Oncology Grand Rounds
Breast Cancer
Nurse and Physician Investigators Discuss New Agents, Novel Therapies and Actual Cases from Practice

Thursday, May 4, 2017
12:15 PM – 1:45 PM

Faculty

Emily Olson, APRN, CNP, MSN
Elizabeth O'Reilly, RN, NP, MSN, MPH
Joyce O'Shaughnessy, MD
Denise A Yardley, MD

Moderator

Neil Love, MD

Research To Practice®

Oncology Grand Rounds Series

Wednesday	**Non-Small Cell Lung Cancer** 6:00 PM – 8:00 PM
Thursday	**Cancer Immunotherapy** 6:00 AM – 7:30 AM
	Breast Cancer 12:15 PM – 1:45 PM
	Lymphomas and CLL 6:00 PM – 8:00 PM
Friday	**Myeloproliferative Neoplasms** 6:00 AM – 7:30 AM
	Ovarian Cancer 12:15 PM – 1:45 PM
	Gastrointestinal Cancers 6:00 PM – 8:00 PM

Oncology Grand Rounds: Themes

Identifying and understanding oncology clinical scenarios

- Key determining factors; natural history and treatment
- Evaluating and managing clinical symptoms
- Patient and caregiver education

Integrating new agents and treatment strategies into practice

- Benefits and risks
- Prevention, identification and management of side effects/toxicity
- Identifying patients at high risk for toxicity

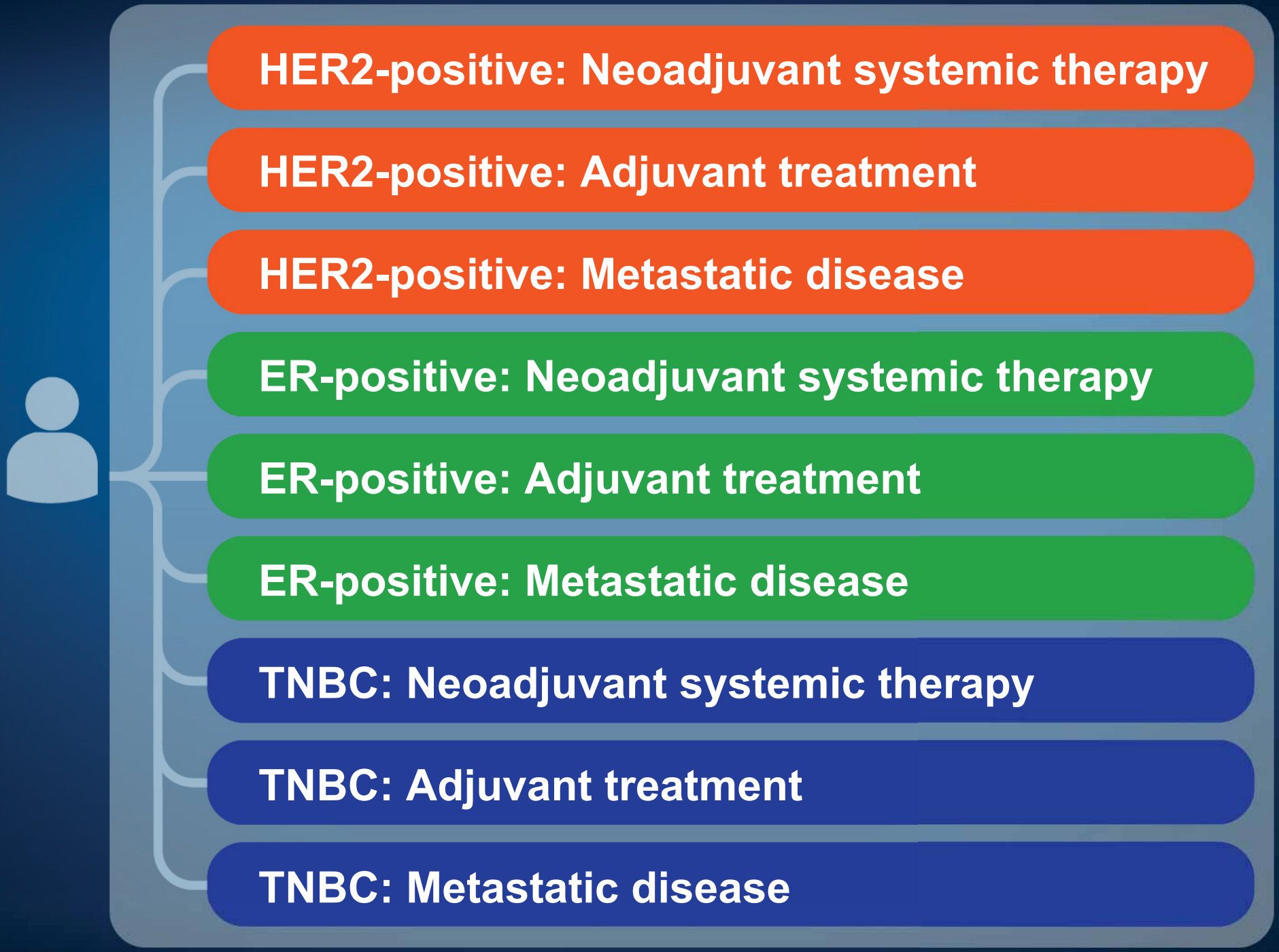
Psychosocial issues in clinical oncology

- Caring for family and loved ones, including minor children and grandchildren
- Job satisfaction and disappointment
- The bond that heals

Novel Agents Approved by the FDA in the Past 9 Weeks

Agent	Approval Date	FDA-Approved Use on Approval Date
Telotristat ethyl (tryptophan hydroxylase inhibitor)	February 28th	In combination with somatostatin analogue (SSA) therapy for the treatment of adults with carcinoid syndrome diarrhea inadequately controlled by SSA therapy alone
Ribociclib (CDK4/6 inhibitor)	March 13th	In combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer
Avelumab (anti-PD-L1 antibody)	March 23rd	For the treatment of patients (≥12 years) with metastatic Merkel cell carcinoma, including those who have not received prior chemotherapy
Niraparib (PARP inhibitor)	March 27th	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer whose tumors have completely or partially shrunk in response to platinum-based chemotherapy
Brigatinib (ALK inhibitor)	April 28th	For the treatment of patients with ALK-positive metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib
Midostaurin (FLT3 inhibitor)	April 28th	For the treatment of adults with newly diagnosed FLT3-positive acute myeloid leukemia in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
Durvalumab (anti-PD-L1 antibody)	May 1st	For the treatment of patients with PD-L1-positive inoperable or metastatic urothelial bladder cancer that has progressed during or after one standard platinum-based regimen

https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm537040.htm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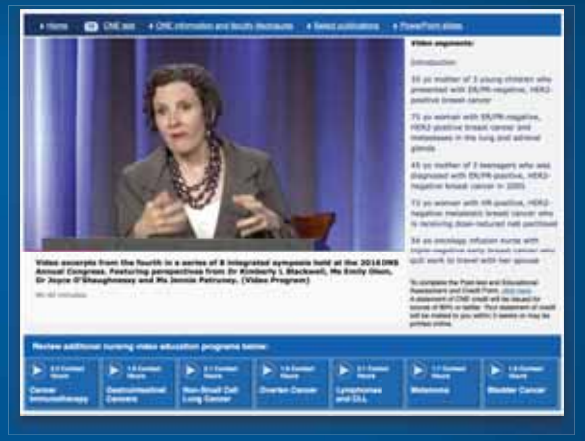
About the Enduring Program

- The proceedings from this 7-part CNE series will be video recorded and used in a virtual meeting archive including a downloadable version of the slides.



- An email will be sent to all attendees when the web activity is available.
- To learn more about our education programs visit our website, www.ResearchToPractice.com

Download the RTPLive app on your smartphone or tablet to access program information, including slides being presented during the program:

www.ResearchToPractice.com/RTPLiveApp

Make the Meeting Even More Relevant to You

Submit a challenging case or question for discussion during the program.

Email to **DrNeilLove@ResearchToPractice.com**

Text to **(786) 759-1458**

(Your phone number will remain confidential and will not be disclosed.)

If you are unable to text or email, please complete a question/comment card located on your conference table and drop it in one of the designated bins located throughout the meeting room.

Make the Meeting Even More Relevant to You

Join the conversation by sharing photos and videos using the hashtag #RTPLive

Facebook **@researchtopractice**

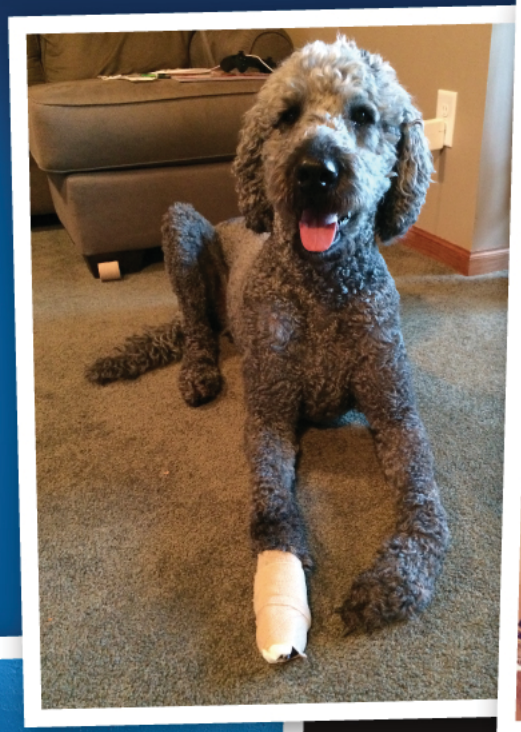
Twitter **@DrNeilLove**

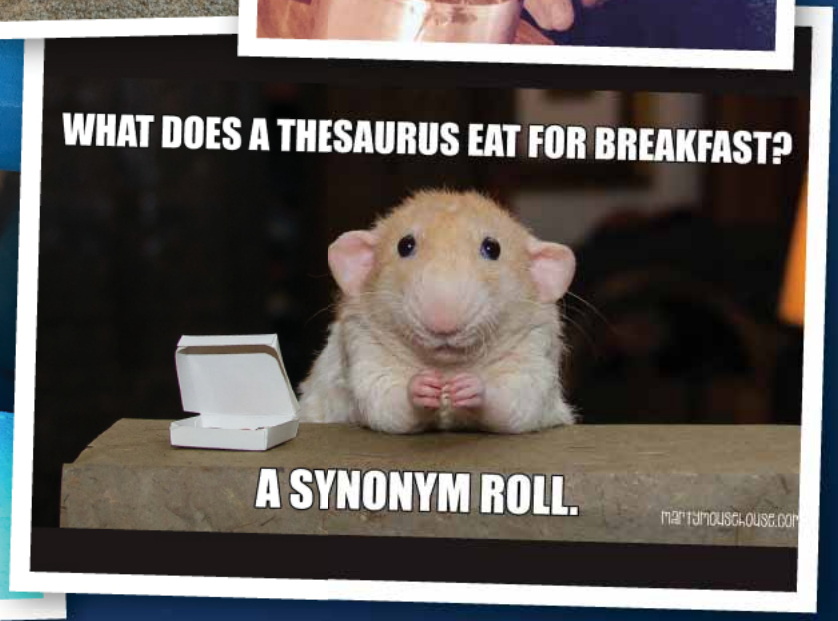
Instagram **@researchtopractice**

And get here early to participate in a brief video interview, where you can tell us about your experiences with oncology nursing. You may even see your post on the big screen during the events!

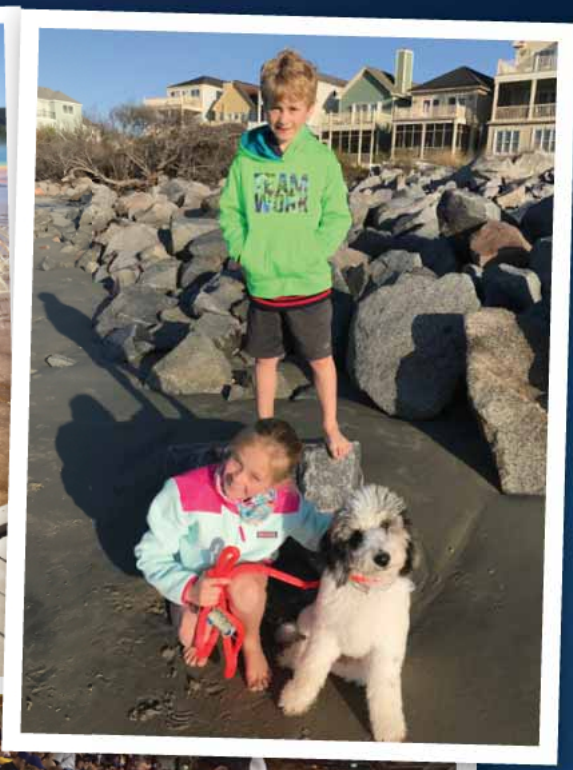
Elizabeth A O'Reilly, RN, NP, MSN, MPH
Dana-Farber Cancer Institute
Boston, Massachusetts

Emily Olson, APRN, CNP, MSN
Mayo Clinic
Rochester, Minnesota

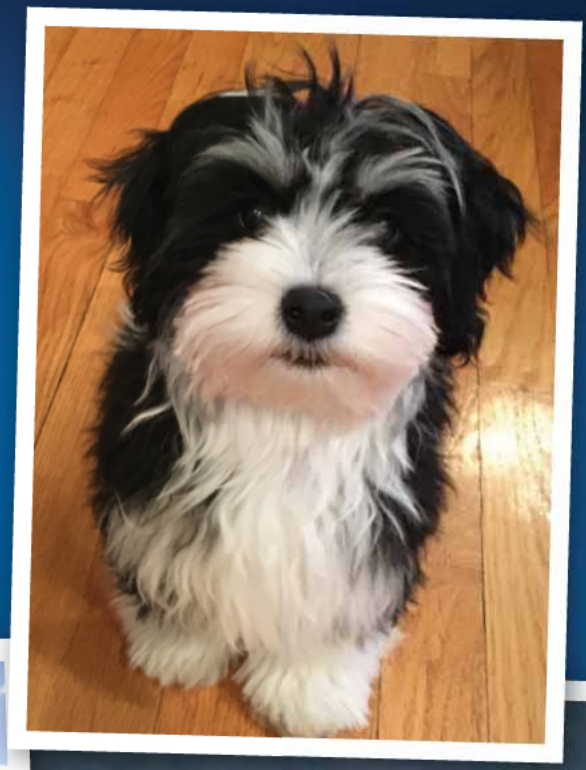




Denise A Yardley, MD
Sarah Cannon Research Institute
Nashville, Tennessee



Joyce O'Shaughnessy, MD
Texas Oncology-Baylor Charles A
Sammons Cancer Center
Dallas, Texas



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Module 1:
Overview of Breast Cancer

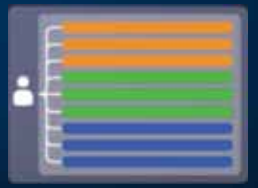
Overview of Breast Cancer

- Estimated number of new cases and deaths in 2017:
  - New cases = 255,180
  - Deaths = 41,070
- Stage at diagnosis:
  - Localized disease = 60%
  - Regional disease = 33%
  - Metastatic disease = 5%
  - Unstaged disease = 2%
- Five-year survival estimates (2006-2012) = 91%

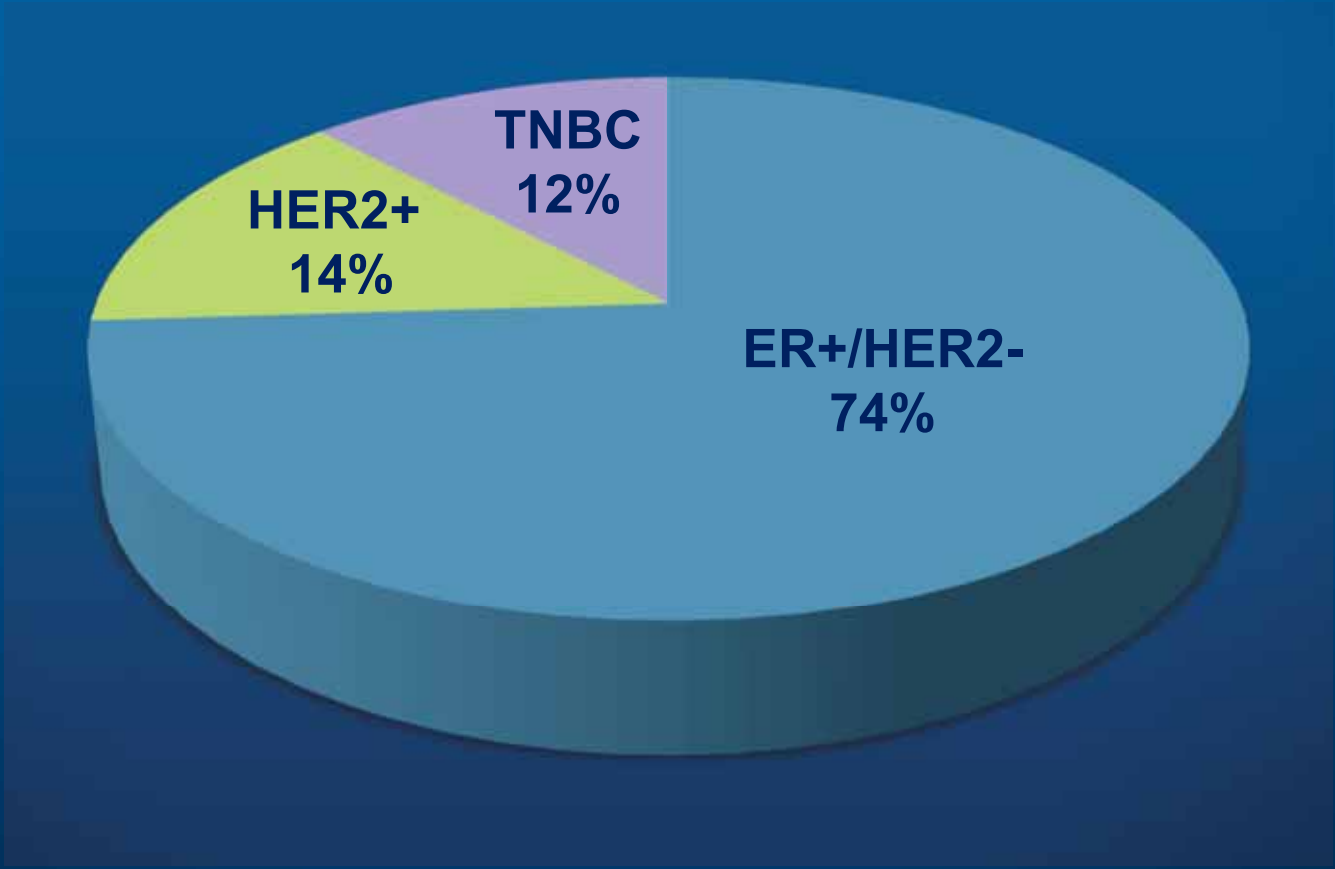
Cancer Facts and Figures 2017; American Cancer Society Surveillance Research 2011; SEER Stat Fact Sheet.

