Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Triple-Negative Breast Cancer

Friday, December 11, 2020
8:30 PM – 10:00 PM ET

Faculty

P Kelly Marcom, MD
Joyce O'Shaughnessy, MD
Hope S Rugo, MD
Professor Peter Schmid, MD, PhD

Moderator

Neil Love, MD

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eisai Inc, Genentech, a member of the Roche Group, and Merck.

Dr Love — Disclosures

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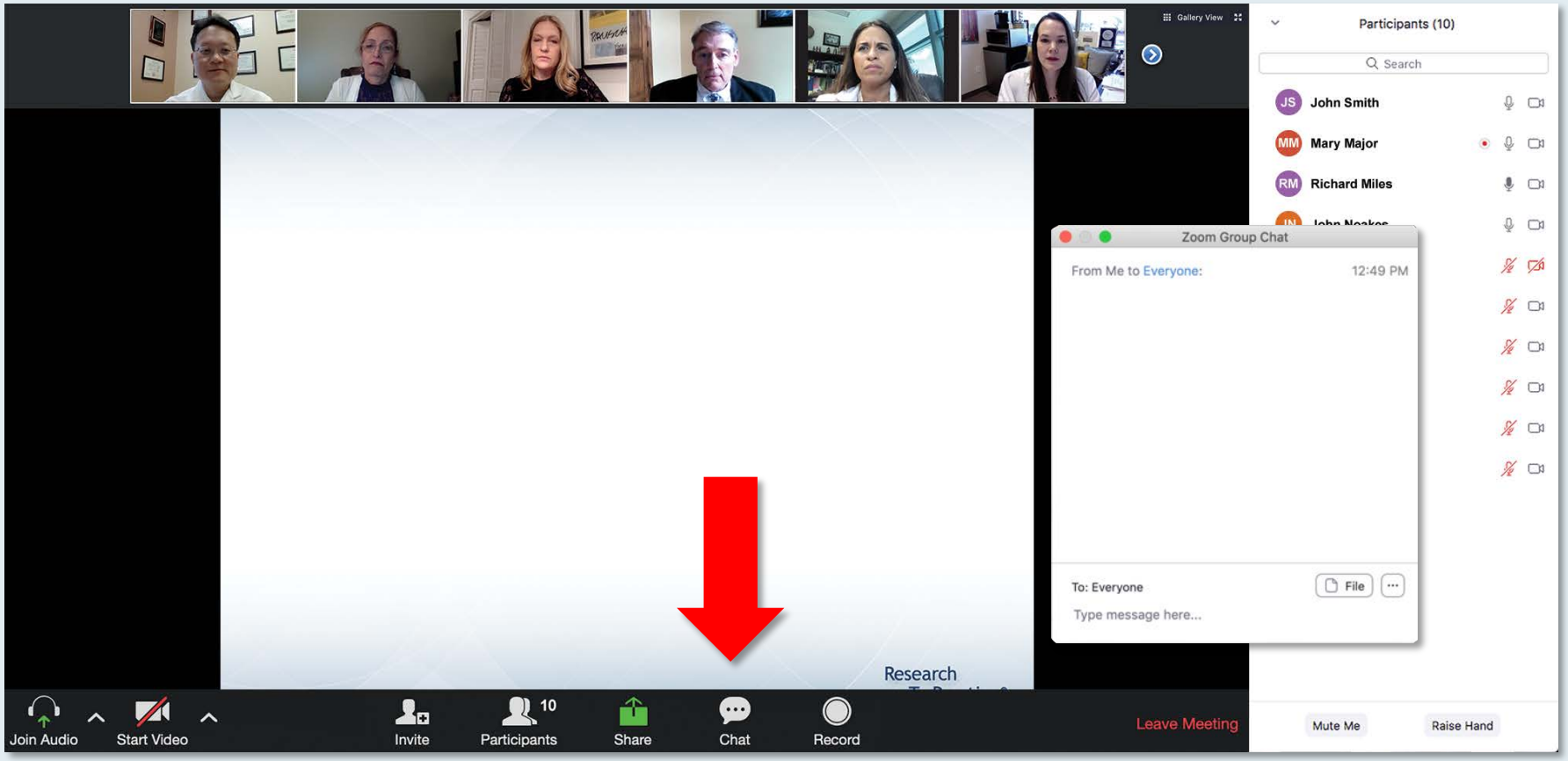

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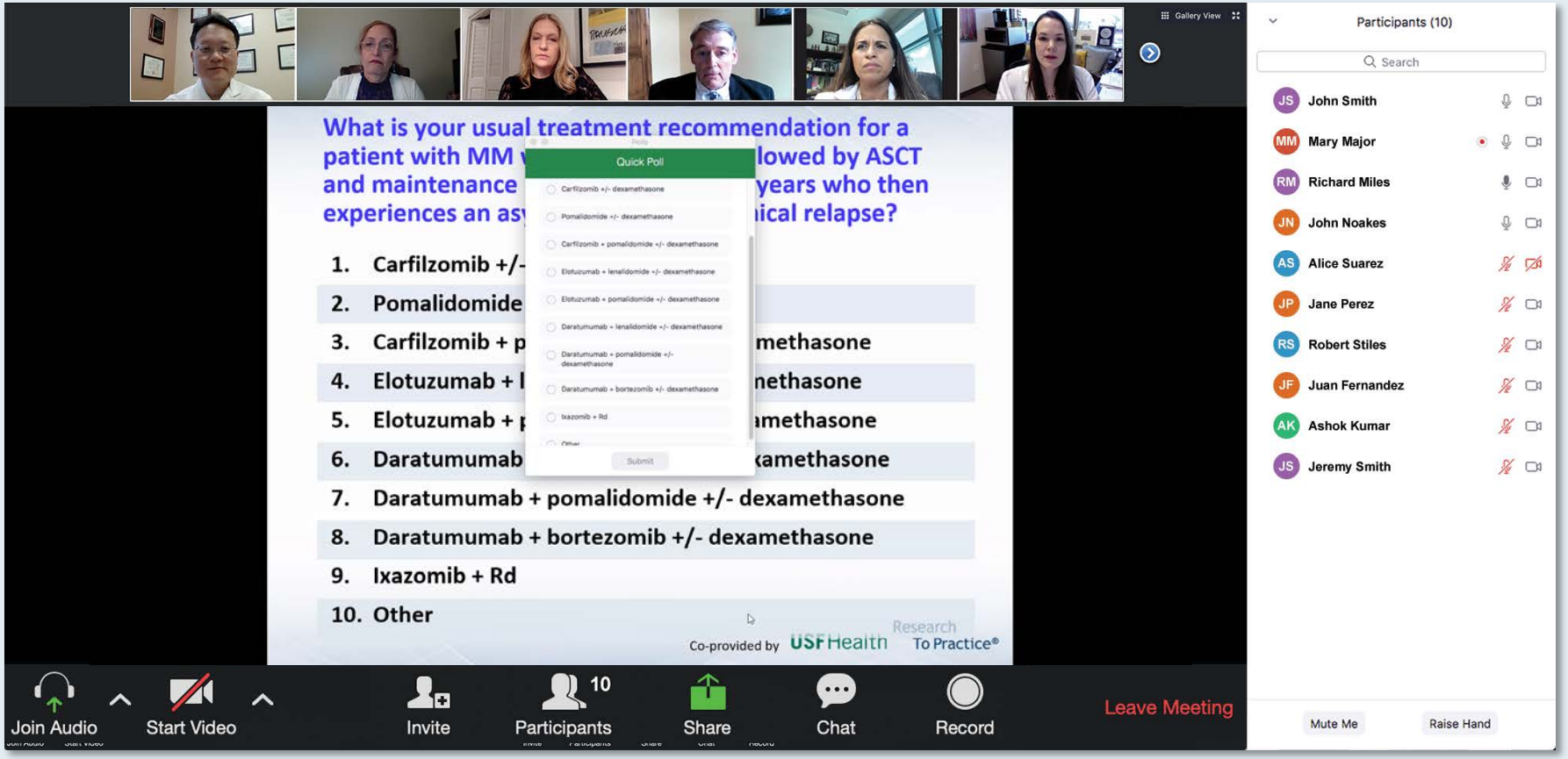

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Year in Review: Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology

Hepatobiliary and Pancreatic Cancers

Tuesday, December 15, 2020
5:00 PM – 6:00 PM ET

Faculty

Tanios Bekaii-Saab, MD
Lipika Goyal, MD, MPhil

Moderator

Neil Love, MD

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Meet The Professor
Management of Multiple Myeloma

Wednesday, December 16, 2020
12:00 PM – 1:00 PM ET

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Peter Voorhees, MD

Moderator

Neil Love, MD

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Meet The Professor

Management of Chronic Lymphocytic Leukemia

Wednesday, December 16, 2020
2:00 PM – 3:00 PM ET

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Moderator

Neil Love, MD

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Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.

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WITH DR NEIL LOVE

IMMUNE CHECKPOINT INHIBITION IN BREAST CANCER

DR SYLVIA ADAMS

PERLMUTTER CANCER CENTER

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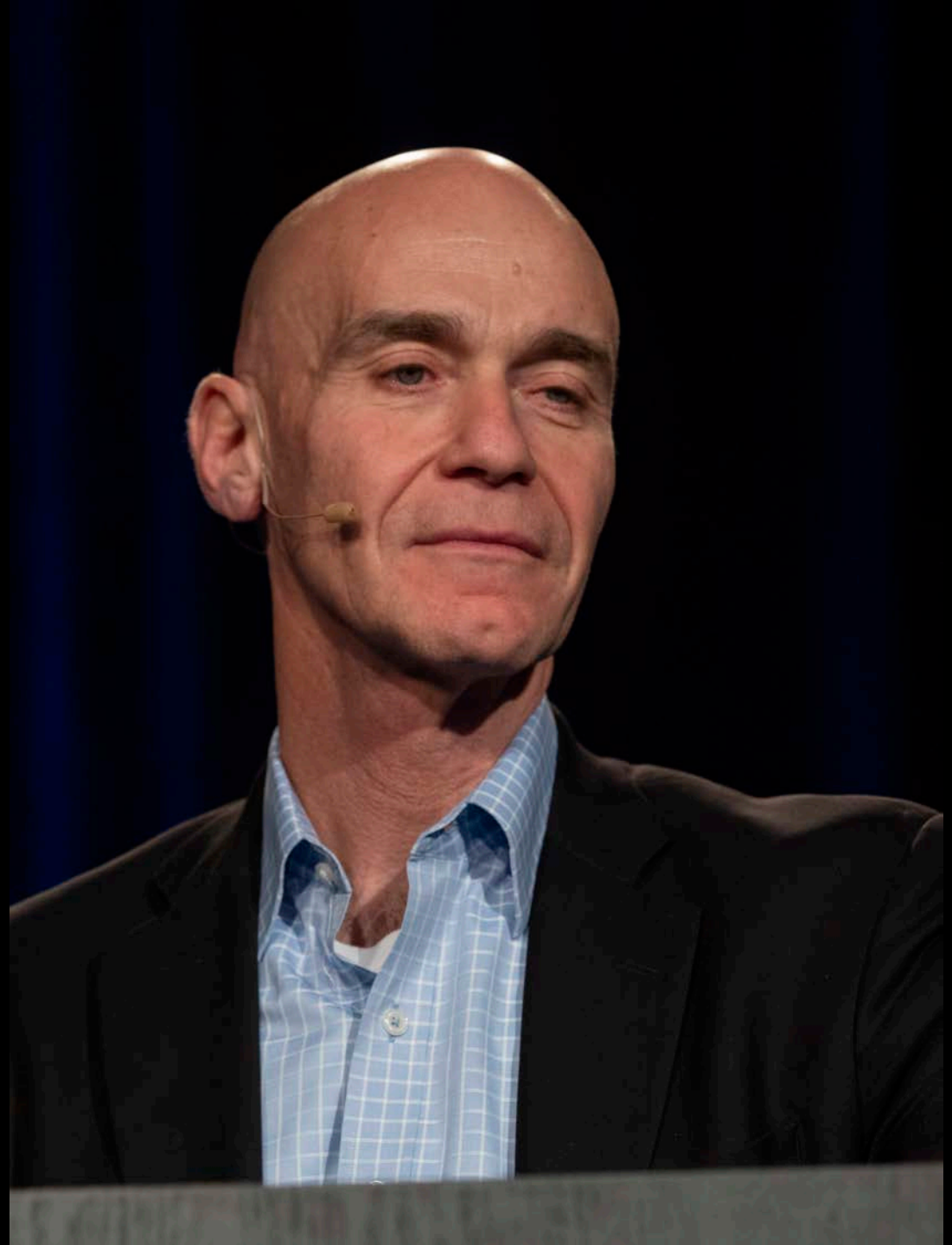
INSTITUUT
Adjuvant and Extended-Adjuvant Therapy for Patients with Localized HER2-Positive Breast Cancer
Martine J Piccart-Gebhart, MD, PhD
Scientific Director




KEYNOTE 522: NEOADJUVANT CHEMO + PEMBROLIZUMAB IN TNBC
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Management of Triple-Neg
Thursday, December 12, 2019
7:30 PM – 9:00 PM
San Antonio, Texas
Moderator
Neil Love, MD
Faculty
Erika Hamilton, MD


Sparano et al. N Engl J Med 2019;380(25):2395-2405.
Integrated Risk: Potential Clinical Utility of Integrated RS and Clinical Risk for Guiding Treatment in Women ≤ 50 Years
Integrated RS and Clinical Risk (CR)
Low Integrated Risk (58%)
< 5% Distant Recurrence
High Integrated Risk (31%)
> 10% Distant Recurrence
Tamoxifen alone adequate
No Chemotherapy
Consider chemotherapy or OFS + AI as an alternative to chemotherapy
Chemotherapy and consider OFS + AI in addition to chemotherapy
Prediction: Hazard Ratio for Chemotherapy Benefit as a Function of Continuous RS and Age (SEER)
Cox proportional hazards regression with propensity weighting (N=70,087)
Age ≤ 50 Years
Age > 50 Years


A 65-year-old postmenopausal woman completes 5 years of adjuvant anastrozole for an ER-positive, HER2-negative IDC but develops asymptomatic biopsy-proven bone and liver metastases 2 years later. Which systemic treatment would you most likely recommend?


