courtesy of Lisa Carey, MD

Lin N et al, JCO 2020

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

HER2CLIMB: CNS Cohort Results





	1y CNS-PFS	1y CNS-PFS Active BM	1y OS Active BM	ORR-CNS (n=75)
Tucatinib (+XH)	40%	35%	72%	47%
Placebo (+XH)	0%	0%	41%	20%

Courtesy of Lisa Carey, MD

Lin N et al, JCO 2020

DESTINY-Breast01

Background: Trastuzumab deruxtecan (DS-8201a, T-DXd) is an antibody-drug conjugate (ADC) of an anti-HER2 antibody, cleavable linker, and topoisomerase I inhibitor payload.

It was designed to have a) a much higher drug-to-antibody ratio than T-DM1 (8 vs <4), b) permeable payload that crosses the cell membrane so can kill bystander cells, and c) short half-life to minimize toxicity.

In early studies it was very active in heavily pretreated patients with HER2-positive MBC.

Objective: Examine safety and ORR of T-DXd in third-line+ setting.

Methods: Single arm two-part Phase II trial of T-DXd in HER2+ MBC patients previously treated with T-DM1 (was a heavily pretreated population, median # prior treatments = 6).

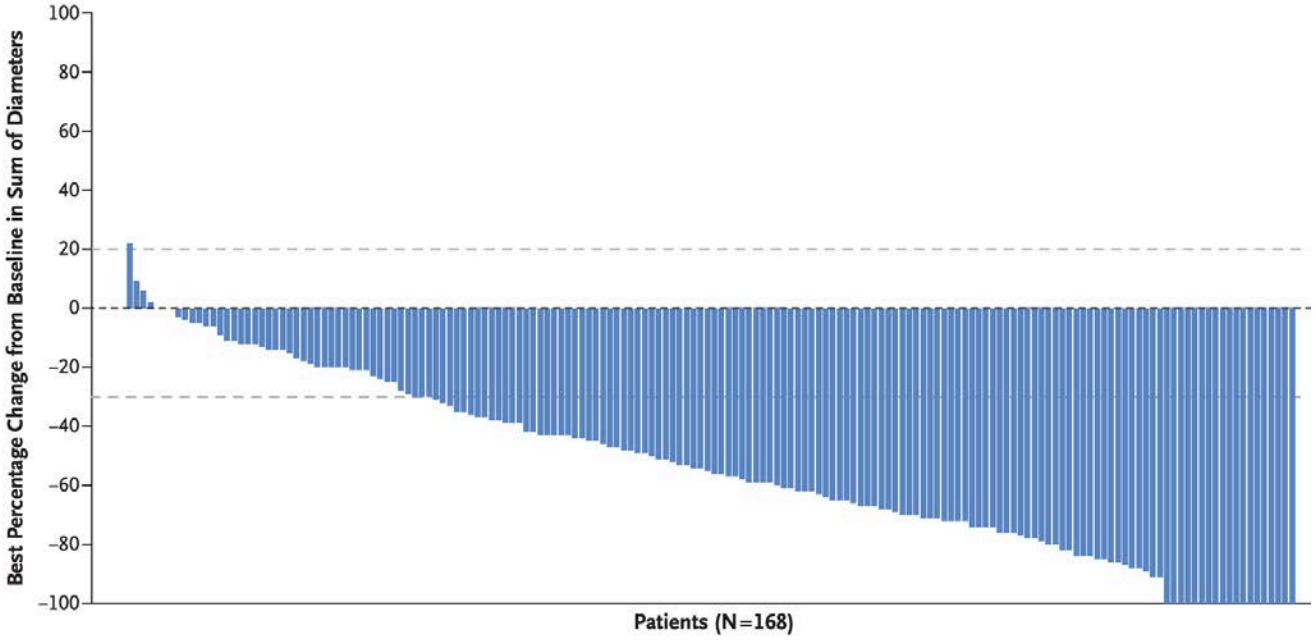
DESTINY-Breast01: Results

N=253 in Parts 1 (dose-finding, PK analysis) and 2 (efficacy by ORR, n=184 Rx@ 5.4 mg/kg) @ 11m

ORR 62% (same across subsets)
PFS 16m
1y OS 86%

Toxicity:

- Grade 3+: ANC (21%), anemia (9%), nausea (8%)
- Discontinuation: 15%
- ILD: 14%, mostly grade 1/2
  - 4 (2.2%) deaths
  - Median onset 193d
  - Reversible in ~ 50% (?)



24 had stable CNS metastases; ORR 58%
CNS site of progression in overall trial 8%

Modi S et al, NEJM 2020; Jerusalem G et al, ESMO 2020

Courtesy of Lisa Carey, MD

NALA

Background: Neratinib, an irreversible pan-HER small molecule inhibitor, delayed CNS progression when added to a taxane in 1st-line HER2+ MBC (NeferTT), and is active as single agent in CNS mets (TBCRC 022) and as extended adjuvant therapy (ExteNET).

Capecitabine plus lapatinib is an older approved regimen in pretreated HER2+ MBC with some evidence of activity in CNS-involved HER2+ MBC (EGF100151).

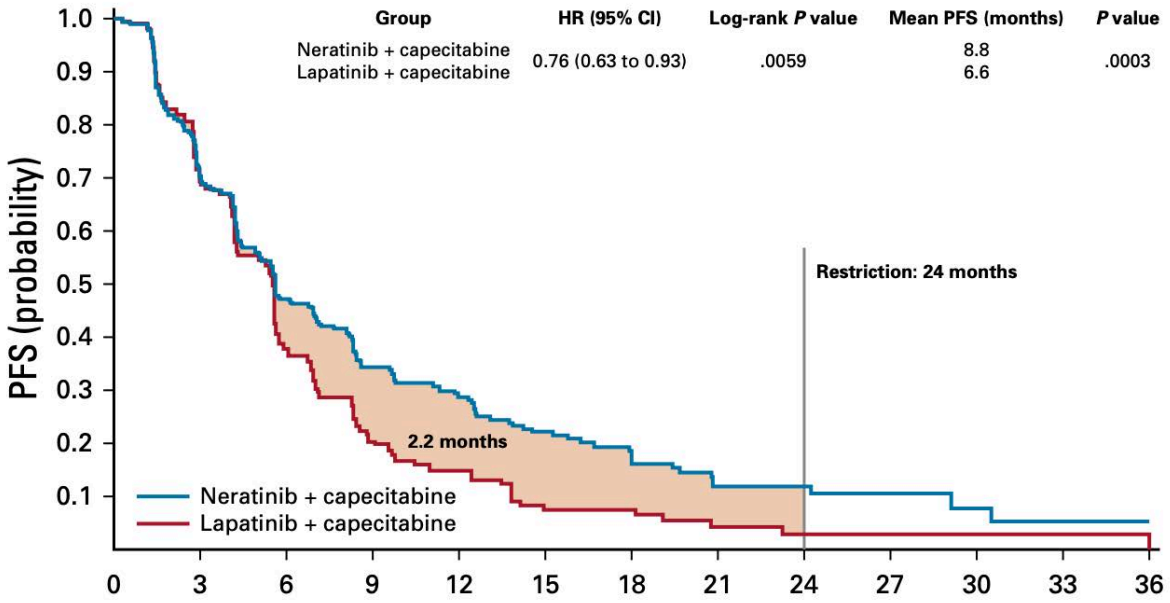
Objective: Compare neratinib to lapatinib when added to capecitabine in third-line+ setting.

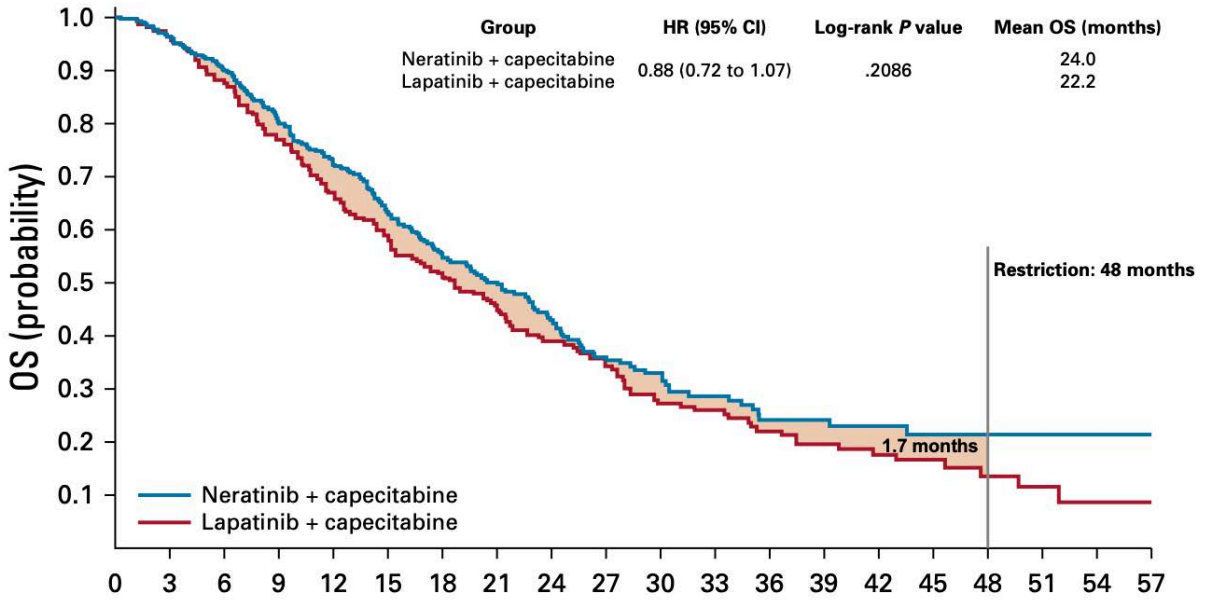
Methods: Randomized Phase III trial of neratinib versus lapatinib added to capecitabine in HER2+ MBC patients previously treated with ≥ 2 prior anti-HER2 regimens (one-third prior trastuzumab, pertuzumab, T-DM1). Stable brain mets allowed.

