Thank you for joining us.
The program will commence momentarily.

Recent Advances in Medical Oncology: Triple-Negative Breast Cancer

Monday, July 20, 2020

5:00 PM – 6:30 PM ET

Faculty

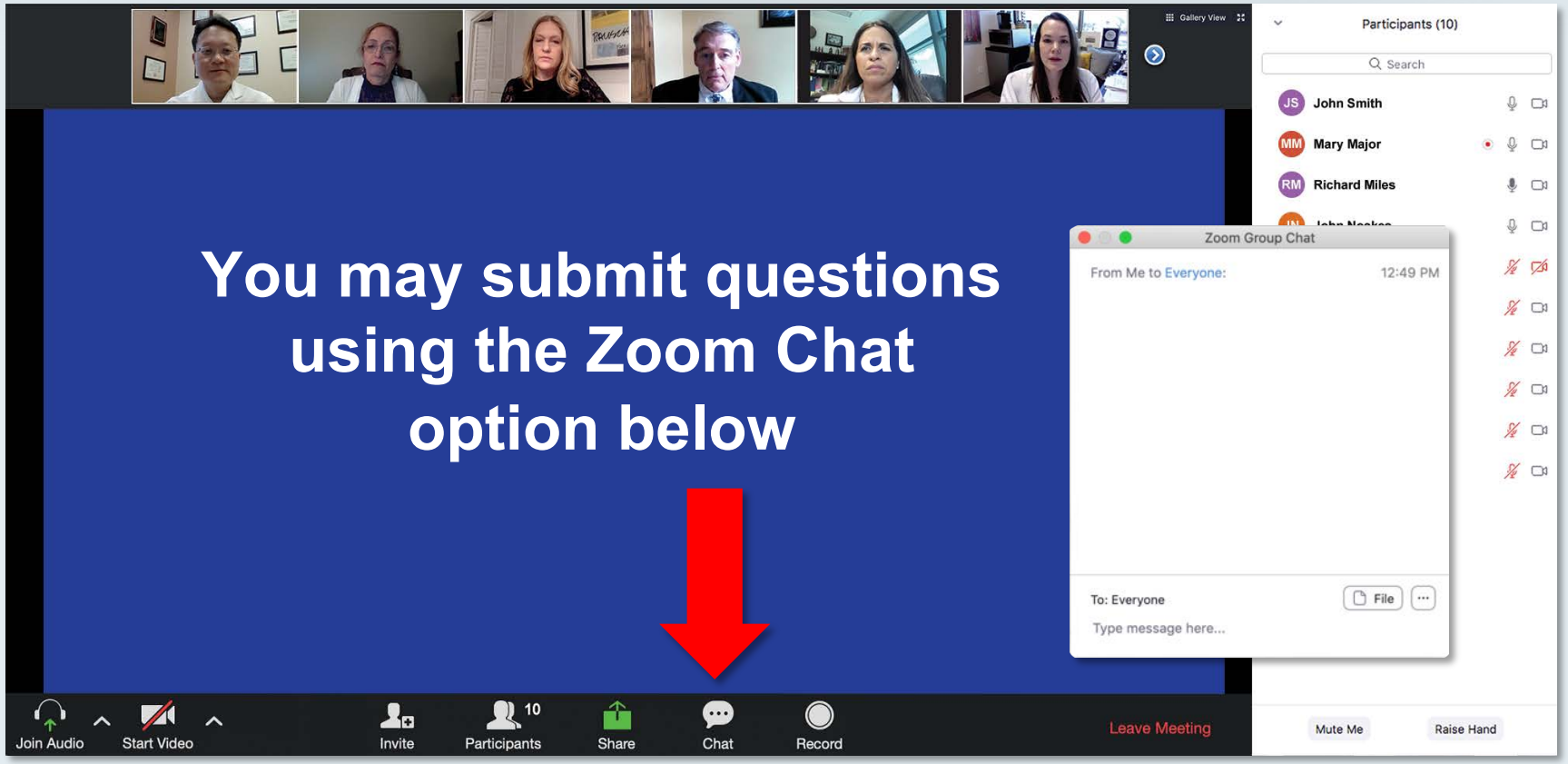
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Moderator

Neil Love, MD

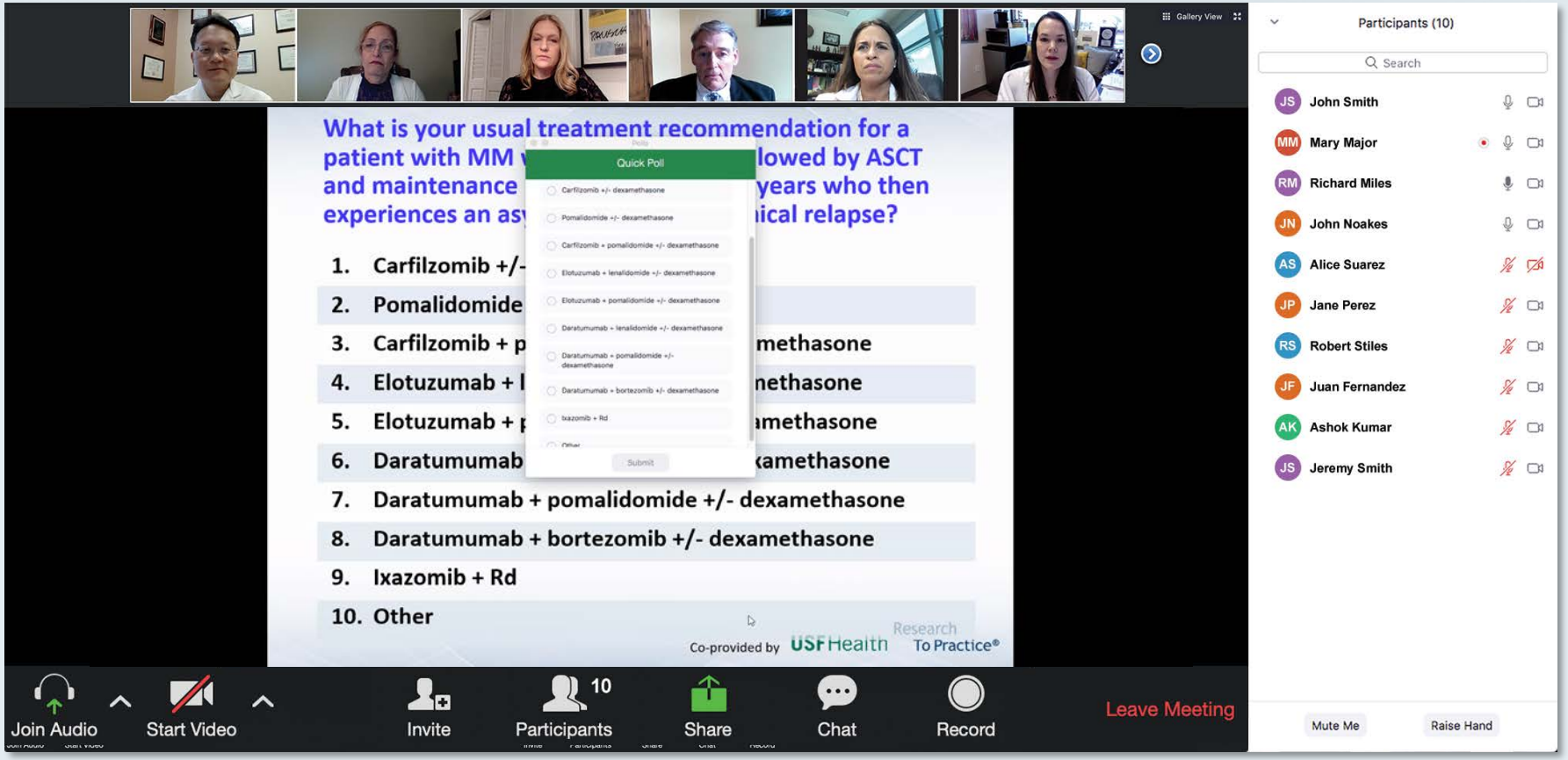
RTP RESEARCH TO PRACTICE

Dr Love and Faculty Encourage You to Ask Questions



Feel free to submit questions **now before** the program commences and **throughout the program.**

Familiarizing yourself with the Zoom interface
How to answer poll questions



When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.

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Dr O’Shaughnessy — Disclosures

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Dr Rugo — Disclosures

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Upcoming Live Webinars

Tuesday, July 21, 2020
12:00 PM – 1:00 PM ET

MEET THE PROFESSORS
Clinical Investigators Discuss Existing and Emerging Treatment Strategies for Patients with Ovarian, Cervical and Endometrial Cancer

Faculty
Joyce F Liu, MD, MPH
David M O'Malley, MD

Moderator
Neil Love, MD

Wednesday, July 22, 2020
5:00 PM – 6:00 PM ET

Recent Advances in Medical Oncology: Melanoma

Faculty
Michael B Atkins, MD
Professor Georgina Long AO, BSc, PhD, MBBS
Jason J Luke, MD

Moderator
Neil Love, MD

Upcoming Live Webinars

Thursday, July 23, 2020
12:00 PM – 1:00 PM ET

MEET THE PROFESSOR
Current Questions and Controversies in the Management of Lung Cancer

Faculty
Joel W Neal, MD, PhD

Moderator
Neil Love, MD

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Faculty

Joyce O'Shaughnessy, MD
Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Director, Breast Cancer Research Program
Texas Oncology
US Oncology
Dallas, Texas

Hope S Rugo, MD
Professor of Medicine
Director, Breast Oncology and Clinical Trials Education
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
San Francisco, California

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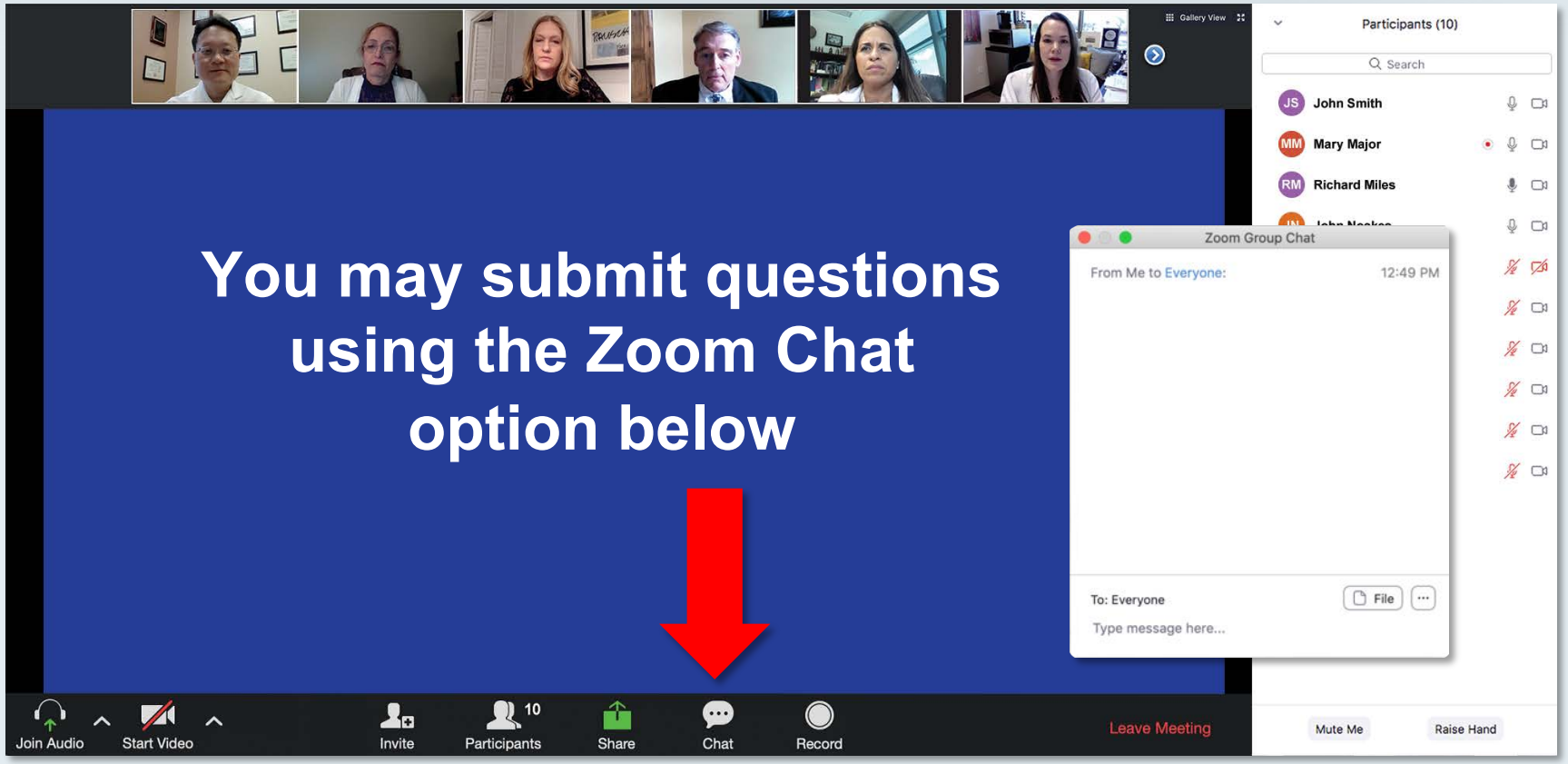