Critical Scenario/Pathway Factors

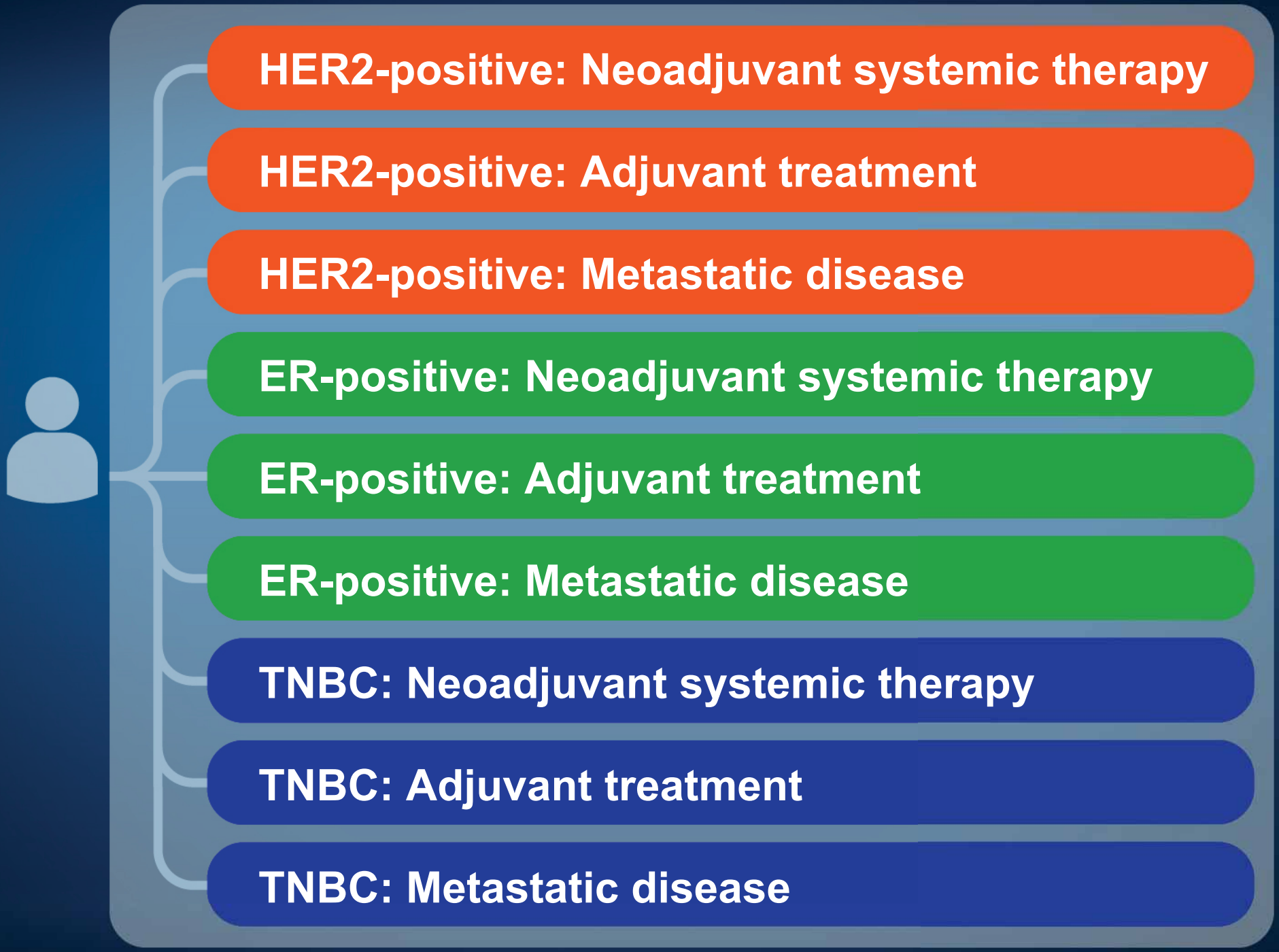
- Disease stage:
  - Localized (neoadjuvant/adjuvant)
  - Locally advanced
  - Metastatic
- ER/PR and HER2 status
- Disease symptomatology, patient performance status



Distribution of Breast Cancer Subtypes



DeSantis CE et al. *CA Cancer J Clin* 2016;66(1):31-42.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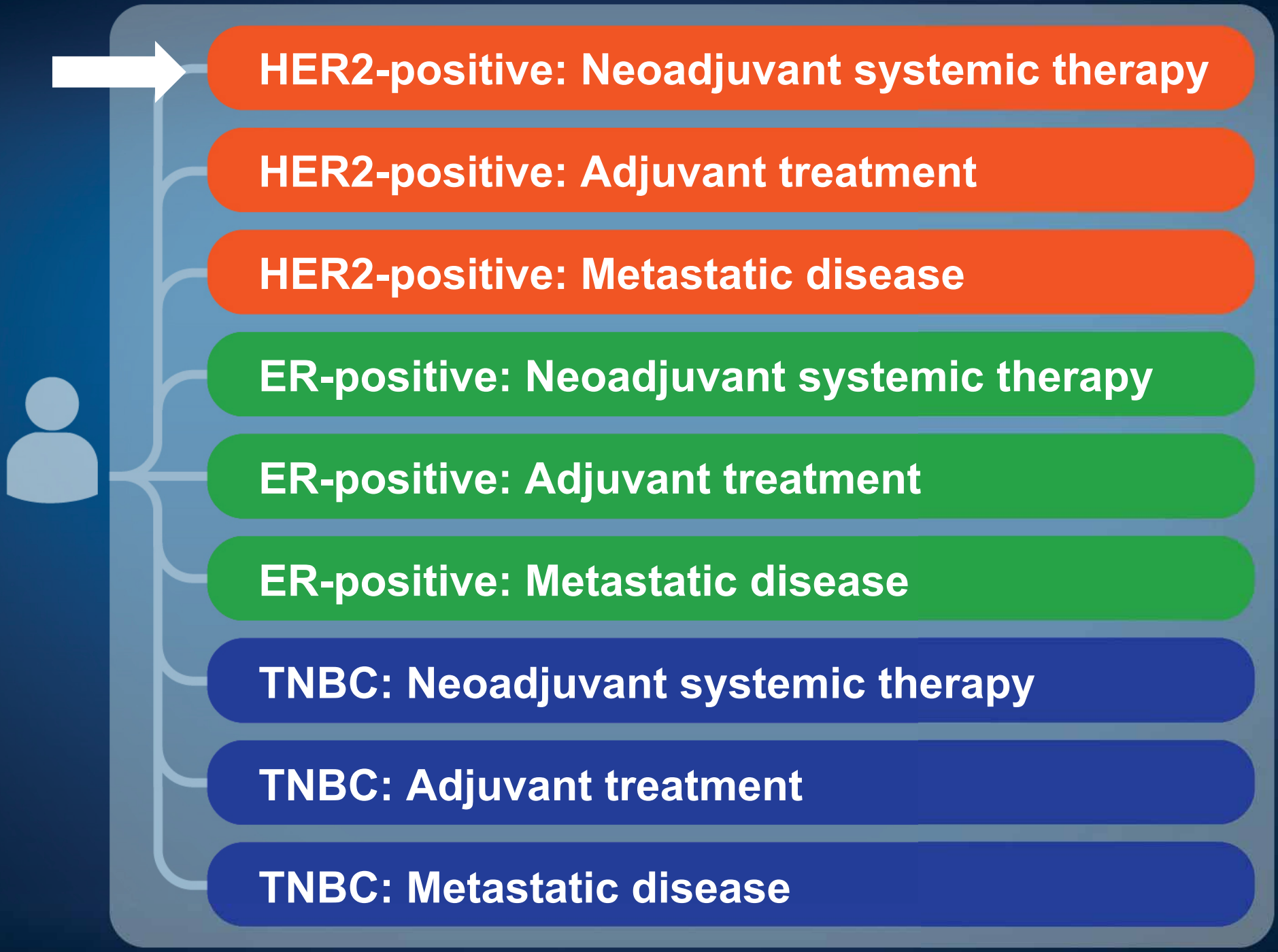
Module 2:
HER2-Positive Breast Cancer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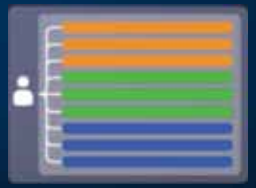
Key Considerations in Neoadjuvant Systemic Therapy (NST) for HER2-Positive Breast Cancer

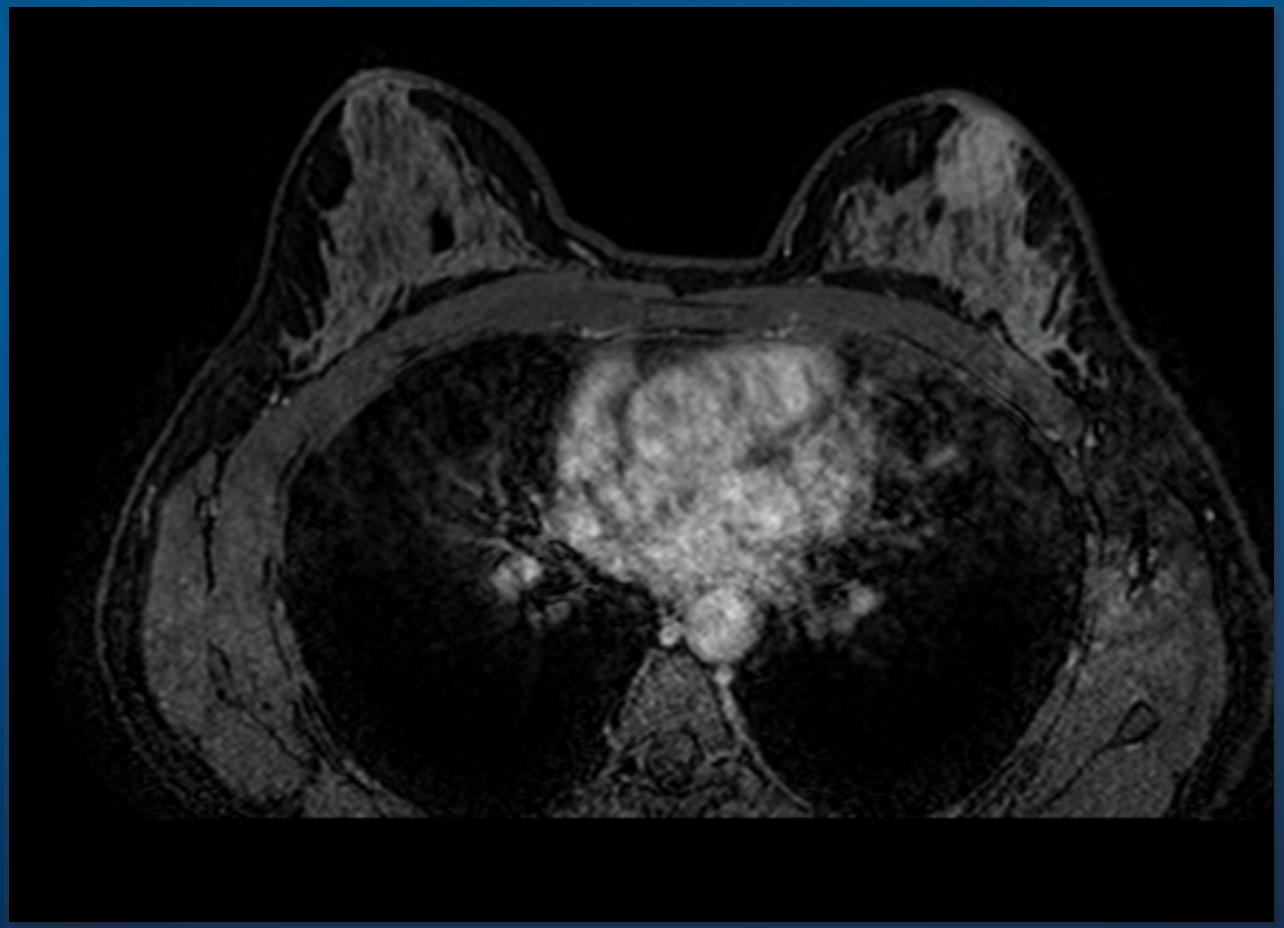
- Impact of NST on type of surgical approach for breast and axilla
- Use of NST in patients who are borderline candidates for breast-conserving surgery based on tumor-to-breast size ratio
- NST as a research tool to identify new therapies
- Ensure early access to pertuzumab



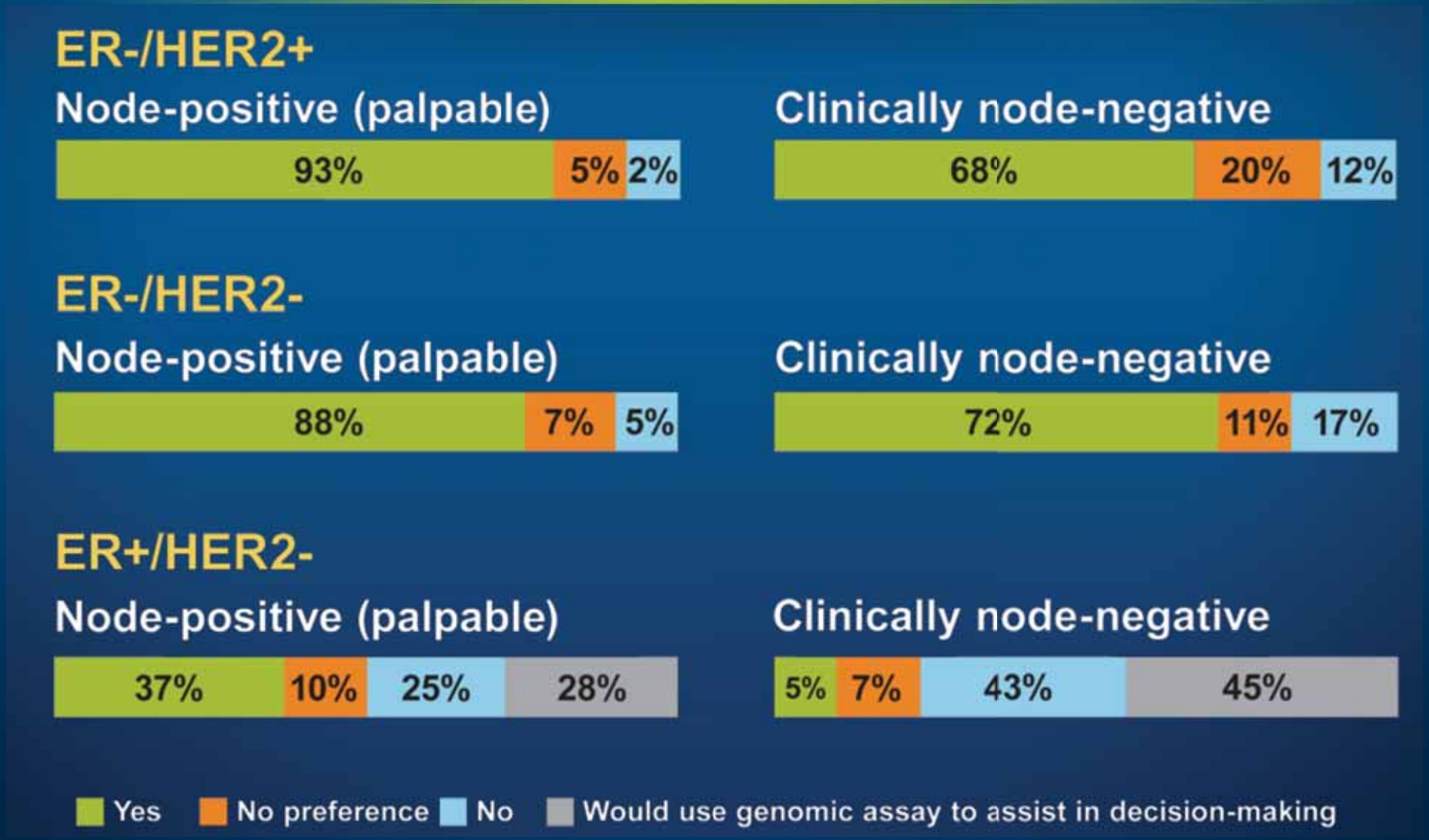
44-Year-Old Woman with ER-Positive, HER2-Positive Breast Cancer (Ms O'Reilly)

- January 2017: Neoadjuvant TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab)
  - Excellent clinical response
  - Grade 2 diarrhea, nonpruritic acneiform rash, severe fatigue
- Single woman, working full time
- Transition to being a patient and requesting support from friends and family

44-Year-Old Woman with ER-Positive, HER2-Positive Breast Cancer (Ms O'Reilly)



Would You Recommend Neoadjuvant Chemotherapy? (2.1- to 3.0-cm tumor)



Love N et al. SABCS 2015;Abstract P1-14-20.

Commonly Used Adjuvant and Neoadjuvant Regimens for HER2-Positive Breast Cancer

Preferred Regimens

- AC → taxane/trastuzumab ± pertuzumab
- TCH ± pertuzumab

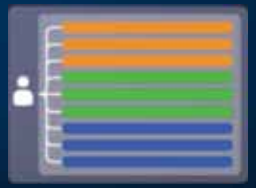
Other Regimens

- Docetaxel/cyclophosphamide + trastuzumab
- AC → docetaxel/trastuzumab ± pertuzumab
- Paclitaxel + trastuzumab
- FEC → taxane + trastuzumab/pertuzumab
- Trastuzumab/pertuzumab/taxane → FEC

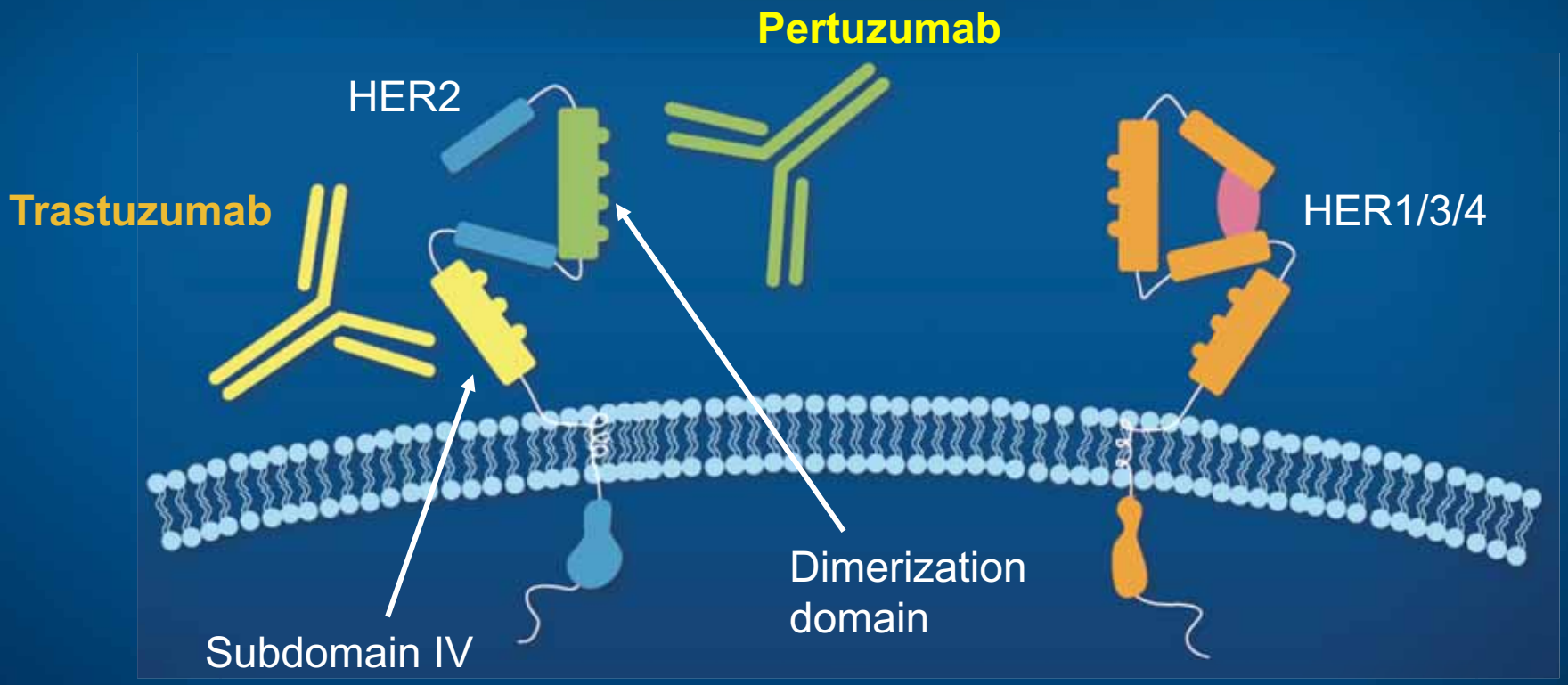
NCCN Guidelines Breast Cancer v2.2017

Available Anti-HER2 Agents

Agent	Mechanism of action
Trastuzumab	HER2-targeted antibody
Pertuzumab	Antibody that prevents HER2 dimerization and signaling
Lapatinib	Tyrosine kinase inhibitor
T-DM1	Antibody-drug conjugate



Pertuzumab and Trastuzumab: Mechanisms of Action



Trastuzumab:

- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

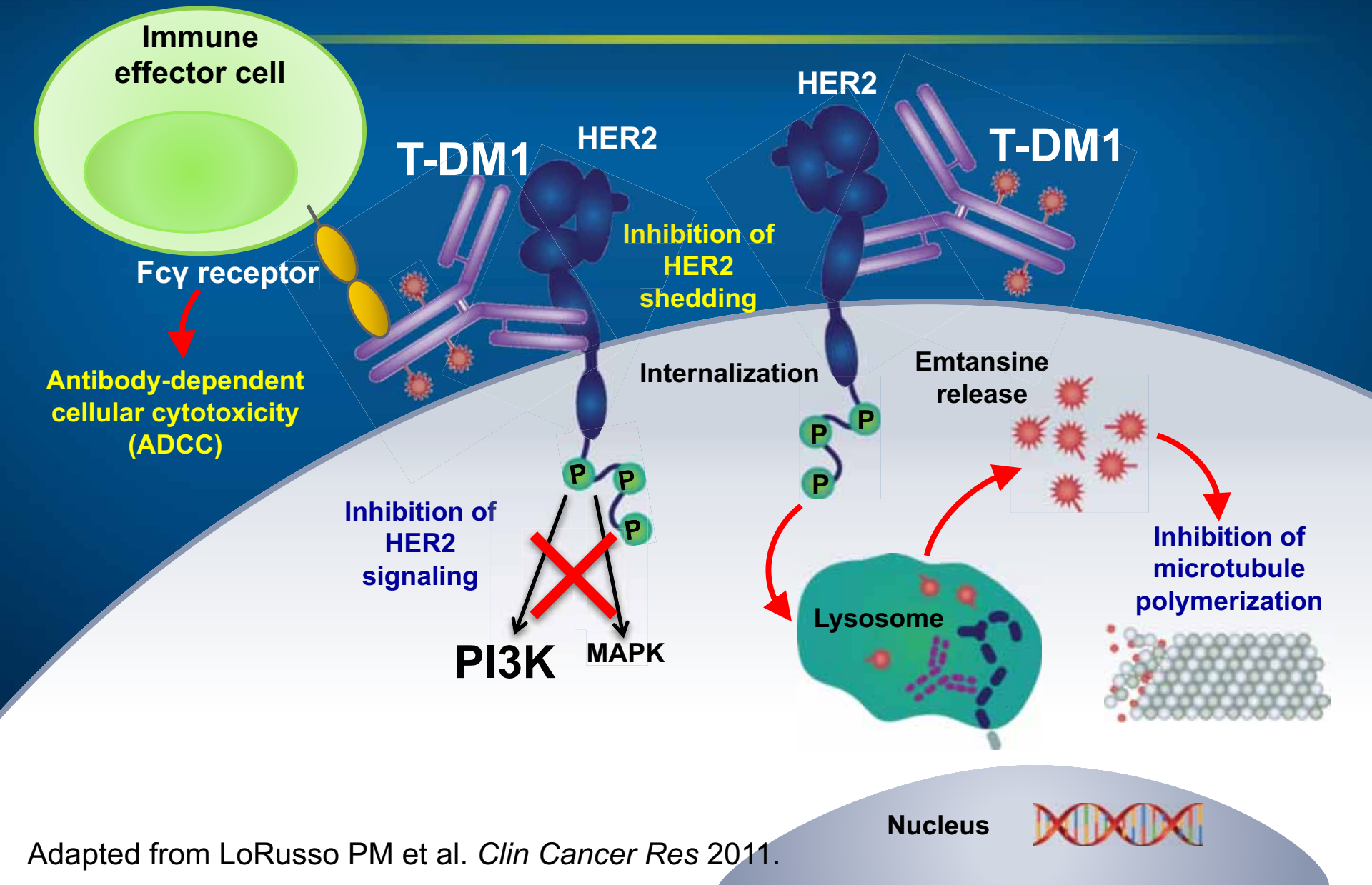
Pertuzumab:

- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

ADCC = antibody-dependent cell-mediated cytotoxicity; ECD = extracellular domain

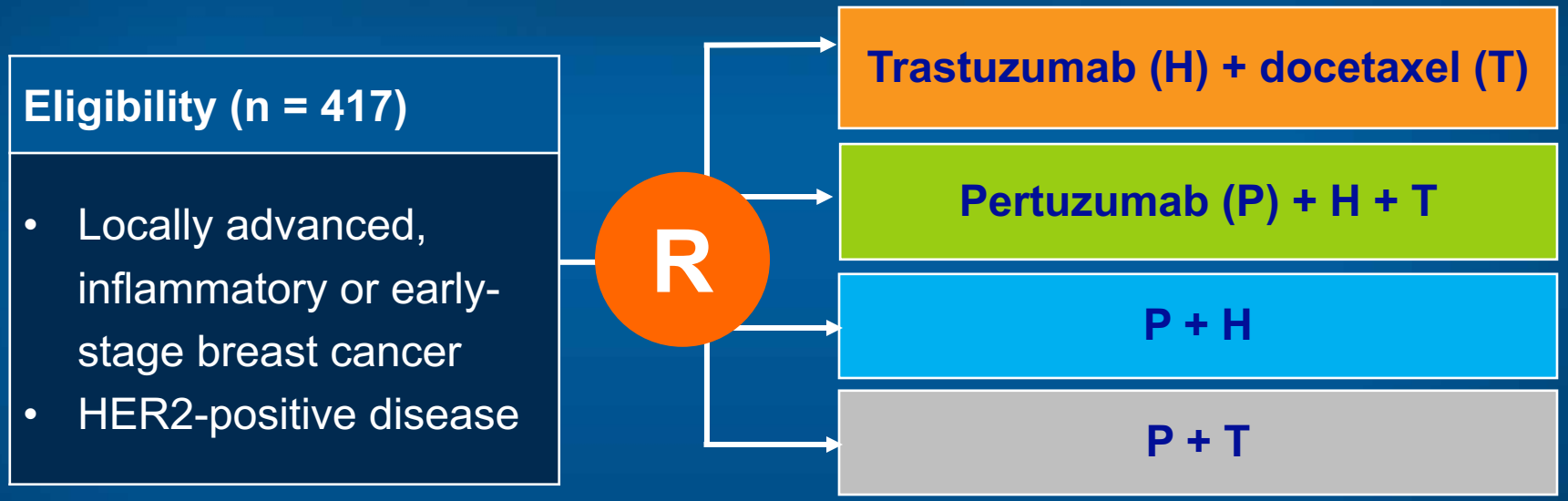
Harbeck N et al. *Breast Care (Basel)* 2013;8(1):49-55.

Trastuzumab Emtansine (T-DM1): Mechanisms of Action



Adapted from LoRusso PM et al. *Clin Cancer Res* 2011.

NEOSPHERE: Analysis of Neoadjuvant Pertuzumab and Trastuzumab



Outcome	H + T (n = 107)	P + H + T (n = 107)	P + H (n = 107)	P + T (n = 96)
pCR	29.0%	45.8%	16.8%	24.0%
5-year PFS	81%	86%	73%	73%
5-year DFS	81%	84%	80%	75%

Gianni L et al. *Lancet Oncol* 2016;17(6):791-800; *Lancet Oncol* 2012;13(1):25-32.

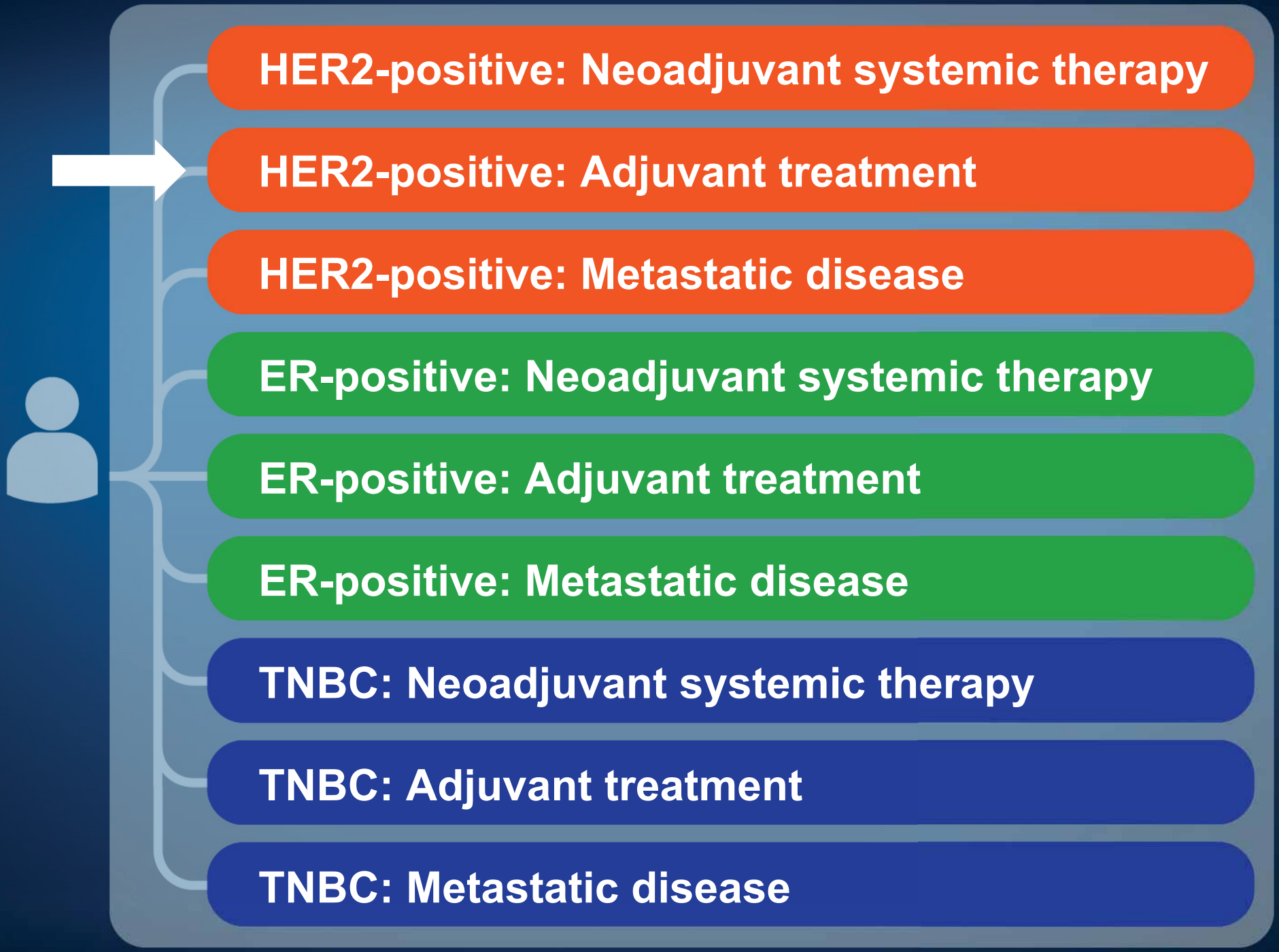
NCCN Clinical Practice Guidelines — Breast Cancer v2.2017

Sept 30, 2013: FDA granted accelerated approval to pertuzumab for use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory or early-stage breast cancer as part of a complete treatment regimen for early breast cancer.

"A pertuzumab-containing regimen may be administered preoperatively to patients with ≥T2 or ≥N1, HER2-positive early-stage breast cancer."

"Patients who have not received a pertuzumab-containing regimen can receive adjuvant pertuzumab."

NCCN Guidelines Breast Cancer v2.2017; www.fda.gov.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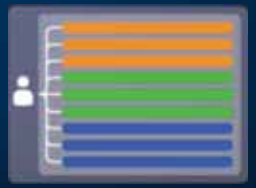
Key Considerations in Adjuvant Therapy for HER2-Positive Breast Cancer

- Selection of patients: Risk criteria for treatment
- Response to neoadjuvant therapy and presence of residual disease
- Anthracyclines or not
- Current and future use of adjuvant pertuzumab
- Duration and potential role of extended adjuvant therapy

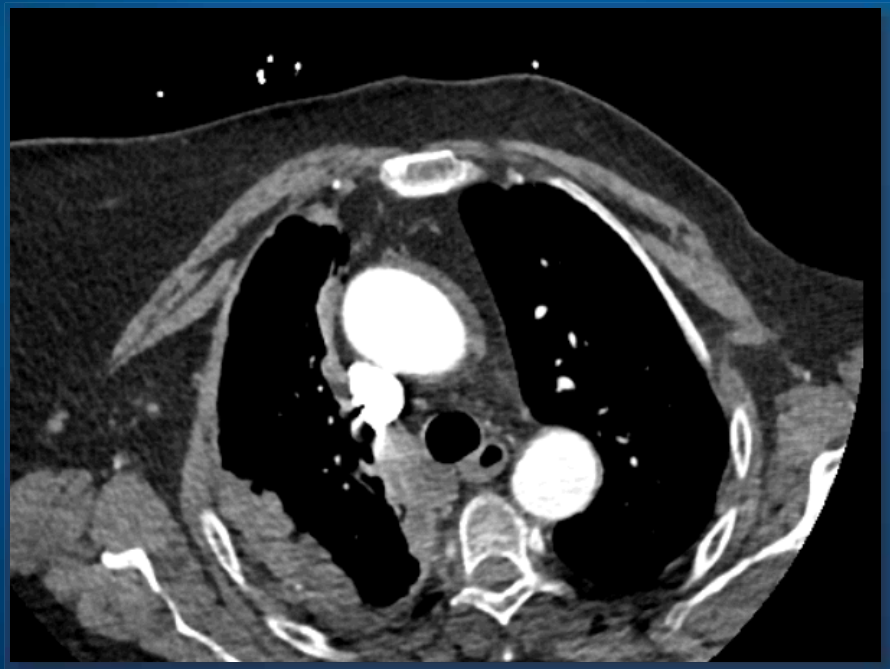


61-Year-Old Saudi Arabian Woman with ER-Positive, HER2-Positive Metastatic Breast Cancer (Ms Olson)

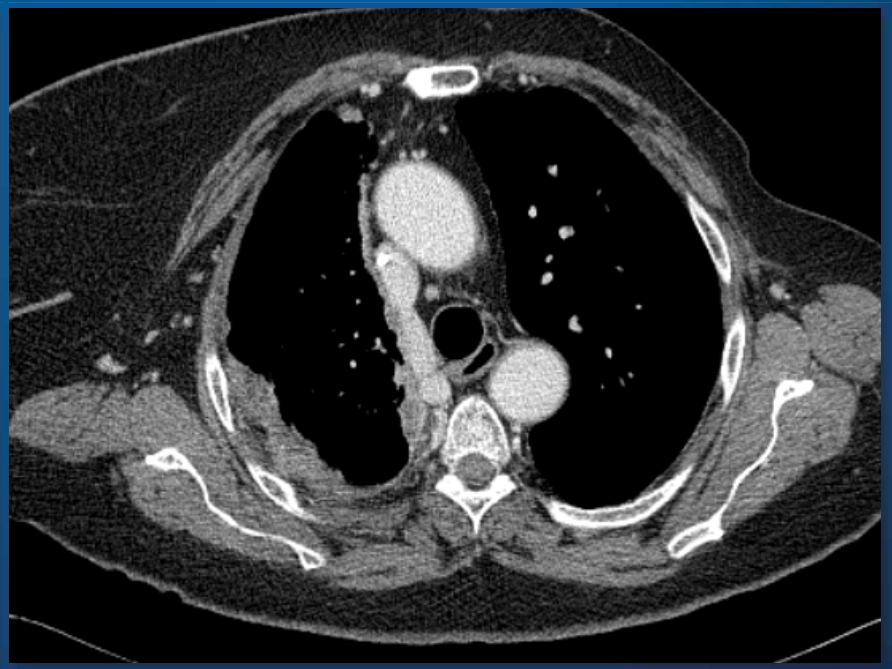
- 2008: T3N2 ER-positive, HER2-positive BC
  - Mastectomy
  - Adjuvant AC/docetaxel (taxane pneumonitis) + trastuzumab (T)
  - RT, tamoxifen
- 2013: Extended adjuvant letrozole
- 2014: Rising tumor markers, PET/CT: lung mass not biopsy confirmed
  - 2014-2016: Capecitabine/lapatinib; vinorelbine/TP; fulvestrant/TP
- Sep 2016: Increase in SOB, progression in lungs, new pleural effusion
  - T-DM1 initiated
- Nov 2016 restaging: Response and improvement in symptoms
- Dec 2016: Lost to follow-up due to embassy revocation of coverage

P = pertuzumab

61-Year-Old Saudi Arabian Woman with ER-Positive, HER2-Positive Metastatic Breast Cancer (Ms Olson)



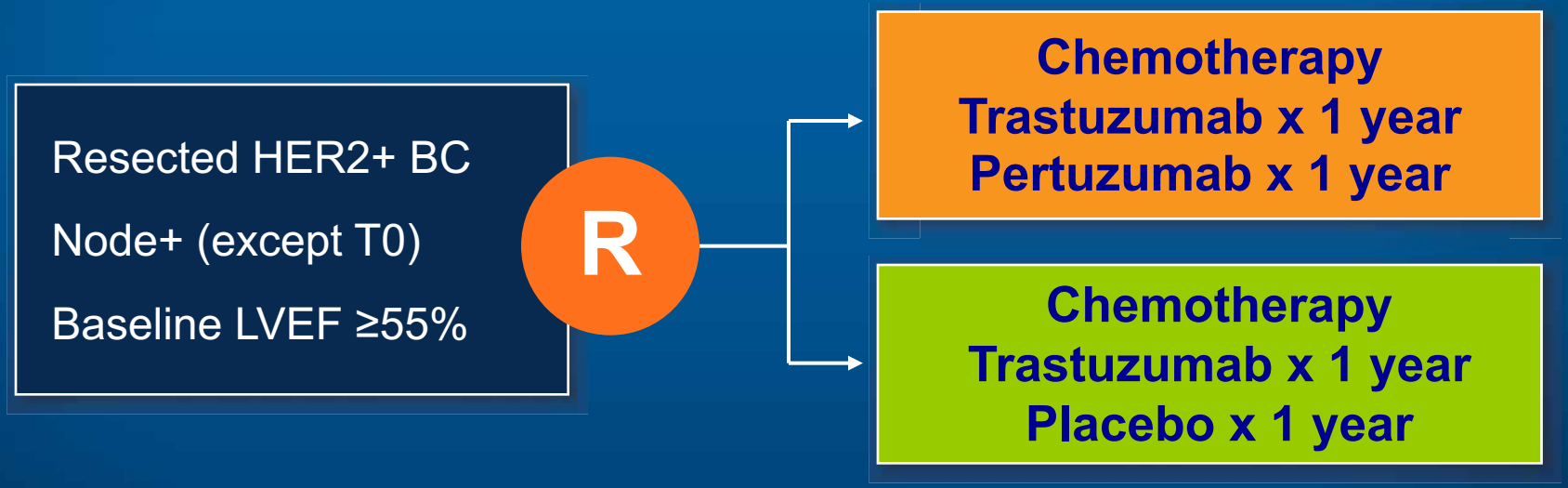
Before T-DM1: Pleural thickening and nodularity



After 3 cycles of T-DM1: Reduction in pleural nodularity

APHINITY: A Phase III Adjuvant Study

Target accrual: 4,805



Primary endpoint: Invasive disease-free survival

www.clinicaltrials.gov (NCT01358877); www.ibcsg.org

Phase III APHINITY Study Met Its Primary Endpoint

Press release March 1, 2017:

- Adjuvant treatment with the combination of pertuzumab, trastuzumab and chemotherapy achieved a statistically significant reduction in the risk of recurrence of invasive disease or death (invasive disease-free survival) in patients with HER2-positive early breast cancer compared to trastuzumab and chemotherapy alone.

- The safety profile of the pertuzumab regimen was consistent with that seen in previous studies, with no new safety signals identified.