Co-primary endpoints: PFS and OS. CNS intervention prespecified endpoint.

NALA: Results

N=621 @ 30m. Met PFS endpoint (HR 0.76), but not OS endpoint (0.88)





- **HR- benefited more than HR+ (opposite of ExteNET); N. America, Europe little benefit.**
- **CNS intervention incidence: 23% neratinib + cape, 29% lapatinib + cape**
- **Toxicity: gr3+ diarrhea 25% despite prophylaxis. Only 3% discontinuation rate.**

Courtesy of Lisa Carey, MD

Saura C et al, J Clin Oncol 2020

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

FDA Approves Margetuximab for HER2-Positive mBC

Press Release: December 16, 2020

"The Food and Drug Administration approved margetuximab-cmkb in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

Efficacy was evaluated in SOPHIA (NCT02492711), a randomized, multicenter, open-label trial of 536 patients with IHC 3+ or ISH-amplified HER2+ metastatic breast cancer who had received prior treatment with other anti-HER2 therapies. Patients were randomized (1:1) to margetuximab plus chemotherapy or trastuzumab plus chemotherapy. Randomization was stratified by chemotherapy choice (capecitabine, eribulin, gemcitabine, or vinorelbine), number of lines of therapy in the metastatic setting (≤ 2, > 2), and number of metastatic sites (≤ 2, > 2)."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-margetuximab-metastatic-her2-positive-breast-cancer

SOPHIA

Background: Margetuximab is a novel Fc-engineered anti-HER2 antibody with enhanced affinity for activating Fc gamma receptor (FcR) CD16A and decreased affinity for inhibitory FcR CD32B. This may increase activation of innate and adaptive anti-HER2 immune responses. Promising activity as monotherapy in pretreated HER2+ MBC phase I trial.

85% of people carry lower-affinity CD16A FV and FF genotypes, 15% have high-affinity VV.

Objective: Compare margetuximab (M) to trastuzumab (H) when added to chemotherapy in third-line+ setting.

Methods: Randomized open-label Phase III trial of M vs H added to chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in HER2+ MBC patients previously treated with ≥ 2 prior anti-HER2 regimens. > 90% had received prior T-DM1, most were 3rd line.

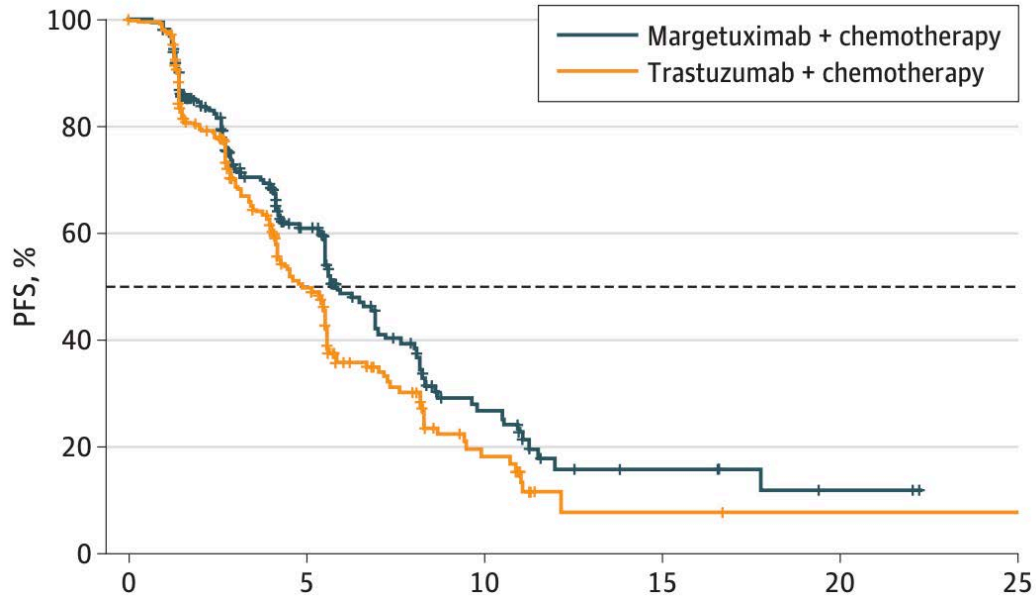
Sequential primary endpoints: centrally assessed PFS and OS

Courtesy of Lisa Carey, MD

Rugo H et al, JAMA Oncol 2021

SOPHIA: Results

N=536 @ 16m. Met primary endpoint for PFS (HR 0.76), OS immature (HR 0.89)



	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	130	135
Median PFS (95% CI)	5.8 mo (5.52-6.97)	4.9 mo (4.17-5.59)
3-mo PFS rate	72% (65%-77%)	70% (63%-76%)
6-mo PFS rate	48% (41%-56%)	36% (28%-44%)
9-mo PFS rate	30% (22%-38%)	22% (15%-30%)

HR by stratified Cox model, 0.76 (95% CI, 0.59-0.98)

- **Well-tolerated, same discontinuation rate as trastuzumab.**
- **Exploratory analysis by CD16A genotype:**

M vs H	PFS
FV or FF (lower-affinity, 86%)	6.9 vs 5.1m
VV (higher-affinity, 14%)	4.8 vs 5.6m

Courtesy of Lisa Carey, MD

Rugo H et al, JAMA Oncol 2021

Agenda

ER-Positive, HER2-Negative Breast Cancer

- Module 1: CDK4/6 inhibitors
- Module 2: PI3K inhibitors
- Module 3: Genomic assays

HER2-Positive Breast Cancer

- Module 4: Early-stage disease; neoadjuvant therapy
- Module 5: Metastatic disease

Triple-Negative Breast Cancer

- **Module 6: Immunotherapy for advanced disease**
- Module 7: Immunotherapy in the neoadjuvant setting
- Module 8: PARP inhibition
- Module 9: Sacituzumab govitecan

A 32-year-old woman who completed neoadjuvant FEC-T and postoperative radiation therapy 21 months ago for localized TNBC now presents with small-volume liver and nodal metastases: BRCA wild-type, PD-L1-positive. What therapy would you recommend?

1. Chemotherapy
2. Atezolizumab/*nab* paclitaxel
3. Atezolizumab/paclitaxel
4. Pembrolizumab/*nab* paclitaxel
5. Pembrolizumab/paclitaxel
6. Pembrolizumab/gemcitabine/carboplatin
7. Other

Module 6: Immunotherapy for advanced advanced triple-negative breast cancer

- **Key Relevant Data Sets**
  - IMpassion130: Final OS analysis with atezolizumab + *nab* paclitaxel
  - IMpassion131: First-line paclitaxel +/- atezolizumab
  - KEYNOTE-355: First-line pembrolizumab + chemotherapy

IMpassion130

Background: This is the pivotal trial responsible for anti-PDL1 immune checkpoint inhibitor (ICI) atezolizumab added to chemotherapy in PDL1+ metastatic TNBC (mTNBC). The OS endpoint was updated in 2020.

Objective: Update the PFS and survival benefit of atezo added to nab paclitaxel in first-line setting.

Methods: Randomized placebo-controlled Phase III trial of atezo added to nab paclitaxel in mTNBC who have not been treated for metastatic disease. Half had previously received taxane for early disease; 12m PFI was required.

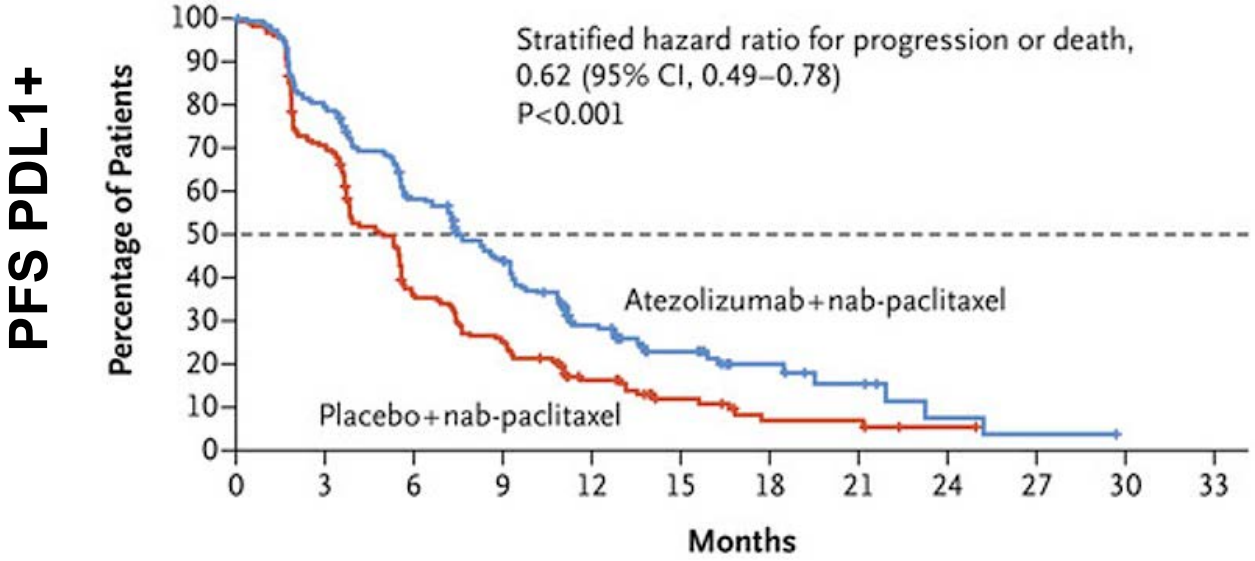
Co-primary endpoints: PFS and OS, hierarchically tested in ITT and PDL1+ (41%) populations.

Courtesy of Lisa Carey, MD

Schmid P et al, Lancet Oncol 2020

IMpassion130: Results

	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo+Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)



Nab paclitaxel + atezolizumab in PDL1+:

- **PFS advantage = 2.5m**
- **OS advantage @ 20m f/u = 7.5m**
- **No impact in PDL1-**

Courtesy of Lisa Carey, MD

Schmid P et al, Lancet Oncol 2020

IMpassion131

Background: Building on the success of IMpassion130, this trial used the same approach in the same setting but with a different chemotherapy backbone, the more conventional paclitaxel.