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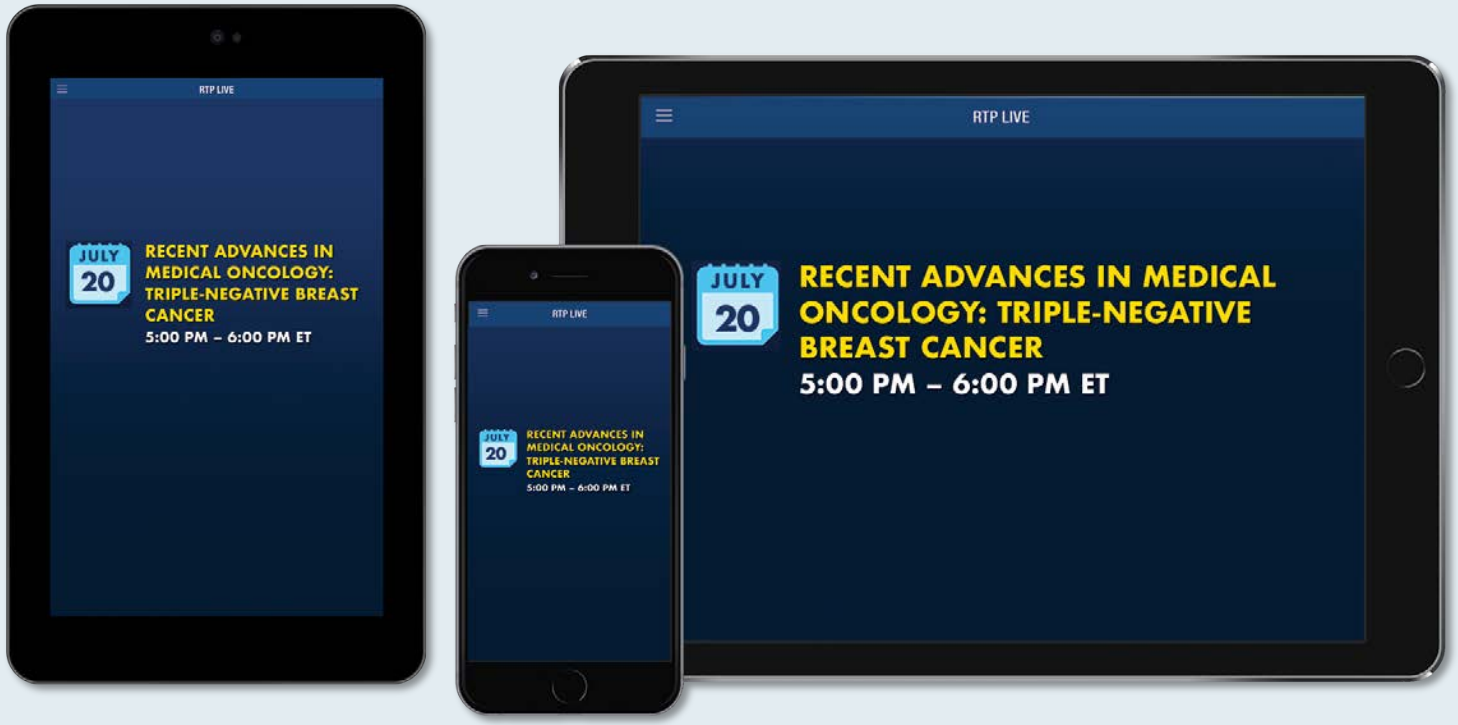

About the Enduring Program

- This webinar is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
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RTP RESEARCH TO PRACTICE

Community Oncologists

Patricia A DeFusco, MD
Director, Breast Program
Hartford HealthCare Cancer Institute
Hartford Hospital
Hartford, Connecticut

Sulfi Ibrahim, MD
Hematology/Oncology
Reid Health
Richmond, Indiana

Maen Hussein, MD
Advent Health Waterman
Central Florida Health Alliance
(Leesburg and The Villages)
Tavares, Florida

Nick C Leasure, MD
Assistant Section Chief
Section of Hematology and Oncology
Tower Health Medical Group
Reading, Pennsylvania

Current Management of Triple-Negative Breast Cancer

Module 1: Immune Checkpoint Inhibition — Dr Rugo

- Key Recent Data Sets
  - IMpassion130
  - KEYNOTE-355
- Cases/Questions from General Medical Oncologists
- Faculty Cases

Module 2: PARP Inhibition and Other Novel Agents/Strategies — Dr O'Shaughnessy

- Key Recent Data Sets
  - OlympiAD, EMBRACA and BROCADE3
  - SWOG-S1416
  - Sacituzumab govitecan
- Cases/Questions from General Medical Oncologists
- Faculty Cases

Conclusions

- Immunotherapy in metastatic disease
  - Improvement in overall survival in IMpassion130
  - Efficacy with different chemotherapy partners in KEYNOTE-355
  - Efficacy appears limited to tumors expressing PD-L1
  - Novel combinations to enhance response
- The role of immunotherapy in the neoadjuvant setting
  - KEYNOTE-522: success in treating earlier line independent of PD-L1 positivity
    - Await EFS results
  - Await full data from IMpassion031
    - Nab-paclitaxel vs paclitaxel/carboplatin?
  - Balancing cost and toxicity in clinical practice is critical
    - Reserve treatment for poor responders?
- Role in HER2+ and ER+ disease also being actively explored

Courtesy of Hope S Rugo, MD

Selected Phase III Trials with IO in Metastatic TNBC

Relapse >6 months after neo/adjuvant chemotherapy

- KEYNOTE-355: await OS data

Relapse >12 months after neo/adjuvant chemotherapy

- IMpassion131:
  - Paclitaxel + atezolizumab or placebo

Relapse ≤12 months after neo/adjuvant chemotherapy

- IMpassion132:
  - Gemcitabine/carboplatin or capecitabine (mandatory if prior carbo) + atezolizumab or placebo

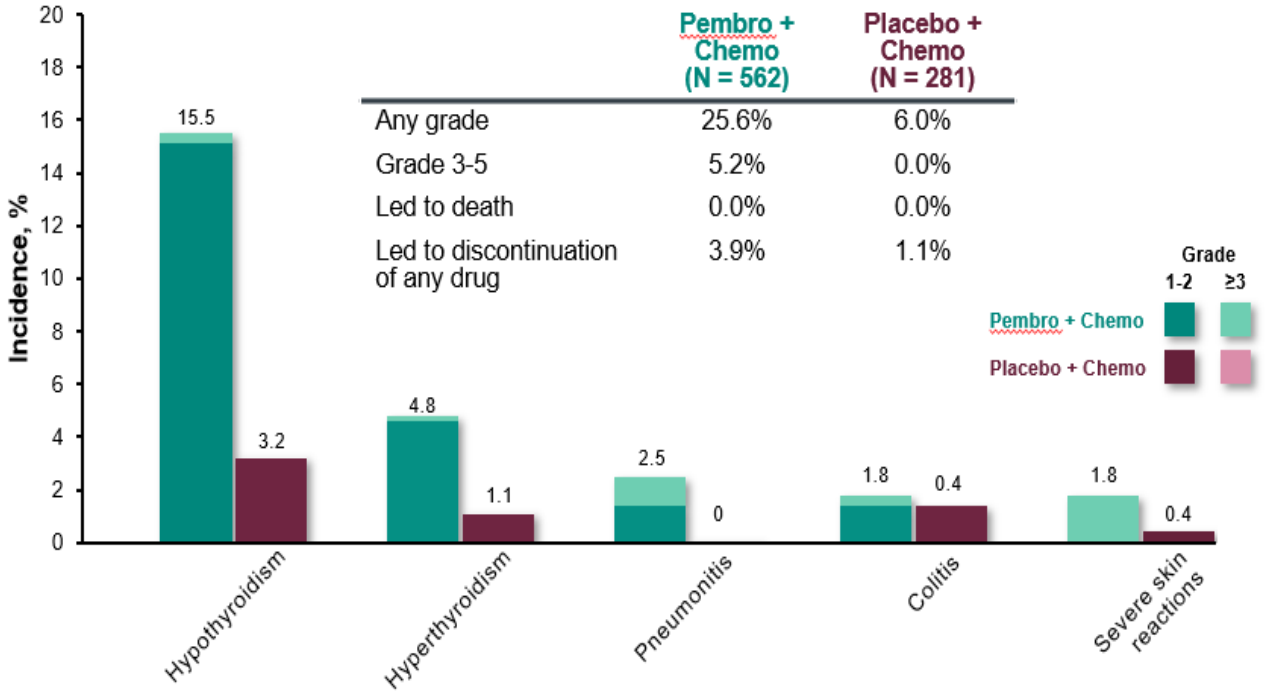
Courtesy of Hope S Rugo, MD

Courtesy of Hope S Rugo, MD

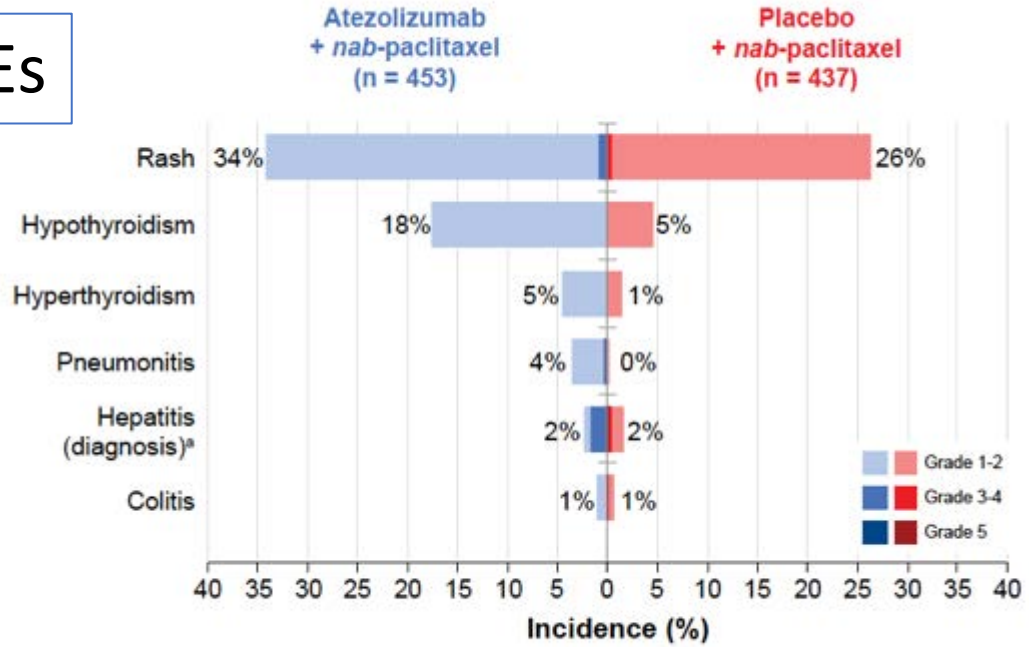
IMpassion130 irAEs

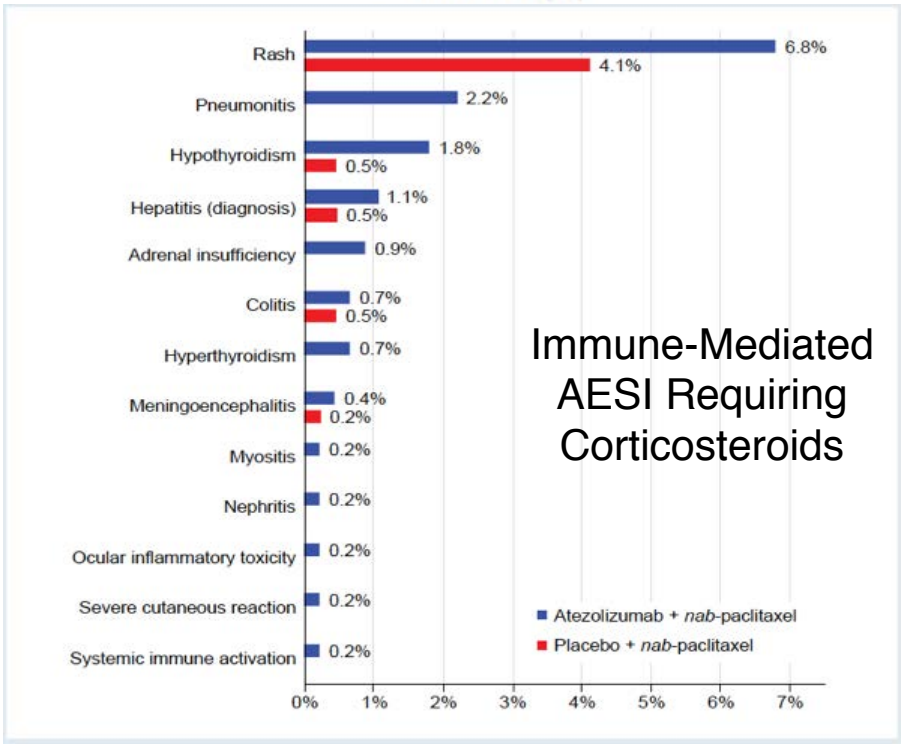
KEYNOTE-355 Immune-Mediated AEs

	Pembro + Chemo (N = 562)	Placebo + Chemo (N = 281)
Any grade	25.6%	6.0%
Grade 3-5	5.2%	0.0%
Led to death	0.0%	0.0%
Led to discontinuation of any drug	3.9%	1.1%