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)

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London, United Kingdom

Moderator
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Miami, Florida

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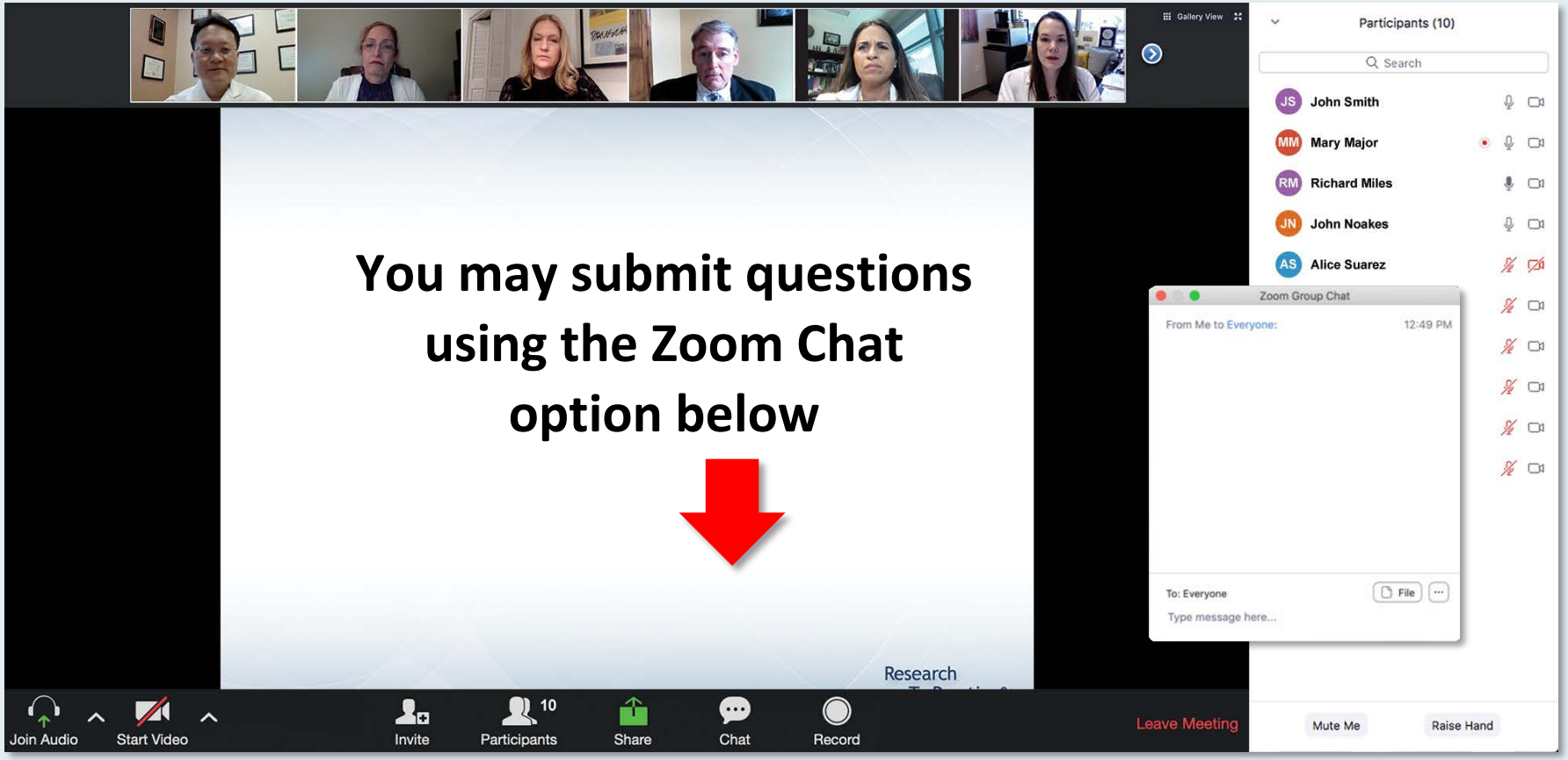

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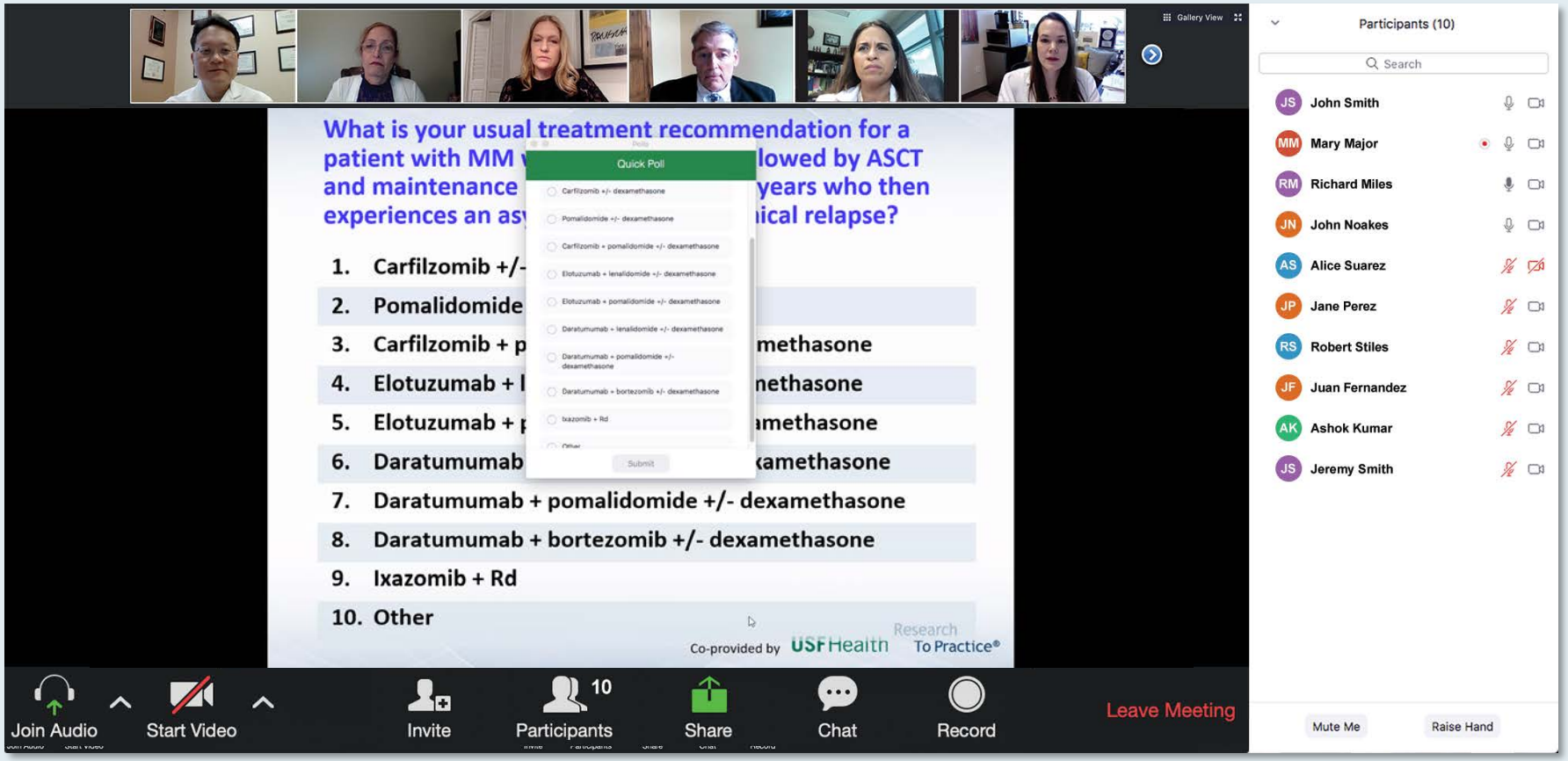

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Presentation Library

Triple-Negative Breast Cancer, Friday, December 11, 2020

Optimal Integration of Immune Checkpoint Inhibitors into the Management of Metastatic Triple-Negative Breast Cancer (mTNBC)
Professor Peter Schmid, MD, PhD

Download Slides

Novel Applications of Immune Checkpoint Inhibitors for Patients with Early TNBC
Hope S Rugo, MD

Download Slides

Current and Future Role of PARP Inhibitors for Patients with TNBC and a BRCA Mutation
P Kelly Marcom, MD

Download Slides

Current and Future Management of PD-L1-Negative mTNBC
Joyce O'Shaughnessy, MD

Download Slides

Triple-Negative Breast Cancer Survey Participants

1. Sylvia Adams, MD
2. Carey K Anders, MD
3. Aditya Bardia, MD, MPH
4. Joanne L Blum, MD, PhD
5. Adam M Brufsky, MD, PhD
6. Howard A Burris III, MD
7. Harold J Burstein, MD, PhD
8. Lisa A Carey, MD
9. Matthew Goetz, MD
10. Erika Hamilton, MD
11. Sara Hurvitz, MD
12. Virginia Kaklamani, MD, DSc
13. Hannah M Linden, MD
14. P Kelly Marcom, MD
15. Jennifer M Matro, MD
16. Kathy D Miller, MD
17. Rita Nanda, MD
18. Ruth O'Regan, MD
19. Joyce O'Shaughnessy, MD
20. Mark D Pegram, MD
21. Lajos Pusztai, MD, DPhil
22. Hope S Rugo, MD
23. Professor Peter Schmid, MD, PhD
24. Joseph A Sparano, MD
25. Sara M Tolaney, MD, MPH

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Agenda

Module 1: Optimal Integration of Immune Checkpoint Inhibitors into the Management of Metastatic Triple-Negative Breast Cancer – Prof Schmid

Module 2: Novel Applications of Immune Checkpoint Inhibitors for Patients with Early TNBC – Dr Rugo

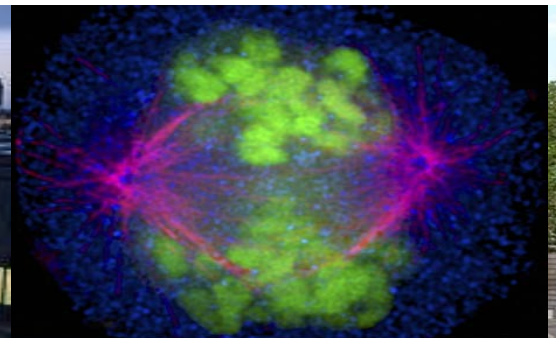
Module 3: Current and Future Role of PARP Inhibitors for Patients with TNBC and a BRCA Mutation – Dr Marcom

Module 4: Current and Future Management of PD-L1-Negative Metastatic Triple Negative Breast Cancer – O'Shaughnessy

Optimal Integration of Immune Checkpoint Inhibitors into the Management of Metastatic Triple-Negative Breast Cancer

PROFESSOR PETER SCHMID, MD PHD FRCP

LEAD, CENTRE FOR EXPERIMENTAL CANCER MEDICINE
BARTS CANCER INSTITUTE, ST BARTHOLOMEW'S HOSPITAL
QUEEN MARY UNIVERSITY OF LONDON

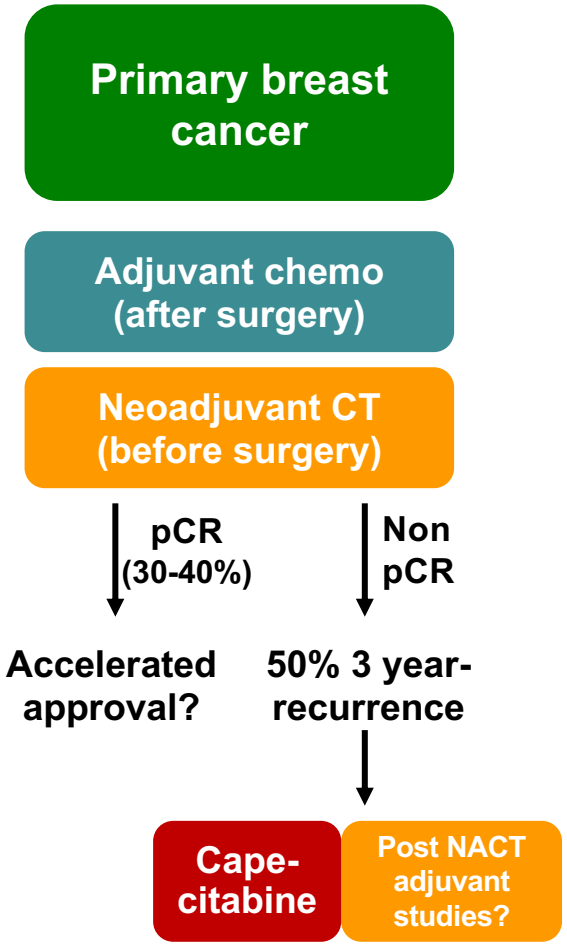




Queen Mary University of London

Barts Health NHS Trust

Triple Negative Breast Cancer – Management in 2017

Median OS for met. TNBC 12-18 months!