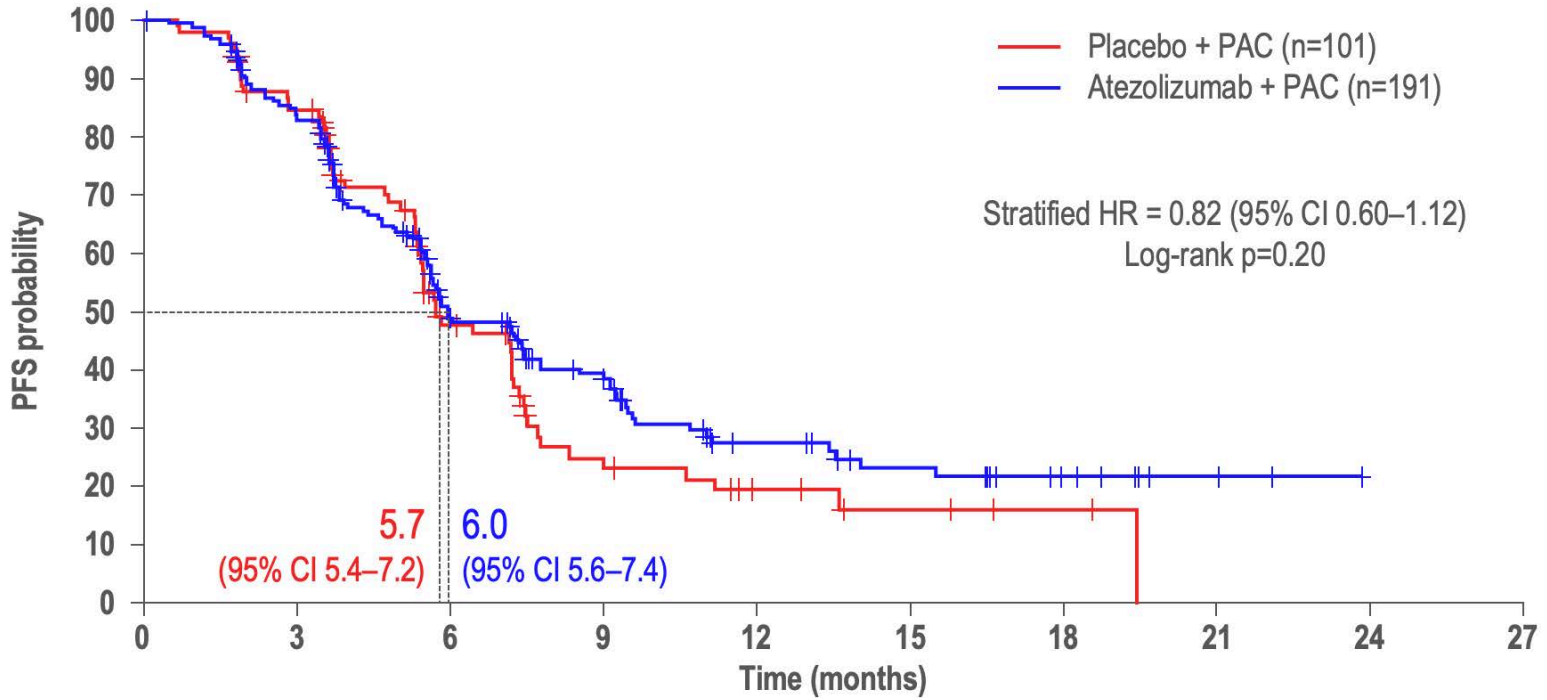
Objective: Examine the impact of atezolizumab added to paclitaxel in first-line mTNBC

Methods: Randomized placebo-controlled Phase III trial of atezo added to paclitaxel in mTNBC who have not been treated for metastatic disease. As in IMpassion130, half had previously received taxane for early disease; 12m PFI was required.

Co-primary endpoints: PFS and OS, hierarchically tested in ITT and PDL1+ (41%) populations.

IMpassion131: Results

N=651, followup 8.6m, met desired # events



PFS
PDL1+ population: 6.0 vs 5.7m
ITT population: 5.6 vs 5.7m

- **ORR PDL1+: 63% vs 55%**
- **Toxicity:** hyper/hypothyroid 13% vs 4%, difficult-to-treat immune AE 8.4% vs 2.8%
- **Discontinuation 20% vs 15%**

Courtesy of Lisa Carey, MD

Miles DW et al, ESMO 2020

FDA Grants Accelerated Approval to Pembrolizumab for Locally Recurrent Unresectable or Metastatic TNBC

Press Release: November 13, 2020

"The Food and Drug Administration granted accelerated approval to pembrolizumab in combination with chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (CPS ≥10) as determined by an FDA approved test. FDA also approved the PD-L1 IHC 22C3 as a companion diagnostic for selecting patients with TNBC for pembrolizumab.

Approval was based on KEYNOTE-355 (NCT02819518), a multicenter, double-blind, randomized, placebo-controlled trial in patients with locally recurrent unresectable or metastatic TNBC, who had not been previously treated with chemotherapy in the metastatic setting. Patients were randomized (2:1) to receive pembrolizumab 200 mg on day 1 every 3 weeks or placebo in combination with different chemotherapy treatments (paclitaxel protein-bound, or paclitaxel, or gemcitabine plus carboplatin) via intravenous infusion."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-pembrolizumab-locally-recurrent-unresectable-or-metastatic-triple

KEYNOTE-355

Background: The anti-PD1 ICI pembrolizumab significantly augmented pCR in I-SPY2 added to neoadjuvant therapy, but has modest activity as a single agent in mTNBC especially in pretreated patients. This is the pivotal trial of pembro added to chemotherapy in mTNBC.

Objective: Examine the PFS and OS impact of pembrolizumab added to chemotherapy in first-line mTNBC

Methods: Randomized placebo-controlled Phase III trial of pembro added to chemotherapy (”taxane” = nab paclitaxel or paclitaxel, or gemcitabine + carboplatin) in mTNBC who have not been treated for metastatic disease. 22% had received “same class” chemo in the early setting; only 6m PFI was required.

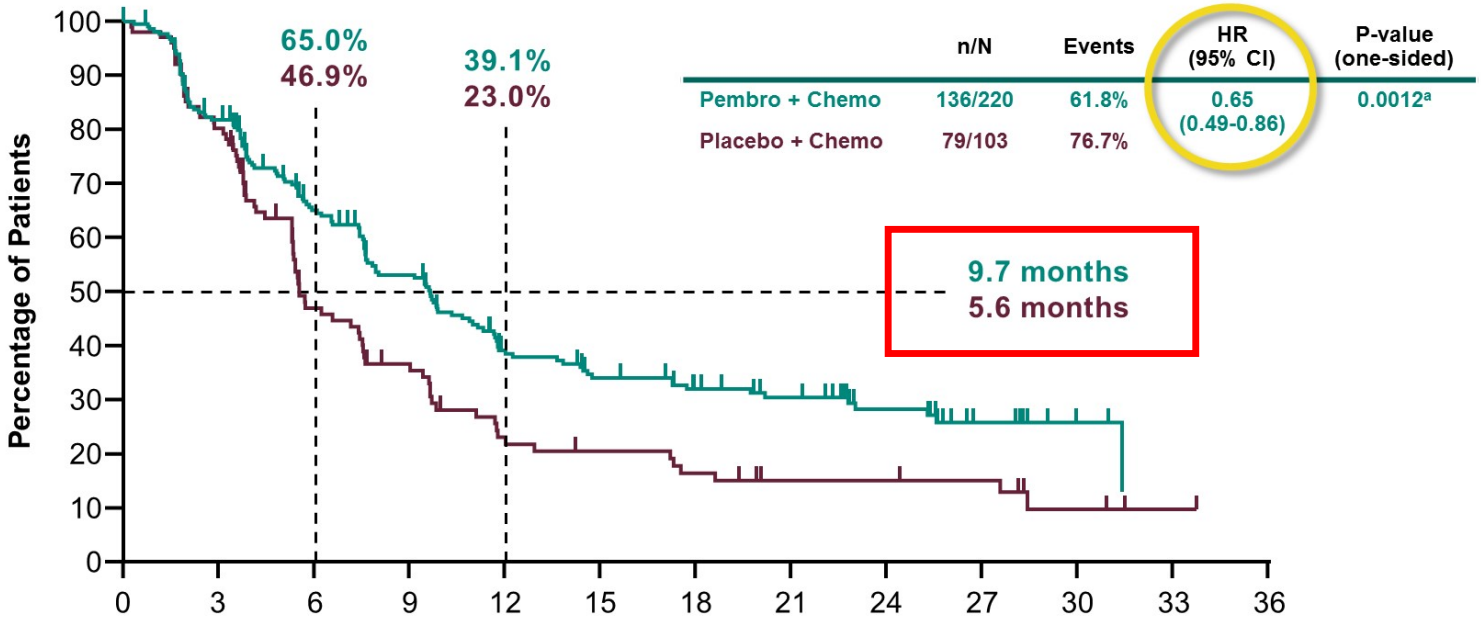
Co-primary endpoints: PFS and OS, hierarchically tested in strongly PDL1+ (38%+ CPS $\geq$10 in 22C3 IHC) and less strongly PDL1+ populations.