Immune-Mediated AEs with Incidence ≥10 Patients in Either Treatment Group





Immune-Mediated AESI Requiring Corticosteroids

J. Cortes et al. ASCO 2020; Schneeweiss, Rugo et al, ASCO 2019

Current Management of Triple-Negative Breast Cancer

Module 1: Immune Checkpoint Inhibition — Dr Rugo

- Key Recent Data Sets
  - IMpassion130
  - KEYNOTE-355
- Cases/Questions from General Medical Oncologists
  - A 52-year-old woman with node-positive early TNBC
  - A 49-year-old woman with a PD-L1-positive locoregional recurrence on adjuvant therapy
  - A 55-year-old woman develops leptomeningeal metastases on atezolizumab/*nab*-paclitaxel
  - A 59-year-old woman on atezolizumab/*nab*-paclitaxel experiences adrenal insufficiency
- Faculty Cases

Have you added or would you add an anti-PD-1/PD-L1 antibody to chemotherapy as neoadjuvant treatment for triple-negative breast cancer (TNBC) outside of a clinical trial setting?

a. I have
b. I have not but would for the right patient
c. I have not and would not

Case Presentation — Dr Ibrahim: A 52-Year-Old Woman with Early TNBC

- A 52-year-old woman presents to her primary care provider with a palpable mass in breast and clinically positive lymph node
- Imaging: 3.5 – 4.0-cm mass in breast
  - No evidence of systemic disease
- ddAC x 4 → weekly paclitaxel
- Good response to neoadjuvant therapy

Sulfi Ibrahim, MD

Which neoadjuvant systemic therapy, if any, would you generally recommend for a 48-year-old woman with a 3-cm, triple-negative IDC with 1 positive axillary node on biopsy?

Regulatory and reimbursement issues aside, would you attempt to access an anti-PD-1/PD-L1 antibody as part of neoadjuvant therapy for the patient in the scenario above?

	Neoadjuvant tx	Access PD-1/PD-L1 ab?
 LISA A CAREY, MD	ddAC → weekly paclitaxel/carboplatin	No
 VIRGINIA KAKLAMANI, MD, DSC	AC → weekly paclitaxel (may add carbo if poor response to AC)	Yes
 IAN E KROP, MD, PHD	ddACT	No
 JOYCE O'SHAUGHNESSY, MD	ddAC → weekly paclitaxel/carboplatin	No
 HOPE S RUGO, MD	Weekly paclitaxel (add carbo after cycle 3 if poor response) → AC	Yes – only if slow/poor response
 SARA M TOLANEY, MD, MPH	ddACT	Yes

A 54-year-old woman receives neoadjuvant dose-dense AC → paclitaxel for a 3.5-cm, triple-negative, node-positive, PD-L1-negative IDC and experiences a clinical response to therapy but has significant residual disease in the breast and axilla. Regulatory and reimbursement issues aside, would you attempt to access an anti-PD-1/PD-L1 antibody as part of adjuvant therapy for this patient?

Regulatory and reimbursement issues aside, would you attempt to access an anti-PD-1/PD-L1 antibody if she had PD-L1-positive disease?

	PD-L1-negative	PD-L1-positive
 LISA A CAREY, MD	No	No
 VIRGINIA KAKLAMANI, MD, DSC	No	No
 IAN E KROP, MD, PHD	No	No
 JOYCE O'SHAUGHNESSY, MD	No	No
 HOPE S RUGO, MD	No	No
 SARA M TOLANEY, MD, MPH	No	No

Case Presentation – Dr Rugo: A woman in her 60s with mTNBC

- A woman in her early 60s is diagnosed with Stage I TNBC and received TC
- Three years later, she presents with metastases to the lung and soft tissue
  - Tumor biopsied, PD-L1 positive
- Atezolizumab/*nab*-paclitaxel for 6 cycles
  - Complete response
  - Some neuropathy and diarrhea
  - Patient hates coming in for atezolizumab q2wks
- After 6 cycles, continued with atezolizumab alone, q2wks
  - She is still doing well a year after stopping the *nab*-paclitaxel
- Switch to q3wks dosing of atezolizumab?

A 49-year-old woman with TNBC (BRCA wild type, HRD-negative) s/p neoadjuvant anthracycline/taxane followed by surgery with residual disease develops extensive skin recurrence on adjuvant capecitabine. Tumor is PD-L1-positive. What is your likely treatment?

a. Atezolizumab/*nab* paclitaxel
b. Atezolizumab/other chemotherapy
c. Pembrolizumab/carboplatin/gemcitabine
d. Pembrolizumab/other chemotherapy
e. Other

Case Presentation — Dr DeFusco: A 49-Year-Old Woman with mTNBC

- A 49-year-old woman with Stage 1 TNBC undergoes lumpectomy and radiation therapy
- Ipsilateral recurrence soon after completion of radiation
  - Neoadjuvant chemotherapy followed by surgery → residual disease
- Adjuvant capecitabine initiated
- Macular, patchy rash developed over chest wall and abdomen that is biopsy confirmed TNBC
  - Staging reveals no evidence of disease elsewhere
- Tumor is PD-L1-positive

Patricia A DeFusco, MD

A woman with a triple-negative IDC (BRCA wild type) receives neoadjuvant taxane/anthracycline-based chemotherapy, has residual disease at surgery and begins adjuvant capecitabine. She then presents with diffuse biopsy-proven PD-L1-positive skin recurrence on the chest wall and abdomen. Regulatory and reimbursement issues aside, what treatment would you recommend? (Dr DeFusco)

 LISA A CAREY, MD	Pembrolizumab/gemcitabine/carboplatin
 VIRGINIA KAKLAMANI, MD, DSC	Pembrolizumab/gemcitabine/carboplatin
 IAN E KROP, MD, PHD	Pembrolizumab/gemcitabine/carboplatin
 JOYCE O'SHAUGHNESSY, MD	Pembrolizumab/gemcitabine/carboplatin
 HOPE S RUGO, MD	Atezolizumab/*nab* paclitaxel or pembrolizumab/gemcitabine/carboplatin
 SARA M TOLANEY, MD, MPH	Atezolizumab/*nab* paclitaxel or pembrolizumab/gemcitabine/carboplatin

Case Presentation — Dr Hussein: A 55-Year-Old Woman with mTNBC

- A 55-year-old woman is diagnosed with TNBC and lung metastases
- Atezolizumab/*nab*-paclitaxel initiated → good response
  - Lung metastases disappeared, improved QOL
  - Complete remission after 6 months of therapy
- *nab*-paclitaxel stopped due to peripheral neuropathy
- Atezolizumab continued alone for a few cycles
- Leptomeningeal metastases detected

Maen A Hussein, MD

A 78-year-old woman with diabetes and preexisting Grade 1 peripheral neuropathy presents with de novo metastatic triple-negative breast cancer (BRCA wild type). Regulatory and reimbursement issues aside, what treatment would you recommend if she had PD-L1-positive disease?

 LISA A CAREY, MD	Pembrolizumab/carboplatin
 VIRGINIA KAKLAMANI, MD, DSC	Atezolizumab/*nab* paclitaxel
 IAN E KROP, MD, PHD	Atezolizumab/*nab* paclitaxel
 JOYCE O'SHAUGHNESSY, MD	Pembrolizumab/gemcitabine/carboplatin
 HOPE S RUGO, MD	Consider atezolizumab with lower-dose *nab* paclitaxel
 SARA M TOLANEY, MD, MPH	Paclitaxel/pembrolizumab

Have you observed adrenal insufficiency in any of your patients with cancer who are receiving a checkpoint inhibitor?

a. No
b. Yes, 1 patient
c. Yes, 2 patients
d. Yes, more than 2 patients

Case Presentation — Dr Leasure: A 59-Year-Old Woman with mTNBC

- 9/2019: A 59-year-old woman with PD-L1-positive mTNBC receives atezolizumab/n*ab*-paclitaxel
  - Responding/stable disease for 9 months
- Presents to office visit tired and hypotensive
- Imaging reveals disease is stable
- Lab workup shows low cortisol and ACTH stimulation test results
- Patient hospitalized due to adrenal insufficiency

Nick C Leasure, MD

A patient who is experiencing a good response to atezolizumab/*nab* paclitaxel for PD-L1-positive triple-negative metastatic breast cancer presents with severe adrenal insufficiency requiring hospitalization. After symptoms resolve, would you resume the atezolizumab/*nab* paclitaxel? (Dr Leasure)

 LISA A CAREY, MD	Yes
 VIRGINIA KAKLAMANI, MD, DSC	Yes
 IAN E KROP, MD, PHD	Yes
 JOYCE O'SHAUGHNESSY, MD	No
 HOPE S RUGO, MD	Yes
 SARA M TOLANEY, MD, MPH	Yes

A 55-year-old woman with metastatic triple-negative breast cancer (BRCA wild type) has experienced disease progression on multiple lines of therapy, including anthracyclines, taxanes, capecitabine, eribulin, carboplatin and gemcitabine. Her tumor is PD-L1-negative, but next-generation sequencing (NGS) reveals a tumor mutational burden of 12. Would you offer this patient an anti-PD-1/PD-L1 antibody at this point?

 LISA A CAREY, MD	Yes
 VIRGINIA KAKLAMANI, MD, DSC	Yes, if MSI-high tumor
 IAN E KROP, MD, PHD	Yes
 JOYCE O'SHAUGHNESSY, MD	Yes
 HOPE S RUGO, MD	No, would offer sacituzumab govitecan first
 SARA M TOLANEY, MD, MPH	Yes

Current Management of Triple-Negative Breast Cancer

Module 1: Immune Checkpoint Inhibition — Dr Rugo

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- Faculty Cases
  - A woman in her early 60s with mTNBC
  - A 42-year-old woman with mTNBC

Case Presentation – Dr Rugo: A 42-year-old woman with mTNBC

- A woman with Stage II TNBC and received neoadjuvant AC/T, 1.7 cm residual disease
- Has recurrence in lung with multiple nodules at 18 months
- Received capecitabine and 3 months later has disease progression
- Enrolled on KEYNOTE-86
- Dramatic response to pembrolizumab, complicated by mild colitis treated with budesonide and mild psoriasis treated with topical steroid
- At 18 months radiation to residual 1 cm lung lesion
- At 2 yrs of pembrolizumab required to stop study therapy
- Able to continue pembrolizumab on compassionate use
- She continues to do well 4 1/2 years later and is NED