Results from the APHINITY trial will be presented at ASCO 2017 on June 5th at 9:45 AM by Von Minckwitz G et al (Abstract LBA500).

https://www.gene.com/media/press-releases/14655/2017-03-01/phase-iii-aphinity-study-shows-genentech

ATEMPT: A Phase II Trial for Stage I HER2-Positive BC

Target Accrual: 500

Eligibility

- Stage I HER2-positive breast cancer
- No prior chemotherapy or trastuzumab

T-DM1 q3wk x 17

Paclitaxel + Trastuzumab Weekly x 12 → Trastuzumab q3wk x 13

Primary endpoint: Disease-free survival

www.clinicaltrials.gov (NCT01853748)

KATHERINE: A Phase III Adjuvant Study

Target accrual: 1,487

- HER2+ BC
- Completion of preop trastuzumab- and taxane-based treatment
- Residual invasive cancer

R

Trastuzumab

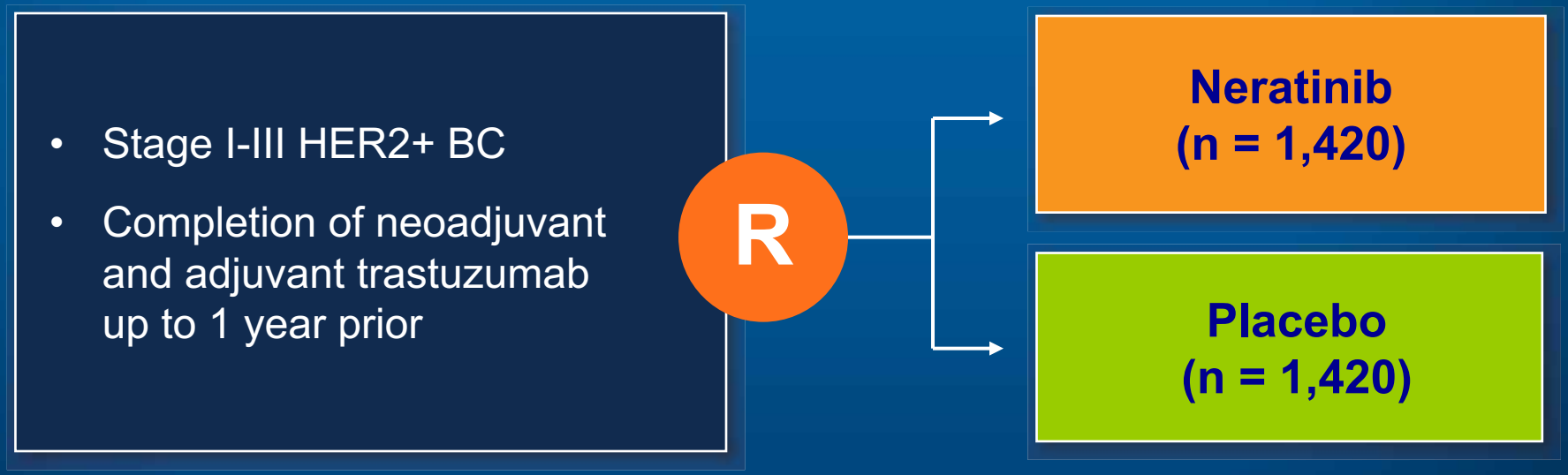
T-DM1

Radiation per standard guidance;
Hormone therapy if ER+ or PR+

Primary endpoint: Invasive disease-free survival

www.clinicaltrials.gov (NCT01772472)

ExteNET: A Phase III Study of Neratinib After Trastuzumab-Based Adjuvant Therapy



Primary endpoint: Invasive disease-free survival

Chan A et al. *Lancet Oncol* 2016;17(3):367-77.

ExteNET: DFS at 2-Year Follow-Up (Intent to Treat)

	Neratinib (n = 1,420)	Placebo (n = 1,420)	Hazard ratio	*p*-value
DFS including DCIS	93.9%	91.0%	0.63	0.0017
Invasive DFS (IDFS)	93.9%	91.6%	0.67	0.0091
HR-positive	95.4%	91.2%	0.51	0.0013
HR-negative	92.0%	92.2%	0.93	0.74
Grade 3/4 AEs	**Neratinib (n = 1,408)**		**Placebo (n = 1,408)**	
Diarrhea	40%		2%	
Vomiting	3%		<1%	
Nausea	2%		<1%	

DFS = disease-free survival; DCIS = ductal carcinoma in situ; AE = adverse event

- Neratinib for 12 mo after trastuzumab significantly improved 2-y IDFS
- Grade 3 or 4 diarrhea was the most common adverse event, leading to dose reductions/discontinuation of neratinib in 26%/17% of patients

Chan A et al. *Lancet Oncol* 2016;17(3):367-77.

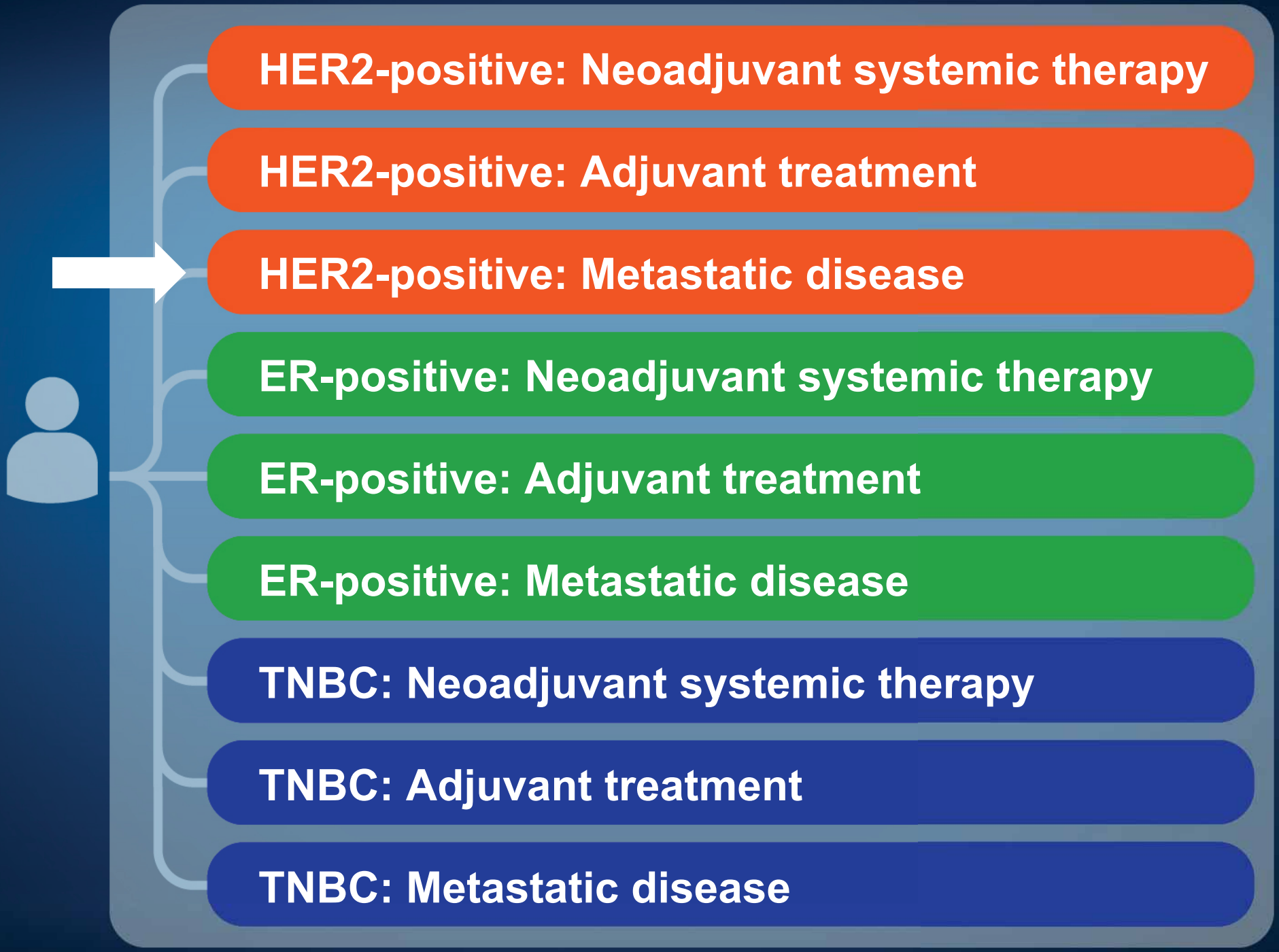
CONTROL: Loperamide Prophylaxis for Neratinib-Associated Diarrhea

- Patients with HER2-positive early BC treated with neratinib
- Loperamide prophylaxis either alone or with budesonide (corticosteroid)

Diarrhea	CONTROL		ExteNET (n = 1,408)
	Loperamide (n = 135)	Loperamide + budesonide (n = 40)	
Any grade	75.6%	65.0%	95.4%
Grade 3/4	28.1%	15.0%	39.9%

- Loperamide prophylaxis reduced the incidence, severity and duration of diarrhea compared to no prophylaxis on the ExteNET trial
- Adding budesonide may further diminish the duration and number of episodes of diarrhea

Barcenas C et al. SABCS 2016;Abstract P2-11-03; Chan A et al. *Lancet Oncol* 2016;17(3):367-77.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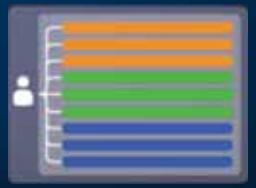
Key Considerations in Systemic Therapy for HER2-Positive Metastatic Breast Cancer

- Choice of therapy in patients who receive pertuzumab in the (neo)adjuvant setting (time since prior therapy)
- Sequencing of therapies
- “CLEOPATRA” regimens as first-line treatment
- CLEOPATRA versus T-DM1 in patients with early recurrence
- Nonchemotherapy regimens
- Integration of endocrine treatment for patients with “triple-positive” tumors
- Presence of CNS metastases



Pertuzumab for HER2-Positive Metastatic Breast Cancer

- Pertuzumab was approved in 2012 for use in combination with trastuzumab and docetaxel for patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease
- Approval was based on the pivotal CLEOPATRA study:
  - Trastuzumab/docetaxel with or without pertuzumab
    - Setting: First-line, HER2-positive metastatic breast cancer
    - Results: Significant survival advantage in favor of pertuzumab (median overall survival 56.5 mo vs 40.8 mo, $p < 0.001$)
  - Most common toxicity: Diarrhea

Baselga J et al. *N Engl J Med* 2012;366(2):109-19; Swain SM et al. *N Engl J Med* 2015;372(8):724-34.

CNS Metastases in HER2-Positive Breast Cancer

VOLUME 32 · NUMBER 19 · JULY 1 2014

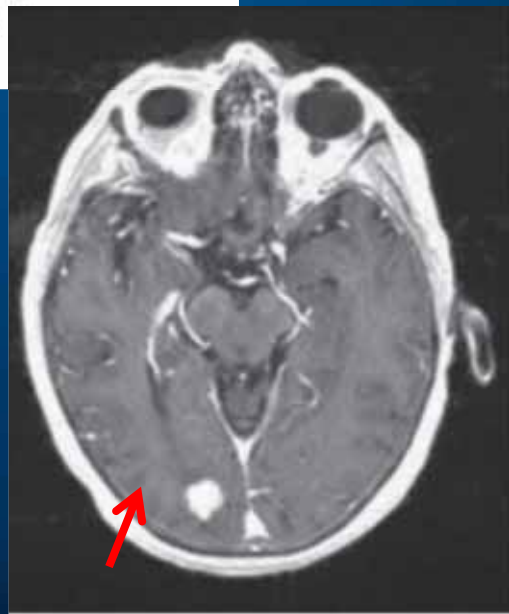
JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Recommendations on Disease Management for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases: American Society of Clinical Oncology Clinical Practice Guideline

Naren Ramakrishna, Sarah Temin, Sarat Chandarlapaty, Jennie R. Crews, Nancy E. Davidson, Francisco J. Esteva, Sharon H. Giordano, Ana M. Gonzalez-Angulo, Jeffrey J. Kirshner, Ian Krop, Jennifer Levinson, Shanu Modi, Debra A. Patt, Edith A. Perez, Jane Perlmutter, Eric P. Winer, and Nancy U. Lin

"Brain metastases are common in patients with advanced HER2-positive breast cancer, with up to half of patients (40%-50%) experiencing brain relapse before death."



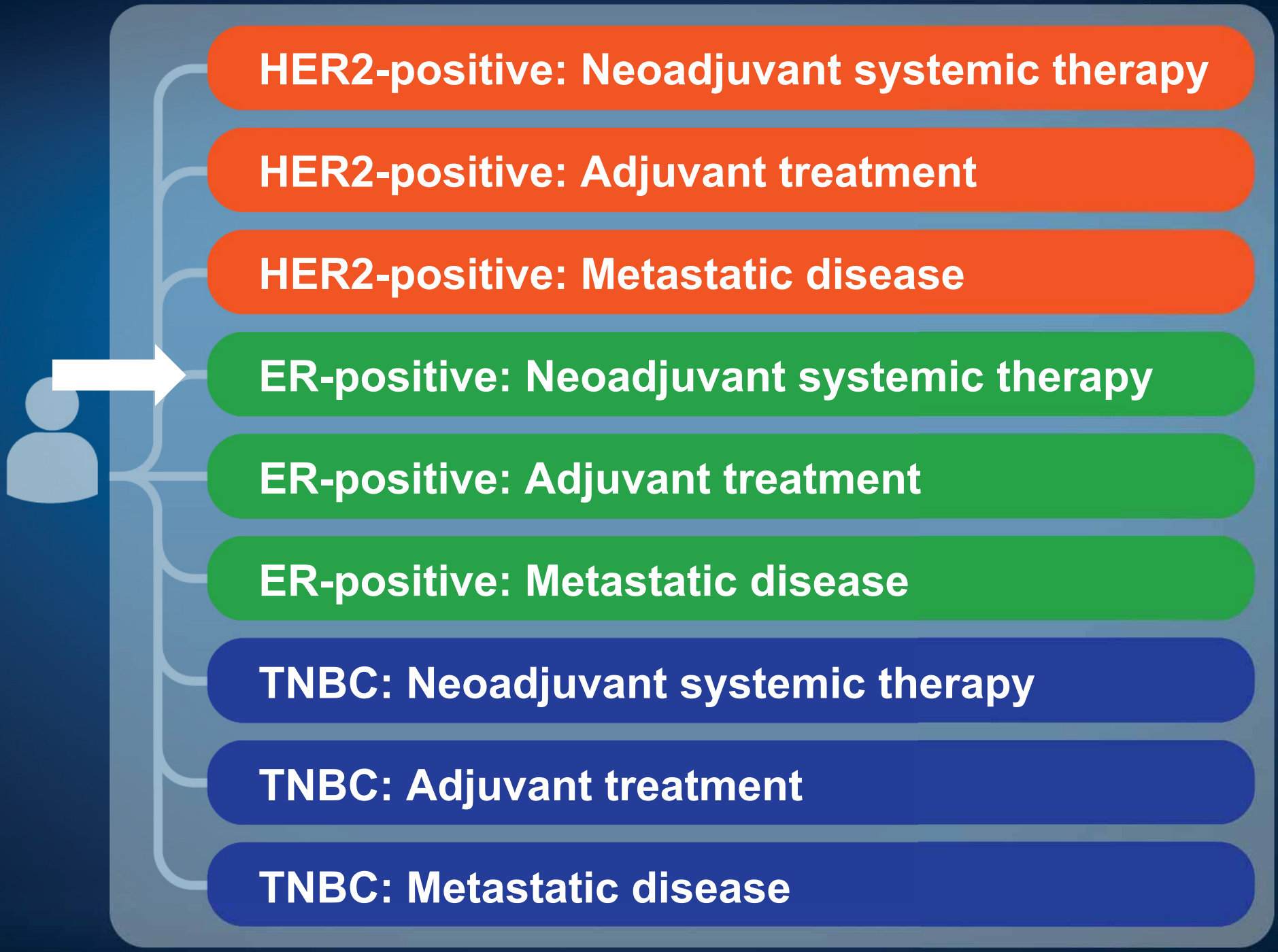
Ramakrishna N et al. *J Clin Oncol* 2014;32(19):2100-8.

Systemic Therapy for Patients Who Receive Local Brain Therapy

"For a patient who receives a standard surgical- or radiotherapy-based approach to treat brain metastases and is receiving anti-HER2–based therapy and whose systemic disease is not progressive at the time of brain metastasis diagnosis, clinicians should not switch systemic therapy."

Ramakrishna N et al. *J Clin Oncol* 2014;32(19):2100-8.

Module 3:
ER-Positive Breast Cancer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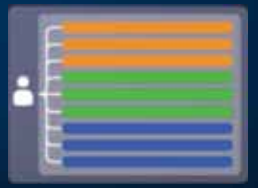
TNBC: Neoadjuvant systemic therapy
TNBC: Adjuvant treatment
TNBC: Metastatic disease

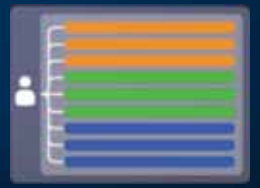
Key Considerations in Neoadjuvant Therapy for ER-Positive Breast Cancer

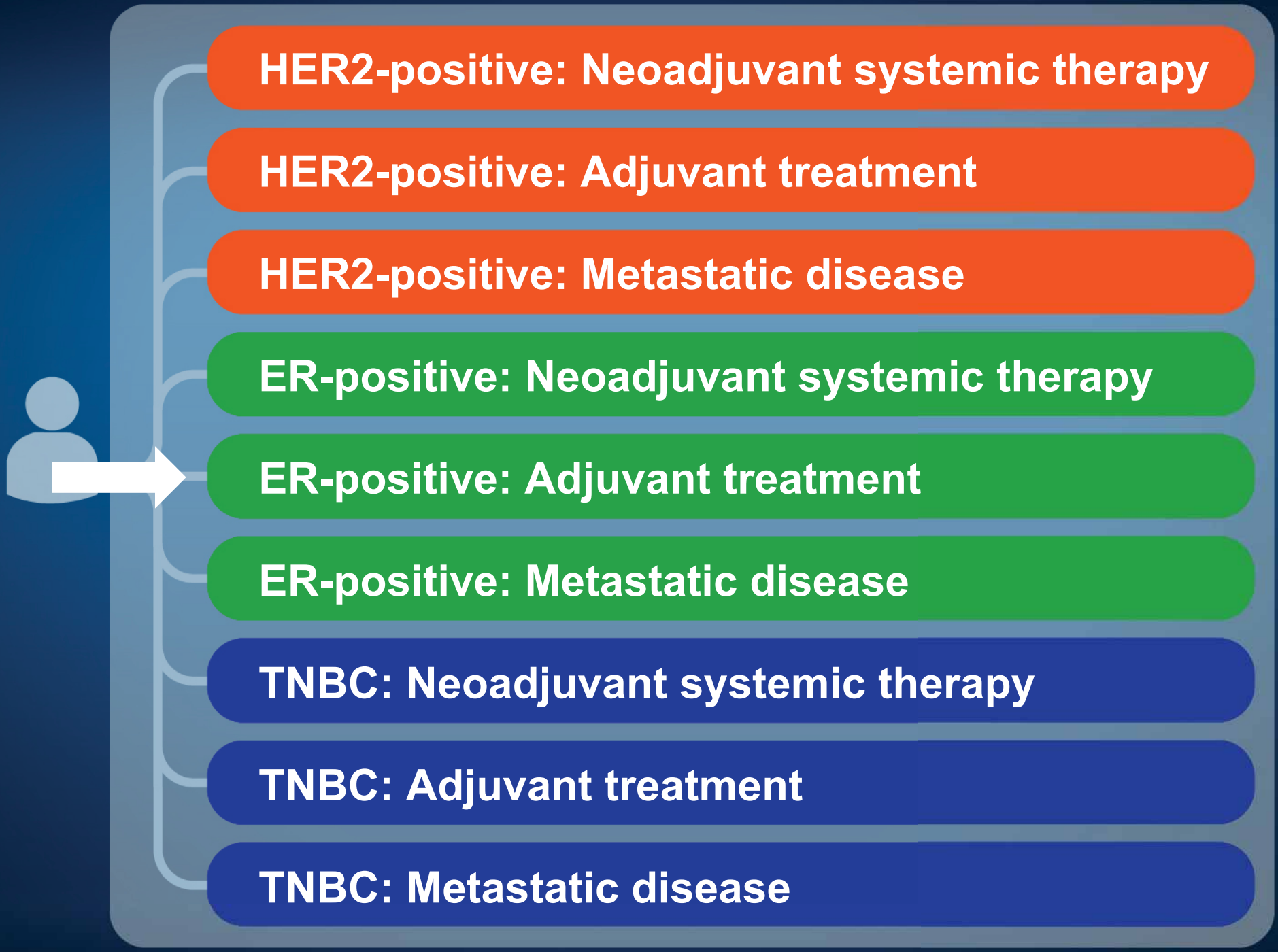
- Use of neoadjuvant chemotherapy
- Use of neoadjuvant endocrine treatment
- Role, if any, of genomic assays in decision-making
- Menopausal status