Courtesy of Lisa Carey, MD

Cortes J et al, Lancet 2020

KEYNOTE-355: Results

N=847 @ 26m
PDL1+ (CPS ≥ 10):



- **CPS ≥ 1: PFS 7.6 vs 5.6m, ns. ITT also ns.**
- **IRAE: 26% (5% gr 3+) vs 6% (0 gr 3+). Mostly skin.**

Similar HR as IMpassion130 PDL1+

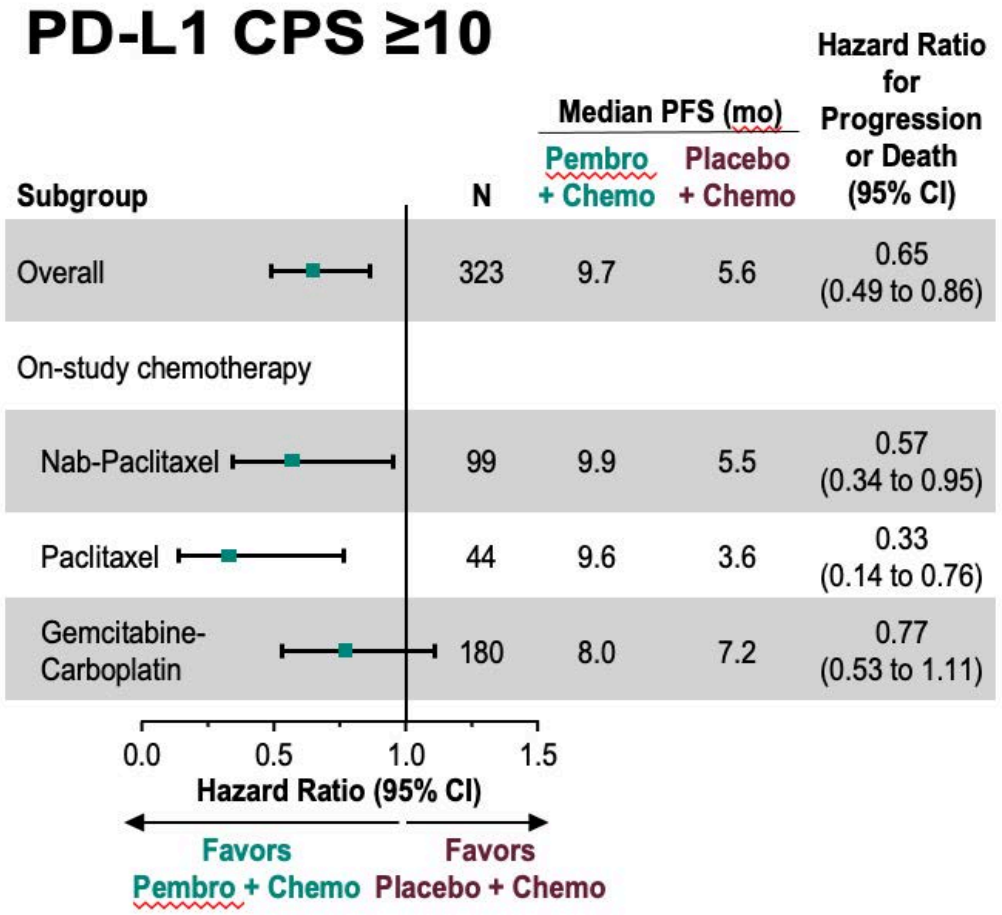
PFS subgroups:

- **Chemotherapy backbone:**
  - **Taxane (n=143): HR 0.51 (0.33-0.78)**
    - **Nab pac (n=99): HR 0.57 (0.34-0.95)**
    - **Paclitaxel (n=44): HR 0.33 (0.14-0.76)**
  - **Gem/carbo (n=180): HR 0.77 (0.53-1.11)**
- **DFI:**
  - **De novo (n=103): HR 0.48 (0.29-0.79)**
  - **< 12m DFI (n=66): HR 1.00 (0.51-1.95)**
  - **> 12m DFI (n=153): HR 0.64 (0.43-0.95)**

Courtesy of Lisa Carey, MD

Cortes J et al, Lancet 2020

KEYNOTE-355: Additional Efficacy Endpoints



Chemotherapy backbone: taxane appears to > doublet. *NB: paclitaxel does not appear to underperform.*

Other secondary endpoints of ORR, DCR, and DOR also favored pembrolizumab arm.

Rugo H et al. SABCS 2020; Cortes J et al, Lancet 2020

Courtesy of Lisa Carey, MD

Agenda

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Regulatory and reimbursement issues aside, have you attempted or would you attempt to access an anti-PD-1/PD-L1 antibody as part of neoadjuvant therapy for a 60-year-old patient with TNBC, a 6-cm tumor?

1. I have
2. I haven't but would for the right patient
3. I haven't and would not

Module 7: Neoadjuvant immunotherapy for TNBC

- **Key Relevant Data Sets**
  - KEYNOTE-522: Pembrolizumab for early-stage disease
  - KEYNOTE-173: Neoadjuvant pembrolizumab + chemotherapy for high-risk disease
  - IMpassion031: Neoadjuvant atezolizumab + *nab* paclitaxel and anthracycline-based chemotherapy

KEYNOTE-522

Background: Immune checkpoint inhibitors (ICI) in TNBC were disappointing as single agents but better combined with immunomodulatory chemotherapy as demonstrated by the success of first-line metastatic trials.

Objective: Examine impact on pCR and outcome of adding pembrolizumab (P) to neoadjuvant anthracycline/taxane/platinum-based chemotherapy for TNBC and continuing it into the adjuvant phase for a total of one year.

Methods: Randomized (2:1) placebo-controlled phase III trial of P concurrently with preoperative paclitaxel + carboplatin followed by AC, then up to 9 cycles of adjuvant P.

Mostly clinical stage II patients, ~ 50% N+.

Endpoints: pCR, EFS in ITT comparing P to placebo arms. Only pCR endpoint is currently mature.

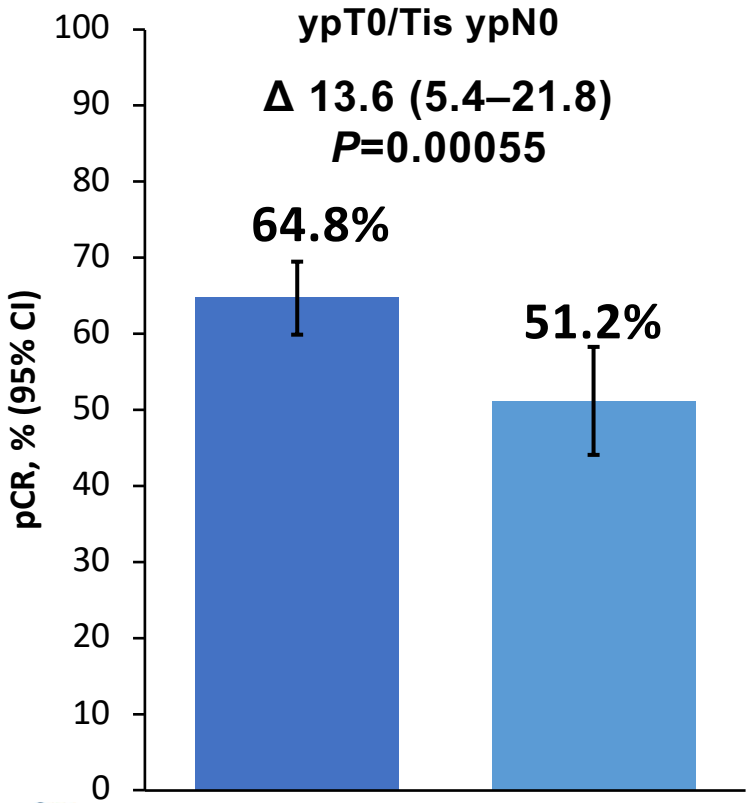
Courtesy of Lisa Carey, MD

Schmid P et al, NEJM 2020

KEYNOTE-522: Results

N= 1174, followup ~18m

Primary Endpoint #1: pCR



Courtesy of Lisa Carey, MD

No apparent relationship to PDL1 status

(higher pCR both arms in PDL1+)

- **Primary endpoint #2 (EFS) immature**

  (HR 0.63 @ 18m, ns)

- **Grade 3+ AE of interest (all the "itis" + immune complications): 13% vs 2%**
  - **Thyroid < 1%**

Schmid P et al, NEJM 2020

KEYNOTE-173

Background: I-SPY2 suggested improved pCR with addition of pembrolizumab to chemotherapy. KN-522 later confirmed this, but the optimal anthracycline/taxane-based chemotherapy schedule is uncertain. GeparNuevo suggested that pCR is augmented with a lead-in window of ICI alone.

Objective: Determine optimal schedule and dose of neoadjuvant taxane (with or without carboplatin) followed by AC (all after a lead-in 3-week pembro alone window).

Methods: Six neoadjuvant cohorts, all with 1 cycle pembrolizumab to start, then 4 cycles of taxane + carboplatin (nab paclitaxel, paclitaxel, weekly or q3wk, ± carbo) followed by q3wk AC x 4, then surgery.

Endpoints: Primary — safety, recommended dose/schedule (RPh2D). Secondary — pCR, other clinical, predictive biomarkers

Courtesy of Lisa Carey, MD

Schmid P et al, Ann Oncol 2020

KEYNOTE-173

N=60, followup 20m.

Chemotherapy cohorts:

- Cohort A: nab paclitaxel weekly alone (IMpassion031)
- Cohort E: paclitaxel weekly + carboplatin AUC5 (KN-522, also allowed weekly carbo)
- Rest failed for toxicity, including the NeoTRIP regimen (nab pac + carbo weekly, 25% d/c early)

Toxicity:

- DLT= ANC (not surprisingly)
- Immune-related toxicity in 30%
- Pembro d/c in 13% for hepatitis (3), fatigue (2), SLE, colitis, hyperthyroidism.

- **pCR 60% all cohorts. EFS trend towards association with pCR but # small, short f/u.**
  - Suggestion of higher pCR in PDL1+ but widely overlapping 95% CI (unlike larger trials)
  - Higher sTILs pre- and on-treatment (after window) associated with pCR (but underpowered)

Courtesy of Lisa Carey, MD

IMpassion031

Background: Atezolizumab added to nab paclitaxel in first-line PDL1+ metastatic TNBC was the first ICI approved in breast cancer. Atezo added to paclitaxel in same setting had no impact on outcomes. Early TNBC was unmet need.

Objective: Examine impact on pCR and outcome of adding atezolizumab (Atezo) to neoadjuvant nab paclitaxel followed by anthracycline chemotherapy for TNBC and continuing it into the adjuvant phase for a total of one year.

Methods: Randomized (1:1) placebo-controlled phase III trial of Atezo concurrently with preoperative nab paclitaxel followed by AC; then additional 11 cycles adjuvant Atezo (unblinded).