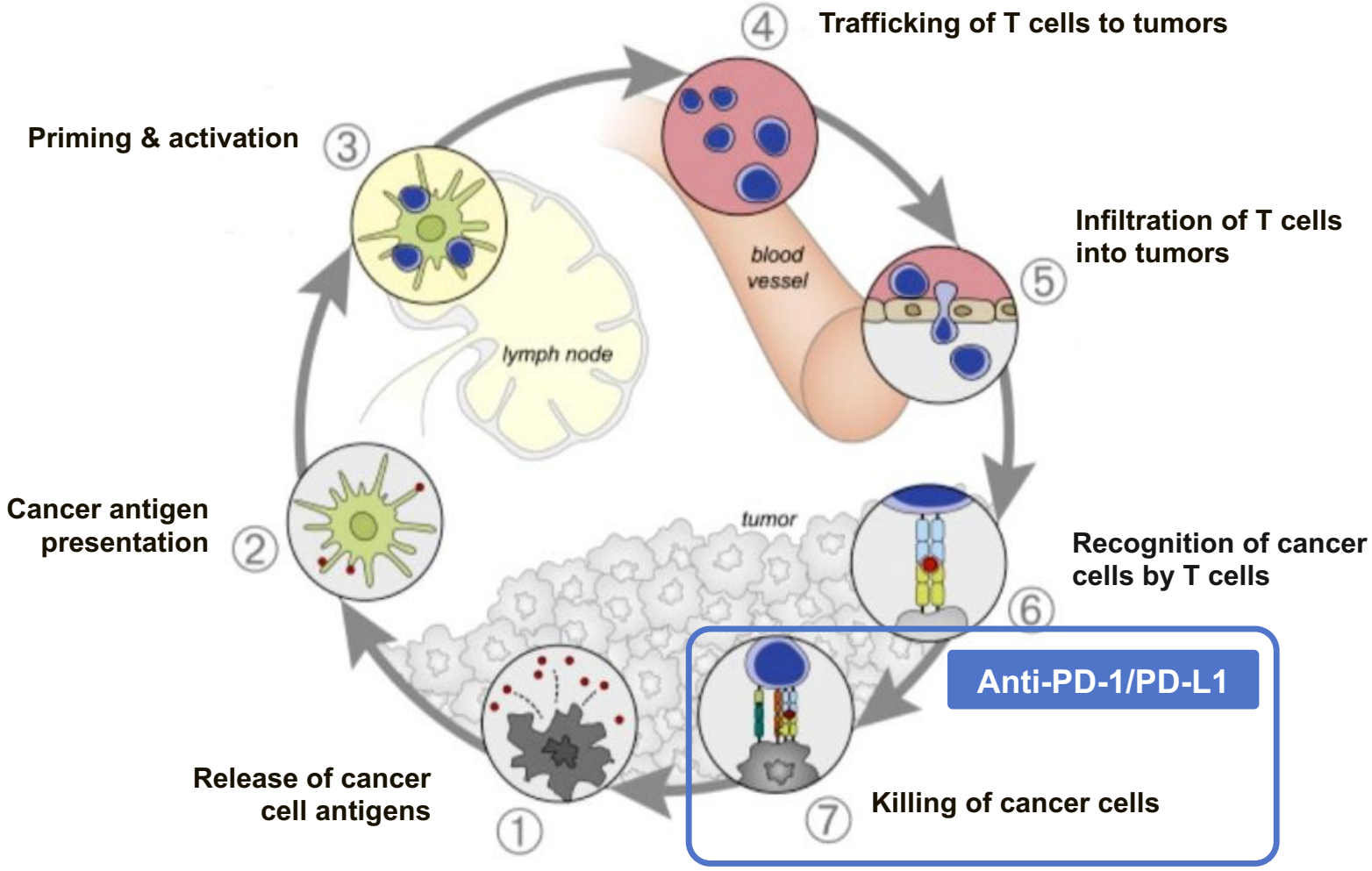


MBC 1st line	MBC 2nd line	MBC >2nd line
Taxanes (if DFI >1a)	Capecitabine	Eribulin
Platinum Combinations (CarboTax, GC)	Platinum Combinations (CarboTax, GC)	BSC
Taxanes + Bevacizumab	Eribulin	

Schmid P, et al. Personal Communication

Courtesy of Professor Peter Schmid, MD, PhD

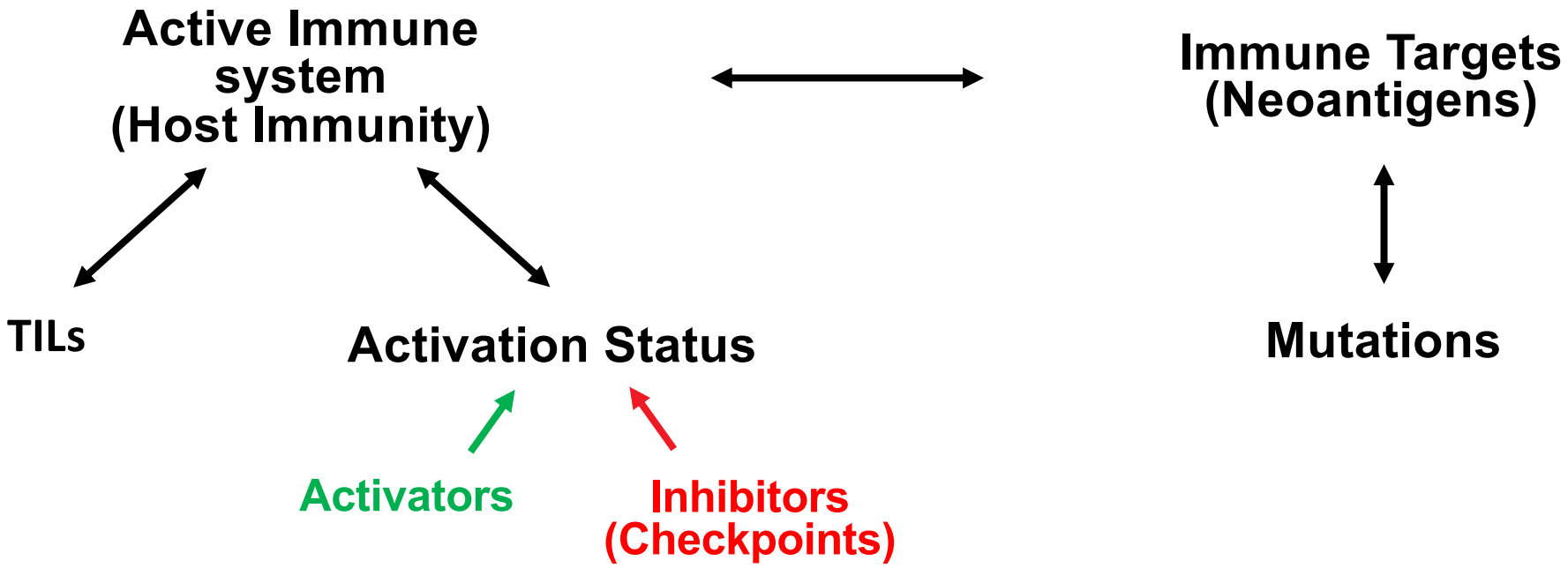
Antitumor Immunity Is a Dynamic Process



Courtesy of Professor Peter Schmid, MD, PhD

1. Chen and Mellman 2013; 2. Liakou et al. 2008; 3. Herr and Morales 2008; 4. Bajorin et al. 2014

Cancer and Immunity



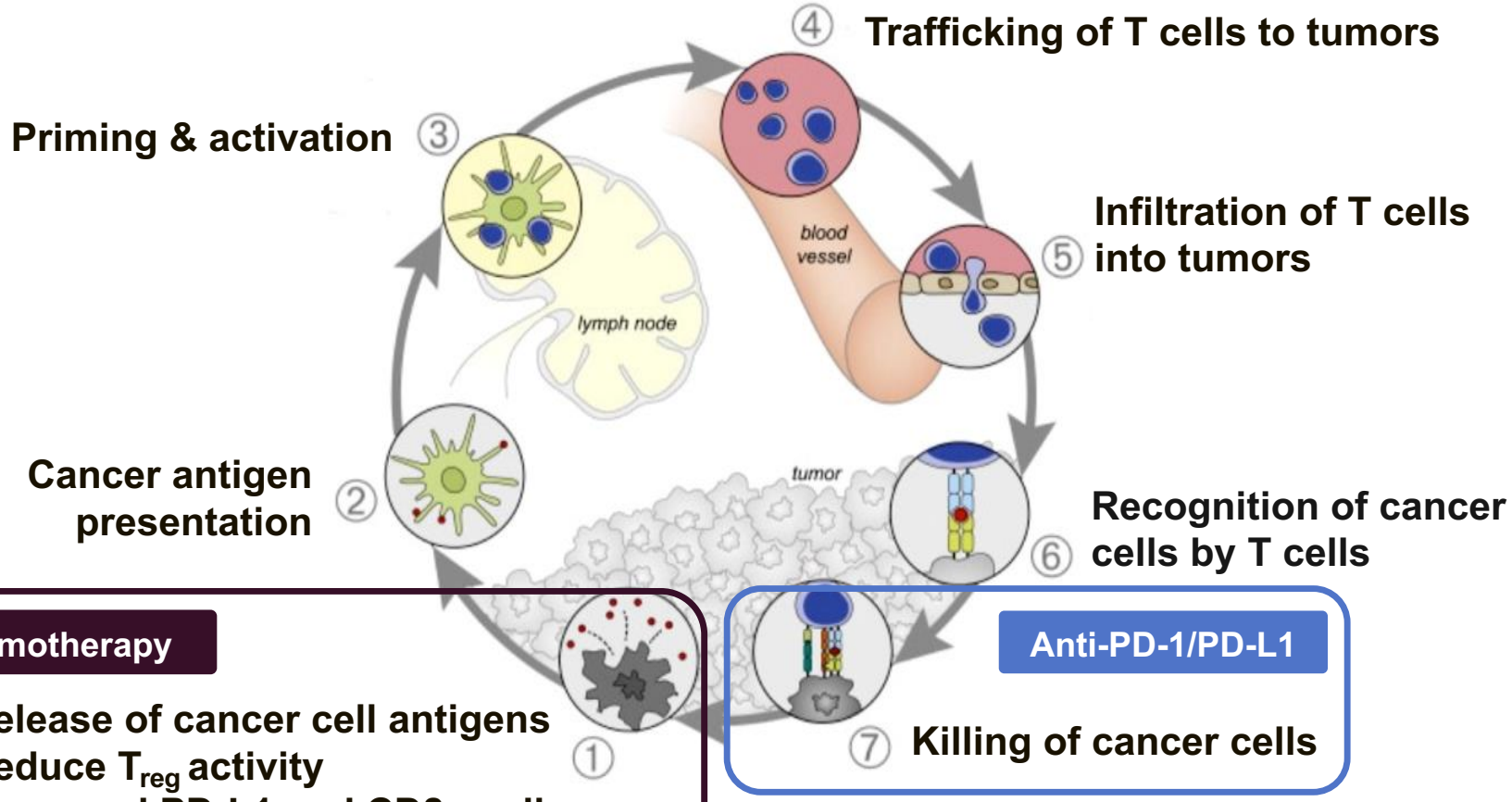
Courtesy of Professor Peter Schmid, MD, PhD