Targeted Therapies for HR-Positive Breast Cancer

Agent	Mechanism of action	Main toxicities
Tamoxifen	Antiestrogen	Menopausal symptoms, stroke, DVT
LHRH agonists	Ovarian suppression	Menopausal symptoms, joint and muscle pain
Aromatase inhibitors	Block aromatase	Menopausal symptoms, joint and muscle pain
Fulvestrant	Estrogen receptor antagonist	Hot flashes, bone and muscle pain, GI symptoms
CDK4/6 inhibitors	Block cell cycle progression	GI symptoms, myelosuppression
Everolimus	mTOR inhibitor	Stomatitis, infection, hepatotoxicity

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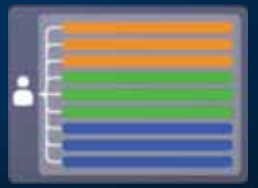
Key Considerations in Adjuvant Therapy for ER-Positive Breast Cancer

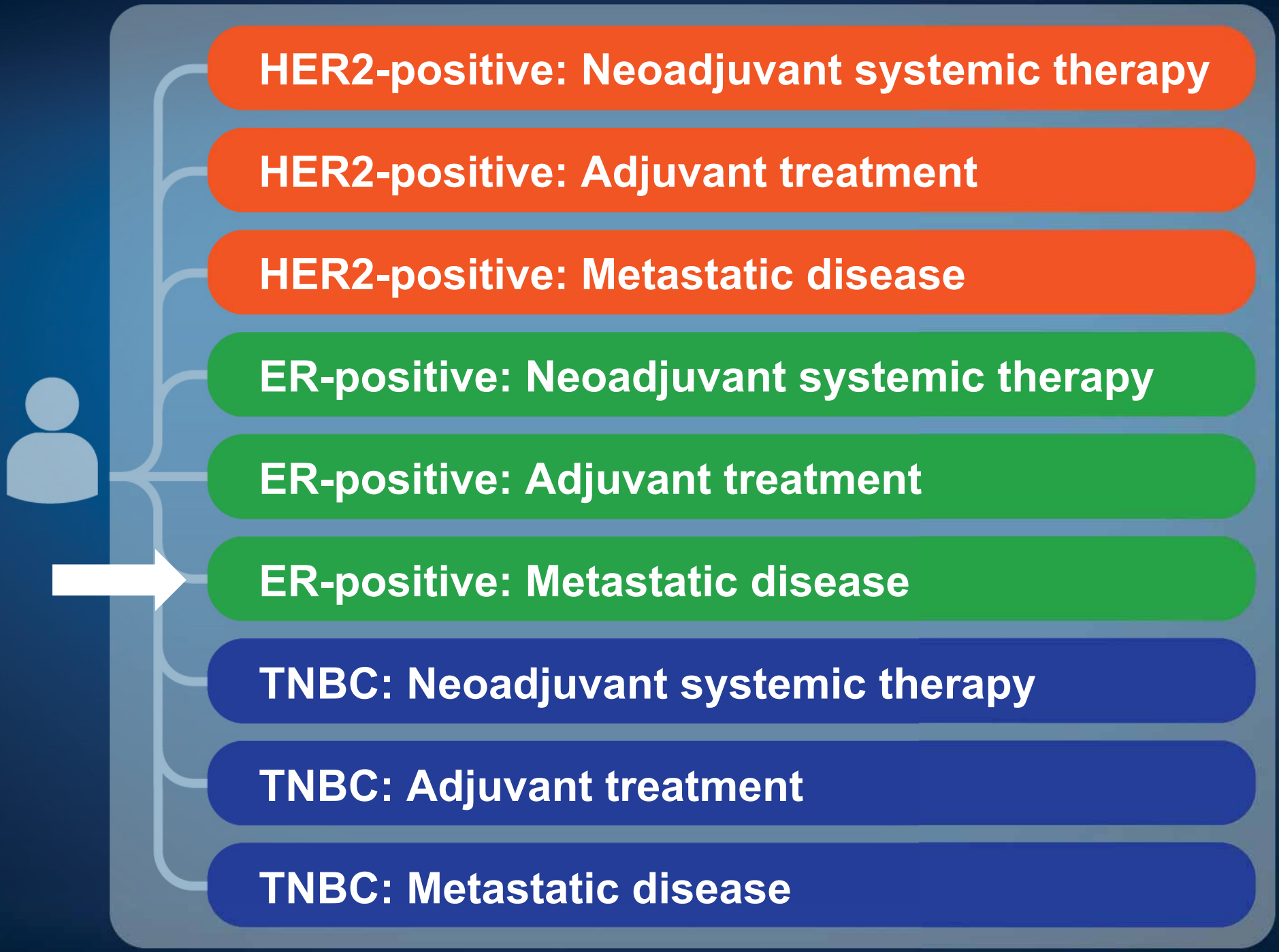
- Selection of patients: Risk criteria for treatment
- Use of genomic assays in node-positive disease
- Choice of endocrine therapy based on menopausal status
- Chemotherapy or not: Role of genomic assays (21-gene Recurrence Score®, 70-gene assay)
- Continuation of endocrine therapy at 5 years: Role of genomic assays (Breast Cancer Index)



Genomic Assays in Breast Cancer

- Onco*type* DX®
- IHC4
- MammaPrint®
- PAM50/risk of recurrence/Prosigna®
- Genomic grade index
- Breast Cancer Index
- EndoPredict®

Győrffy B et al. *Breast Cancer Res* 2015;17:11.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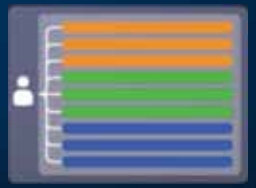
Key Considerations in Systemic Therapy for ER-Positive Metastatic Breast Cancer

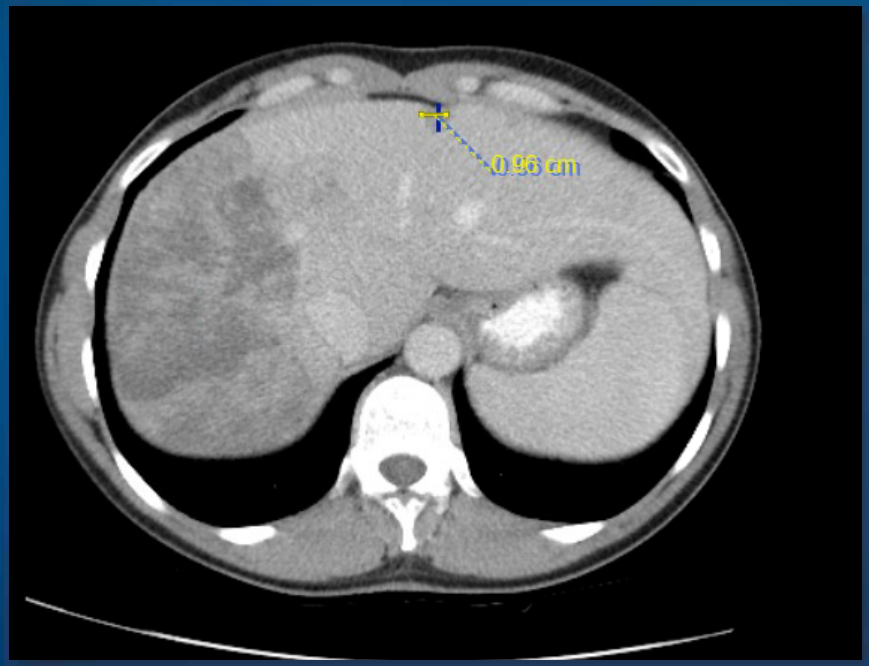
- Choice of endocrine therapy; implications of menopausal status
- Single-modality endocrine therapy with a biologic agent
- Endocrine therapy in combination with a CDK4/6 inhibitor or everolimus
- Chemotherapy versus endocrine therapy: The symptomatic patient who needs an antitumor response

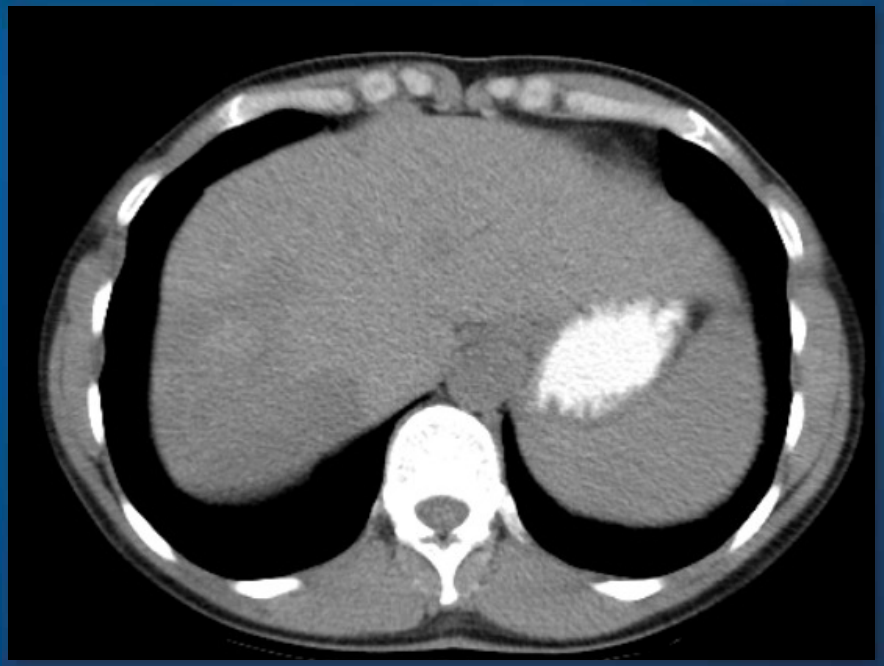


47-Year-Old Woman with ER-Positive, HER2-Negative Metastatic Breast Cancer (Ms O'Reilly)

- 2009: 3-cm, node-positive, ER-positive, PR-positive, HER2-negative infiltrating ductal carcinoma
  - Neoadjuvant AC/taxane
  - Bilateral mastectomy with residual DCIS and 1/17 nodes positive
  - Adjuvant tamoxifen
- March 2016: Recurrent chest wall disease; ER-positive, HER2-negative liver metastases
- April 2016: Ovarian suppression (OS), letrozole, palbociclib
  - Significant reduction in liver metastases, dramatic decline in tumor markers
  - Palbociclib dose reduced for neutropenia and thrombocytopenia

47-Year-Old Woman with ER-Positive, HER2-Negative Metastatic Breast Cancer (Ms O'Reilly)





Before OS/palbociclib/letrozole

After 10 months of OS/palbociclib/letrozole

Significant reduction in liver metastases

Comparison of CDK4/6 Inhibitors

	Palbociclib		Abemaciclib		Ribociclib	
Dosing	125 mg qd 3 wk on, 1 wk off		200 mg BID continuously		600 mg qd 3 wk on, 1 wk off	
ORR (monotherapy)	6%		17%		3%	
CNS penetration	No		Yes		No	
Common adverse events	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Neutropenia Thrombocytopenia	95% 76%	54% 19%	88% 42%	27% 2%	46% 37%	29% 10%
Diarrhea Nausea Vomiting	16% 23% 5%	0 0 0	90% 65% 35%	20% 5% 2%	22% 46% 25%	3% 2% 0

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

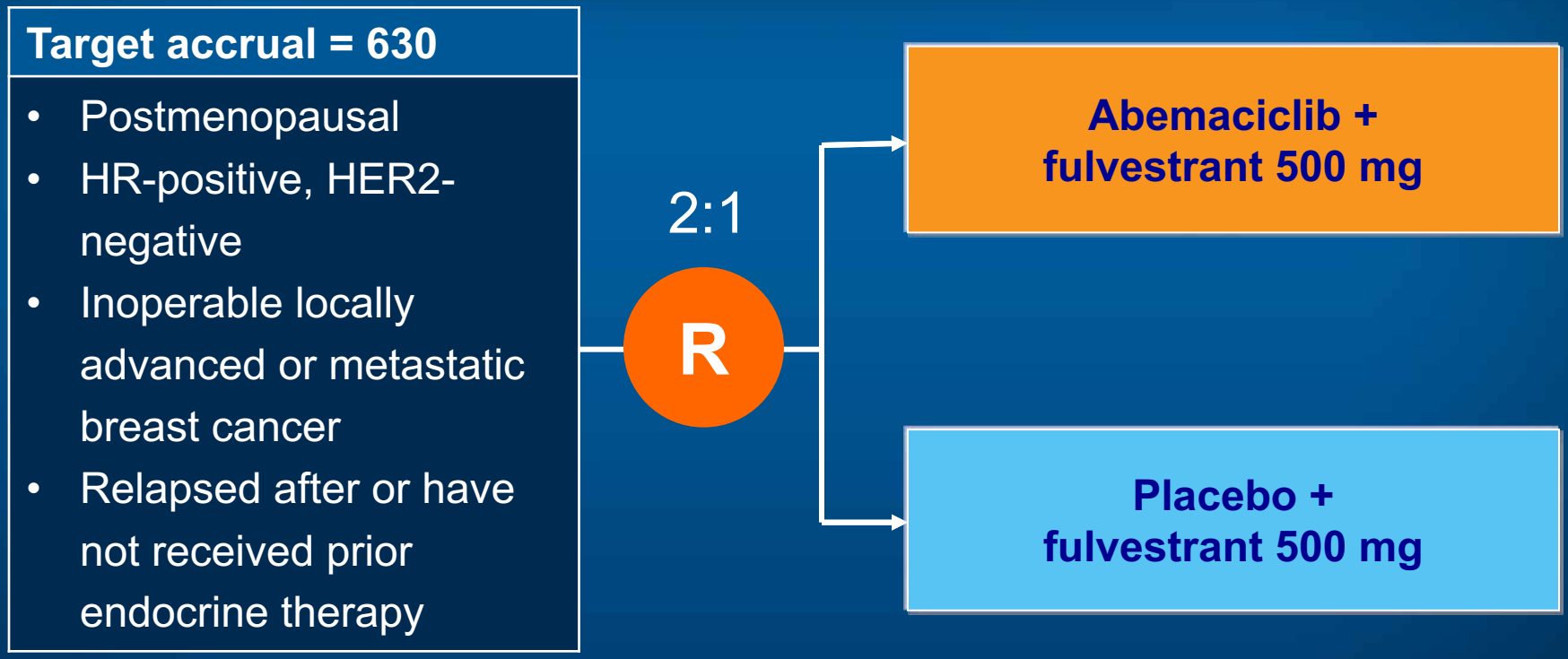
Key Efficacy Data with CDK4/6 Inhibitors

Agent	Indication	Key efficacy data
Palbociclib (approved)	• First line, postmenopausal, HR+, HER2-, advanced BC, with an aromatase inhibitor • Second line, HR+, HER2-, advanced BC, with FULV	• PALOMA-2: Median PFS with PALB + LET 24.8 mo vs LET 14.5 mo ($p < 0.0001$) • PALOMA-3: Median PFS with PALB + FULV 9.5 mo vs FULV 4.6 mo ($p < 0.001$)
Ribociclib (approved)	• First line, postmenopausal, HR+, HER2-, advanced BC, with LET	• MONALEESA-2: Median PFS with RIBO + LET not reached vs LET 14.7 mo ($p < 0.0001$)
Abemaciclib (investigational)	• Not approved • Breakthrough designation as monotherapy for heavily pretreated, refractory, HR+, advanced BC	• MONARCH 1: ORR 19.7%, • CBR 42.4%

FULV = fulvestrant; PALB = palbociclib; LET = letrozole; RIBO = ribociclib; ORR = overall response rate; CBR = clinical benefit rate

Finn RS et al. *Proc ASCO* 2016;Abstract 507; *N Engl J Med* 2016;375:1925-36; Cristofanilli M et al. *N Engl J Med* 2016;17(4):425-39; Hortobagyi GN et al. *N Engl J Med* 2016;375(18):1738-48; Dickler MN et al. *Proc ASCO* 2016;Abstract 510.

Phase III MONARCH 2 Schema



Primary endpoint: Progression-free survival

Results from the MONARCH 2 trial will be presented at ASCO 2017 on June 3rd at 1:15 PM by Sledge G et al (Abstract 1000).

Llombart A et al. SABCS 2014;Abstract OT1-01-07; www.clinicaltrials.gov, May 2, 2017.

Phase III MONARCH 2 Study of Abemaciclib with Fulvestrant Met Primary Endpoint of Progression-Free Survival (PFS)

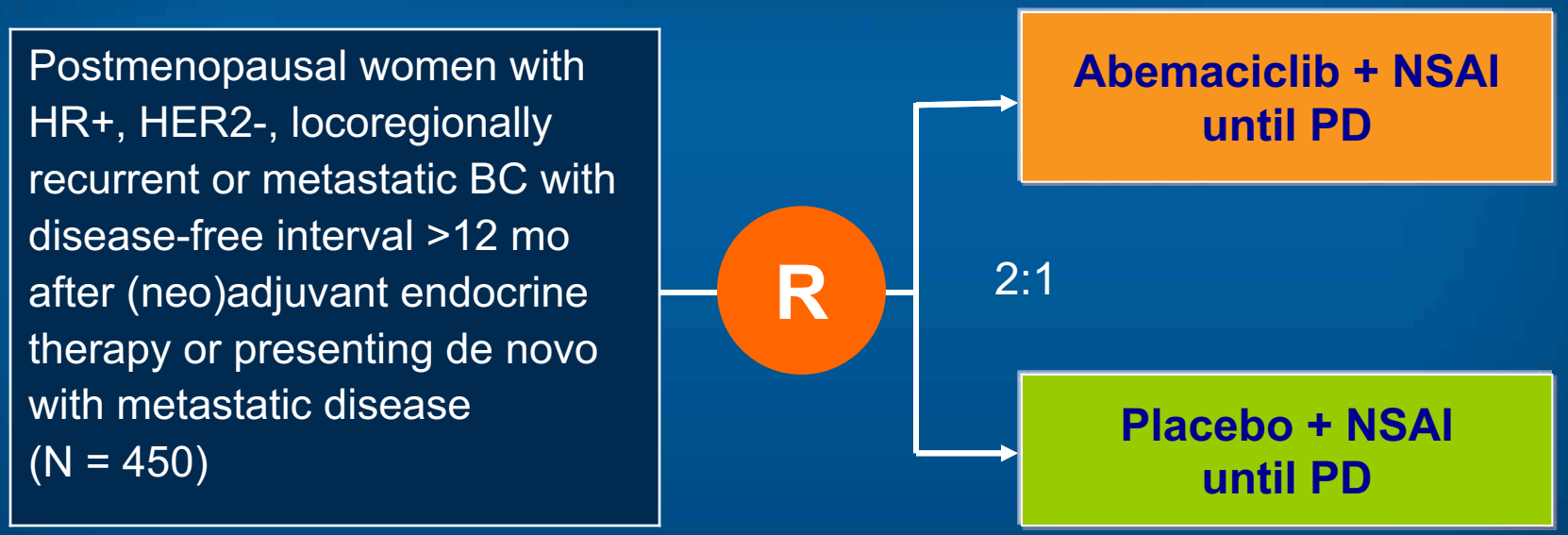
Press release March 20, 2017:

- MONARCH 2 evaluated abemaciclib in combination with fulvestrant in women with HR+, HER2-, advanced breast cancer and disease relapse or progression after endocrine therapy. The addition of abemaciclib to fulvestrant resulted in a statistically significant improvement in PFS when compared to the control arm of placebo with fulvestrant.