Mostly (~75%) clinical stage II patients, ~ 40% N+.

Endpoint: pCR comparing Atezo arm to placebo

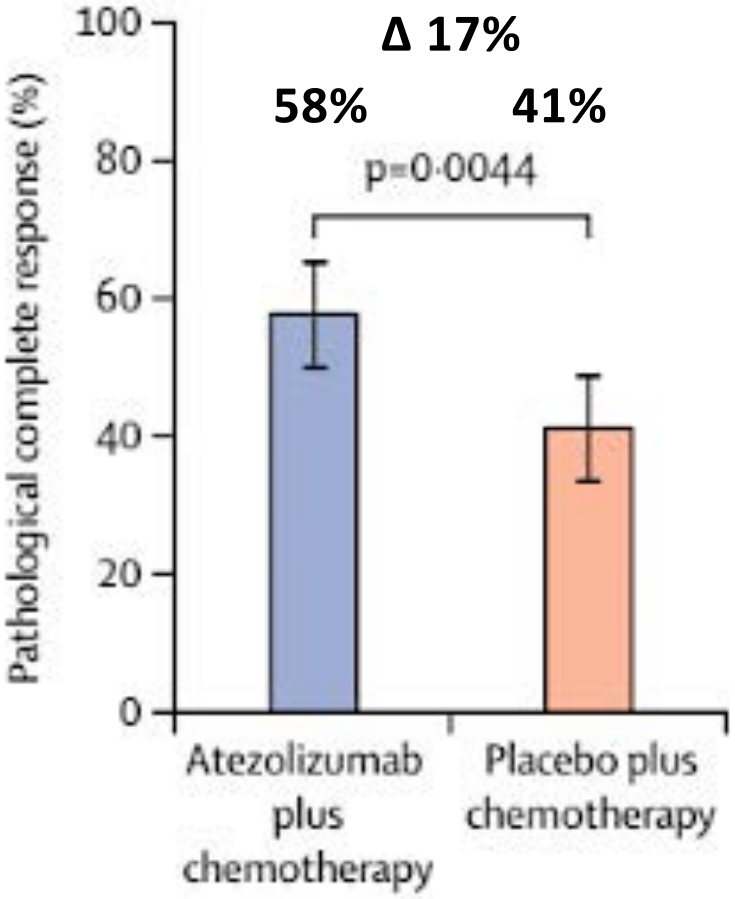
Courtesy of Lisa Carey, MD

Mittendorf E et al, Lancet 2020;396:1090-1100

IMpassion031: Results

N= 333, followup ~20m

pCR breast and axilla



Courtesy of Lisa Carey, MD

No apparent relationship to PDL1 status

(again higher pCR rate both arms in PDL1+)

- **Secondary endpoint EFS HR 0.76, ns**

Toxicity:

- **Treatment-related serious adverse events: 23% vs 16%**
- **Grade 3+ AE of special interest: 7% vs 5%**

Mittendorf E et al, Lancet 2020;396:1090-1100

Agenda

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- Module 3: Genomic assays

HER2-Positive Breast Cancer

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Triple-Negative Breast Cancer

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- **Module 8: PARP inhibition**
- Module 9: Sacituzumab govitecan

In general, what is the optimal approach to mutation testing for possible use of a PARP inhibitor for a patient with metastatic TNBC?

1. Germline BRCA
2. Germline BRCA; if negative, multigene somatic
3. Multigene germline panel
4. Next-generation sequencing
5. Multigene germline and next-generation sequencing
6. Other

What would be your preferred treatment approach for a 60-year-old patient with a BRCA germline mutation and de novo metastatic TNBC that is PD-L1-negative?

1. Olaparib
2. Talazoparib
3. Olaparib or talazoparib — coin flip
4. Nonplatinum chemotherapy
5. Platinum-containing chemotherapy
6. Chemotherapy followed by maintenance PARP inhibitor
7. Chemotherapy combined with a PARP inhibitor
8. Other

Module 8: PARP inhibition for TNBC

- **Key Relevant Data Sets**
  - TBCRC 048: Olaparib for mBC with HRR mutation
  - MEDIOLA: Olaparib + durvalumab for mBC with germline BRCA mutation

Beth Israel Deaconess Medical Center | HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Dana-Farber Cancer Institute

tbcrc Translational Breast Cancer Research Consortium

TBCRC 048: A phase II study of olaparib monotherapy in metastatic breast cancer patients with germline or somatic mutations in homologous recombination (HR) pathway genes (Olaparib Expanded)

Nadine Tung, Mark E. Robson, Steffen Ventz, Cesar Santa-Maria, Paul Kelly Marcom, Rita Nanda, Payal D. Shah, Tarah J. Ballinger, Eddy Yang, Michelle Melisko, Adam Brufsky, Shaveta Vinayak, Michelle DeMeo, Colby Jenkins, Susan Domchek, Gerburg Wulf, Ian E. Krop, Antonio C. Wolff, Eric P. Winer, Judy E. Garber

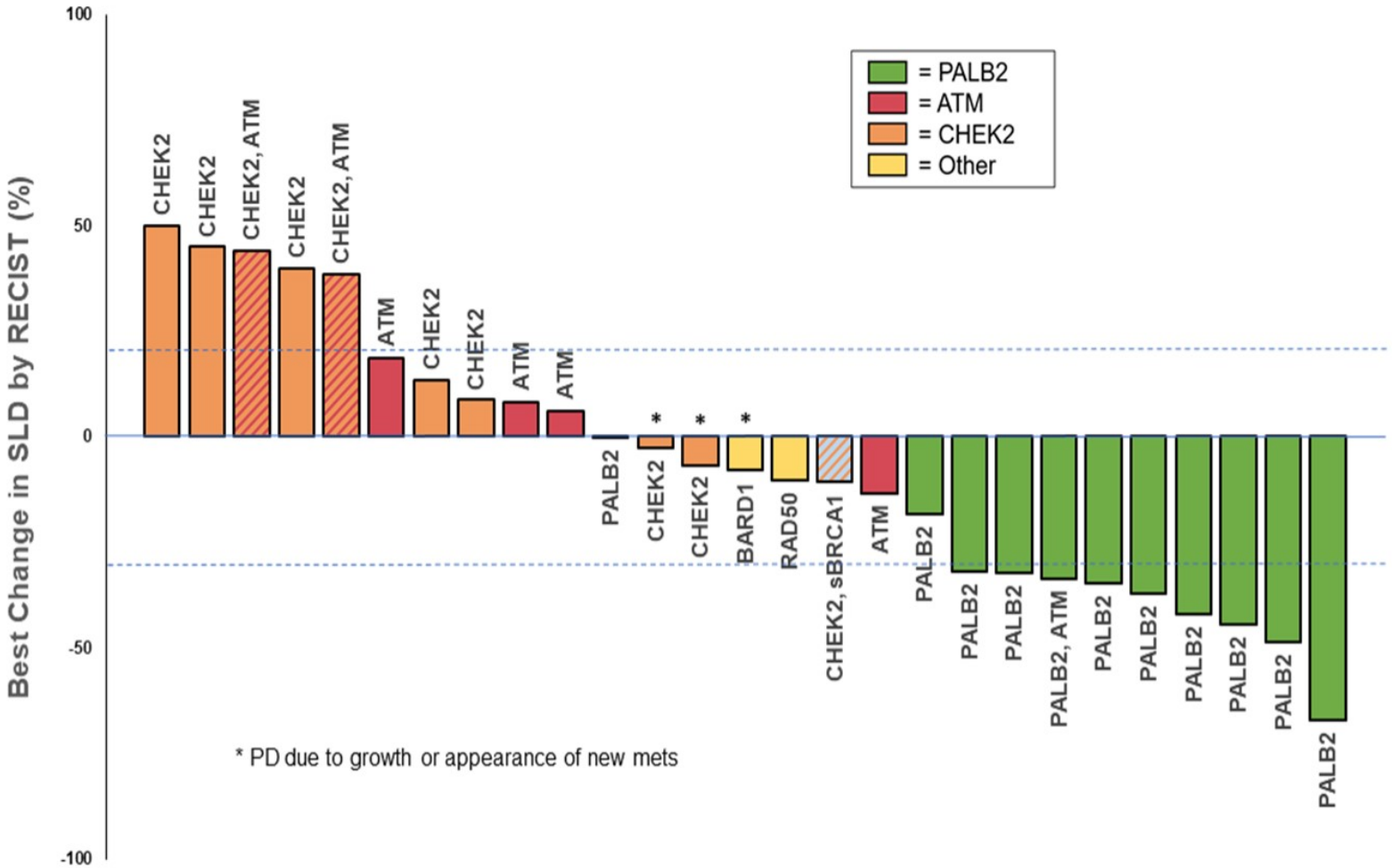
PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Nadine Tung, MD

Presented By Nadine Tung at TBD

Courtesy of Harold J Burstein, MD, PhD

Best Overall Responses: Cohort 1 (Germline)