Schmid P, et al. Personal Communication

CIT can target several steps in the immunity cycle

Combinations to widen the target population and increase efficacy

1. Chemotherapy + CIT
2. CIT + novel targeted agents (eg PARP, MEK)?
3. CIT combination



Courtesy of Professor Peter Schmid, MD, PhD

1. Chen and Mellman 2013; 2. Liakou et al. 2008; 3. Herr and Morales 2008; 4. Bajorin et al. 2014

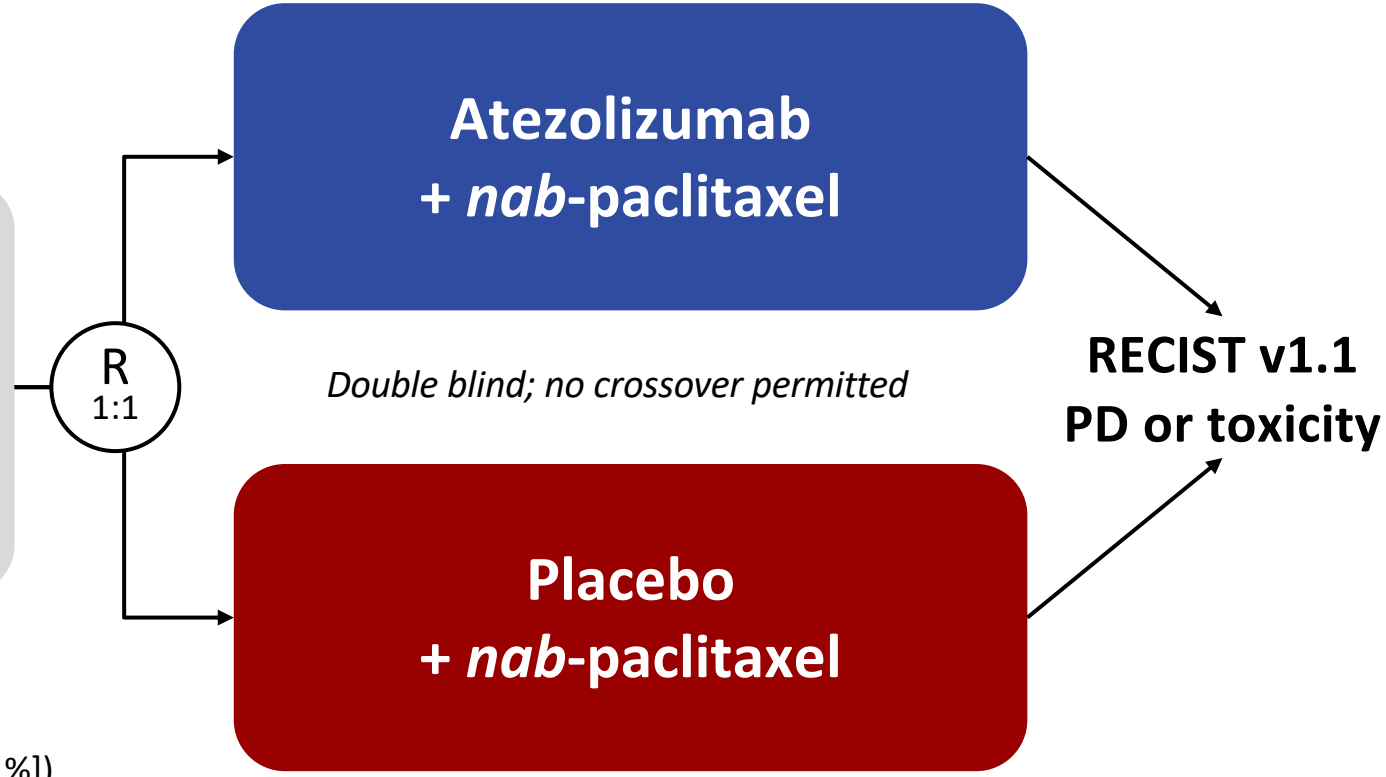
Atezolizumab (anti-PD-L1) plus chemotherapy in TNBC

IMpassion130 study design

- **Metastatic or inoperable locally advanced TNBC**
- **No prior therapy for advanced TNBC**
  - **Prior (neo)adjuvant chemo allowed if TFI ≥ 12 months**
- **ECOG PS 0-1**

Stratification factors:

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

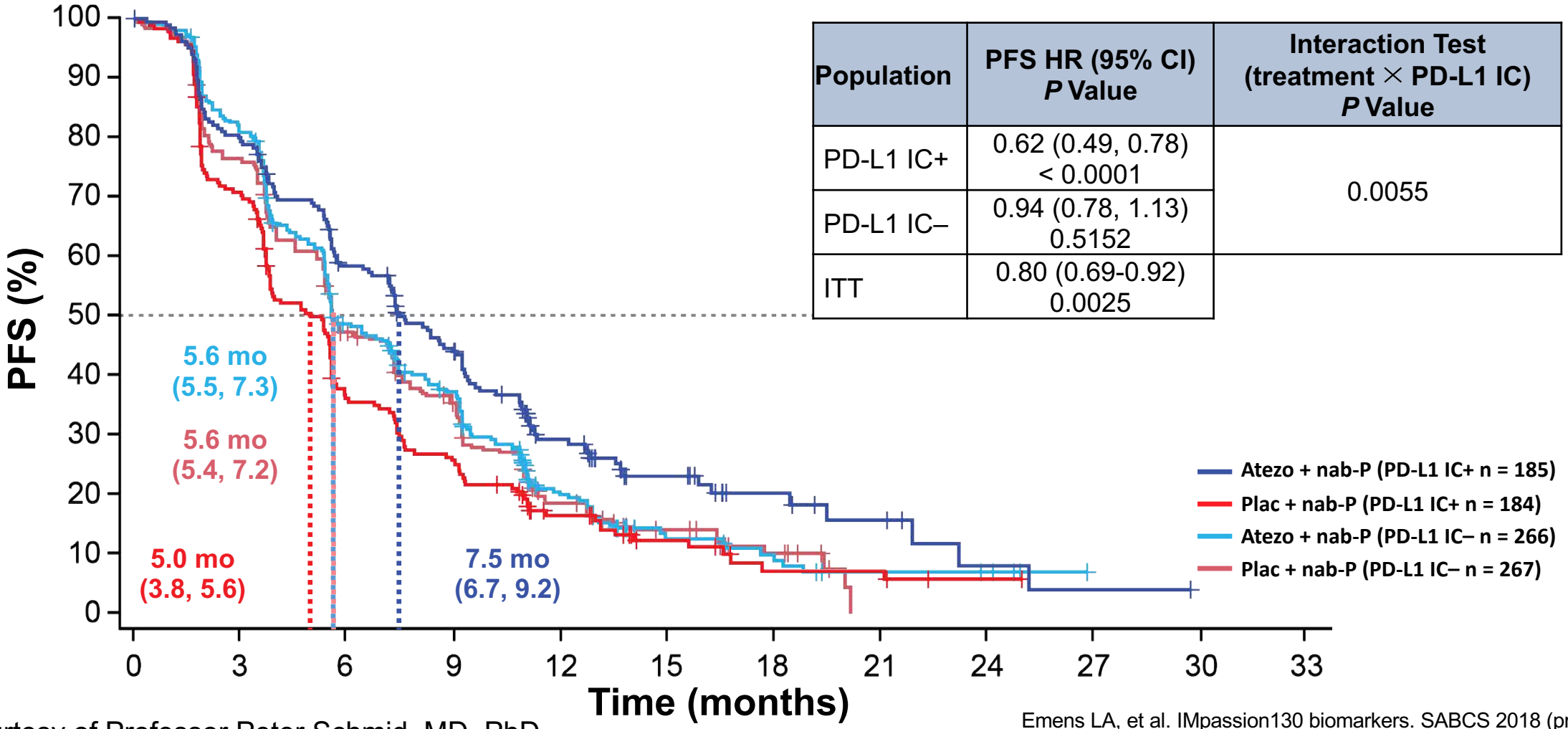


- **Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations**

Courtesy of Professor Peter Schmid, MD, PhD

Schmid P, et al. ESMO 2018 (LBA1); Schmid P, et al NEJM 2018

Progression-free survival: PD-L1 predicts benefit with atezolizumab



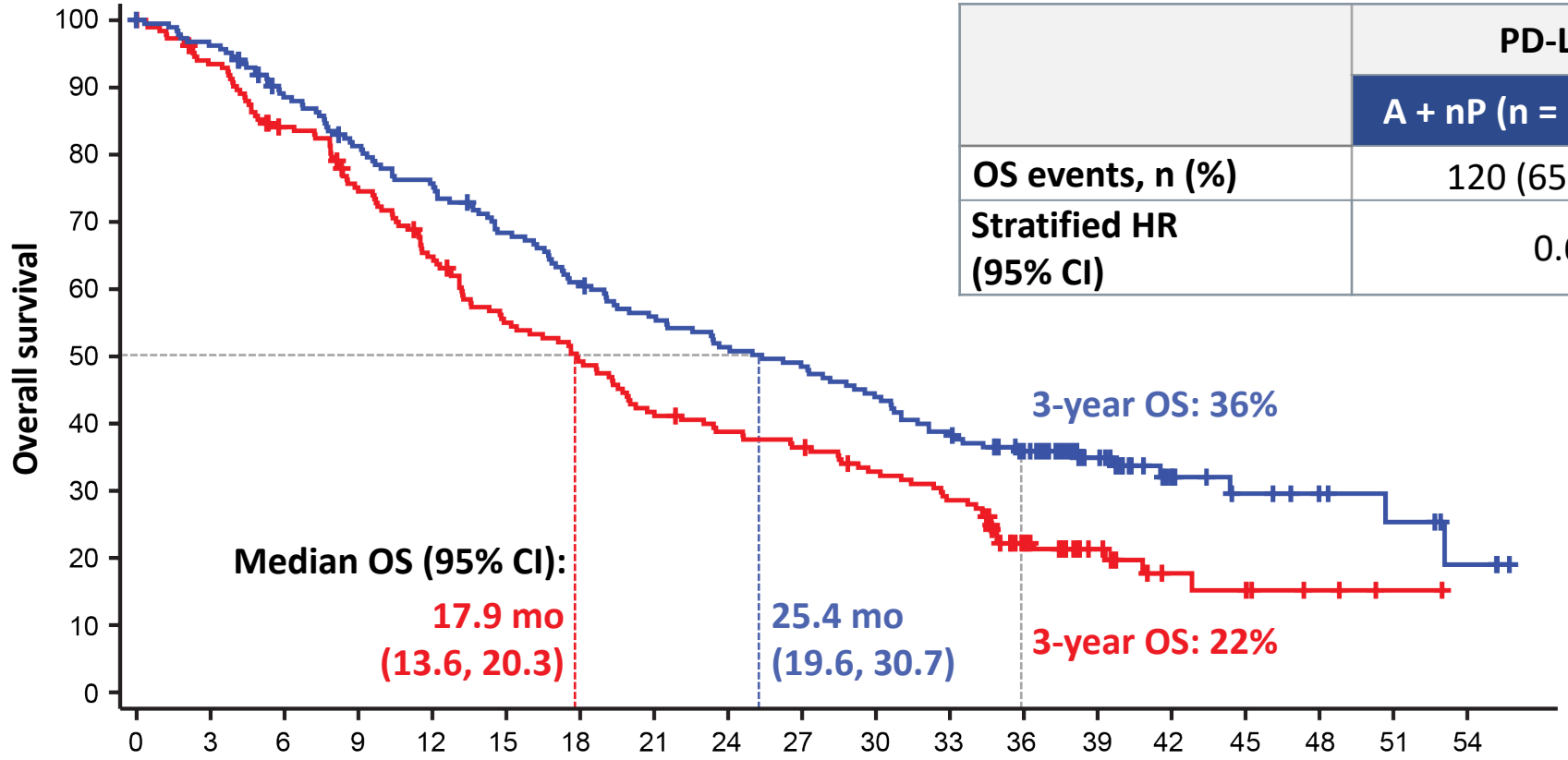
Population	PFS HR (95% CI) *P* Value	Interaction Test (treatment × PD-L1 IC) *P* Value
PD-L1 IC+	0.62 (0.49, 0.78) < 0.0001	0.0055
PD-L1 IC–	0.94 (0.78, 1.13) 0.5152	
ITT	0.80 (0.69-0.92) 0.0025	

Courtesy of Professor Peter Schmid, MD, PhD

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04); Schmid P, et al. ESMO 2018 (LBA1); Schmid P, et al NEJM 2018

Overall survival: PD-L1 status predicts benefit with atezolizumab

	PD-L1 IC+ population	
	A + nP (n = 185)	P + nP (n = 184)
OS events, n (%)	120 (65)	139 (76)
Stratified HR (95% CI)	0.67 (0.53, 0.86)[a]	



No. at risk (PD-L1+ population):																		
A + nP	185	177	160	145	135	121	108	98	90	86	77	67	56	32	17	11	9	6	3
P + nP	184	170	150	132	113	95	85	72	66	62	54	47	28	14	7	6	3	1	NE