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  - SWOG-S1416
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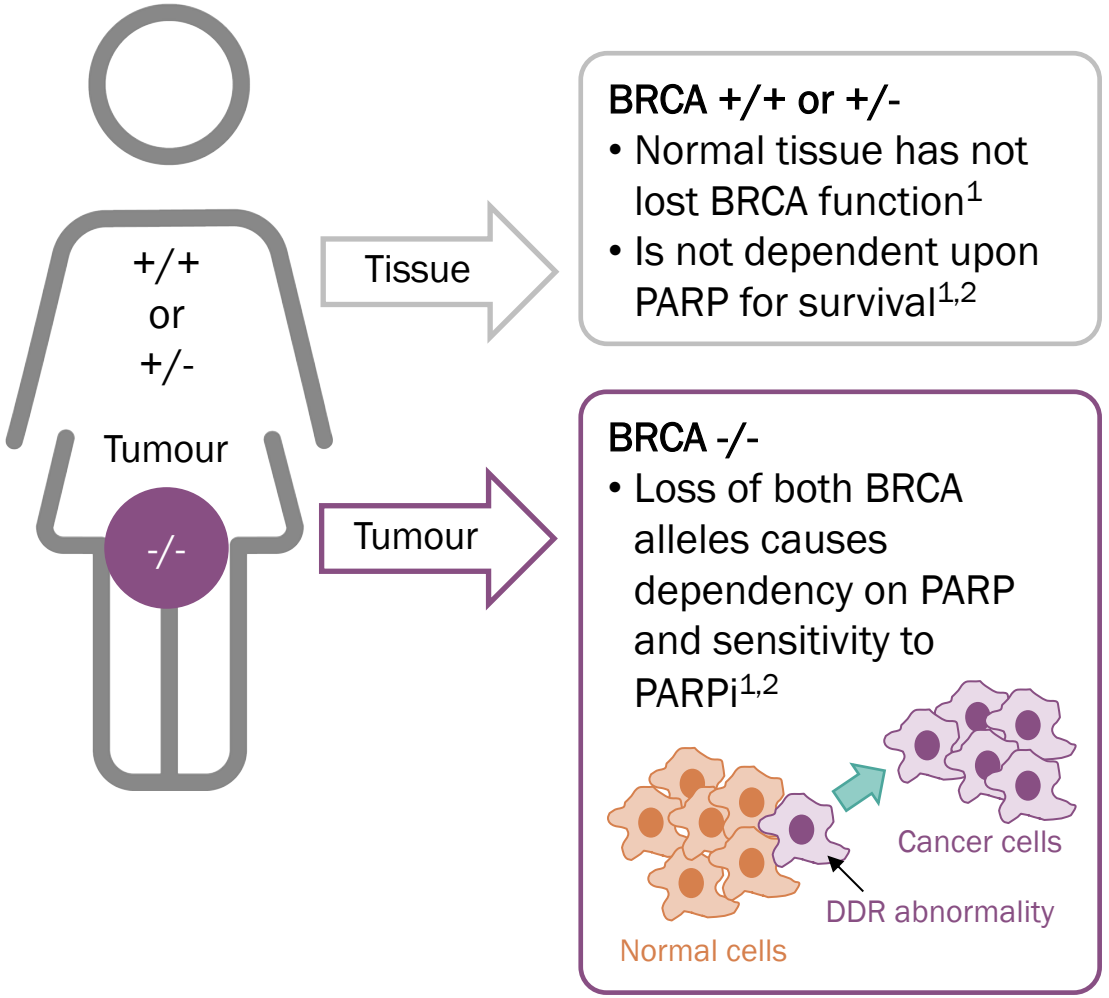
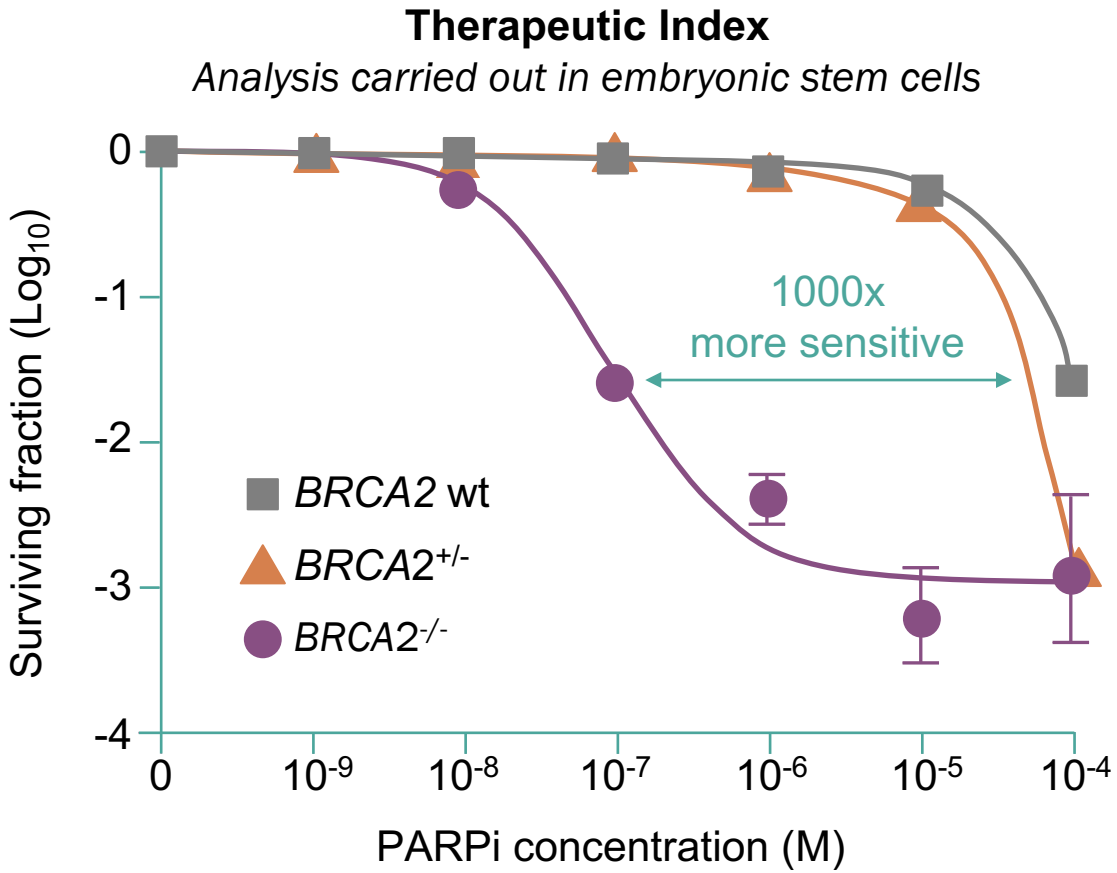
PARP inhibitors selectively target homologous recombination repair deficient cells





Courtesy of Joyce O'Shaughnessy, MD

1. Bryant HE et al. Nature 2005;434:913–917; 2. Farmer H et al. Nature 2005:434:917–921

In general, which PARP inhibitor would you recommend for a patient with metastatic TNBC with a BRCA mutation?

a. Olaparib
b. Talazoparib
c. Either olaparib or talazoparib – coin flip

Regulatory and reimbursement issues aside, would you attempt to access a PARP inhibitor for a patient with metastatic TNBC and either a somatic BRCA mutation or a germline PALB2 mutation?

a. No
b. Yes, somatic BRCA mutation
c. Yes, germline PALB2 mutation
d. Both b and c

Phase III studies of PARP inhibitors gBRCA MBC

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)

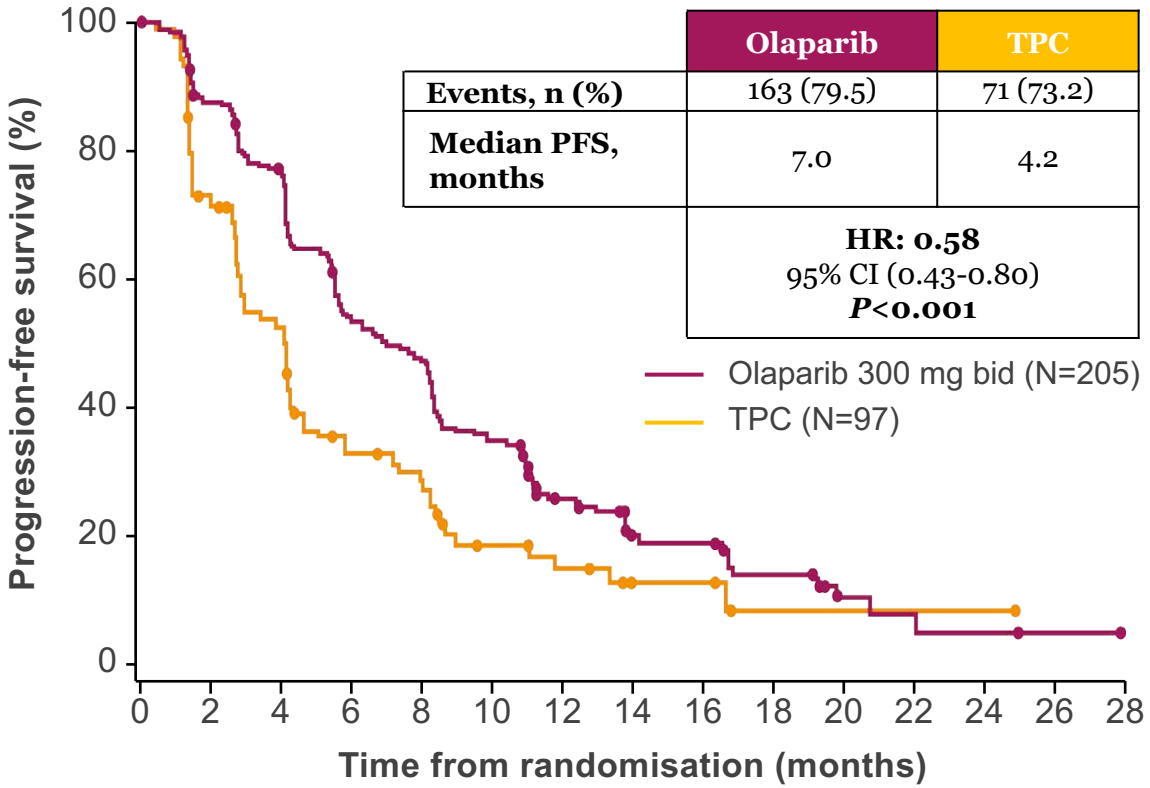
1. Robson et al. N Engl J Med. 2017; 377:523-533; 2. Litton J et al. N Engl J Med 2018; 379:753–763

Courtesy of Joyce O'Shaughnessy, MD

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 physicians' choice

OLYMPIAD: Olaparib PFS[1,2]

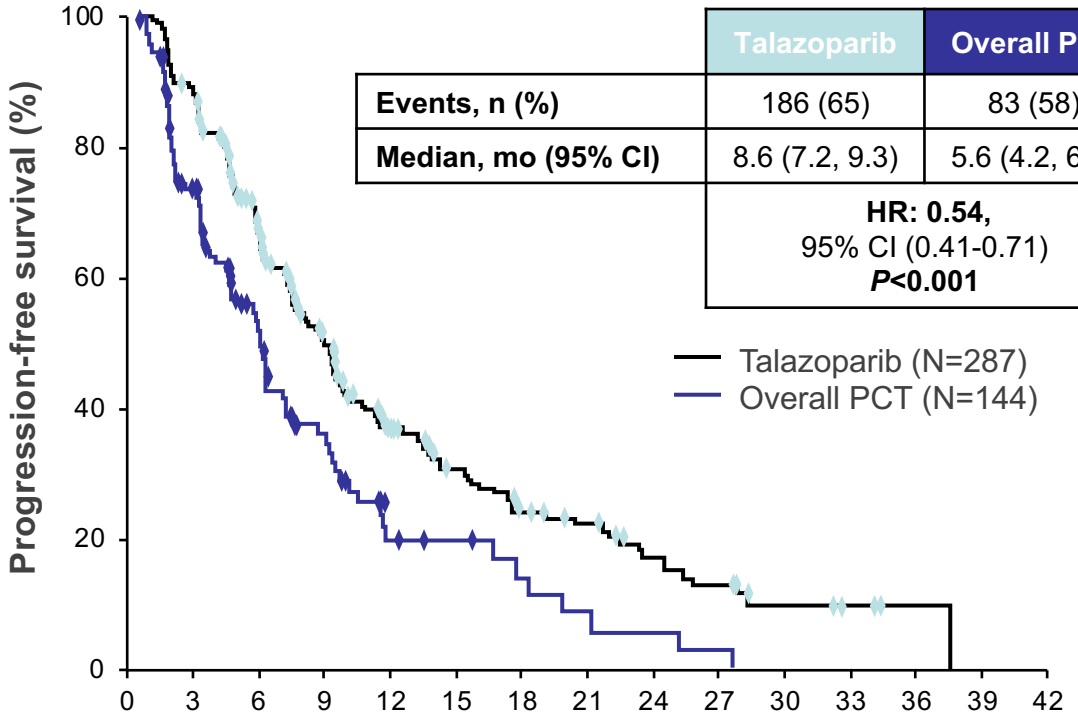


	Olaparib	TPC
Events, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
	HR: 0.58 95% CI (0.43-0.80) *P*<0.001	

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. Lynparza 150mg Film-Coated Tablets, SmPC. 2019; 3. Litton JK, et al. N Engl J Med. 2018;379:753-763 (supplementary appendix)