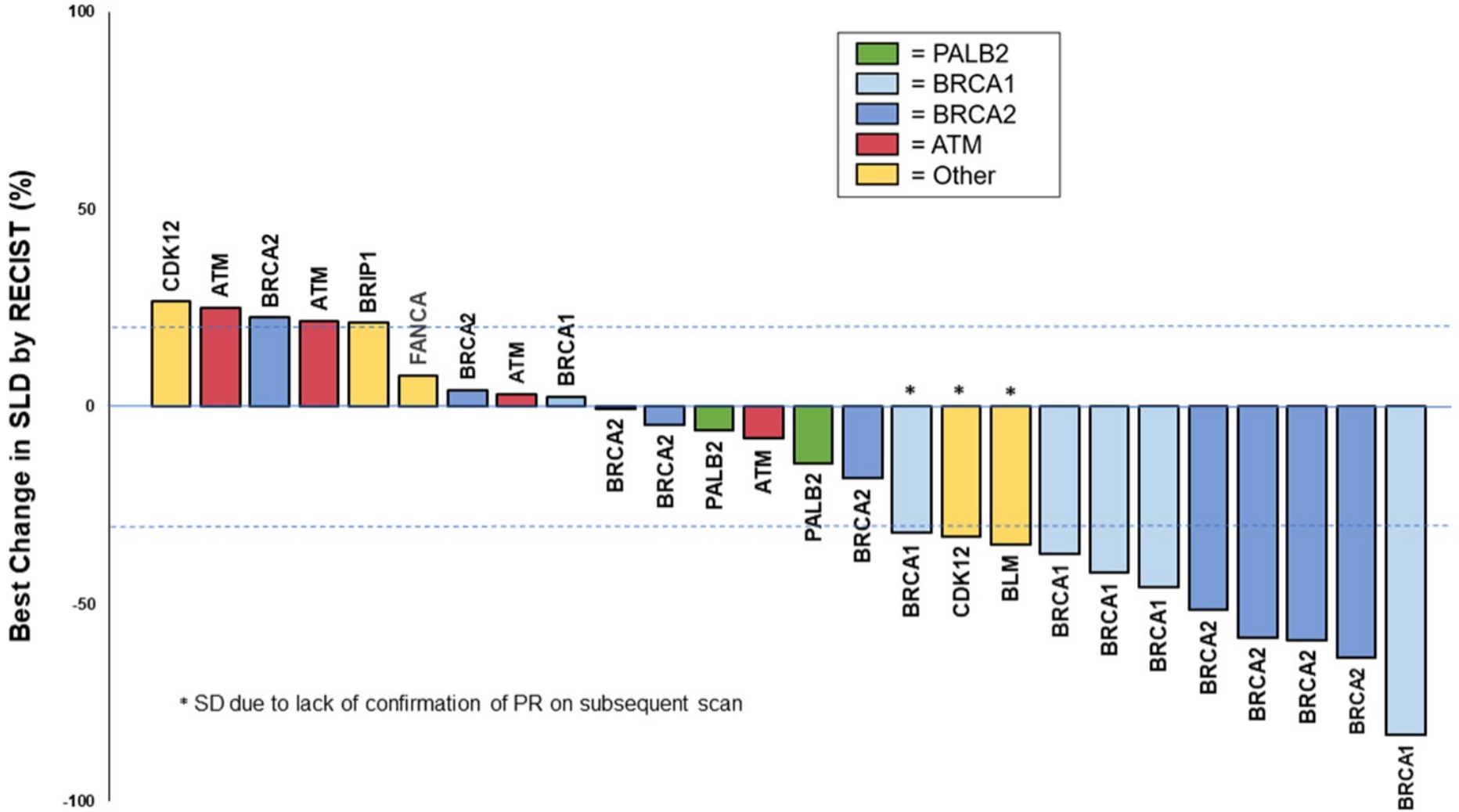


Datacut May 4, 2020

Presented By Nadine Tung at TBD

Courtesy of Harold J Burstein, MD, PhD

Best Overall Responses: Cohort 2 (Somatic)

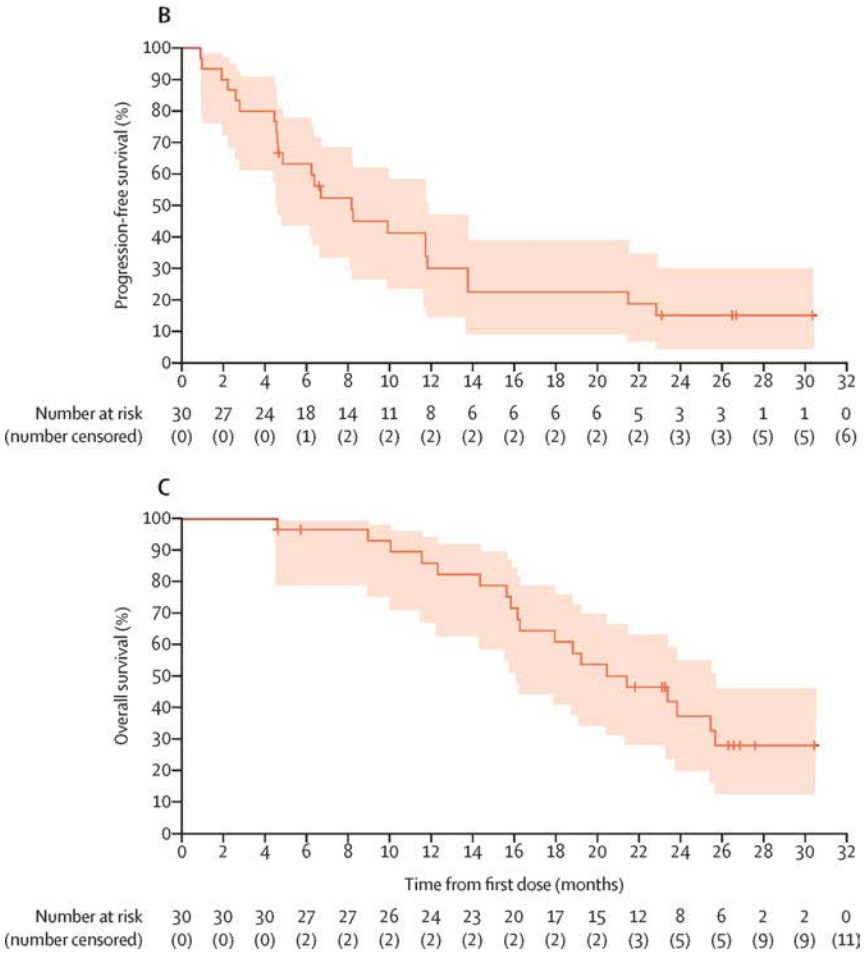


Datacut May 4, 2020

Presented By Nadine Tung at TBD

Courtesy of Harold J Burstein, MD, PhD

MEDIOLA: olaparib plus durvalumab (anti-PD-L1) in BRCA-associated advanced breast cancer



Response rate: 63%

PFS:

TNBC	4.9m
ER+	9.9m

Domchek et al. Lancet Oncol 2020;21:1155

Courtesy of Harold J Burstein, MD, PhD

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- Module 7: Immunotherapy in the neoadjuvant setting
- Module 8: PARP inhibition
- **Module 9: Sacituzumab govitecan**

What treatment would you recommend next for a 60-year-old woman with metastatic TNBC (BRCA wild-type, PD-L1-positive) who experiences disease progression after 7 months of first-line atezolizumab/*nab* paclitaxel?

1. Gemcitabine
2. Capecitabine
3. Vinorelbine
4. Eribulin
5. Sacituzumab govitecan
6. Platinum-based chemotherapy
7. Other chemotherapy
8. Other

Module 9: Sacituzumab govitecan

- **Key Relevant Data Sets**
  - IMMU-132-01: Sacituzumab govitecan for refractory mTNBC
  - ASCENT: Phase III confirmatory study

FDA Grants Accelerated Approval to Sacituzumab Govitecan-hziy for mTNBC

Press Release: April 22, 2020

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

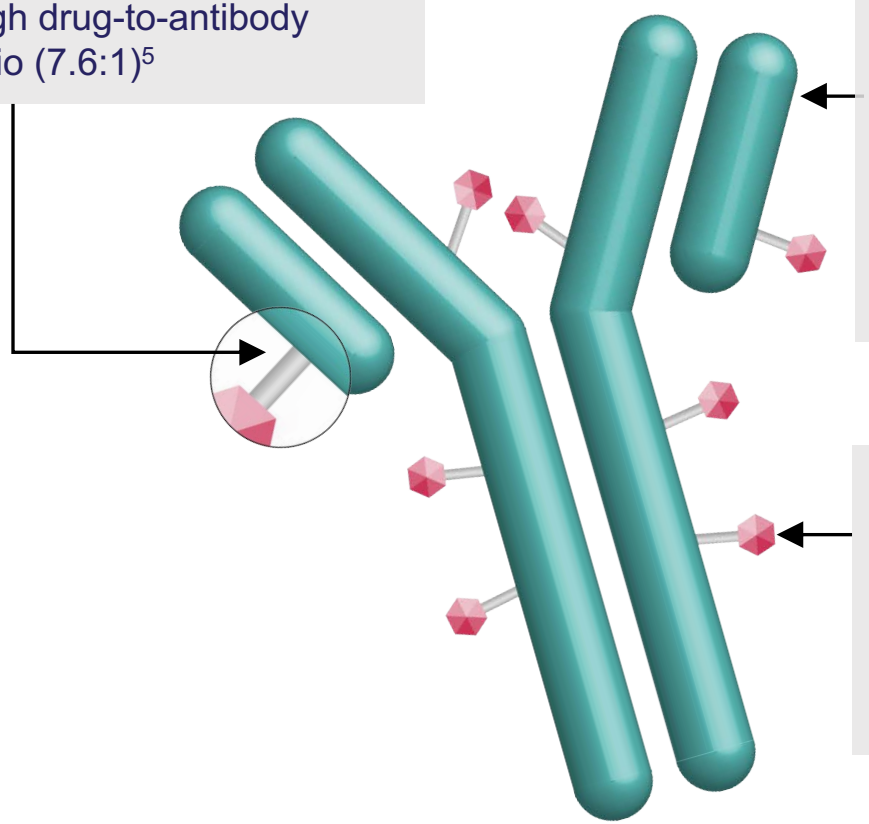
Efficacy was demonstrated in IMMU-132-01 (NCT 01631552), a multicenter, single-arm, trial enrolling 108 patients with metastatic triple negative breast cancer (mTNBC) who received at least two prior treatments for metastatic disease. Patients received sacituzumab govitecan-hziy 10 mg/kg intravenously 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

Sacituzumab Govitecan (SG) Is a First-In-Class Trop-2–Directed ADC

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-5]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and linker cleaver by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC and fast-track designation in metastatic urothelial cancer[6]