Results from the MONARCH 2 trial will be presented at ASCO 2017 on June 3rd at 1:15 PM by Sledge G et al (Abstract 1000).

https://investor.lilly.com/releasedetail.cfm?ReleaseID=1017952

MONARCH 3: A Phase III Study of First-Line Abemaciclib with a Nonsteroidal Aromatase Inhibitor (NSAI)



Primary endpoint: Progression-free survival (PFS)

Stratification factors:

- Nature of disease (visceral metastases versus bone-only metastases versus other)
- Prior (neo)adjuvant endocrine therapy (AI therapy versus other versus no prior endocrine therapy)

Goetz MP et al. *Proc ASCO* 2015;Abstract TPS624; www.clinicaltrials.gov; NCT02246621

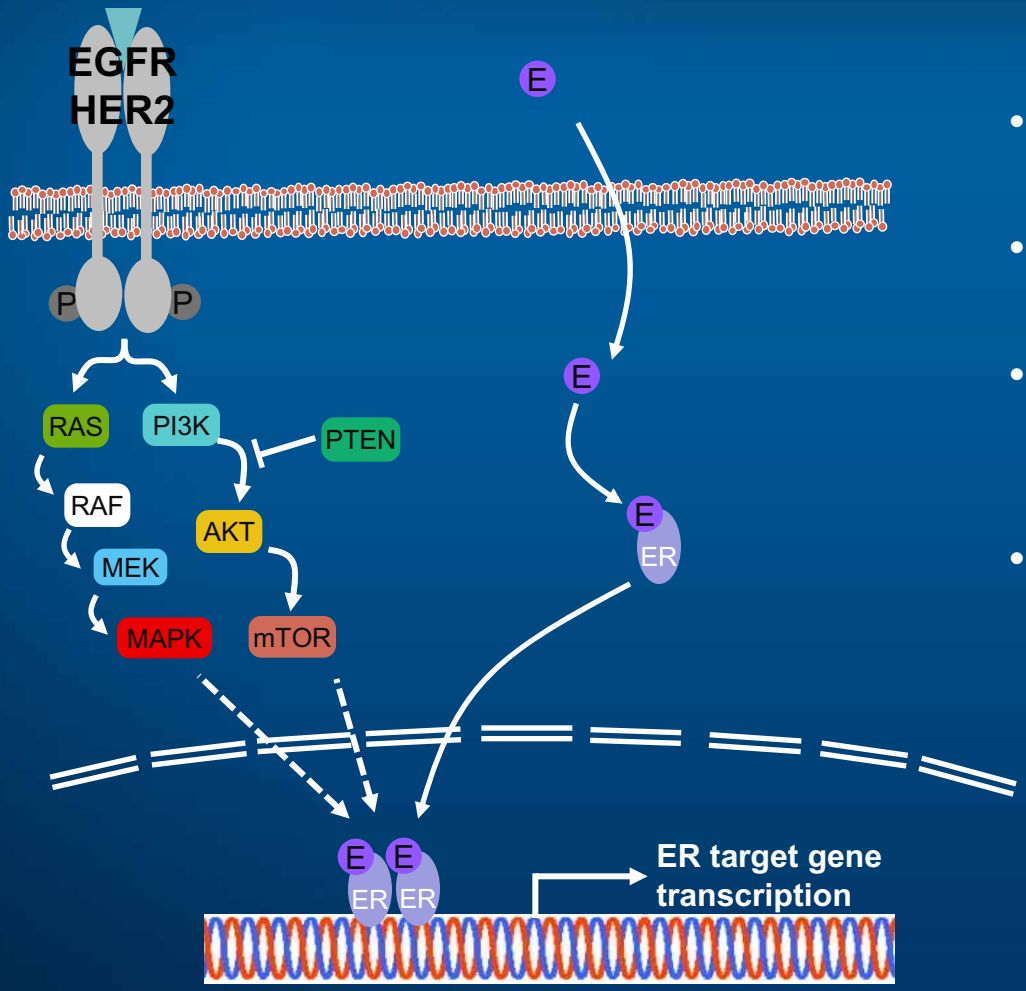
MONARCH 3 Study of Abemaciclib Demonstrated Superior PFS at Interim Analysis

Press release April 24, 2017:

- MONARCH 3 evaluated abemaciclib in combination with an aromatase inhibitor (letrozole or anastrozole) compared to an aromatase inhibitor alone for women with HR-positive, HER2-negative advanced breast cancer.
- A preplanned interim analysis for MONARCH 3 demonstrated that the trial met its primary endpoint of statistically significant improvement in PFS.
- Improvement was also demonstrated in objective response rate, a key secondary endpoint.

https://investor.lilly.com/releasedetail.cfm?ReleaseID=1022428

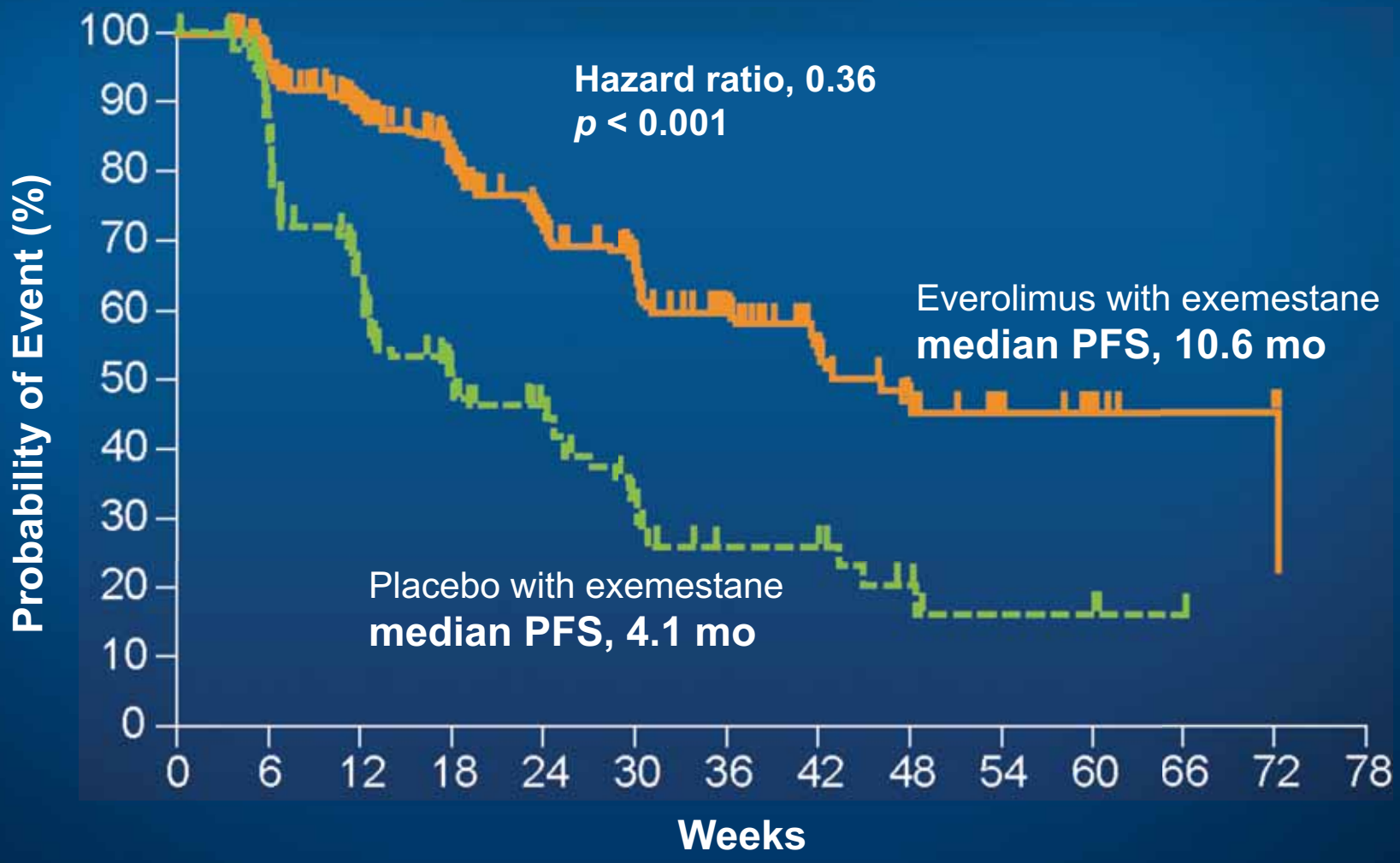
Crosstalk between ER and PI3K/AKT/mTOR Signaling: Rationale for Dual Inhibition



- mTOR activates ER in a ligand-independent manner
- Estradiol suppresses apoptosis induced by mTOR blockade
- Hyperactivation of the mTOR pathway is observed in endocrine therapy-resistant breast cancer cells
- mTOR is a rational target to enhance the efficacy of hormonal therapy

Adapted from: Di Cosimo S, Baselga J. *Nat Rev Clin Oncol* 2010;7:139-47.

BOLERO-2: PFS with Everolimus/Exemestane for HR-Positive Advanced Breast Cancer

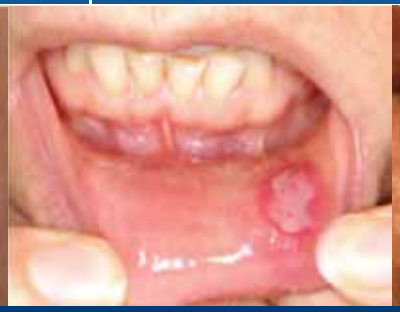


Baselga J et al. *N Engl J Med* 2012;366(6):520-9.

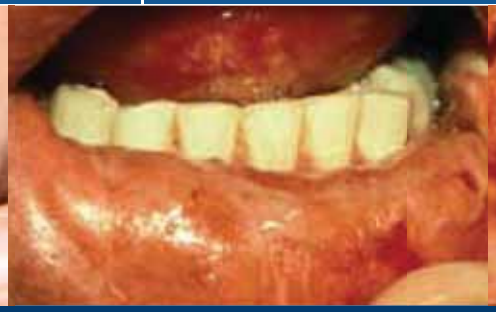
Everolimus-Associated Stomatitis

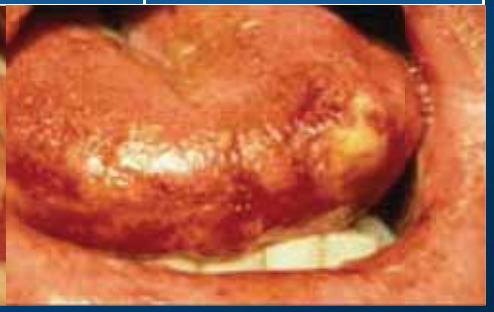
	Grade 1	Grade 2	Grade 3	Grade 4
Clinical exam	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes, bleeding with minor trauma	Tissue necrosis, significant spontaneous bleeding
Functional symptoms	Minimal symptoms, normal diet	Symptomatic but can eat and swallow modified diet	Symptomatic and unable to adequately aliment or hydrate orally	Symptoms associated with life-threatening consequences

de Oliveira MA et al.
Oral Oncol 2011



Ferte C et al.
Eur J Cancer 2011



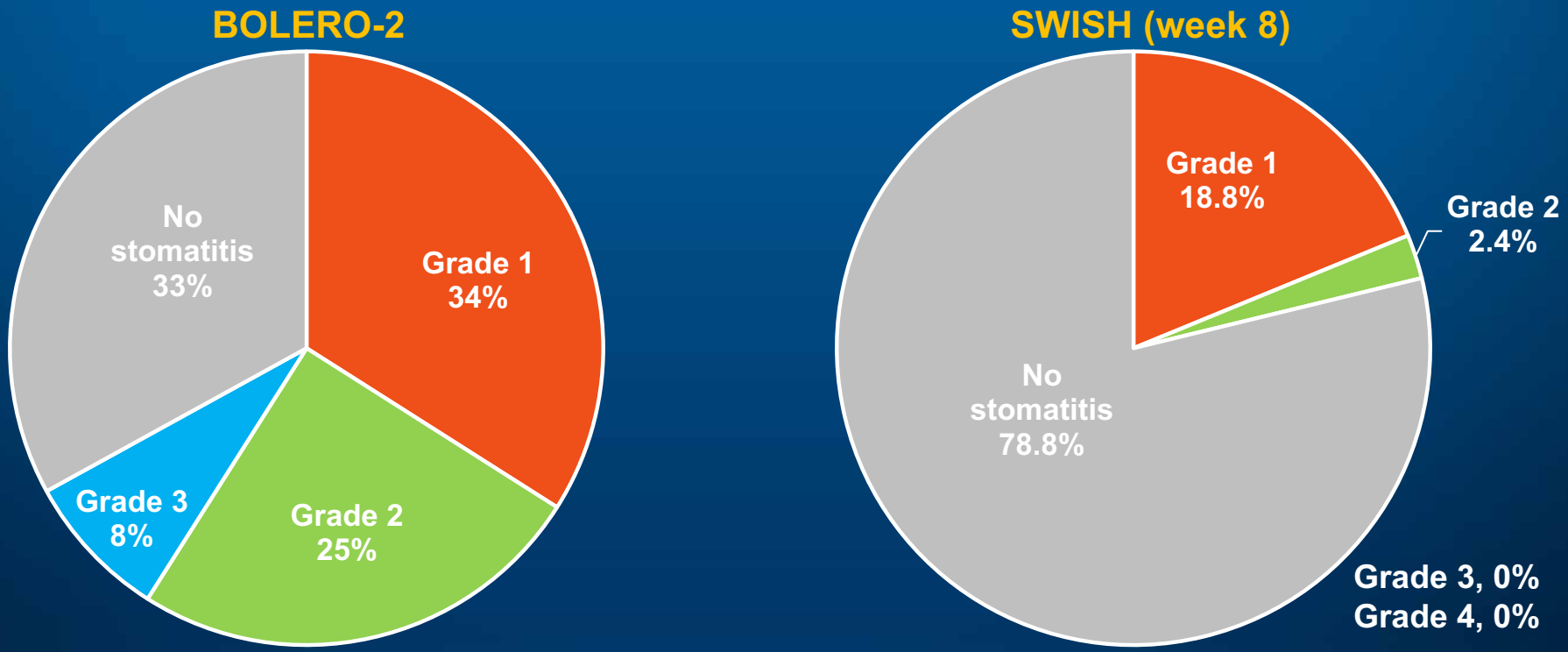


Cawley M et al.
Clin J Oncol Nurs 2005

SWISH: Prevention of Everolimus-Related Stomatitis with a Dexamethasone-Based Mouthwash

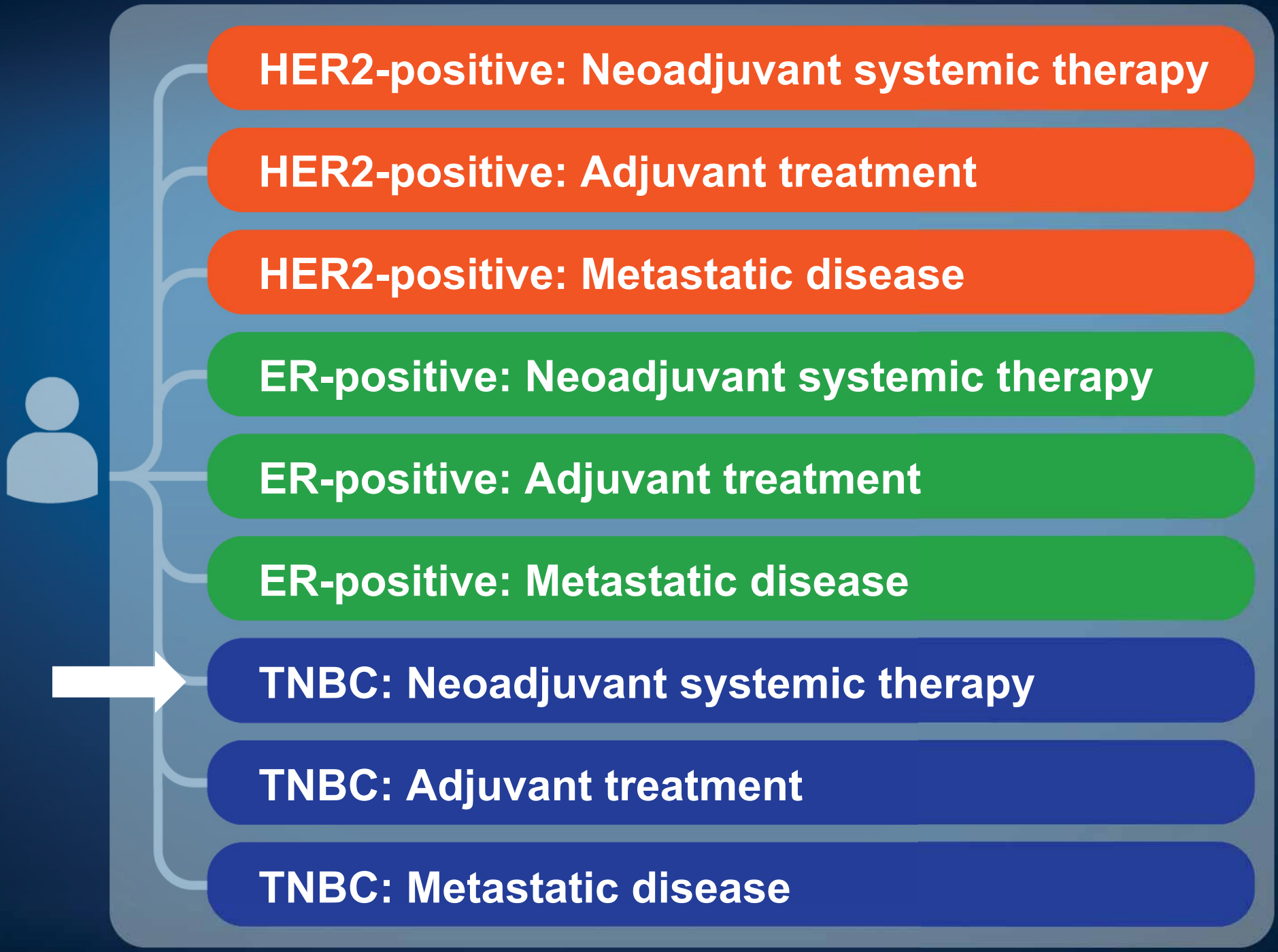
- Patients with HR-positive metastatic BC treated with everolimus/exemestane
- Dexamethasone solution (0.5 mg/5 mL) 10 mL per day for 8 weeks, starting day 1

INCIDENCE OF STOMATITIS



Rugo H et al. *Proc ASCO* 2016;Abstract 525.

Module 4:
Triple-Negative Breast Cancer (TNBC)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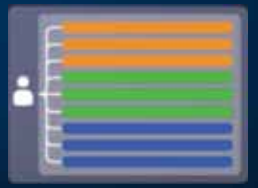
TNBC: Neoadjuvant systemic therapy
TNBC: Adjuvant treatment
TNBC: Metastatic disease

Key Considerations in NST for TNBC

- Role of platinum-based chemotherapy
- High rate of clinical response and downstaging
- Opportunity for less surgery
- BRCA mutation status



Role of Neoadjuvant Platinum in TNBC: Randomized Trials

Study	#	Backbone regimen	pCR in breast/axilla	
			No carboplatin	Carboplatin
GeparSixto[1]	315	Weekly paclitaxel + liposomal doxorubicin + bevacizumab	36.9%	53.2%
CALGB-40603[2]	433	Sequential weekly pac → AC ± bev	41%	54%
Tamura et al[3]	75	Sequential weekly pac ± carboplatin AUC5 → CEF	26.3%	61.2%
Alba et al[4]	94	EC → docetaxel ± carbo AUC6	30%	30%

[1] Von Minckwitz et al. *Lancet Oncol* 2014;15(7):747-56; [2] Sikov et al. *JCO* 2015;33(1):13-21; [3] Tamura et al. *Proc ASCO* 2014;Abstract 1017; [4] Alba et al. *Breast Cancer Res Treat* 2012;136(2):487-93.