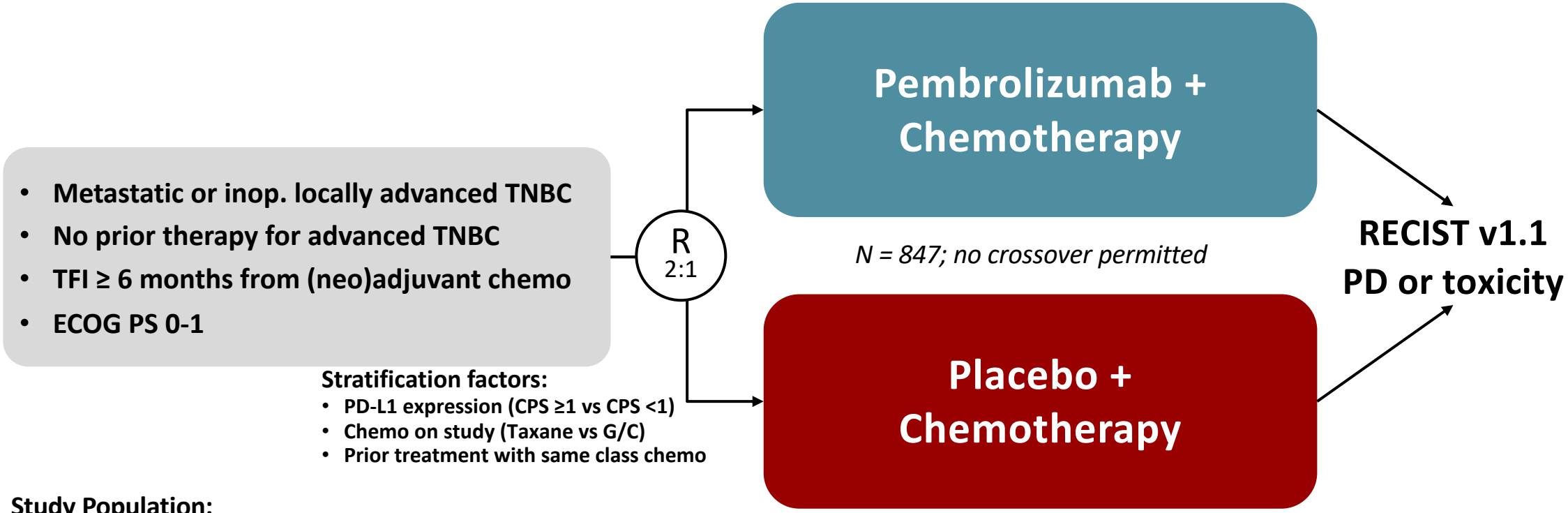
Courtesy of Professor Peter Schmid, MD, PhD

Data cutoff, 14 April 2020. NE, not estimable. [a] *P* value not formally tested per hierarchical study design.

Emens LA. ESMO 2020

Pembrolizumab (anti-PD-1) plus chemotherapy in TNBC

KEYNOTE-355 study design



- Metastatic or inop. locally advanced TNBC
- No prior therapy for advanced TNBC
- TFI ≥ 6 months from (neo)adjuvant chemo
- ECOG PS 0-1

Stratification factors:
- PD-L1 expression (CPS ≥1 vs CPS <1)
- Chemo on study (Taxane vs G/C)
- Prior treatment with same class chemo

Study Population:
- CPS≥10, 75%; CPS≥1, 38%; CPS <1, 25%
- Taxane, 45%; Gem/carboplatin, 55%
- Prior treatment with same class chemo, 22%
- De novo MBC, 30%; DFI 6-12, 21%; DFI >12, 49%

Nab-paclitaxel, 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel, 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine, 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days

- **Co-primary endpoints were PFS and OS in the CPS ≥10, CPS ≥1, and ITT populations**

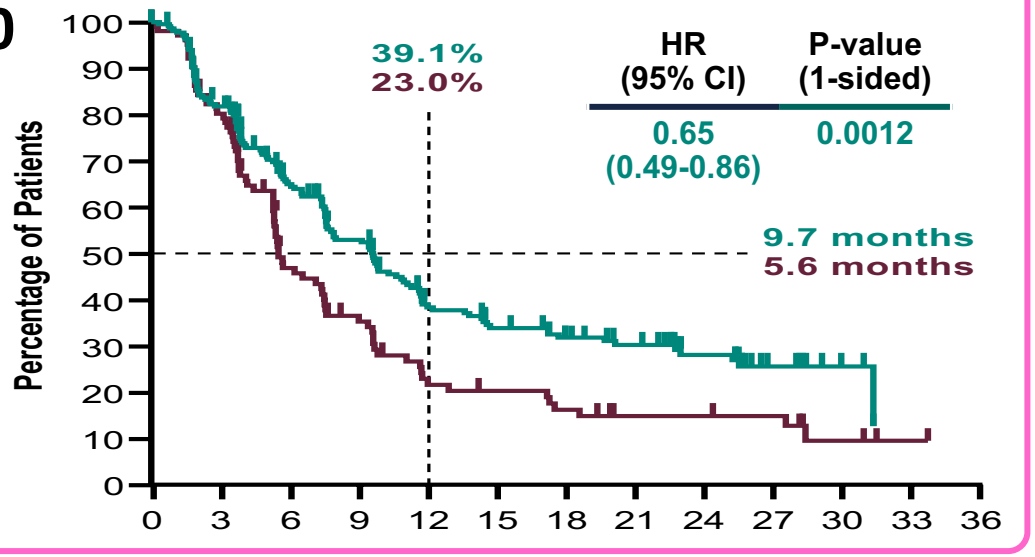
Statistical design: Overall alpha controlled at one-sided 0.025, split among PFS (0.005),OS (0.018), and ORR (0.002); hierarchical testing PFS (CSP10>CP1>ITT)