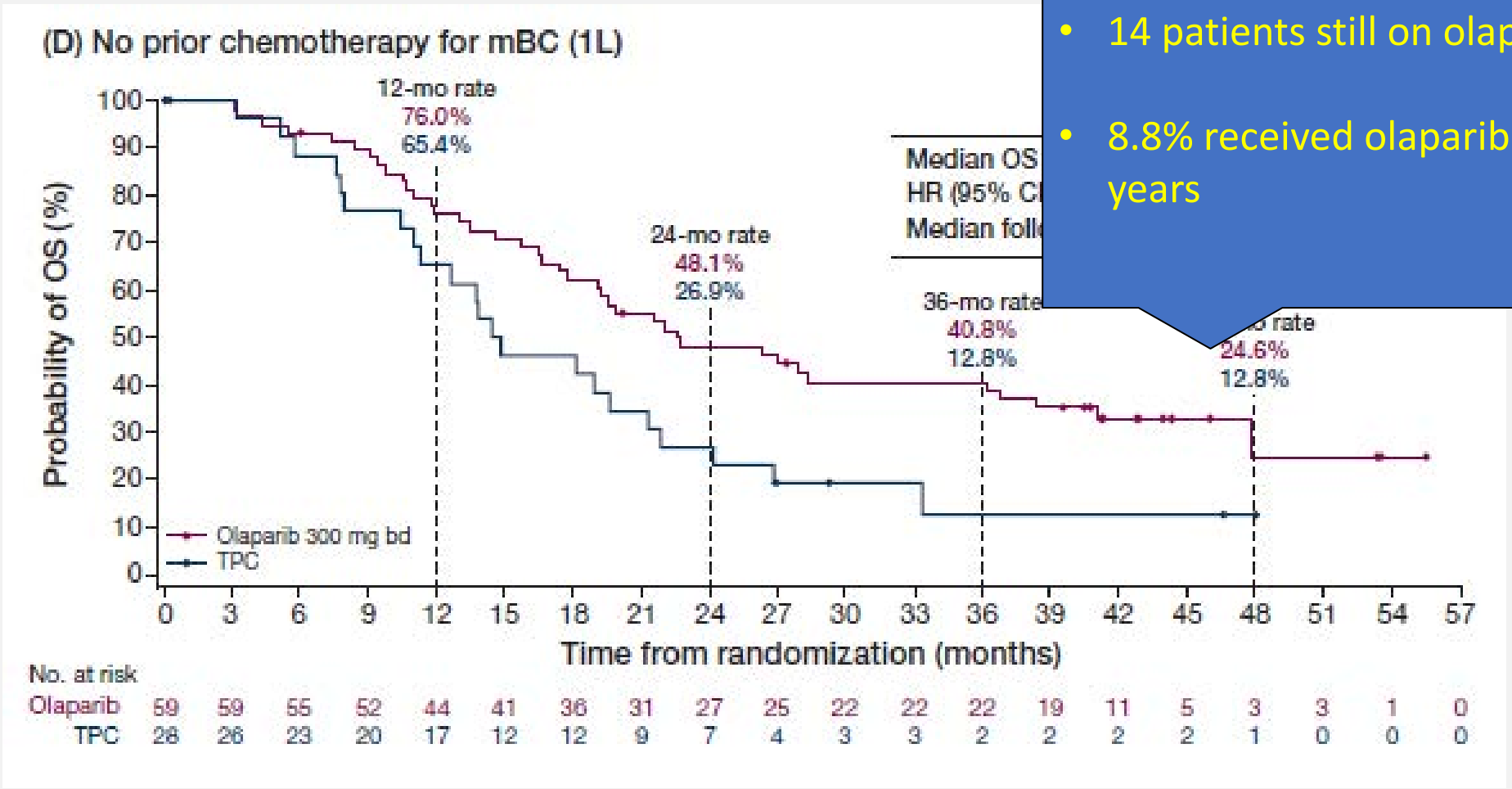
Courtesy of Joyce O'Shaughnessy, MD

OlympiAD Extended Follow-Up

No statistically significant differences in survival curves in:

- Overall population and > 1 line of chemotherapy in metastatic setting
- Tissue receptor subtype
- Prior exposure to platinums

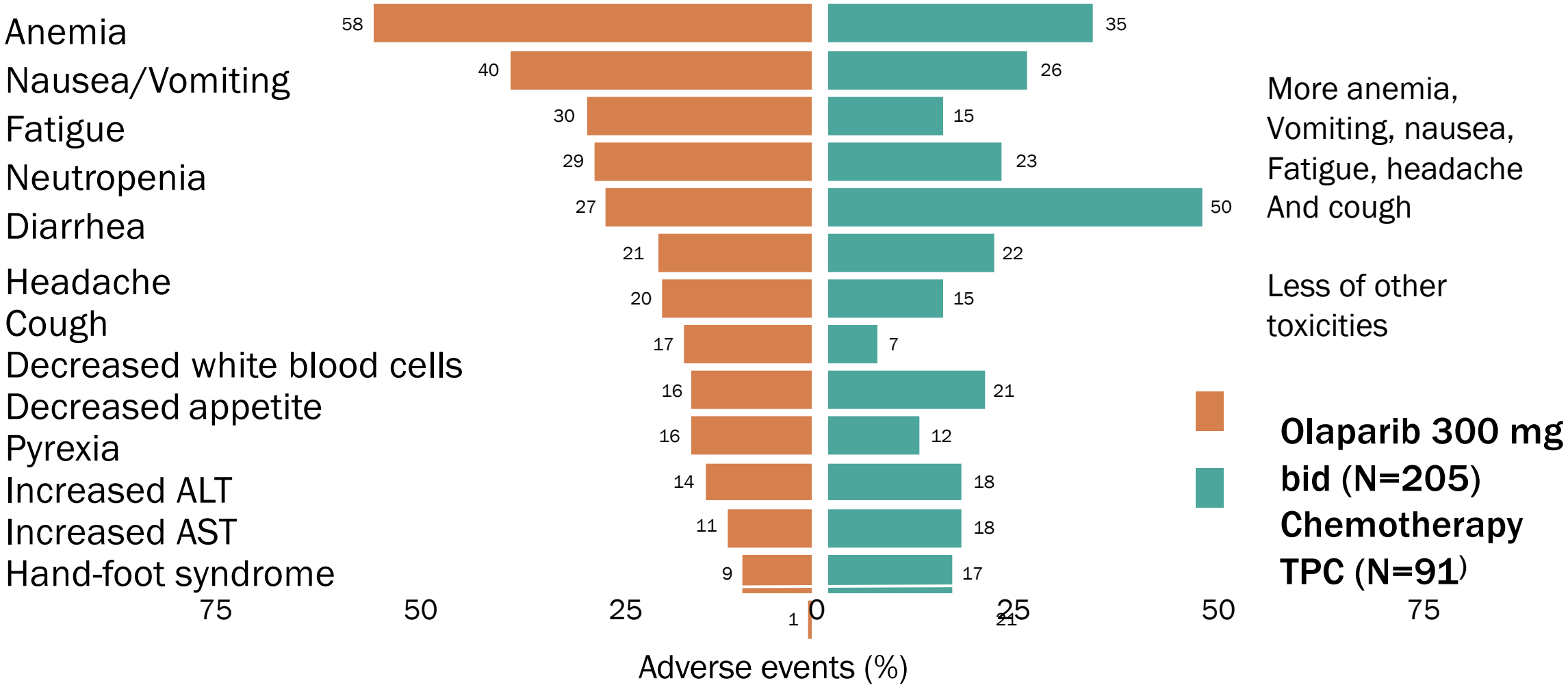
No new safety signal –No AML/MDS



- 14 patients still on olaparib
- 8.8% received olaparib > 3 years

Robson M, et al.
SABCS 2019. Poster PD4-03.

OlympiAD - Adverse events (any grade) in ≥15% of patients



Irrespective of causality. MedDRA preferred terms for adverse events have been combined for 1) anemia and 2) neutropenia
ALT, alanine aminotransferase; AST, aspartate aminotransferase

Robson M et al. NEJM 2017

Courtesy of Joyce O'Shaughnessy, MD

Hematologic Toxicity with Talazoparib in EMBRACA

Adverse reactions (%)	Talazoparib (n=286)			Chemotherapy (n=126)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Anemia	53	38	1	18	4	1
Neutropenia	35	18	3	43	20	16
Thrombocytopenia	27	11	4	7	2	0

Courtesy of Joyce O'Shaughnessy, MD

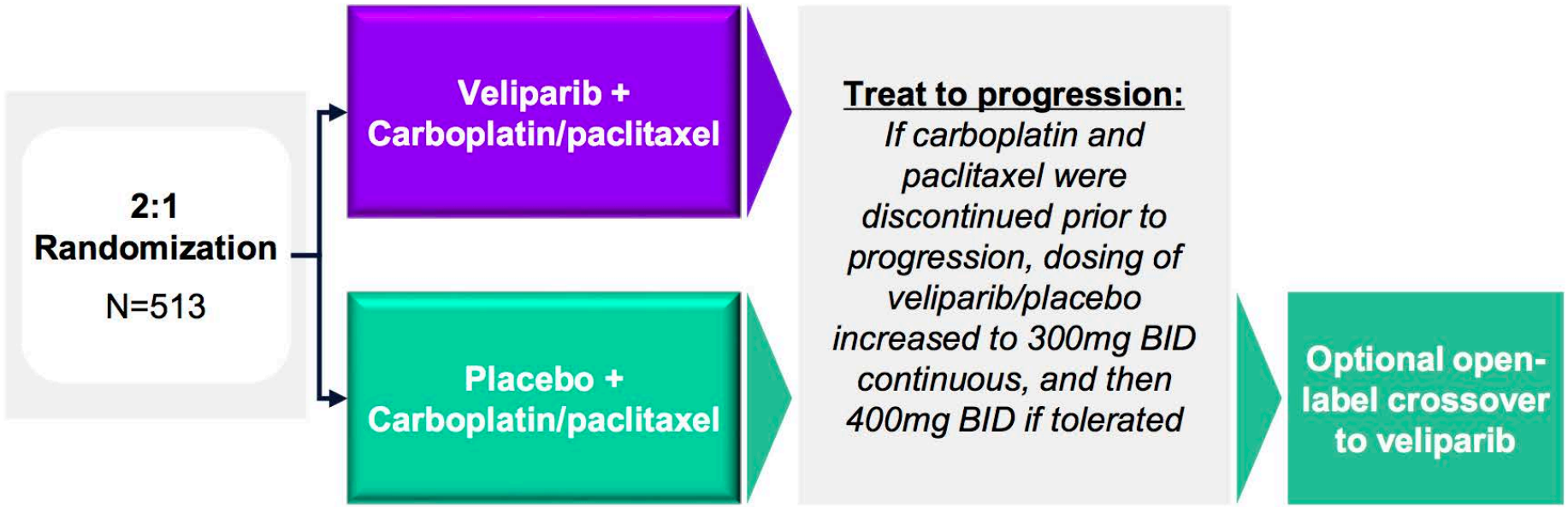
Study Design: BROCADE3 (NCT02163694)

Patient Population

- Advanced HER2-negative breast cancer
- Germline *BRCA1* or *BRCA2* mutation
- ≤2 prior lines cytotoxic therapy for metastatic disease
- ≤1 prior lines of platinum; no progression ≤12 months of completing

Stratification Factors

- Hormone Receptor Expression
- Prior Platinum
- CNS Metastasis



Primary Endpoint:
Investigator-assessed PFS per RECIST 1.1

21-Day Cycles:

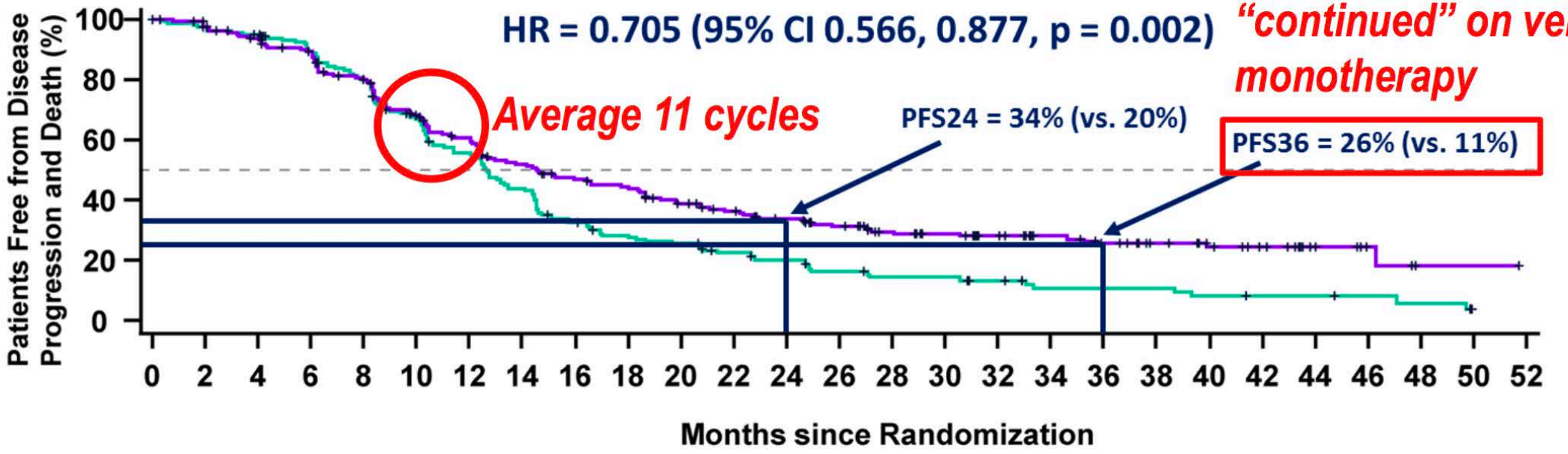
- Carboplatin (C): AUC 6 on Day 1
- Paclitaxel (P): 80 mg/m^2 on Days 1, 8, 15
- Veliparib or Placebo: 120mg BID on Days -2 to 5

Dieras V et al. ESMO 2019

Courtesy of Joyce O'Shaughnessy, MD

Primary endpoint: PFS (investigator-assessed)