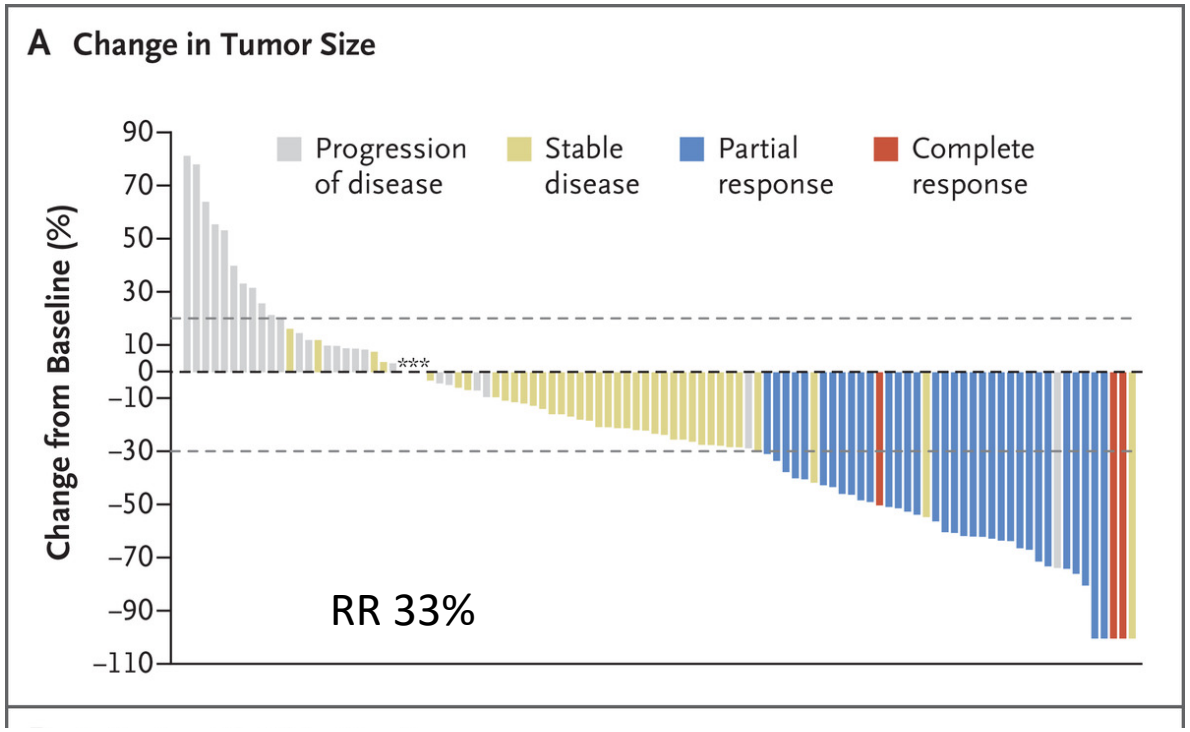


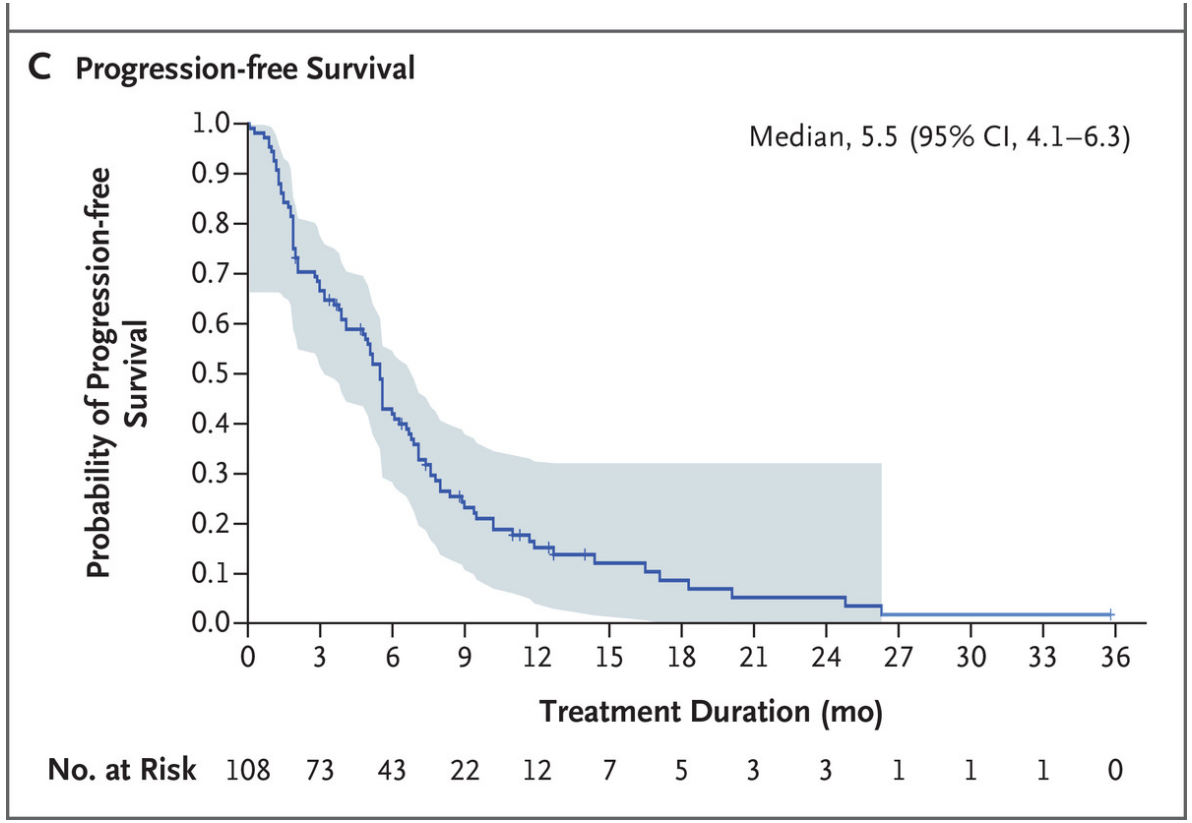
ADC, antibody−drug conjugate; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Vidula et al. *J Clin Oncol.* 2017;35:15(suppl):Abstract 1075. 2. Ambrogi et al. *PLoS One.* 2014;9(5):e96993. 3. Goldenberg DM et al. *Expert Opin Biol Ther*. 2020 Aug;20(8):871-885. 4. Nagayama A, et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 5. Cardillo TM, et al. *Bioconjugate Chem.* 2015;26:919-931. 6. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020.

Courtesy of Harold J Burstein, MD, PhD

Sacituzumab govitecan: Response and Survival among 108 Patients with Metastatic Triple-Negative Breast Cancer.



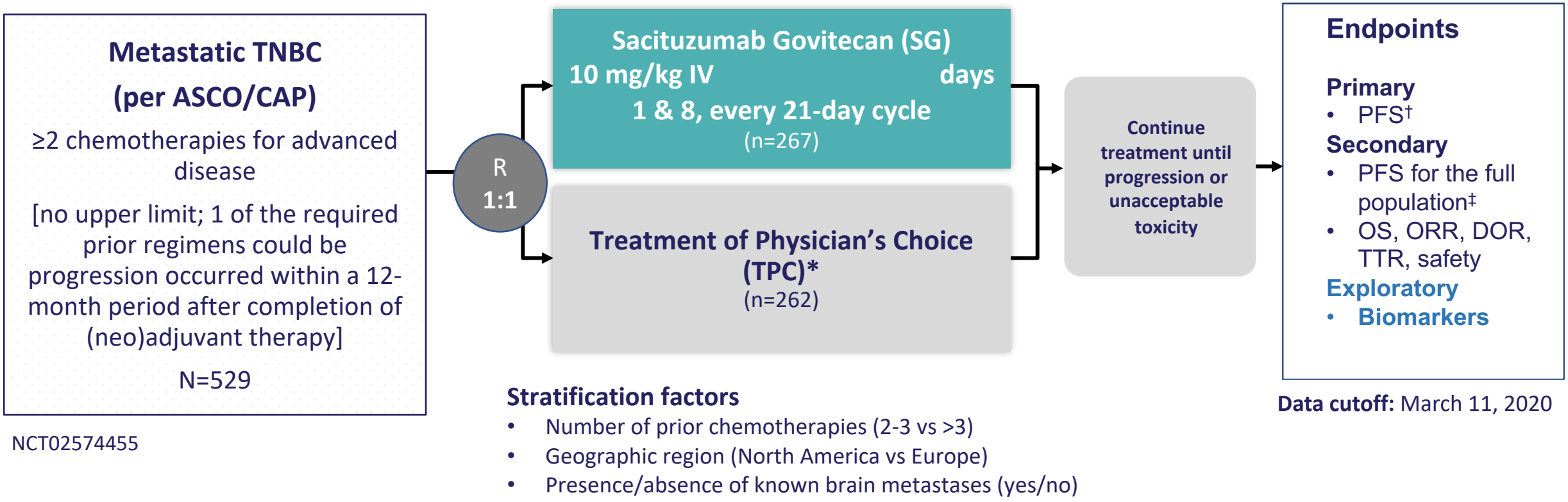


Common side effects: anemia, neutropenia, febrile neutropenia, diarrhea, vomiting/nausea, alopecia

A Bardia et al. N Engl J Med 2019;380:741-751.