Courtesy of Professor Peter Schmid, MD, PhD

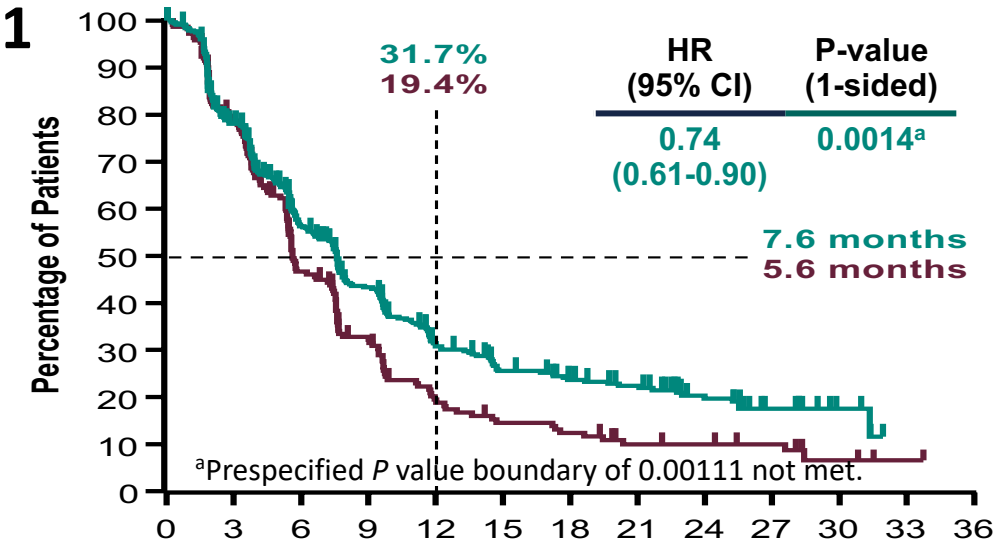
Cortes, et al. ASCO 2020

Pembrolizumab (anti-PD-1) plus chemo: Progression-free Survival

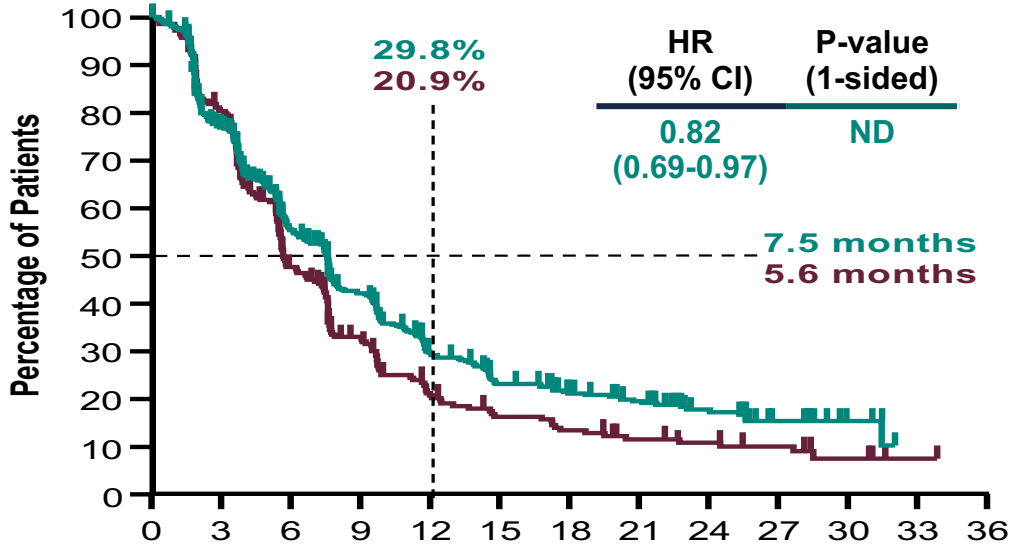
CPS ≥10



CPS ≥1



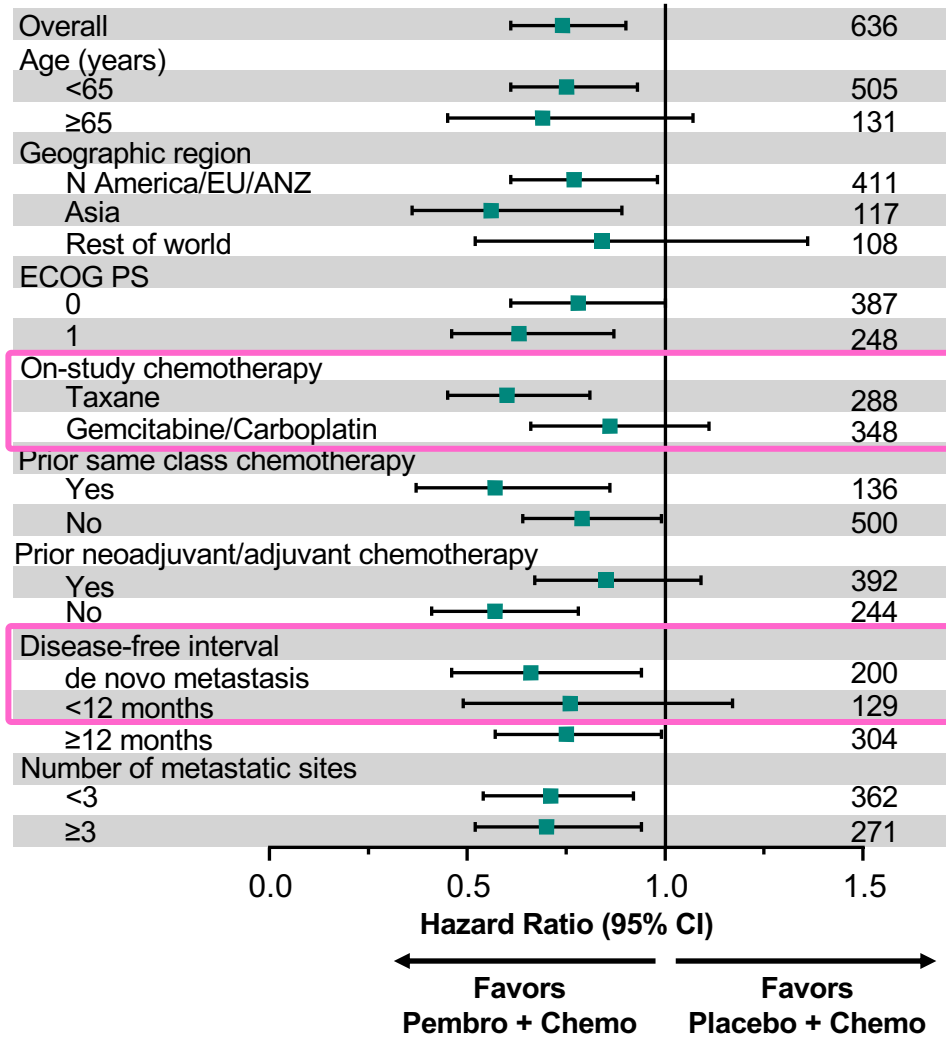
ITT



Courtesy of Professor Peter Schmid, MD, PhD

Cortes, et al. ASCO 2020

Progression-Free Survival in Subgroups: PD-L1 CPS ≥1

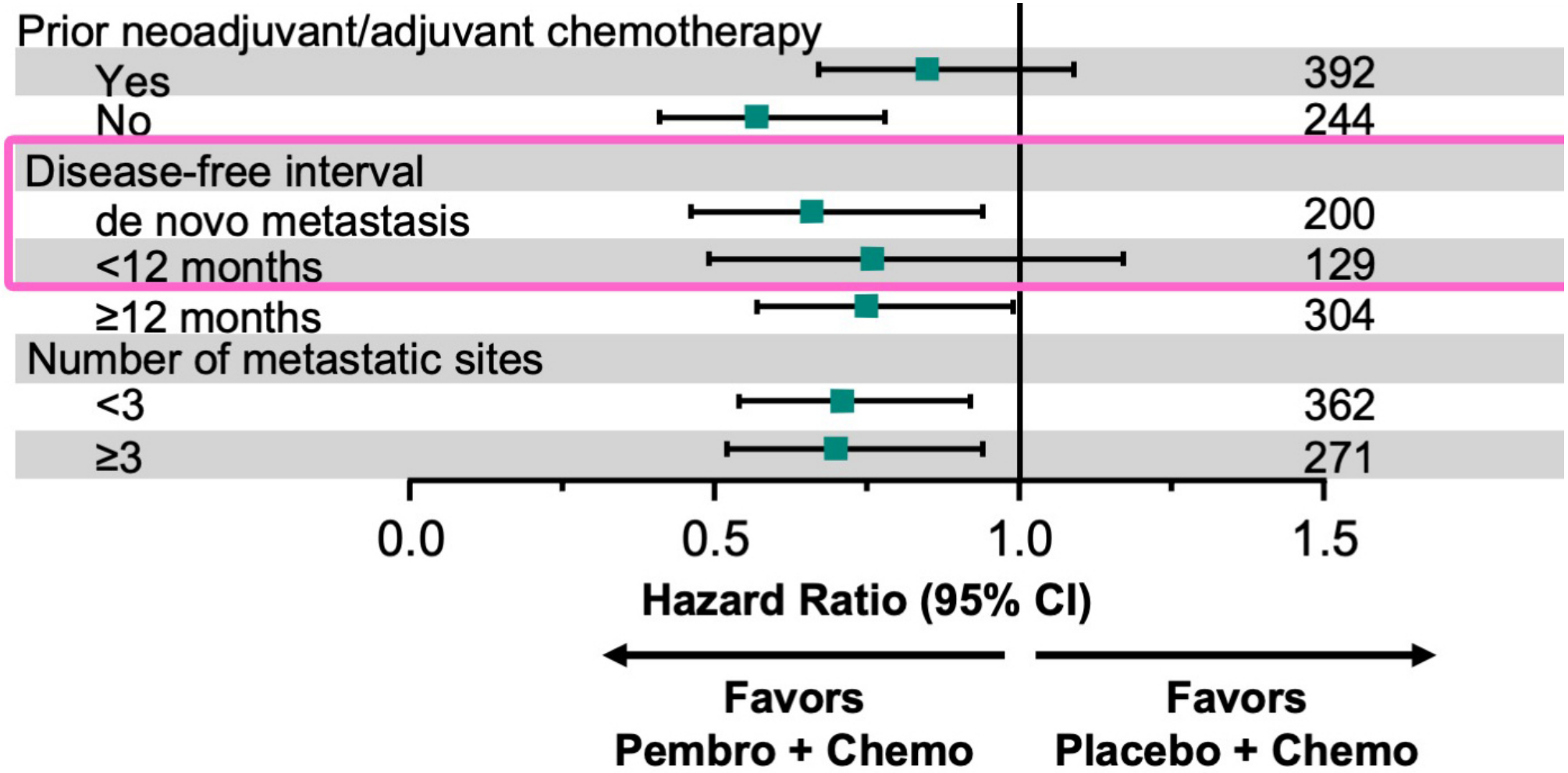


Subgroup	N	Median PFS (mo)		Hazard Ratio for Progression or Death (95% CI)
		Pembro + Chemo	Placebo + Chemo	
Overall	636	7.6	5.6	0.74 (0.61 to 0.90)
Age (years)				
<65	505	7.5	5.6	0.75 (0.61 to 0.93)
≥65	131	8.2	6.6	0.69 (0.45 to 1.07)
Geographic region				
N America/EU/ANZ	411	7.6	5.7	0.77 (0.61 to 0.98)
Asia	117	7.7	5.6	0.56 (0.36 to 0.89)
Rest of world	108	6.6	5.4	0.84 (0.52 to 1.36)
ECOG PS				
0	387	7.7	6.7	0.78 (0.61 to 1.00)
1	248	6.6	5.4	0.63 (0.46 to 0.87)
On-study chemotherapy				
Taxane	288	7.6	5.1	0.60 (0.45 to 0.81)
Gemcitabine/Carboplatin	348	7.5	7.5	0.86 (0.66 to 1.11)
Prior same class chemotherapy				
Yes	136	7.5	5.4	0.57 (0.37 to 0.86)
No	500	7.6	6.6	0.79 (0.64 to 0.99)
Prior neoadjuvant/adjuvant chemotherapy				
Yes	392	6.8	5.7	0.85 (0.67 to 1.09)
No	244	8.0	5.5	0.57 (0.41 to 0.78)
Disease-free interval				
de novo metastasis	200	7.6	5.6	0.66 (0.46 to 0.94)
<12 months	129	5.8	5.4	0.76 (0.49 to 1.17)
≥12 months	304	7.7	6.6	0.75 (0.57 to 0.99)
Number of metastatic sites				
<3	362	9.2	6.7	0.71 (0.54 to 0.92)
≥3	271	6.2	5.3	0.70 (0.52 to 0.94)

Courtesy of Professor Peter Schmid, MD, PhD

Cortes, et al. ASCO 2020

Progression-Free Survival in Subgroups: PD-L1 CPS ≥1



Courtesy of Professor Peter Schmid, MD, PhD

Cortes, et al. ASCO 2020

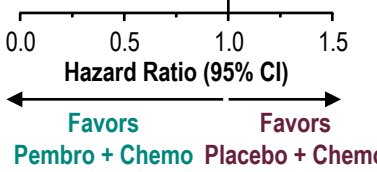
Additional Efficacy Endpoints from the Phase 3 KEYNOTE-355 Study of Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy as First-Line Therapy for Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer

Rugo HS et al. SABCS 2020;Abstract GS3-01

KEYNOTE-355: Progression-Free Survival in Subgroups by On-Study Chemotherapy

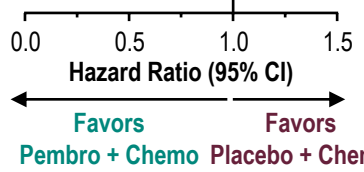
PD-L1 CPS ≥10

Subgroup	N	Median PFS (mo) Pembro + Chemo	Median PFS (mo) Placebo + Chemo	Hazard Ratio for Progression or Death (95% CI)
Overall	323	9.7	5.6	0.65 (0.49 to 0.86)
On-study chemotherapy				
Nab-Paclitaxel	99	9.9	5.5	0.57 (0.34 to 0.95)
Paclitaxel	44	9.6	3.6	0.33 (0.14 to 0.76)
Gemcitabine-Carboplatin	180	8.0	7.2	0.77 (0.53 to 1.11)



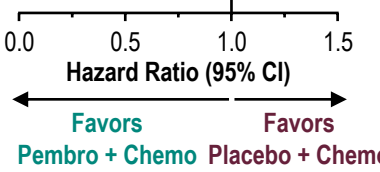
PD-L1 CPS ≥1

Subgroup	N	Median PFS (mo) Pembro + Chemo	Median PFS (mo) Placebo + Chemo	Hazard Ratio for Progression or Death (95% CI)
Overall	636	7.6	5.6	0.74 (0.61 to 0.90)
On-study chemotherapy				
Nab-Paclitaxel	204	6.3	5.3	0.66 (0.47 to 0.92)
Paclitaxel	84	9.4	3.8	0.46 (0.26 to 0.82)
Gemcitabine-Carboplatin	348	7.5	7.5	0.86 (0.66 to 1.11)



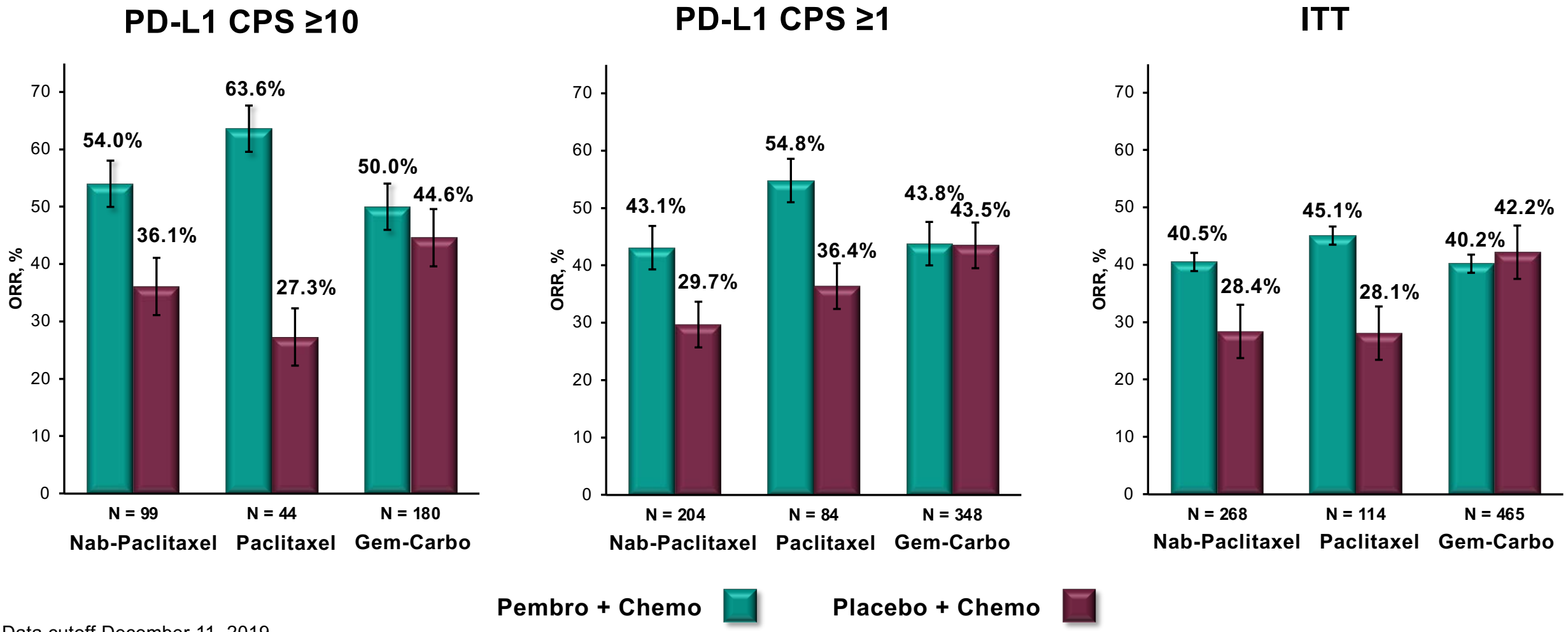
ITT

Subgroup	N	Median PFS (mo) Pembro- + Chemo	Median PFS (mo) Placebo + Chemo	Hazard Ratio for Progression or Death (95% CI)
Overall	847	7.5	5.6	0.82 (0.69 to 0.97)
On-study chemotherapy				
Nab-Paclitaxel	268	7.5	5.4	0.69 (0.51 to 0.93)
Paclitaxel	114	8.0	3.8	0.57 (0.35 to 0.93)
Gemcitabine-Carboplatin	465	7.4	7.4	0.93 (0.74 to 1.16)



The PFS treatment effect was assessed in subgroups descriptively using hazard ratios and 95% CIs; although subgroup analyses by on-study chemotherapy were pre-specified, the trial was not powered to compare efficacy among treatment groups by different chemotherapy regimens. Steroid premedication for paclitaxel was given according to local guidelines and practices and was not restricted by the protocol. Steroid use was also allowed for the management of immune-mediated AEs across the study. Data cutoff December 11, 2019.

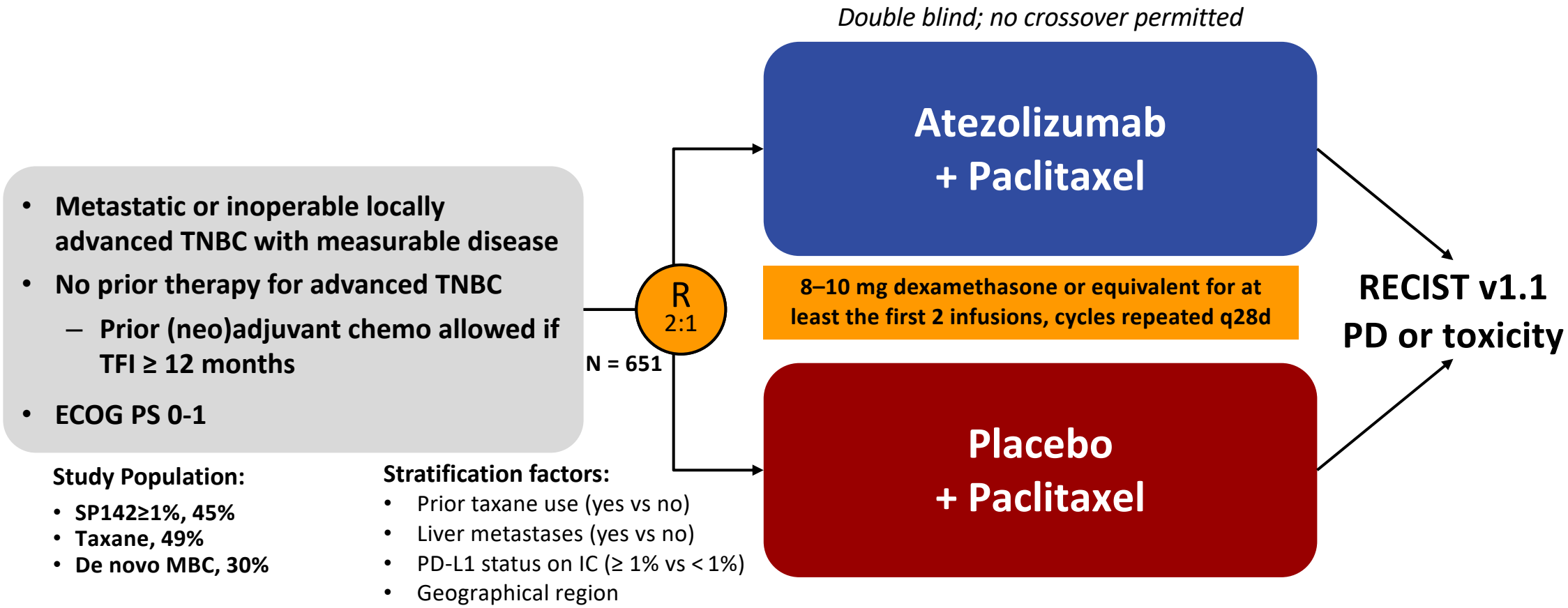
KEYNOTE-355: Response Rate in Subgroups by On-Study Chemotherapy



Data cutoff December 11, 2019.