136/337 patients "continued" on veliparib monotherapy



OS 33.5 mos Veliparib vs 28.2 mos Placebo ; HR 0.945, p=0.666

No. at Risk

Control	172	160	153	140	123	99	82	64	47	39	35	27	23	18	15	15	12	8	8	8	6	5	5	4	3	0
Veliparib	337	316	301	282	250	207	181	154	137	126	107	92	81	72	60	51	45	38	32	25	20	16	8	4	1	1	0

	Veliparib + C/P	Placebo + C/P
PFS events, n/N	217/337	132/172
Median PFS [95% CI]	14.5 [12.5, 17.7]	12.6 [10.6, 14.4]

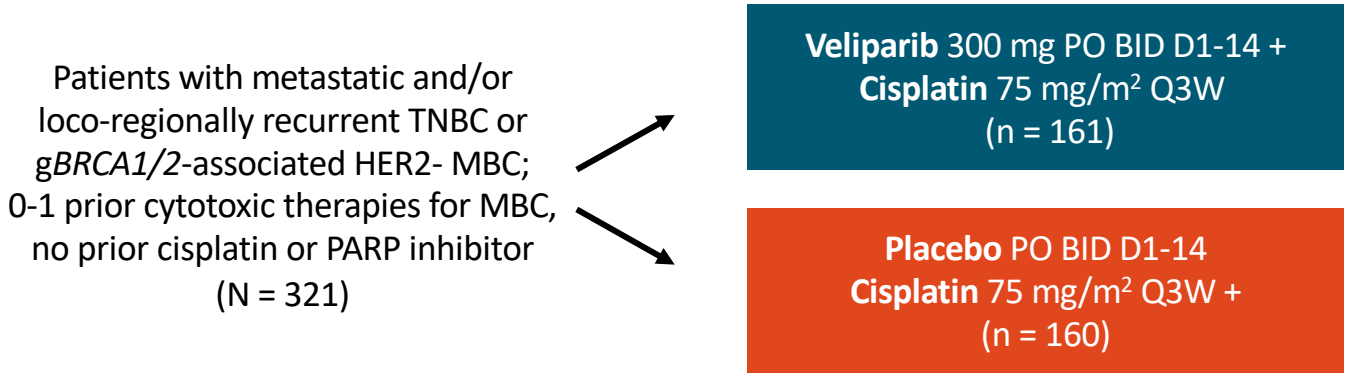
C/P, carboplatin and paclitaxel

Variable	Veliparib +C/P (N = 337)	Placebo + C/P (N = 172)
CBR (at 24 weeks), % [95%CI]	90.7 [87.9, 92.9]	93.2 [89.5, 95.7]
ORR (CR+PR), % [95% CI]	75.8 [70.4, 80.6]	74.1 [66.1, 81.1]

Dieras V et al. ESMO 2019

Courtesy of Joyce O'Shaughnessy, MD

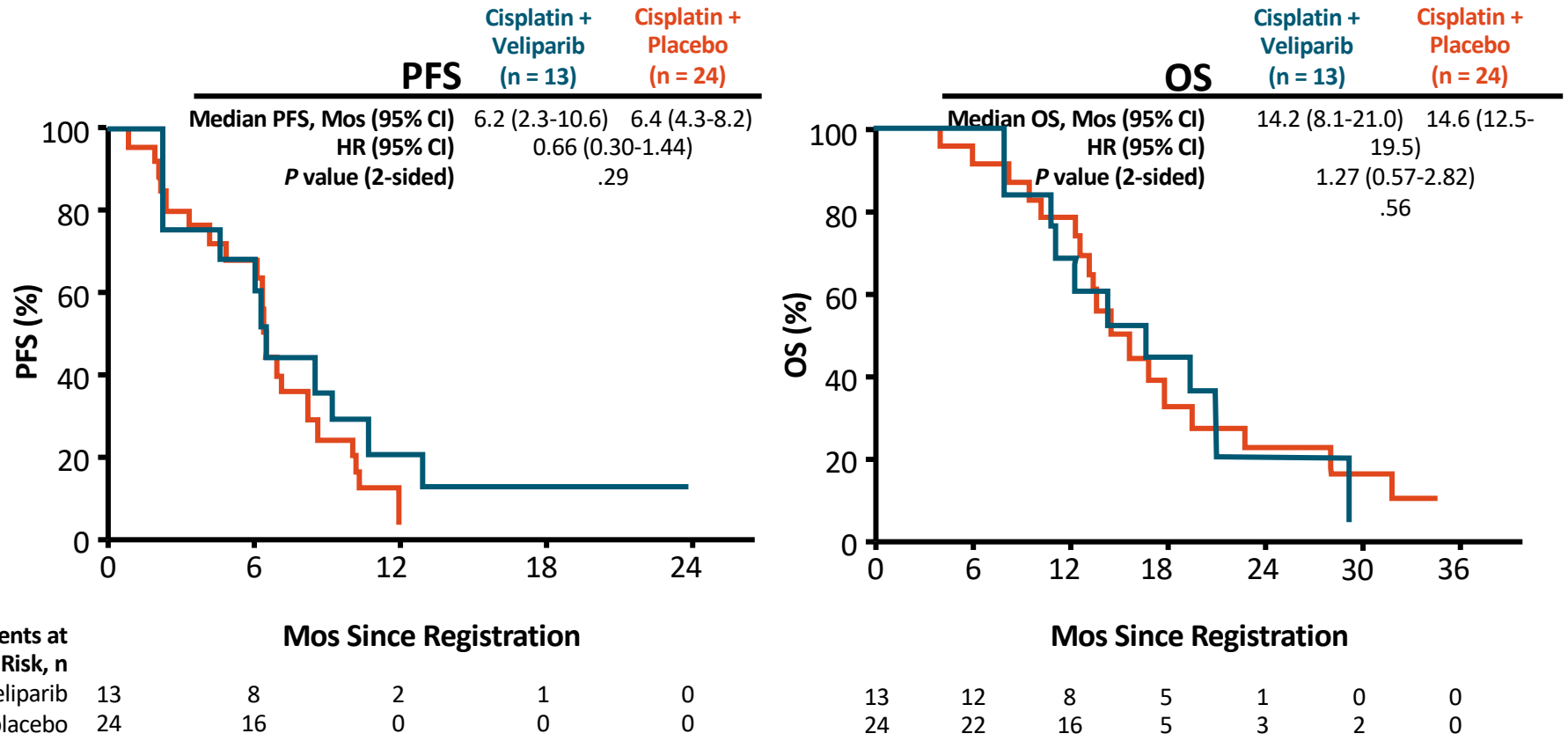
SWOG-S 1416: Study Design



- Primary endpoint: PFS in 3 prespecified groups (gBRCA, BRCA-like, non–BRCA-like)
  - Patients assigned by postrandomization gBRCA, BRCA-like biomarker testing
  - BRCA-like if any of: HRD genomic instability score ≥ 42, somatic BRCA1/2 mutation, BRCA1 promoter methylation, other germline HR repair gene mutation
- Key secondary endpoints: OS, ORR, clinical benefit rate

Sharma. ASCO 2020. Abstr 1001.

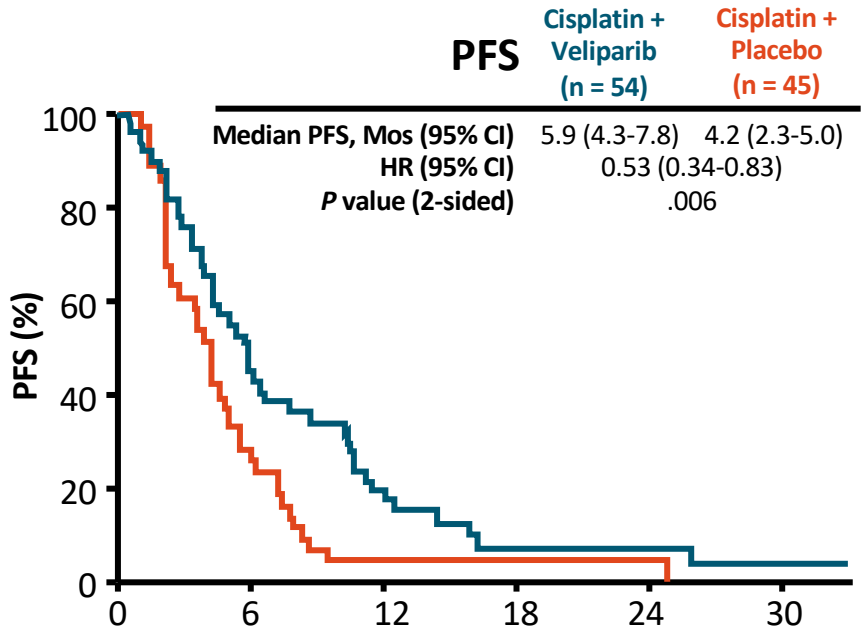
SWOG-S 1416: PFS and OS in Germline *BRCA* Group

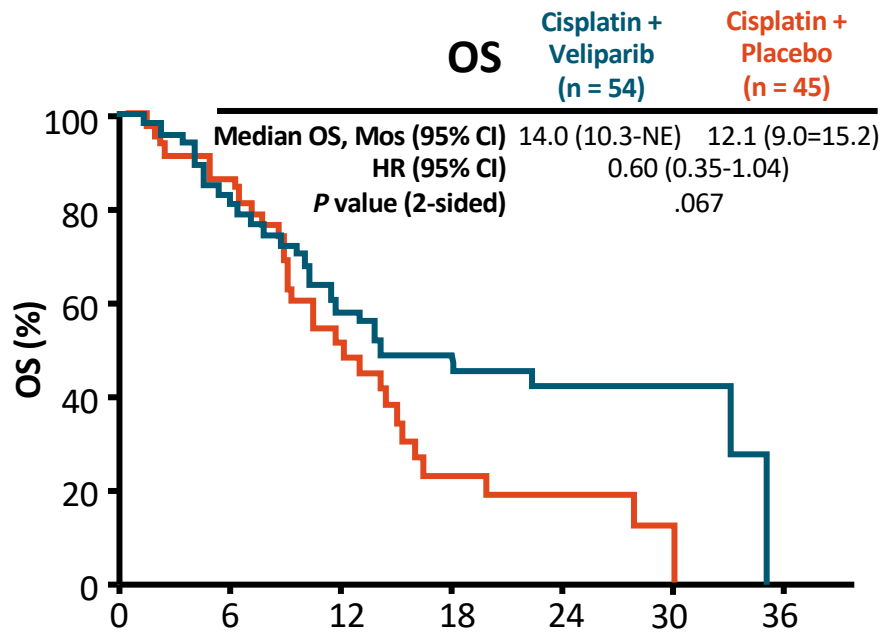


Sharma. ASCO 2020. Abstr 1001. Reproduced with permission.

Courtesy of Joyce O'Shaughnessy, MD

SWOG-S 1416: PFS and OS in BRCA-Like Group





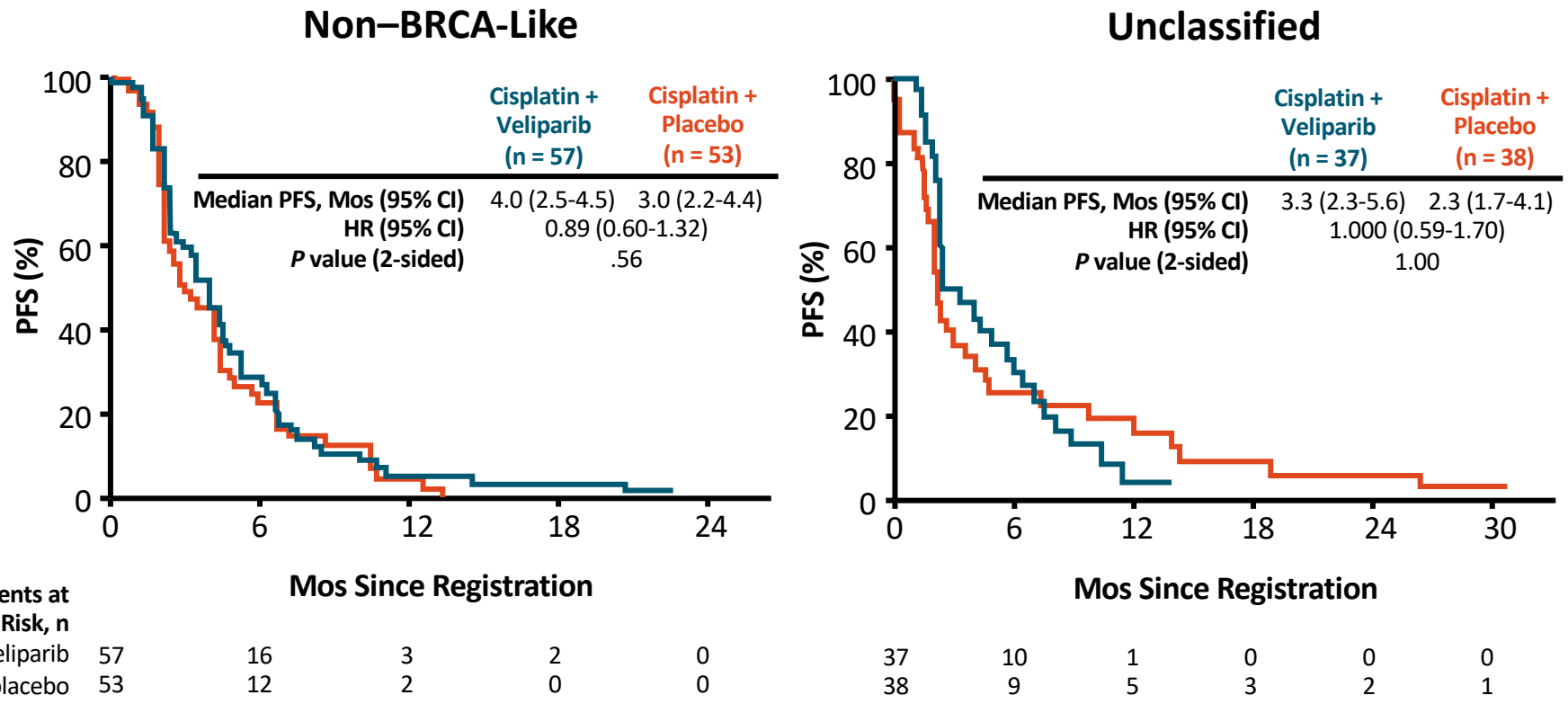
Patients at Risk, n						
Cis + veliparib	54	21	9	3	3	1
Cis + placebo	45	12	2	1	1	0

54	37	22	16	10	6	0
45	36	16	6	4	0	0

Sharma. ASCO 2020. Abstr 1001. Reproduced with permission.