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ER-positive: Neoadjuvant systemic therapy

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ER-positive: Metastatic disease

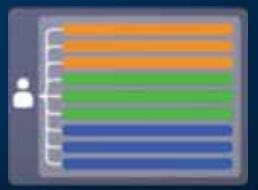
TNBC: Neoadjuvant systemic therapy

TNBC: Adjuvant treatment

TNBC: Metastatic disease

Key Considerations in Adjuvant Systemic Therapy for TNBC

- Choice of chemotherapeutic regimen
- Response to neoadjuvant therapy and presence of residual disease
- BRCA mutation status

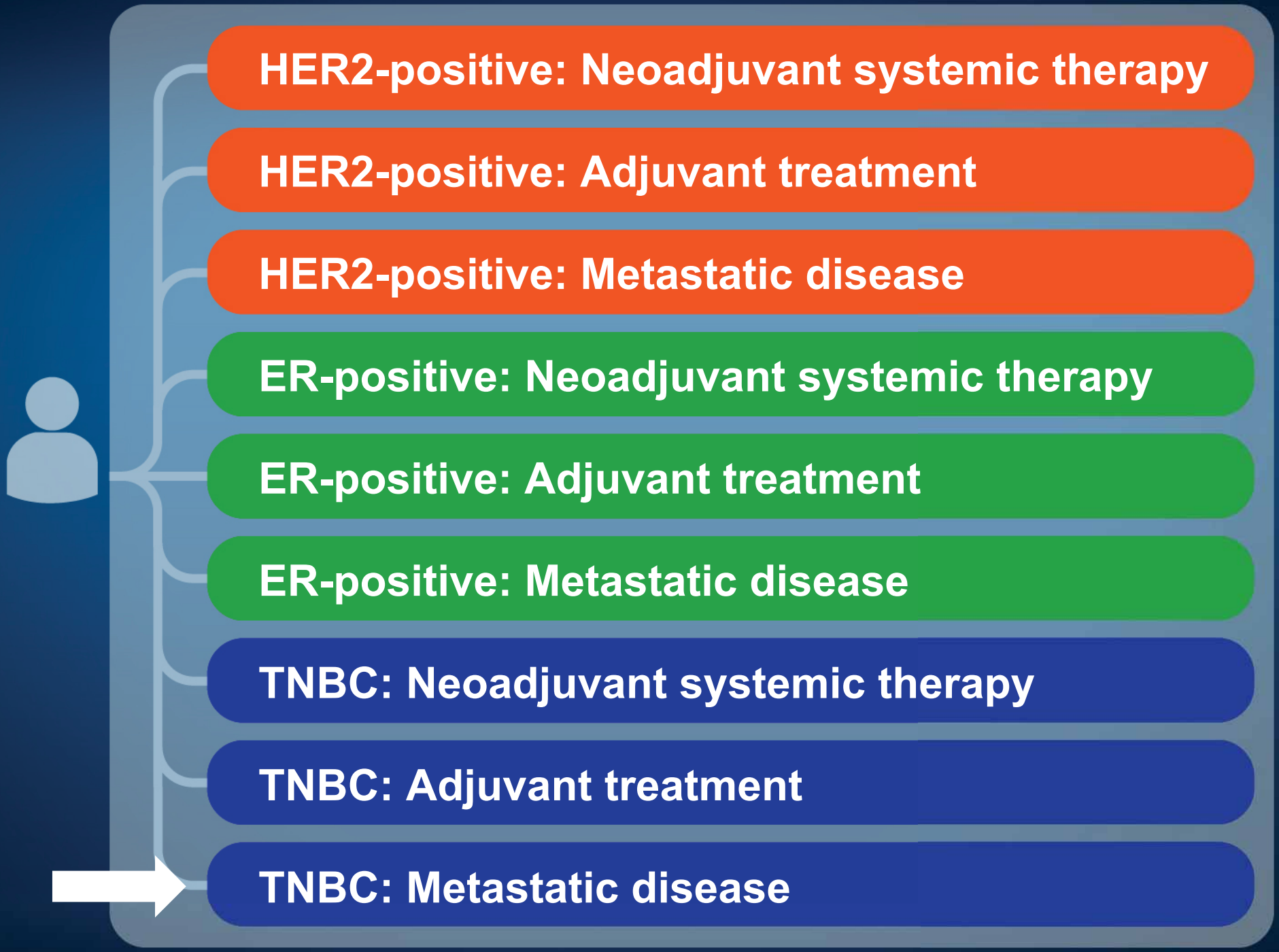


CREATE-X: Adjuvant Capecitabine for Patients with HER2-Negative BC and Residual Invasive Disease After Neoadjuvant Chemotherapy

Efficacy (5 y)	Capecitabine (n = 440)	Control (n = 445)	HR, *p*-value
Disease-free survival	74.1%	67.7%	0.7, 0.00524
Overall survival	89.2%	83.9%	0.6, <0.01

Subgroup analysis of DFS by hormone receptor status:
HR-positive (n = 561), hazard ratio = 0.84
HR-negative (n = 296), hazard ratio = 0.58

Toi M et al. SABCS 2015;Abstract S1-07.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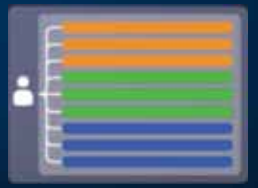
Key Considerations in Metastatic TNBC

- Selection and sequencing of chemotherapeutic agents (eg, capecitabine, eribulin, taxanes)
- Emerging data with antiandrogens in patients with elevated androgen receptor levels
- Ongoing clinical trials and nonresearch role with immune checkpoint inhibitors
- Multiplex tumor testing and next-generation sequencing to identify clinical trial opportunities
- BRCA mutation status



Commonly Used Chemotherapy Agents in TNBC

- Platinum agents (carboplatin, cisplatin)
- Anthracyclines
- Taxanes
- Eribulin
- Gemcitabine
- Capecitabine

NCCN Clinical Practice Guidelines; Breast Cancer v2.2017.

Atezolizumab for Metastatic TNBC

	All patients	Atezo as first line	Atezo after ≥2 lines of therapy
ORR (n = 112, 19, 93)	10%	26%	7%
Median duration of response	21 mo	21 mo	Not evaluable
OS rate (n = 113, 19, 94) 1-year 3-year	 41% 22%	 63% Not evaluable	 37% 18%

Durable clinical benefit observed in responders

Schmid P et al. *Proc AACR* 2017;Abstract 2986.

Atezolizumab with *Nab* Paclitaxel for Metastatic TNBC

Response	First line (n = 13)	Second line (n = 9)	Third line + (n = 10)
Confirmed objective response	46%	22%	40%
Complete response	8%	0	0
Partial response	38%	22%	40%
Stable disease	38%	67%	30%

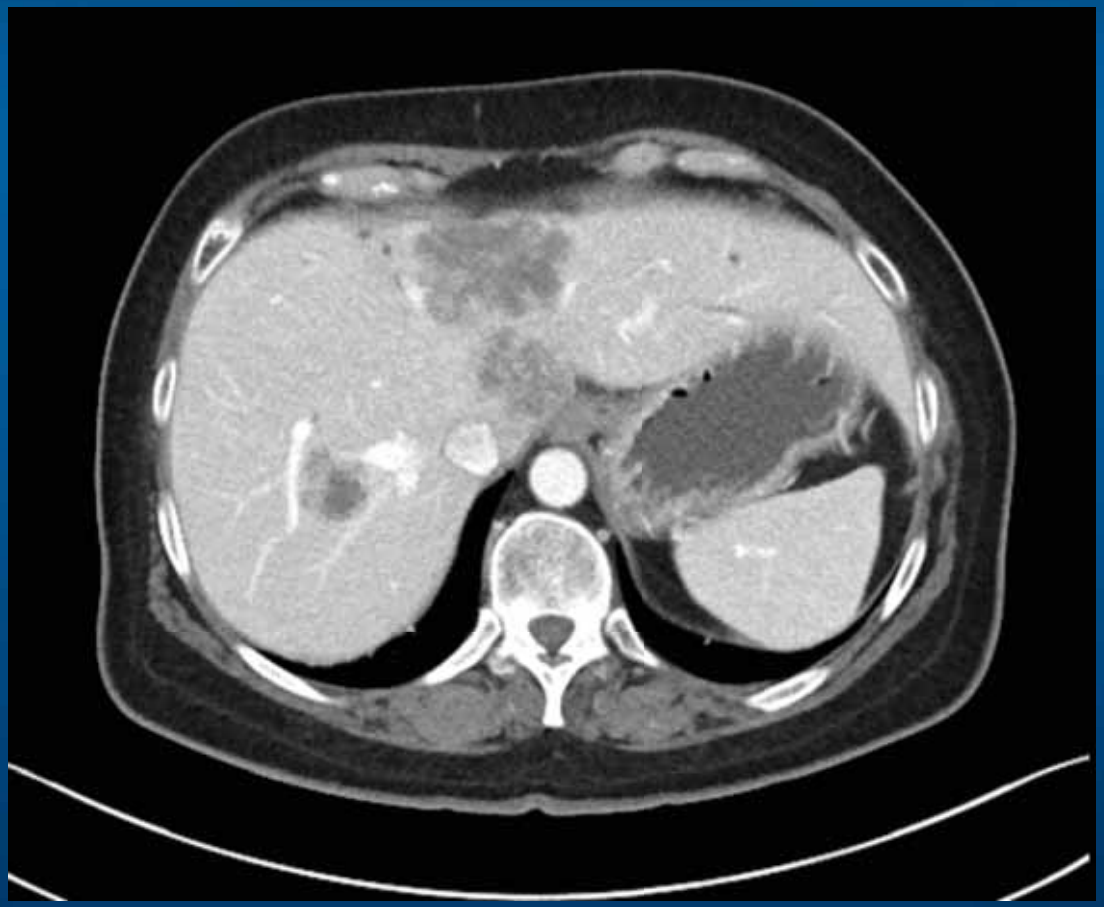
- PFS not mature and median duration of response not reached
- Treatment-related Grade 3-4 adverse events: neutropenia/decreased neutrophil (47%), thrombocytopenia, anemia and diarrhea (6% each)

Adams S et al. *Proc ASCO* 2016;Abstract 1009.

60-Year-Old Divorced Mother with Triple-Negative Metastatic Breast Cancer (Ms Olson)

- Dec 2015: De novo TNBC to liver
- Feb 2016: Clinical trial of pembrolizumab, with PD
- Jun 2016: Carboplatin/paclitaxel
  - Discontinued carboplatin after 2 cycles due to prolonged neutropenia
  - Transitioned to *nab* paclitaxel due to paclitaxel hypersensitivity
- Dec 2016: Liposomal doxorubicin → MATCH trial → carboplatin
- April 2017: Progression in liver, increasingly symptomatic, abdominal pain – chemotherapy versus hospice?... Eribulin initiated
- Unable to work and relies on government assistance
- Extremely supportive brother and children

60-Year-Old Divorced Mother with Triple-Negative Metastatic Breast Cancer (Ms Olson)



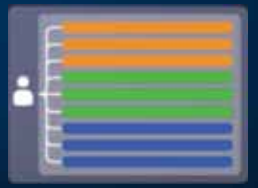
Baseline staging for TNBC: Multiple hepatic lesions

Module 5:

Patients with BRCA Germline Mutations: Role of PARP Inhibitors?

BRCA and PARP Inhibitors

- Incidence and clinical significance of BRCA1/2 mutations
- Available BRCA mutation testing assays
- Current and future (June 2017) indications for BRCA testing
- Preventive implications of positive BRCA results
- PARP inhibitors in patients with BRCA mutations



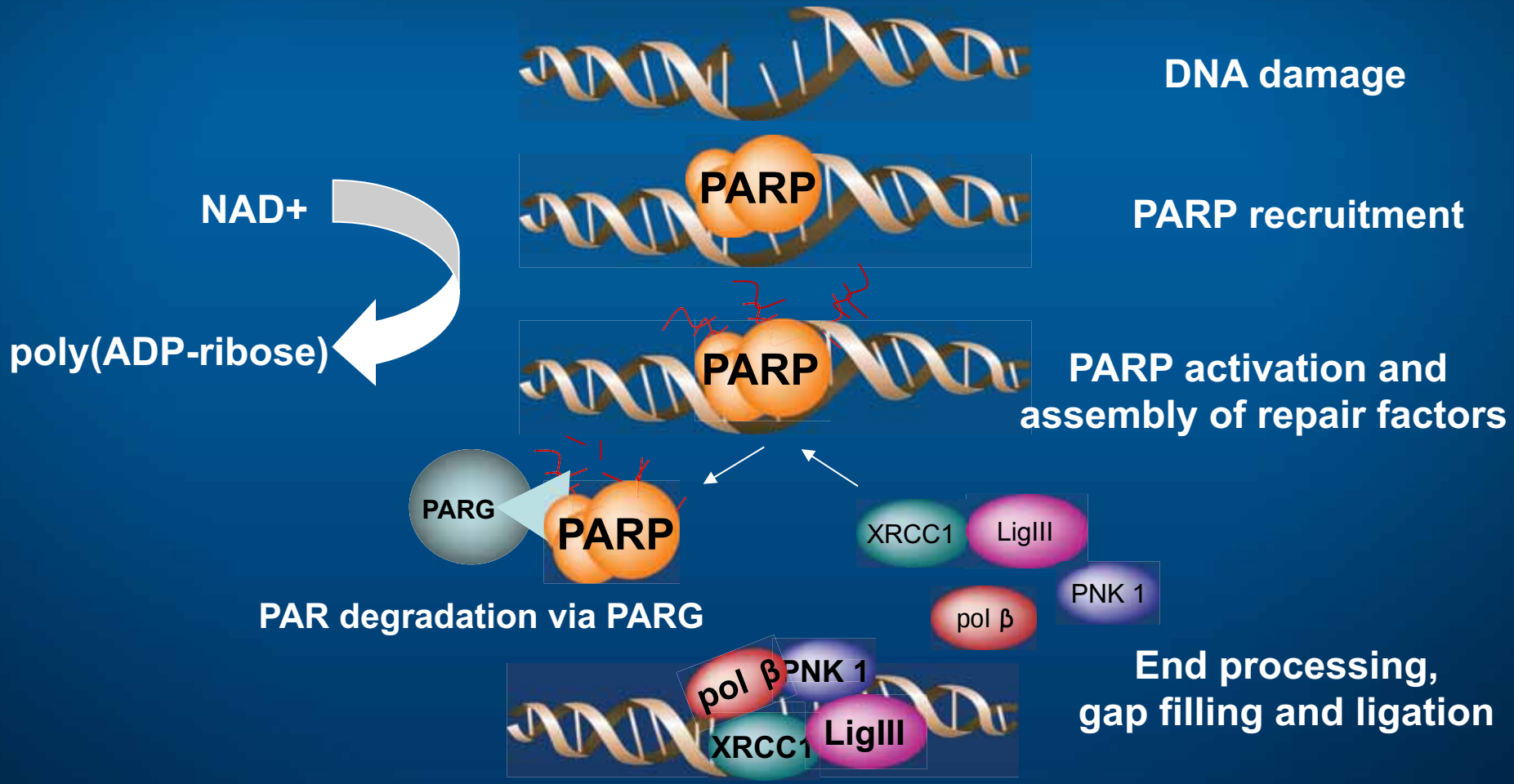
Guidelines for BRCA Testing in Breast Cancer

A breast cancer diagnosis meeting any of the following criteria:

- A known mutation in a cancer susceptibility gene within the family
- Early-age-onset breast cancer
- Triple-negative (ER-, PR-, HER2-) breast cancer diagnosed at age ≤60
- Two breast cancer primaries in a single individual
- Breast cancer at any age and
  - ≥1 close blood relative with breast cancer at 50 or younger
  - ≥1 close blood relative with invasive ovarian cancer at any age
  - ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age
  - Pancreatic cancer at any age
  - From a population at increased risk
- Male breast cancer
- Ashkenazi Jewish descent with breast, ovarian or pancreatic cancer at any age

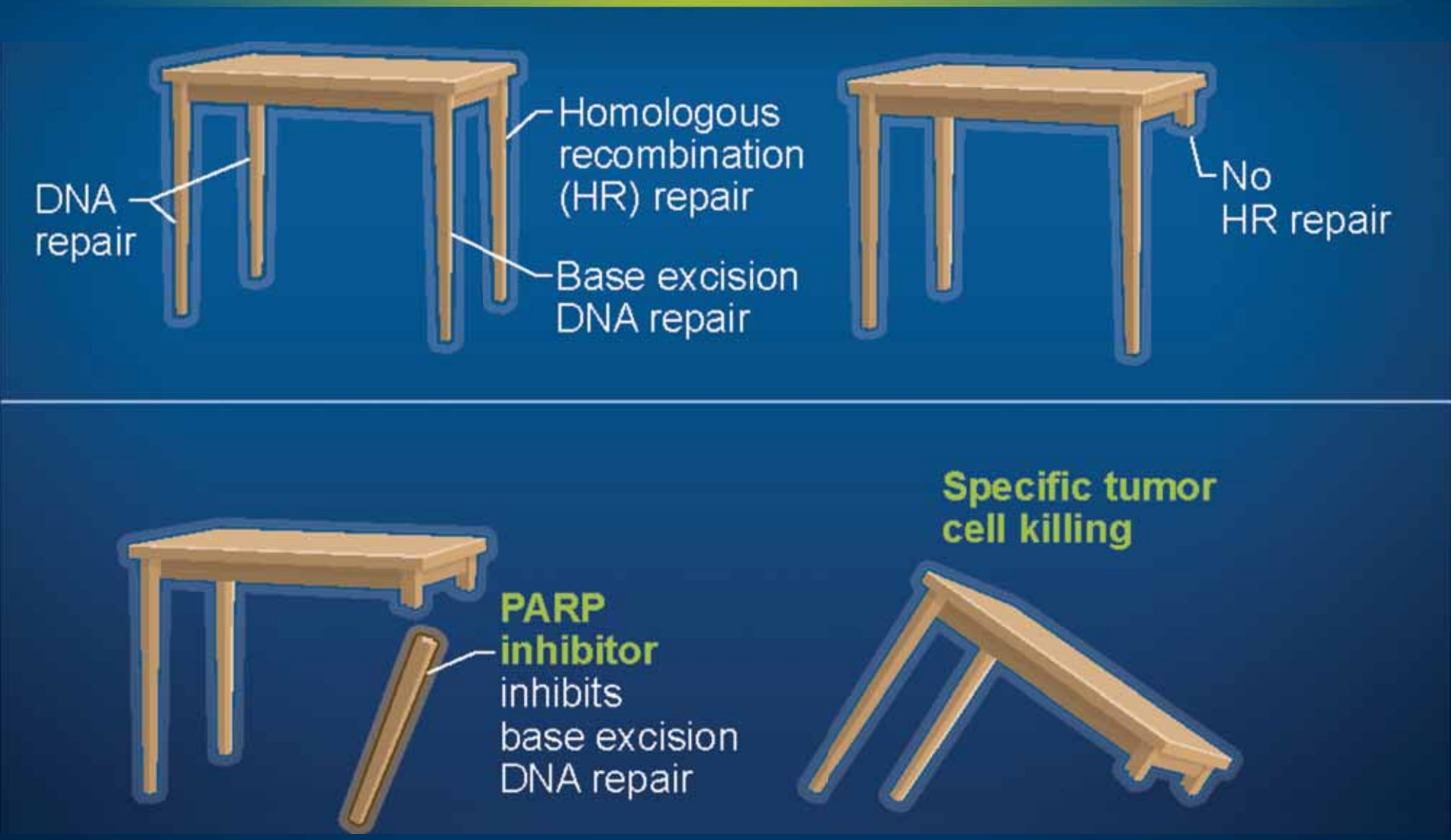
NCCN Guidelines Breast and/or Ovarian Cancer Genetic Assessment v2.2017

PARP and Base Excision Repair



Vergote, ND; Khanna et al, 2001; Sanchez-Perez, 2006; Kennedy et al, 2006.