Atezolizumab (anti-PD-L1) plus Paclitaxel in TNBC

IMpassion131 study design

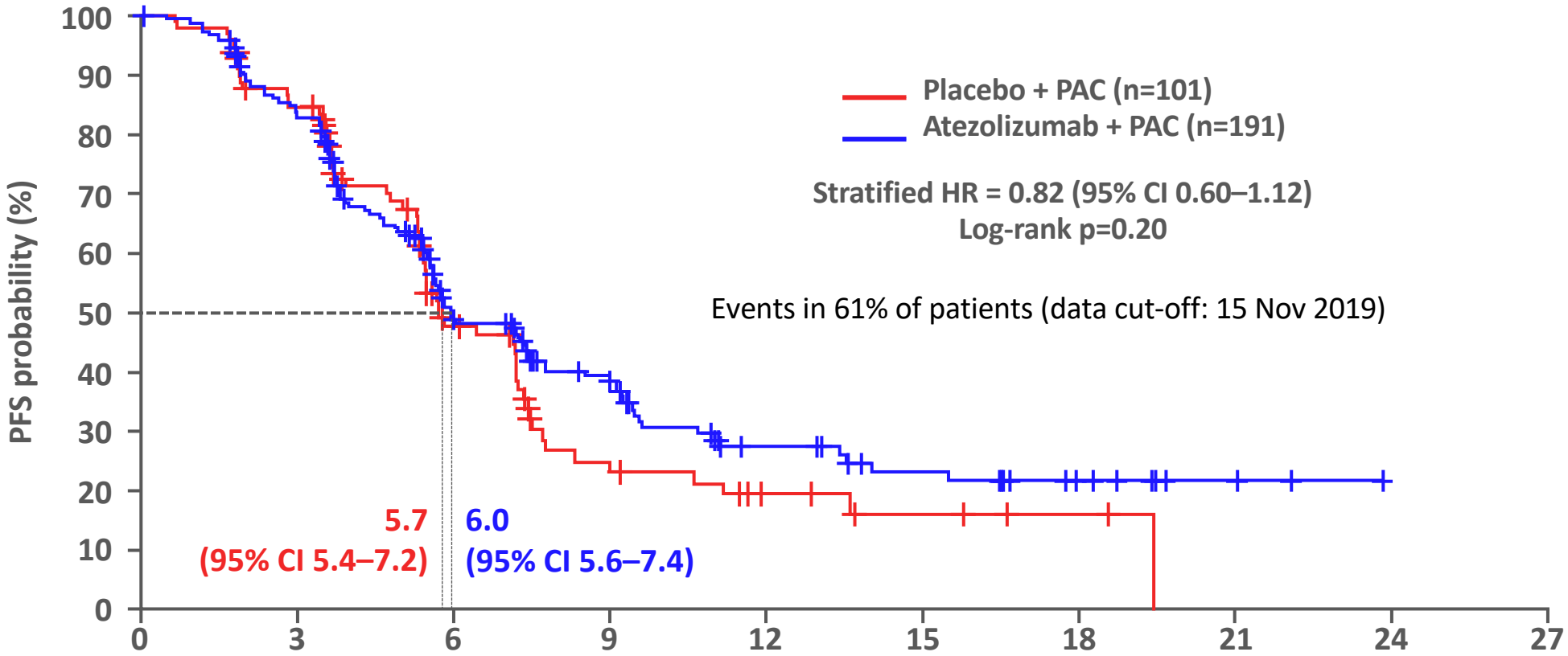


- **Co-primary endpoints were PFS (investigator assessed) in the PD-L1+ and ITT populations**

Courtesy of Professor Peter Schmid, MD, PhD

Miles D, et al. ESMO 2020

Atezolizumab plus Paclitaxel: Progression-free Survival in PD-L1+



Number at risk										
Placebo + PAC	101	81	33	14	7	4	2	0	0	0
Atezolizumab + PAC	191	152	69	44	22	15	8	3	0	0

Courtesy of Professor Peter Schmid, MD, PhD

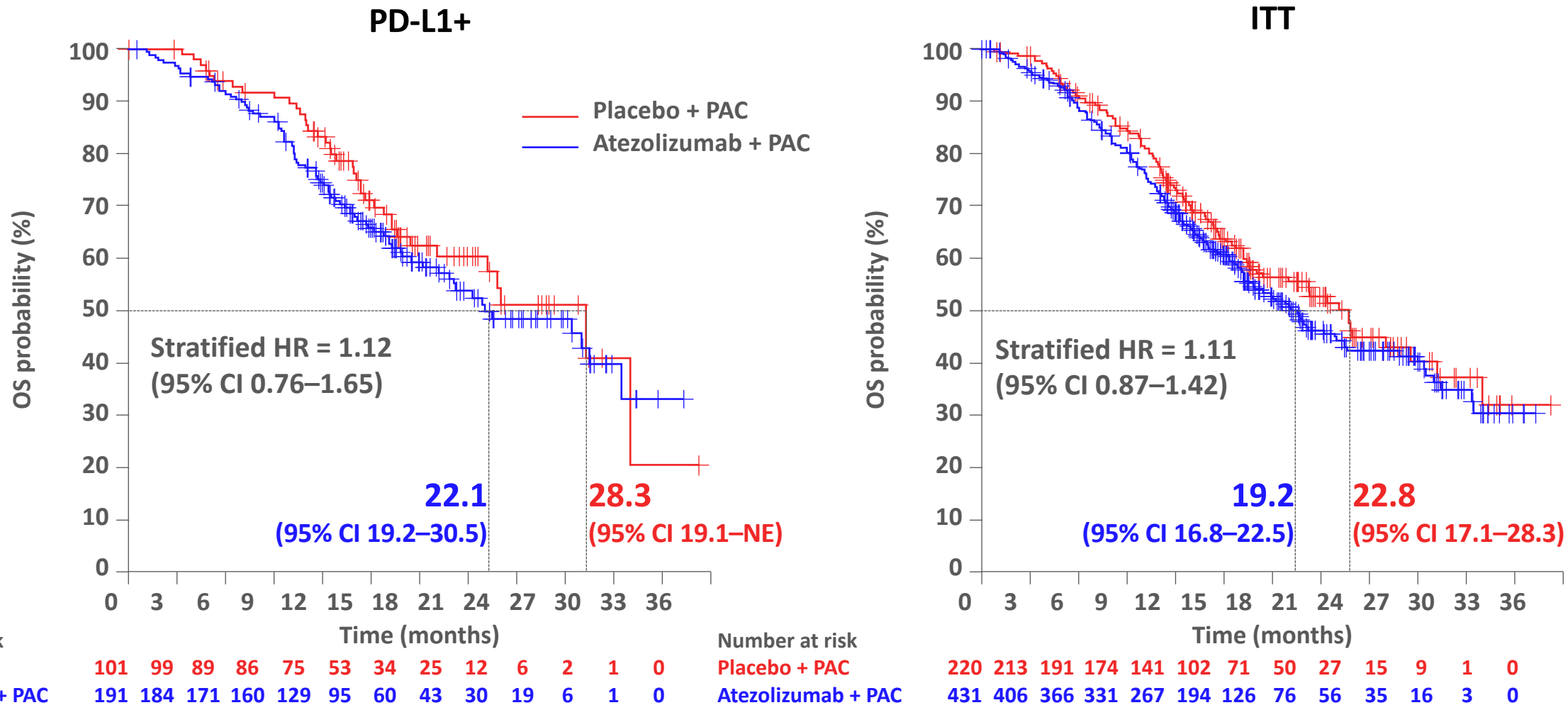
Median duration of follow-up: 8.6 months (placebo + PAC) vs 9.0 months (atezolizumab + PAC). CI = confidence interval

Miles D, et al. ESMO 2020

Atezolizumab plus Paclitaxel: Interim Survival Analysis

Updated interim OS analysis (data cut-off: 19 Aug 2020), events in 47% of the ITT population

Deaths in PD-L1+ 38 (38%) vs 82 (43%)



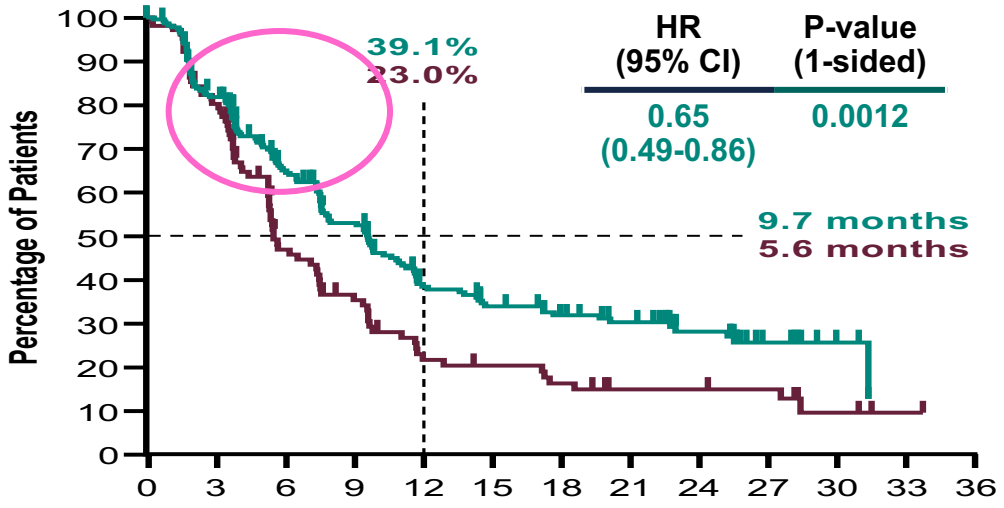
Median duration of follow-up: 14.5 months (placebo + PAC) vs 14.1 months (atezolizumab + PAC) in the ITT population

Prof. P. Schmid, Barts Cancer Institute

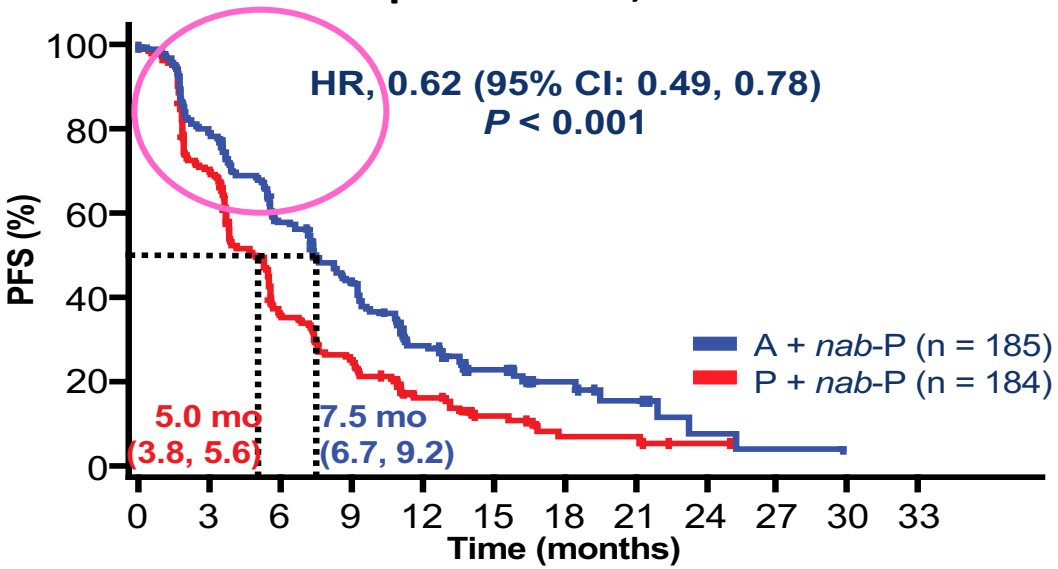
Courtesy of Professor Peter Schmid, MD, PhD