Courtesy of Joyce O'Shaughnessy, MD

SWOG-S 1416: PFS in Non–BRCA-Like and Unclassified



Sharma. ASCO 2020. Abstr 1001. Reproduced with permission.

Courtesy of Joyce O'Shaughnessy, MD

Ongoing PARP Trials for Early Stage Disease

PARP inhibitor (dose)	Phase/Name/NCT	Treatment Arms	Patient Population	Primary Outcome
olaparib (300 mg BID)	III / OlympiA NCT02032823	adjuvant maintenance treatment for high-risk disease after definitive treatment, olaparib for 1 year vs placebo	*gBRCA* w/ high-risk disease (non-pCR)	invasive DFS
olaparib (150 mg BID day -2 to 10 or 150 mg BID day 3 to day 14)	II/III/ PARTNER NCT03150576	olaparib with weekly paclitaxel and carboplatin (AUC=5, q3 weeks) vs paclitaxel and carboplatin (all get anthracycline-based regimen prior to surgery)	TNBC or *gBRCA*	pCR
olaparib (100 mg BID)	II / GeparOla NCT02789332	standard neoadjuvant chemotherapy with either olaparib or carboplatin (AUC=2, weekly)	homologous repair deficient	pCR
niraparib	I / NCT03329937	single arm neoadjuvant niraparib	germline or somatic *BRCA* mutations	safety, change in tumor volume (by MRI)
rucaparib (300 mg to 600 mg BID)	I / NCT03542175	concurrent rucaparib with post-op radiation after definitive chemotherapy and surgery	TNBC and non-pCR	safety, MTD
talazoparib (1 mg daily)	II / NCT03499353	neoadjuvant talazoparib monotherapy for 6 months followed by surgery	*gBRCA* and TNBC	pCR

PARP Inhibition + Immune Checkpoint Blockade

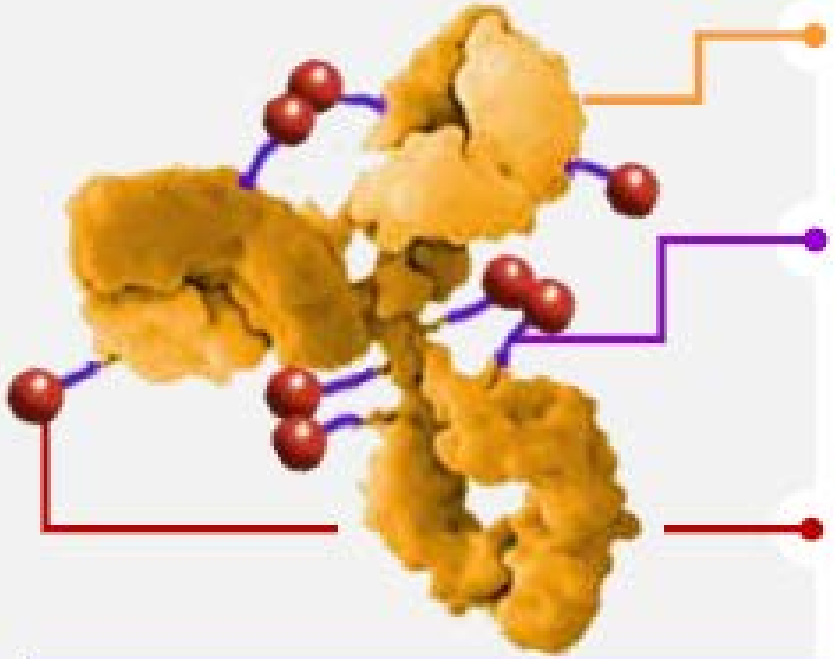
Trial	BRCA1/2 Mutation	Drugs	Selection	N	ORR	1-Year PFS
MEDIOLA	Germline	Olaparib + Durvalumab	Max 2 lines chemo	30	63%	≈ 40%
TOPACIO	Tumor	Niraparib + Pembrolizumab	Max 2 lines chemo	15	47%	≈ 40%
OlympiAD	Germline	Olaparib	Max 2 lines chemo	205	60%	26%
EMBRACA	Germline	Talazoparib	Max 3 lines chemo	287	63%	37%

- Addition of immunotherapy did not ↑ ORR
- Remains to be seen if immunotherapy can extend the tail of the curve

Courtesy of Joyce O'Shaughnessy, MD

Robson M, et al. *N Engl J Med* 2017;377:523-533
Litton JK, et al. *N Engl J Med* 2018;379:753-763
Slide courtesy Sara Tolaney, MD

Sacituzumab Govitecan – Trop-2-Directed ADC



1. Monoclonal antibody (hRS7)

- Binds to Trop-2, a cell surface antigen highly expressed by many cancers, including TNBC

2. Hydrolyzable linker (CL2A)

- Helps to ensure that an active concentration of SN-38 is maintained in the tumor
- Hydrolysis of the linker releases the cytotoxic payload intracellularly and in the tumor microenvironment to kill cells

3. Cytotoxic payload (SN-38)

- Topoisomerase I inhibitor that blocks DNA replication, leading to double-stranded DNA breaks via multiple mechanisms

Favorable Therapeutic Index

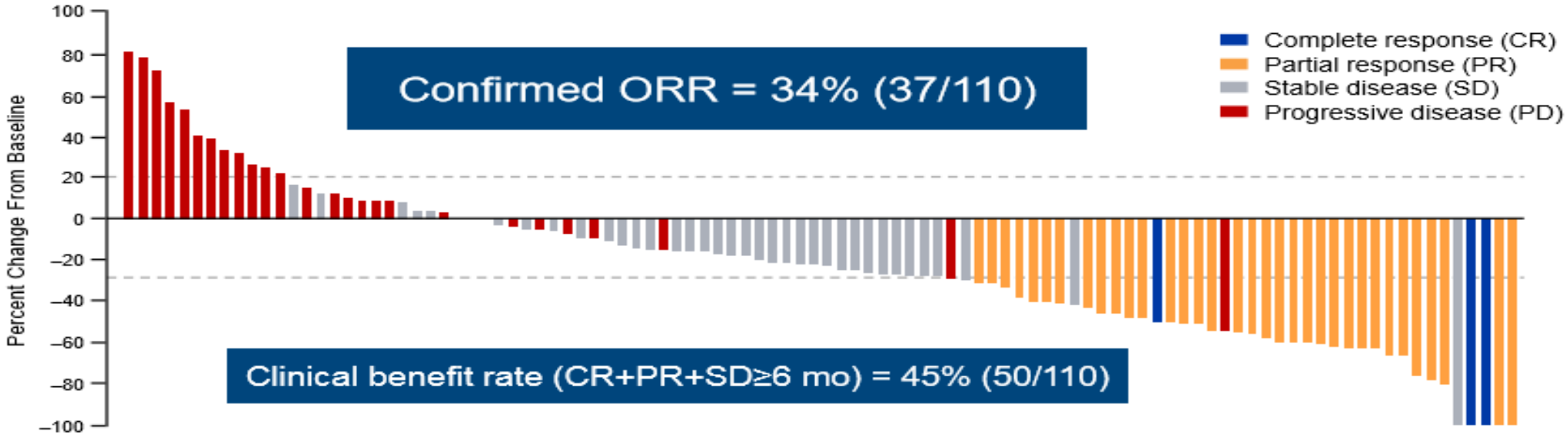
- SG has a high DAR (7.6:1 or 7-8 molecules of SN-38 per antibody), enhancing drug delivery to tumor
  - Other ADCs have 3 or 4 to 1 ratios[2,3]
- Moderate drug potency mitigates toxicity, while increased intratumoral drug release enhances efficacy
  - Other ADCs have highly toxic payloads

Courtesy of Joyce O'Shaughnessy, MD

Phase II Trial Sacituzumab Govitecan

Met TNBC 3/4/5th-line Phase II

Tumor Response to Treatment



- 74% (75/102) of patients with at least one CT response assessment had reduction of target lesions (sum of diameters)
- 102 patients had ≥1 scheduled CT response assessment
- 8 patients withdrew prior to assessment (4 PD, 4 MRI brain mets)

Median DoR 7.6 mos Med PFS 5.5 mos

Courtesy of Joyce O'Shaughnessy, MD

Bardia A et al. NEJM 2018

Toxicities: Phase II Sacituzumab Govitecan in TNBC

Adverse Event	Any Grade N (%)	Grade 3 N (%)	Grade 4 N (%)
Any adverse event	108 (100)	71 (66)	21 (19)
Nausea	72 (67)	7 (6)	0
Diarrhea	67 (62)	9 (8)	0
Neutropenia	69 (64)	28 (26)	17 (16)
Fatigue and asthenia	59 (55)	9 (8)	0
Alopecia	39 (36)	0	0

24% pts had one and 9% pts had two dose reductions
2.8% pts discontinued SG due to toxicity

Courtesy of Joyce O'Shaughnessy, MD

Current Management of Triple-Negative Breast Cancer

Module 2: PARP Inhibition and Other Novel Agents/Strategies — Dr O'Shaughnessy

- Key Recent Data Sets
  - OlympiAD, EMBRACA and BROCADE3
  - SWOG-S1416
  - Sacituzumab govitecan
- Cases/Questions from General Medical Oncologists
  - A 52-year-old with gBRCA mutation-positive TNBC and peritoneal metastases
  - A 63-year-old woman with mTNBC and anemia
- Faculty Cases

Regulatory and reimbursement issues aside, what would be your preferred systemic treatment approach for a patient with PD-L1-positive metastatic TNBC and a BRCA germline mutation?

a. Atezolizumab/*nab* paclitaxel → PARP inhibitor maintenance
b. Olaparib
c. Talazoparib
d. Platinum-based chemotherapy → PARP inhibitor maintenance
e. Chemotherapy
f. Other

Case Presentation — Dr Ibrahim: A 52-Year-Old Woman with mTNBC

- 2019: A 52-year-old woman is diagnosed with Stage II T2N0 TNBC in right breast
  - Genetic testing reveals a germline BRCA mutation
- Bilateral mastectomy → Adjuvant TC
  - Prophylactic hysterectomy
  - No evidence of disease
- July 2020: presents with abdominal discomfort and nausea
- Imaging reveals peritoneal implants; biopsy confirms TNBC
- PD-L1 test results pending

Sulfi Ibrahim, MD

Case Presentation — Dr DeFusco: A 63-Year-Old Woman with mTNBC

- A 63-year-old woman with originally diagnosed ER-positive BC experiences metastatic disease recurrence that is triple-negative
- Previously treated with several lines of chemotherapy, including paclitaxel and capecitabine
- Olaparib initiated
  - Disease progression observed after nearly 1 year of therapy
- Presents for routine office visit with a hematocrit of 17

Patricia A DeFusco, MD

In what line of therapy would you most likely use a PARP inhibitor for a 60-year-old patient with a BRCA germline mutation and de novo metastatic triple-negative breast cancer that is PD-L1-negative?

For a patient with metastatic breast cancer for whom you've made the determination to administer a PARP inhibitor, do you have a preference as to which one?