Courtesy of Harold J Burstein, MD, PhD

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC



NCT02574455

Stratification factors
- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

Data cutoff: March 11, 2020

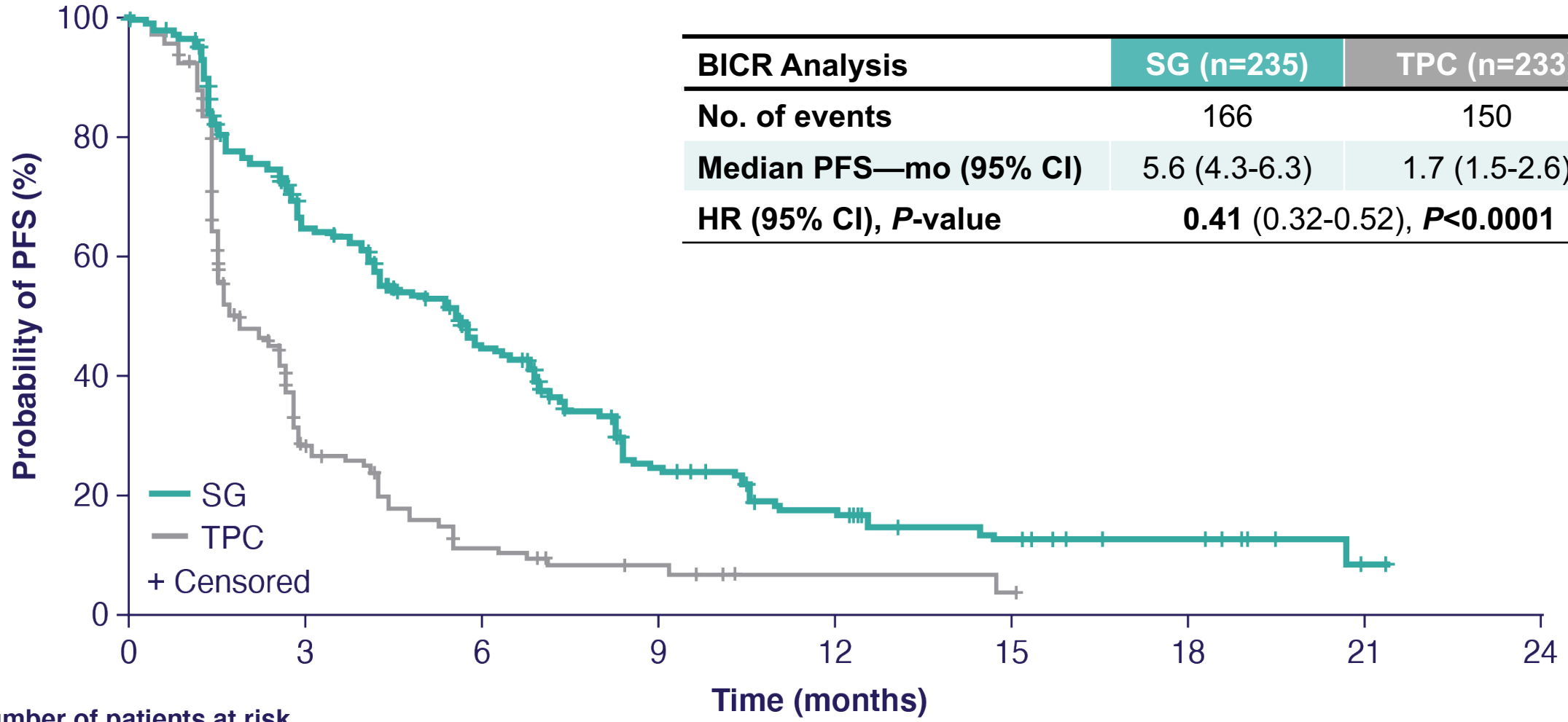
We report the exploratory biomarker analysis in the brain metastases-negative (Brain Mets-Negative) population

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Bardia A et al. ESMO 2020;Abstract LBA17.

Courtesy of Harold J Burstein, MD, PhD

ASCENT: Progression-Free Survival (BICR Analysis)



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

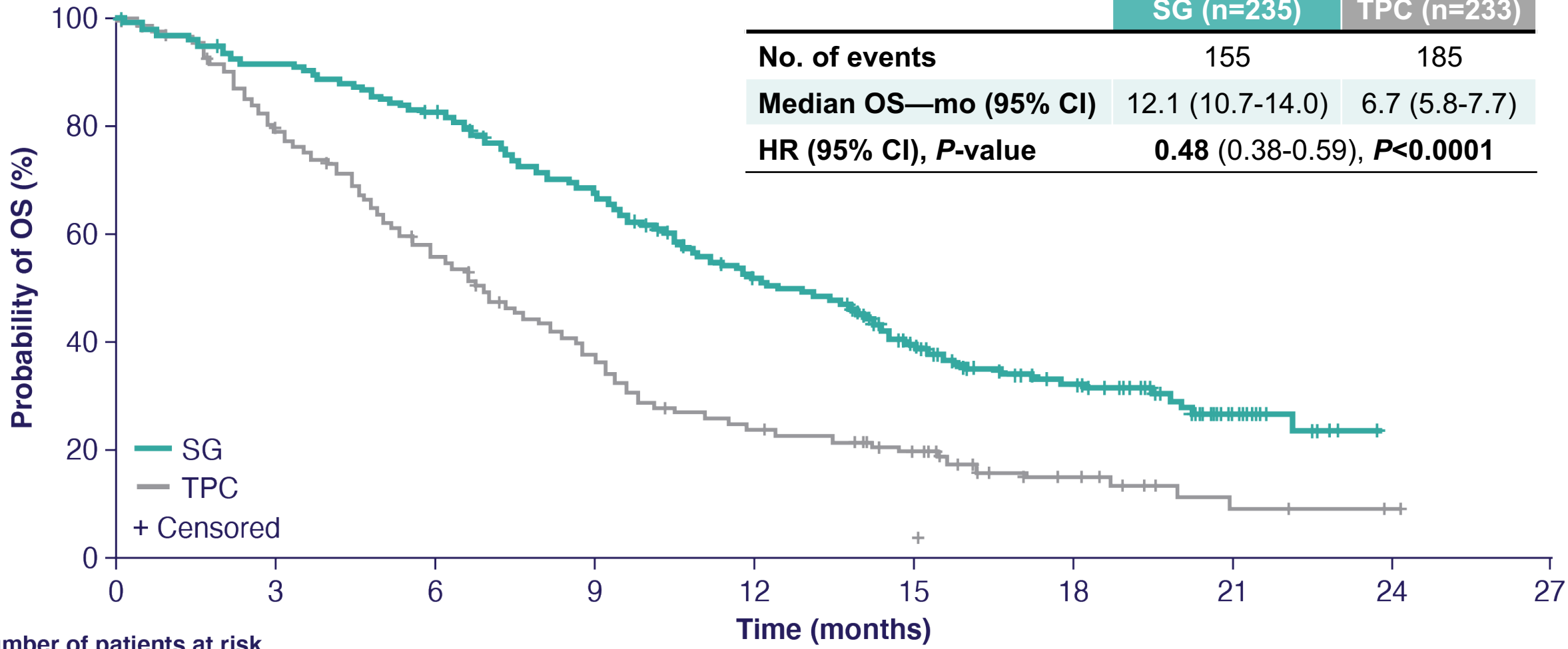
Assessed in the brain metastases-negative population.
BICR, blind independent central review; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician choice.

Bardia A et al. ESMO 2020;Abstract LBA17.

Courtesy of Harold J Burstein, MD, PhD

ASCENT: Overall Survival

	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	



Number of patients at risk

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

Assessed by independent central review in the brain metastases-negative population.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician choice.

Bardia A et al. ESMO 2020;Abstract LBA17.

Courtesy of Harold J Burstein, MD, PhD

ASCENT: TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

		SG (n=258)			TPC (n=224)		
	TRAE*	**All grade %**	**Grade 3, %**	**Grade 4, %**	**All grade, %**	**Grade 3, %**	**Grade 4, %**
Hematologic	**Neutropenia†**	**63**	**46**	**17**	**43**	**27**	**13**
	Anemia‡	**34**	**8**	**0**	**24**	**5**	**0**
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	**Diarrhea**	**59**	**10**	**0**	12	<1	0
	Nausea	**57**	**2**	**<1**	**26**	**<1**	**0**
	Vomiting	29	1	<1	10	<1	0
Other	**Fatigue**	**45**	**3**	**0**	**30**	**5**	**0**
	Alopecia	**46**	**0**	**0**	**16**	**0**	**0**

- Key grade ≥3 TRAEs (SG vs TPC): Neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%)
  - GCSF usage was 49% in the SG arm vs 23% in the TPC arm
- No severe cardiovascular toxicity, no grade >2 neuropathy or grade >3 interstitial lung disease
- No treatment-related deaths with SG; one treatment-related death (neutropenic sepsis) with TPC
- AE leading to treatment discontinuation were low for SG and TPC: 4.7% and 5.4%

*Patients may report more than 1 event per preferred term. AEs were classified according to the MedDRA systems of preferred terms and system organ class and according to severity by NCI CTCAE v4.03. †Combined preferred terms of 'neutropenia' and 'decreased neutrophil count'. ‡Combined preferred terms of 'anemia' and 'decreased hemoglobin'. §Combined preferred terms of 'leukopenia' and 'decreased white blood cell count'.
BMNeg, brain metastasis-negative; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology for AE; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related AE.

Bardia A et al. ESMO 2020;Abstract LBA17.

Courtesy of Harold J Burstein, MD, PhD

Recent Advances in Hematologic Oncology: A 4-Part Live Webinar Series Reviewing Key Data and Presentations from the 62nd ASH Annual Meeting

Part 3 — Multiple Myeloma

Wednesday, February 10, 2021
5:00 PM – 6:00 PM ET

Faculty

Rafael Fonseca, MD
Robert Z Orlowski, MD, PhD
Edward A Stadtmauer, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

A Daylong Clinical Summit Hosted in Partnership with North Carolina Oncology Association (NCOA) and South Carolina Oncology Society (SCOS)

Saturday, February 13, 2021

8:30 AM – 4:30 PM ET

RTP RESEARCH TO PRACTICE

Saturday, February 13, 2021

8:30 AM — Chronic Lymphocytic Leukemia and Lymphomas

John Pagel, Mitchell Smith

9:30 AM — Multiple Myeloma

Paul Richardson, Peter Voorhees

10:45 AM — Genitourinary Cancers

Robert Dreicer, Daniel Petrylak

11:45 AM — Lung Cancer

Justin Gainor, Heather Wakelee

RTP RESEARCH TO PRACTICE

Saturday, February 13, 2021

1:15 PM — Gastrointestinal Cancers

Philip Philip, Eric Van Cutsem

2:15 PM — Breast Cancer

Sara Hurvitz, Ian Krop

3:30 PM — Acute Myeloid Leukemia and Myelodysplastic Syndromes

Courtney DiNardo, Alexander Perl

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

RESEARCH TO PRACTICE 2021 YEAR IN REVIEW