Mechanism of Cell Death from Synthetic Lethality Induced by PARP Inhibition



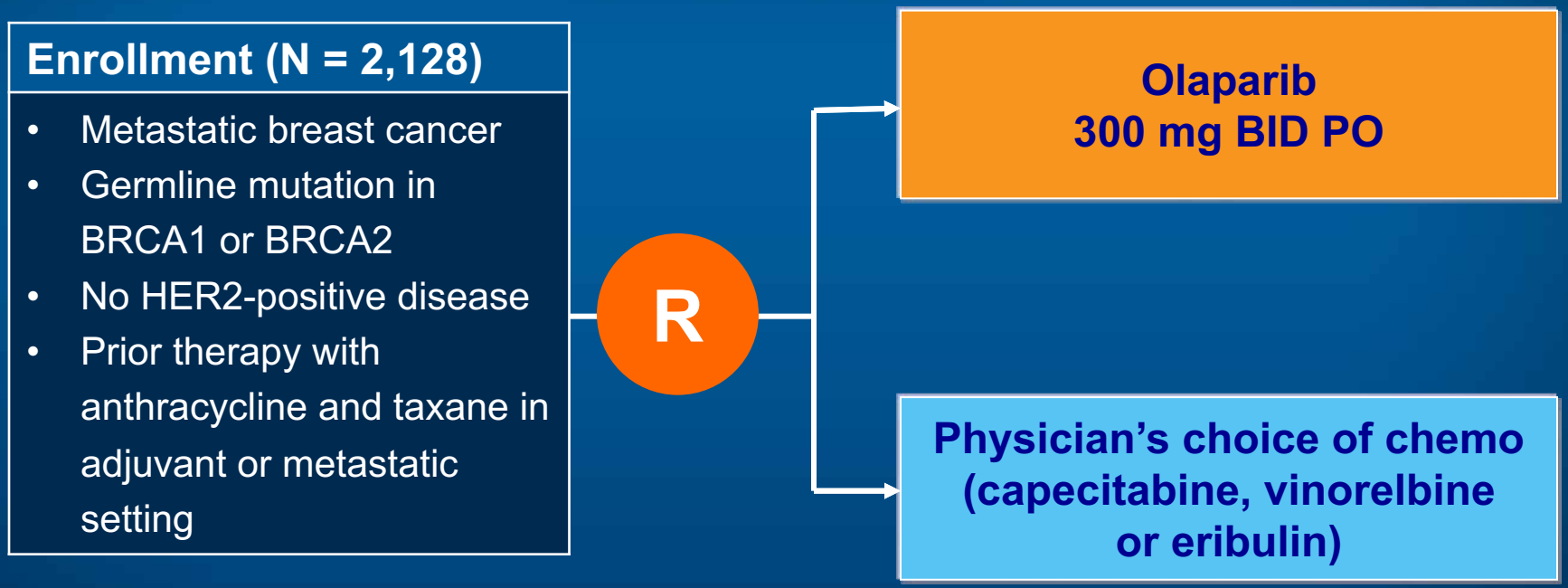
Courtesy of Jenny C Chang, MD

PARP Inhibitors in Clinical Development for Breast Cancer

Agent	Dose	Phase
Olaparib	400 mg orally BID	I, II, III
Rucaparib	600 mg orally BID	II
Veliparib	400 mg orally BID	I, II, III
Niraparib	300 mg orally per day	I, II, III
Talazoparib	1 mg orally per day	I, II, III

www.clinicaltrials.gov

OlympiAD: Phase III Study of Olaparib for Metastatic Breast Cancer with Germline BRCA1/2 Mutations



Primary endpoint: Progression-free survival

www.clinicaltrials.gov (NCT02000622). Accessed May 1, 2017.

Olaparib Meets Primary Endpoint in Phase III Trial in BRCA Mutation-Positive Metastatic BC

Press release February 17, 2017:

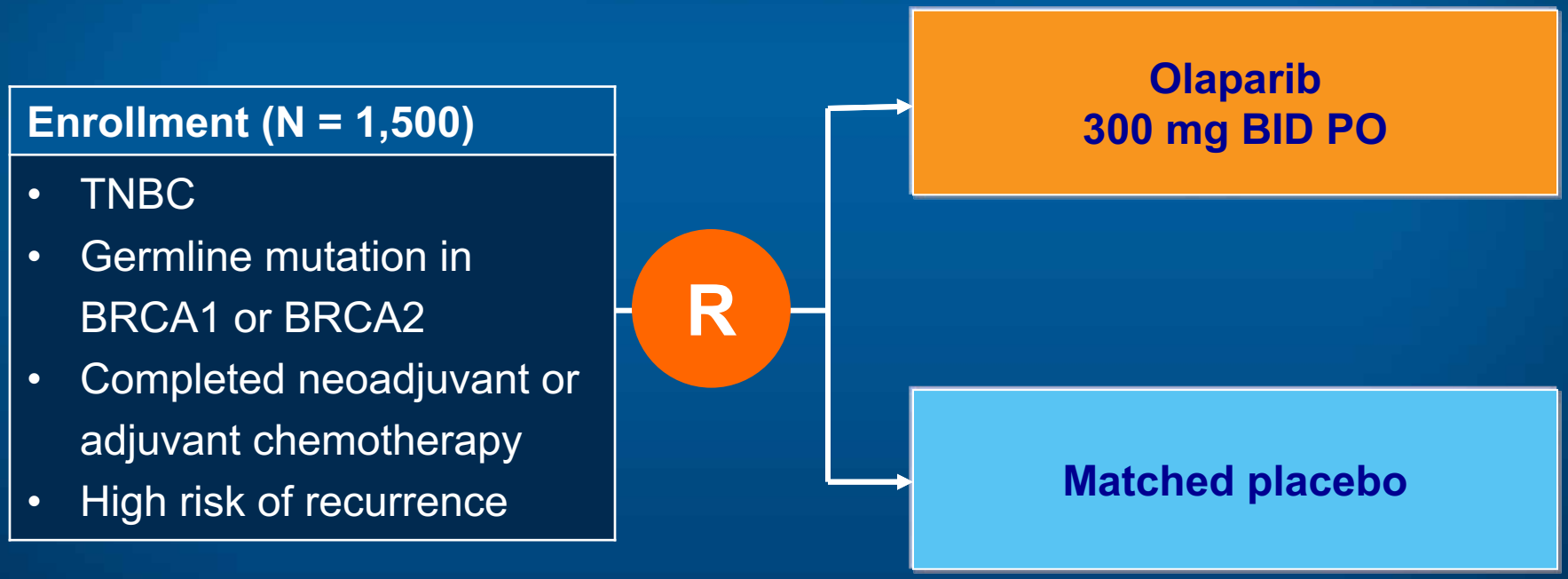
- Patients with HER2-negative metastatic breast cancer and germline BRCA1 or BRCA2 mutations who received olaparib showed a statistically significant and clinically meaningful improvement in PFS compared to those who received chemotherapy (capecitabine, vinorelbine or eribulin).

To be presented at ASCO 2017:

- Results from a phase III clinical trial evaluating the PARP inhibitor olaparib vs standard chemotherapy for women with BRCA-related advanced breast cancer. Abstract LBA4, Plenary

https://www.astrazeneca.com/media-centre/press-releases/2017/lynparza-meets-primary-endpoint-in-phase-iii-trial-in-brca-mutated-metastatic-breast-cancer-17022017.html

OlympiA: Phase III Study of Olaparib as Adjuvant Therapy for High-Risk, HER2-Negative Primary Breast Cancer with Germline BRCA1/2 Mutations



Primary endpoint: Invasive disease-free survival

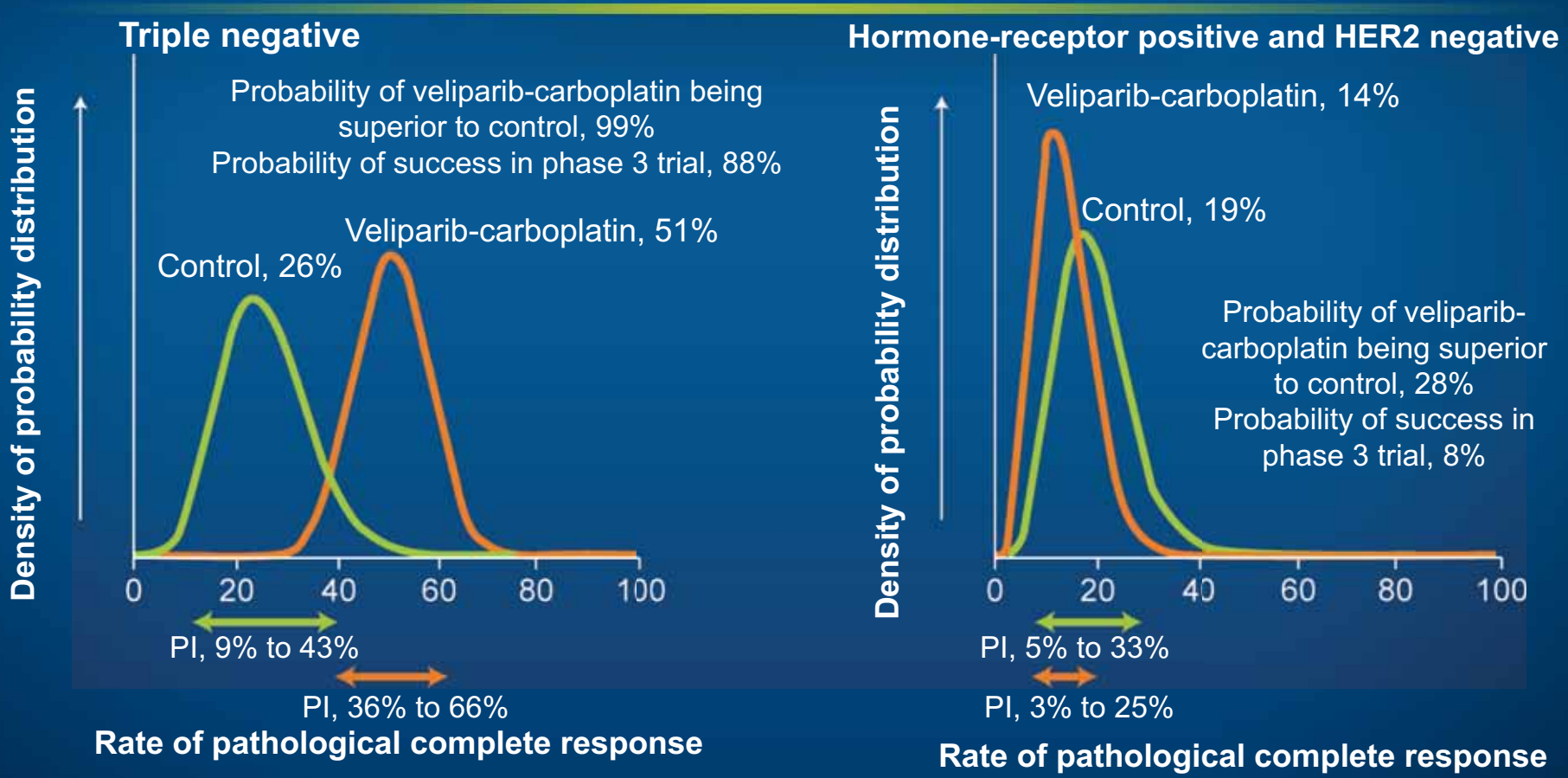
Tutt A et al. *Proc ASCO* 2015;Abstract TPS1109; www.clinicaltrials.gov; NCT02032823.

Olaparib Education: Premeds and Side Effects

- PI side effects: Anemia, fatigue, emesis
- Real life side effects:
  - Fatigue, thrombocytopenia, nausea
- All patients receive weekly CBC, diff for 1st month (pretend they are on clinical trial)
- 8 pills BID — individualize. Start with antiemetic with evening dose and prn during day
- Fatigue, nausea, hematologic side effects common

Courtesy of Paula J Anastasia, RN, MN, AOCN

I-SPY 2: Veliparib/Carboplatin in HER2-Negative BC



PI = probability interval

- Patients with TNBC benefited whereas patients with HER2-negative, hormone receptor-positive tumors did not benefit from veliparib/carboplatin
- Toxic effects were greater with veliparib/carboplatin than with control

Rugo HS et al. *N Engl J Med* 2016;375(1):23-34.

Phase II Study of Veliparib with Carboplatin/Paclitaxel (C/P) for BRCA1/2 Mutation-Positive Metastatic Breast Cancer

Efficacy	Veliparib + C/P (n = 95)	Placebo + C/P (n = 98)	HR, *p*-value
ORR	77.8%	61.3%	—, 0.027
PFS	14.1 mo	12.3 mo	0.789, 0.231
OS	28.5 mo	25.0 mo	0.725, 0.148

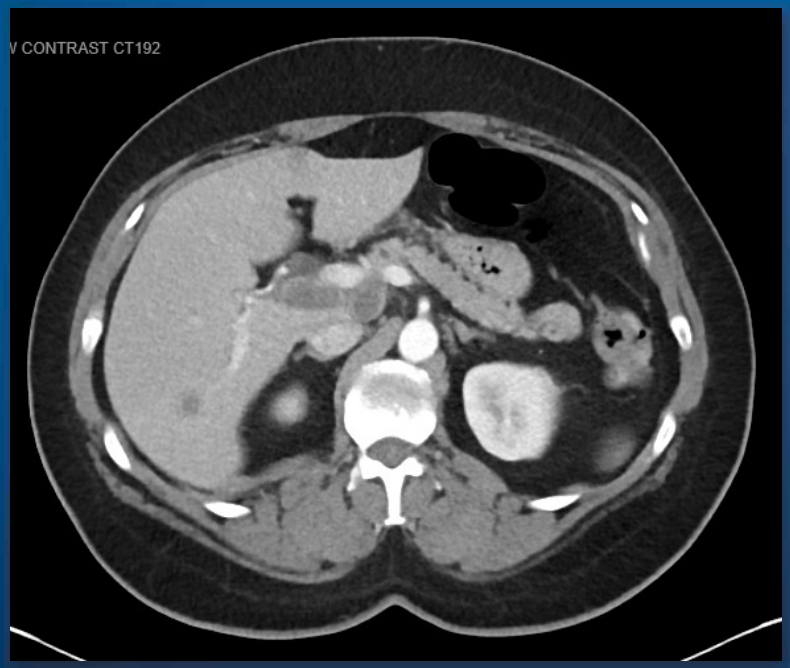
- No meaningful increase in toxicity was observed with the addition of veliparib
- The most common Grade ≥3 adverse events were neutropenia, (placebo 55%, veliparib 56%) and thrombocytopenia (placebo 26%, veliparib 31%)

Han HS et al. SABCS 2016;Abstract S2-05.

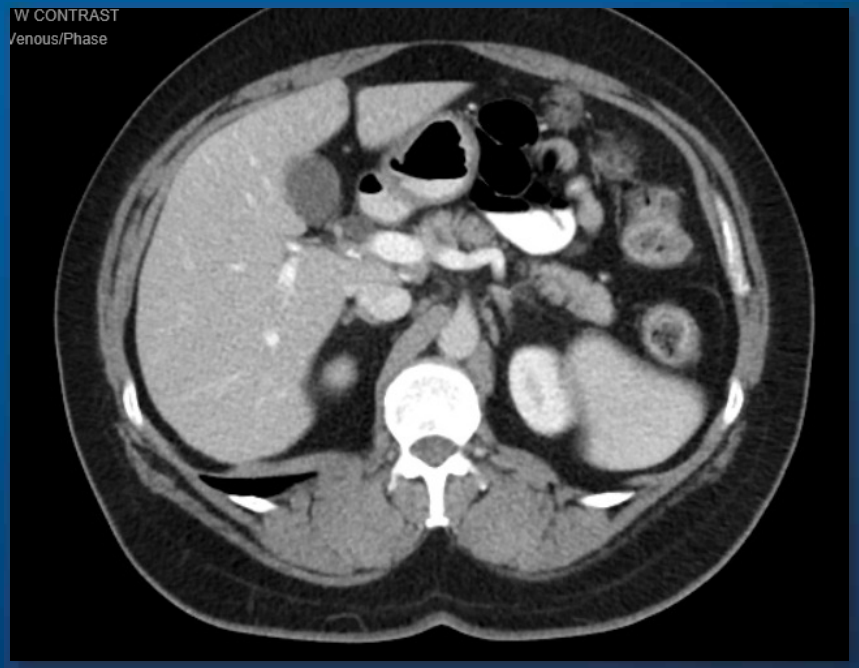
47-Year-Old Woman with Triple-Negative, BRCA Mutation-Positive Metastatic Breast Cancer (Ms O'Reilly)

- Jan 2012: Diagnosed with left-side TNBC with BRCA mutation
  - Neoadjuvant cisplatin, paclitaxel, everolimus on protocol
  - Bilateral mastectomy followed by RT
  - Adjuvant AC x 2, discontinued due to psychosocial difficulties
- May 2014: Left occipital brain metastases
- Jun 2014: Neurosurgical resection and WBRT
- Fall 2014: Liver and lymph node metastases in the porta hepatis
  - Paclitaxel
- Feb 2015: Disease progression, enrollment on OlympiAD, with olaparib
- Complex psychosocial history, including heroin abuse and physical abuse; death of friends and family due to opioid overdoses

47-Year-Old Woman with Triple-Negative, BRCA Mutation-Positive Metastatic Breast Cancer (Ms O'Reilly)

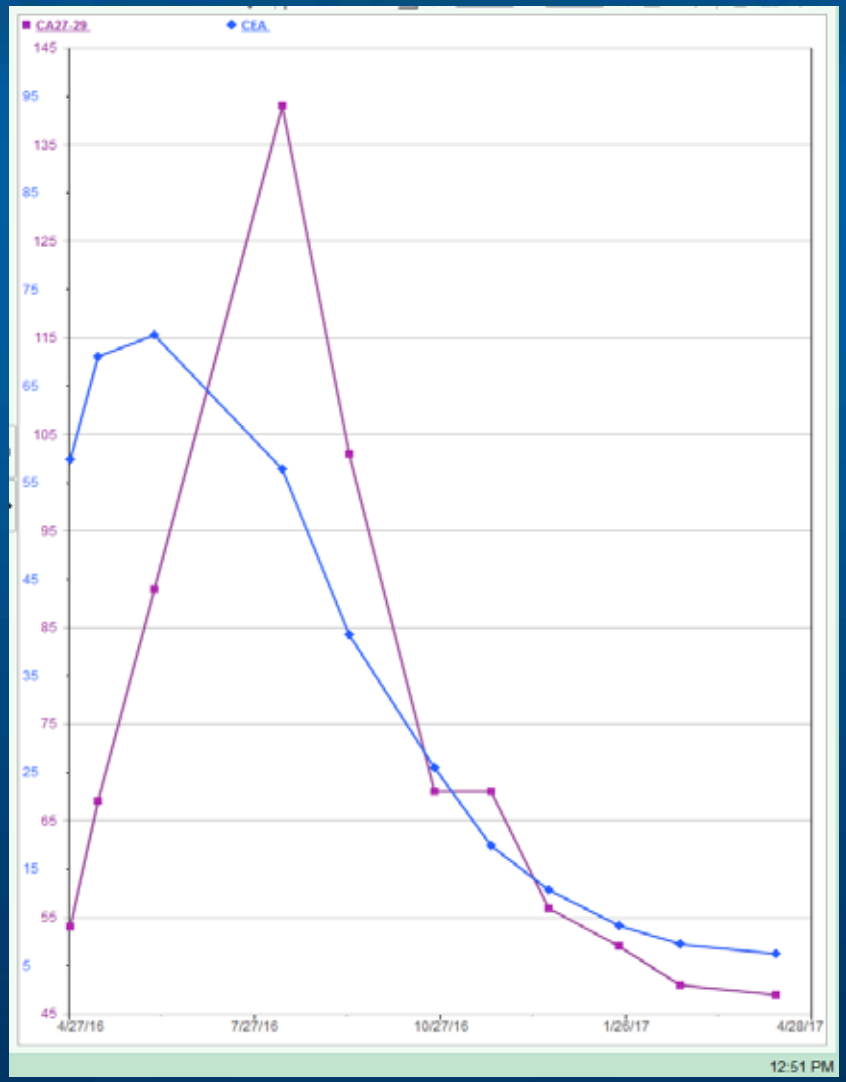


Before olaparib



After 2 years of olaparib

47-Year-Old Woman with ER-Positive, HER2-Negative Metastatic Breast Cancer (Ms O'Reilly)



Reduction in tumor markers

Reminder

Please turn in your CNE course evaluation for credit as you exit the activity.

Thank you for joining us.