	Line of therapy	Preference of PARP inhibitor
 LISA A CAREY, MD	First line	No
 VIRGINIA KAKLAMANI, MD, DSC	First line	No
 IAN E KROP, MD, PHD	First line	Yes, olaparib
 JOYCE O'SHAUGHNESSY, MD	First line	Yes, olaparib
 HOPE S RUGO, MD	First line	No
 SARA M TOLANEY, MD, MPH	First line	No

Regulatory and reimbursement issues aside, have you or would you attempt to access a PARP inhibitor for a patient with metastatic triple-negative breast cancer and a …

	Somatic BRCA mutation	Germline PALB2 mutation
 LISA A CAREY, MD	I have	I have not, but I would for the right patient
 VIRGINIA KAKLAMANI, MD, DSC	I have not, but I would for the right patient	I have not, but I would for the right patient
 IAN E KROP, MD, PHD	I have	I have not, but I would for the right patient
 JOYCE O'SHAUGHNESSY, MD	I have	I have
 HOPE S RUGO, MD	I have	I have not, but I would for the right patient
 SARA M TOLANEY, MD, MPH	I have	I have not, but I would for the right patient

What has been your clinical experience with the diarrhea and neutropenia associated sacituzumab govitecan in the treatment of metastatic triple-negative breast cancer?

 LISA A CAREY, MD	Both manageable with medications and modifications
 VIRGINIA KAKLAMANI, MD, DSC	Both manageable with medications
 IAN E KROP, MD, PHD	Both manageable, with frequent use of growth factors
 JOYCE O'SHAUGHNESSY, MD	Both manageable with dose reduction
 HOPE S RUGO, MD	Easy to manage
 SARA M TOLANEY, MD, MPH	Both manageable with medications

Current Management of Triple-Negative Breast Cancer

Module 2: PARP Inhibition and Other Novel Agents/Strategies — Dr O'Shaughnessy

- Key Recent Data Sets
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- Cases/Questions from General Medical Oncologists
  - A 52-year-old with gBRCA mutation-positive TNBC and peritoneal metastases
  - A 63-year-old woman with mTNBC and anemia
- Faculty Cases
  - A 31-year-old woman with mTNBC and a gRAD51D mutation
  - A 42-year-old woman with mTNBC and a gBRCA1 mutation

Case – Dr O'Shaughnessy: A 31-year-old woman with mTNBC and a g*RAD51D* mutation

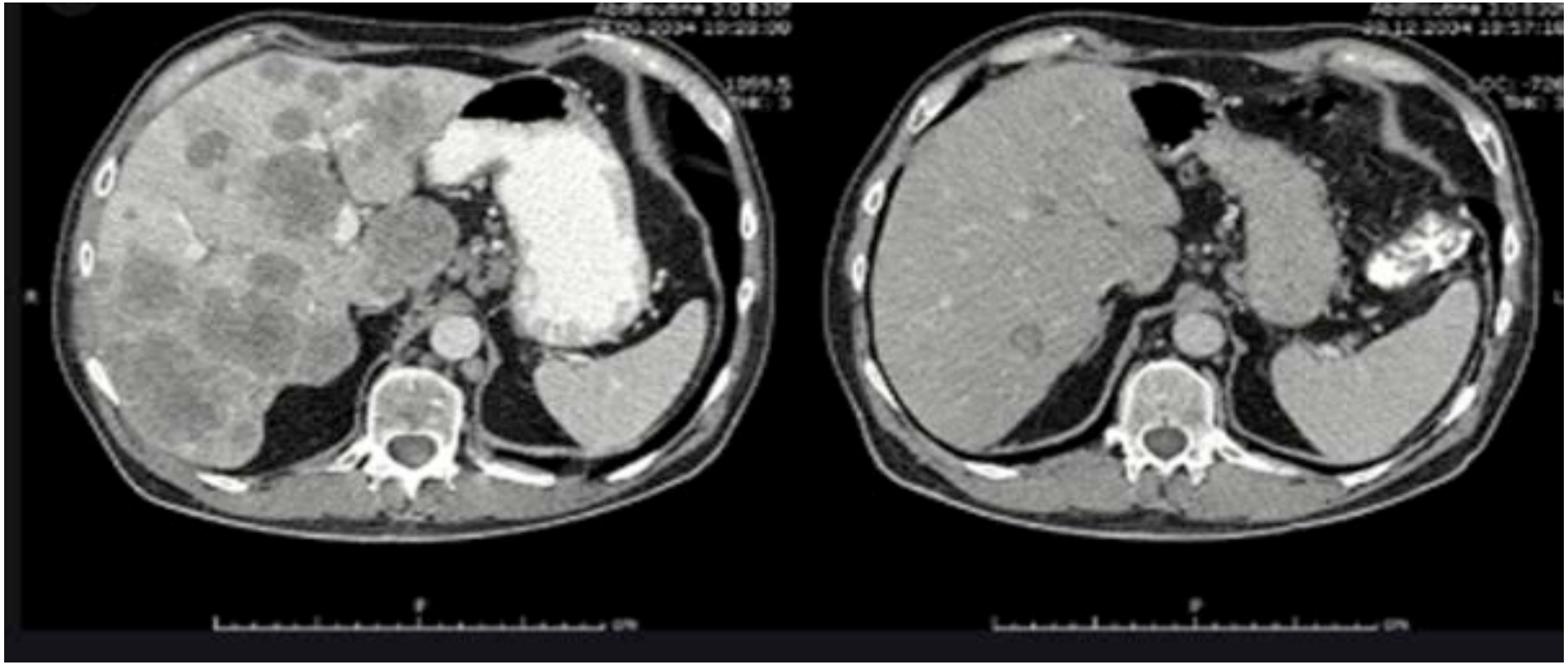
- 31 yo woman whose mother had breast cancer at 40 presented with locally advanced inflammatory TNBC and had a near pathologic complete response with preoperative dose dense AC/paclitaxel and then received post-mastectomy radiation therapy
- 1 year later she developed inflammatory breast cancer recurrence on her chest wall, biopsy-positive for TNBC, and had a complete response with gemcitabine/carboplatin therapy which was stopped, and her chest wall disease never recurred
- Her disease progressed 6 months later in her lungs and she received paclitaxel/carboplatin therapy and had a durable partial response for 12 mos

Case – Dr O'Shaughnessy: A 31-year-old woman with mTNBC and a g*RAD51D* mutation (cont)

- Her disease then progressed in her lungs and liver and she was treated with eribulin and had a partial response for 4 mos followed by progression in her liver
- She developed mild headaches and brain MRI showed 3 metastases up to 2 cm in size and she underwent SRS
- She was then treated on a phase II trial of sacituzumab as 4th-line therapy and had a near complete response in her liver and lung metastases for 18 mos. She had neutropenia that led to dose delay after 3 cycles of therapy and had a dose reduction to 7.5 mg/kg. With the dose reduction she had no significant toxicities and continued teaching school and caring for her family

Case – Dr O'Shaughnessy: A 31-year-old woman with mTNBC and a g*RAD51D* mutation (cont)

Before Sacituzumab After 8 cycles of Sacituzumab



Case – Dr O'Shaughnessy: A 43-year-old woman with mTNBC and a *gBRCA1* mutation

- 36 yo teacher and mother of 3 presented while pregnant with 4th child in 2013 with left cT3N3M0 TNBC
- Age 21 had APML treated with idarubicin, Ara-C and ATRA
- Germline testing revealed a *gBRCA1* mutation
- She was treated with preoperative cisplatin and then bilateral mastectomy which showed minimal RD in breast and 10+ LNs. She received 6 cycles adjuvant TC then PMRT, followed by BSO
- In 2015 her disease recurred in left IM LN and A-P window node. Biopsy showed TNBC. She responded to gemcitabine + carboplatin and then developed progressive disease in left SC and mediastinal LNs

Case – Dr O'Shaughnessy: A 43-year-old woman with mTNBC and a *gBRCA1* mutation (cont)

- She underwent radiation to the SC and mediastinal LNs followed by capecitabine
- In April, 2017 her disease recurred in thoracic, retroperitoneal, inguinal LNs, left anterior rib, and focally around breast implant. Brain MRI showed 11 mm mass cerebellum with edema. Biopsy of inguinal LN showed TNBC, Ki-67 40-50%, PD-L1 negative in tumor and IC with 22C3.
- She underwent SRS to brain metastasis and then was treated on clinical trial of PI3K/TORC1/2 inhibitor PIKTOR (to increase "BRCAness"). After 4 months on PIKTOR she developed progressive disease with multiple, new, small lung metastases, followed by 6 cycles of nab paclitaxel + cisplatin per protocol

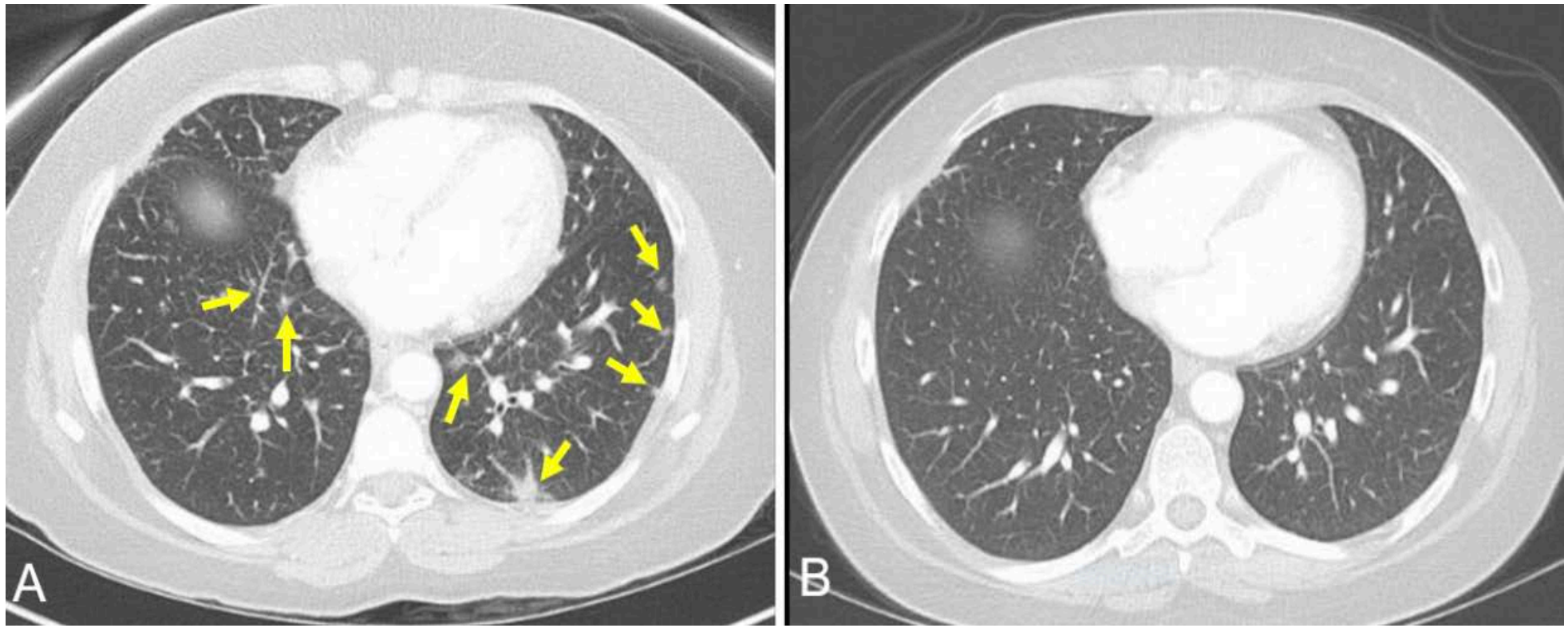
Case – Dr O'Shaughnessy: A 43-year-old woman with mTNBC and a *gBRCA1* mutation (cont)

- Restaging CT scans December 2017 showed complete regression of pulmonary mets and LNs above and below diaphragm
- With nab paclitaxel + cisplatin she developed grade 2 sensory neuropathy in hands and feet and grade 2 fatigue
- She began treatment with single agent pembrolizumab every 3 weeks in April 2018
- Her chest CT scan showed stable small residual lung nodules over 8 mos
- She then developed a tender lower left anterior rib lesion that was lytic and expansile. Biopsy showed TNBC and repeat staging showed no recurrence of the lung, LN or brain metastases

Case – Dr O'Shaughnessy: A 43-year-old woman with mTNBC and a *gBRCA1* mutation (cont)

Following PD on PIKTOR

Post-Cisplatin/Nab Paclitaxel



Case – Dr O'Shaughnessy: A 43-year-old woman with mTNBC and a *gBRCA1* mutation (cont)

- She began treatment with olaparib 300 mg bid December 2018 and continued pembrolizumab
- She had mild nausea for 2 mos with olaparib which then abated, and mild fatigue. She was noted to have a rising TSH (no h/o hypothyroidism). She began thyroid replacement therapy
- After 3 months on olaparib plus pembrolizumab, chest CT scan showed regression of the expansile left rib lesion with sclerosis, no recurrence of lung or LN metastases. Brain MRIs remain negative
- She has now been on combined olaparib plus pembrolizumab for 15 mos, in addition to zoledronic acid, without disease progression, no serious irAEs and excellent PS

Meet The Professors

Clinical Investigators Discuss Existing and Emerging Treatment Strategies for Patients with Ovarian, Cervical and Endometrial Cancer

Tuesday, July 21, 2020

12:00 PM – 1:00 PM ET

Faculty

Joyce F Liu, MD, MPH

David M O'Malley, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

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