Immunotherapy plus chemo in 1L TNBC: Progression-free Survival

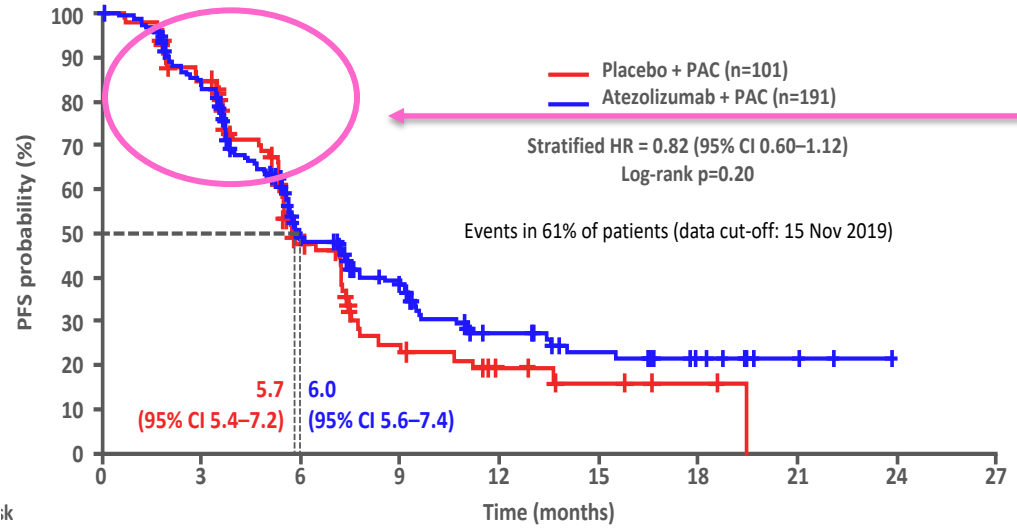
KEYNOTE-355, CPS ≥10



IMpassion130, SP142 ≥1%



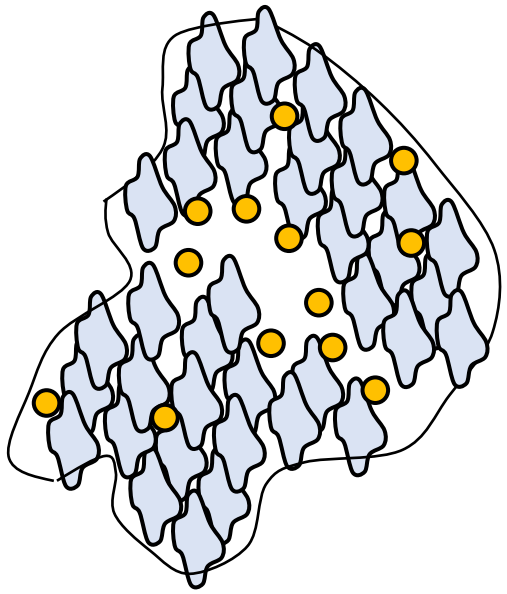
IMpassion131, SP142 ≥1%



- **Investigator-assessed PFS**
- **Late separation of curves**
- **Data from IMpassion130 available in 10/2018**

Courtesy of Professor Peter Schmid, MD, PhD

PD-L1 assessment: key variables to take into account



Tumor cells Immune cells

Type of cell to be considered

- Only tumor cells (TC)
- Only immune cells (IC)
- Both (e.g. CPS)

Modality of the scoring calculation

– Enumeration of positive cells (CPS)
– Area occupied by positive ICs (SP142)

Cut-off value

– ≥1, ≥10, ≥20, >50 …..

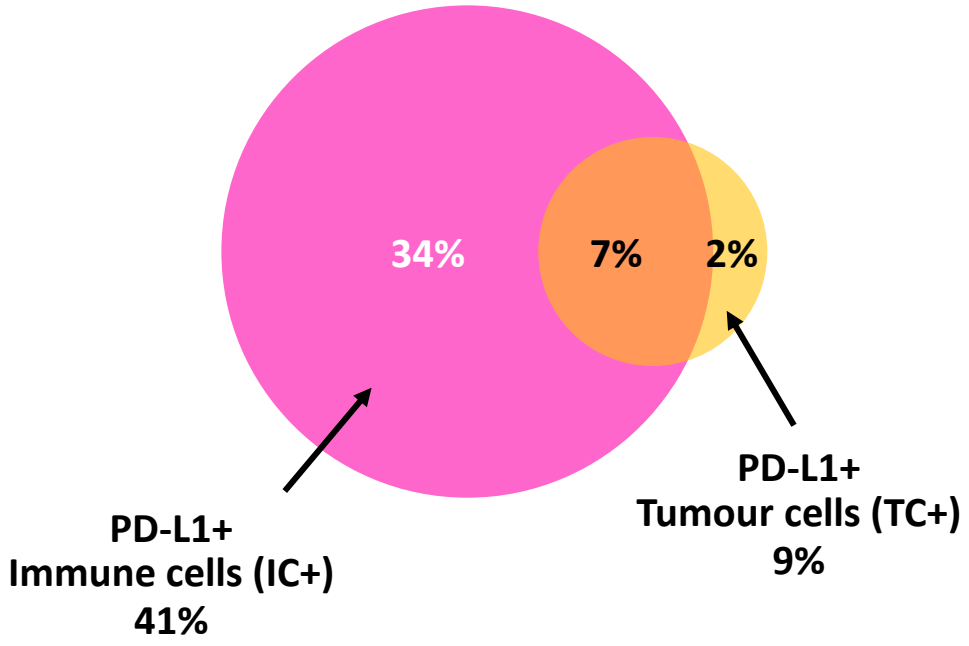
Primary antibody clones

– SP142, SP263 and 22C3

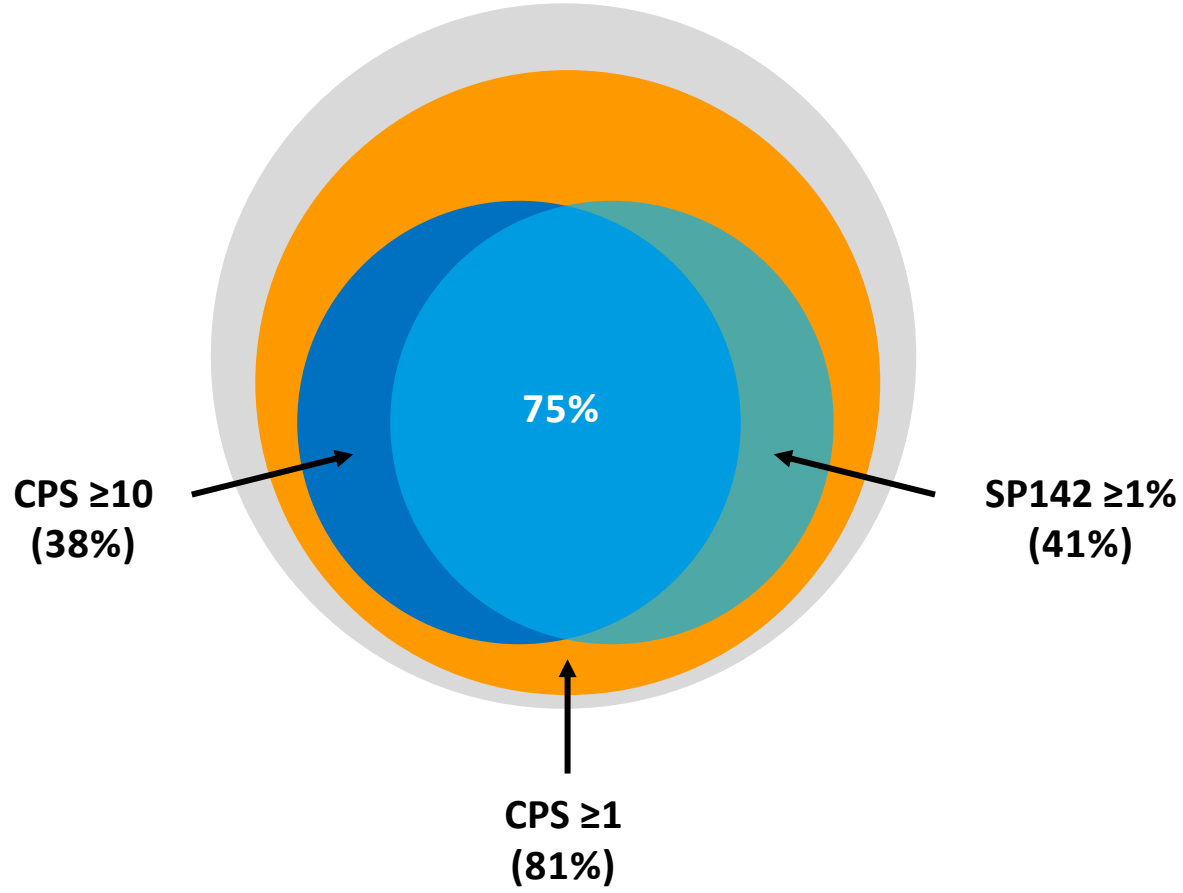
Courtesy of Professor Peter Schmid, MD, PhD

PD-L1-positive TNBC subpopulations

PD-L1 expression in TNBC (SP142 Assay)



Subpopulations in TNBC defined by PD-L1 assays



Courtesy of Professor Peter Schmid, MD, PhD

Schmid P, et al. Personal Communication

Toxicities with Immune Checkpoint Inhibitors

	Chemotherapy	Immunotherapy
Incidence (moderate/severe AEs)	Almost all patients	Majority without
AE profile	Well described	Variable
Affected systems/organs	Few organs affected	Any organ
Time course	Well established	Variable (even after end of Tx)
	Predictable	Relatively unpredictable

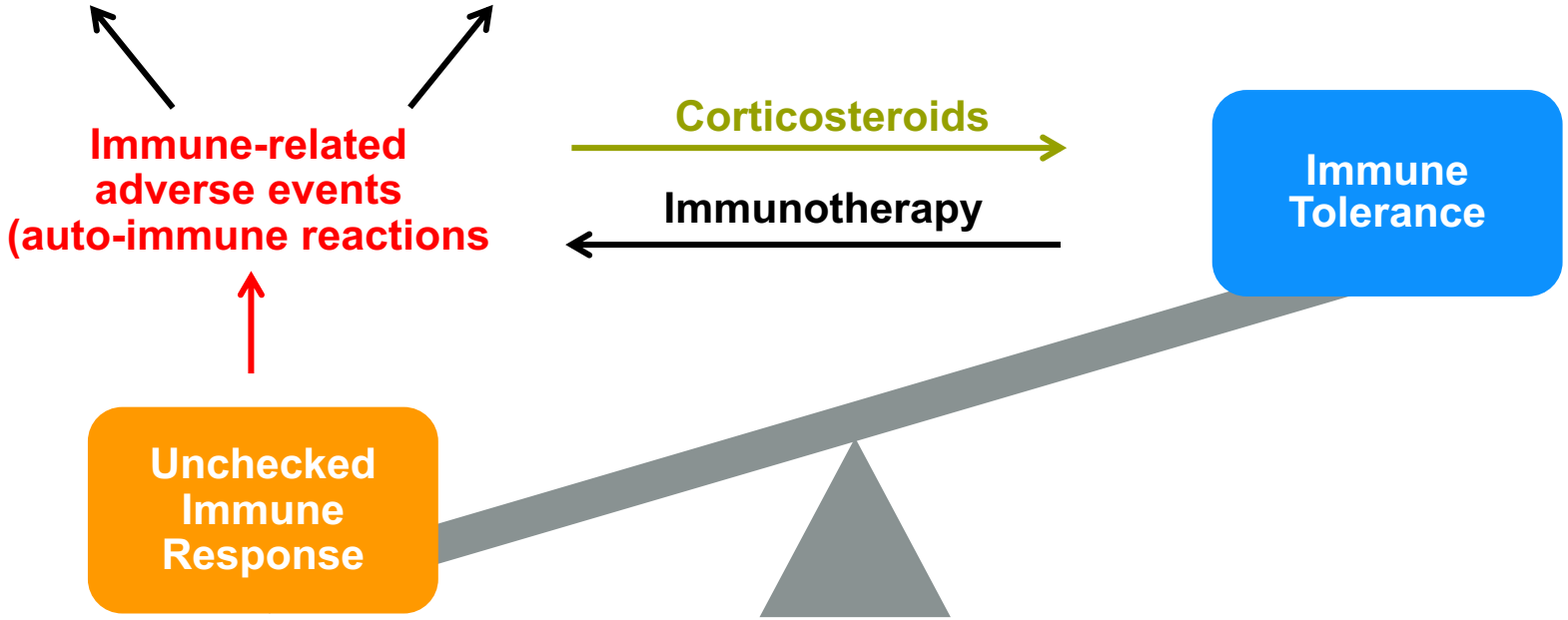
Courtesy of Professor Peter Schmid, MD, PhD

Schmid P, et al. Personal Communication

Toxicities with Immune Checkpoint Inhibitors

Organ-specific events
- Endocrine system
- Skin
- Gastrointestinal
- Liver
- Pulmonary

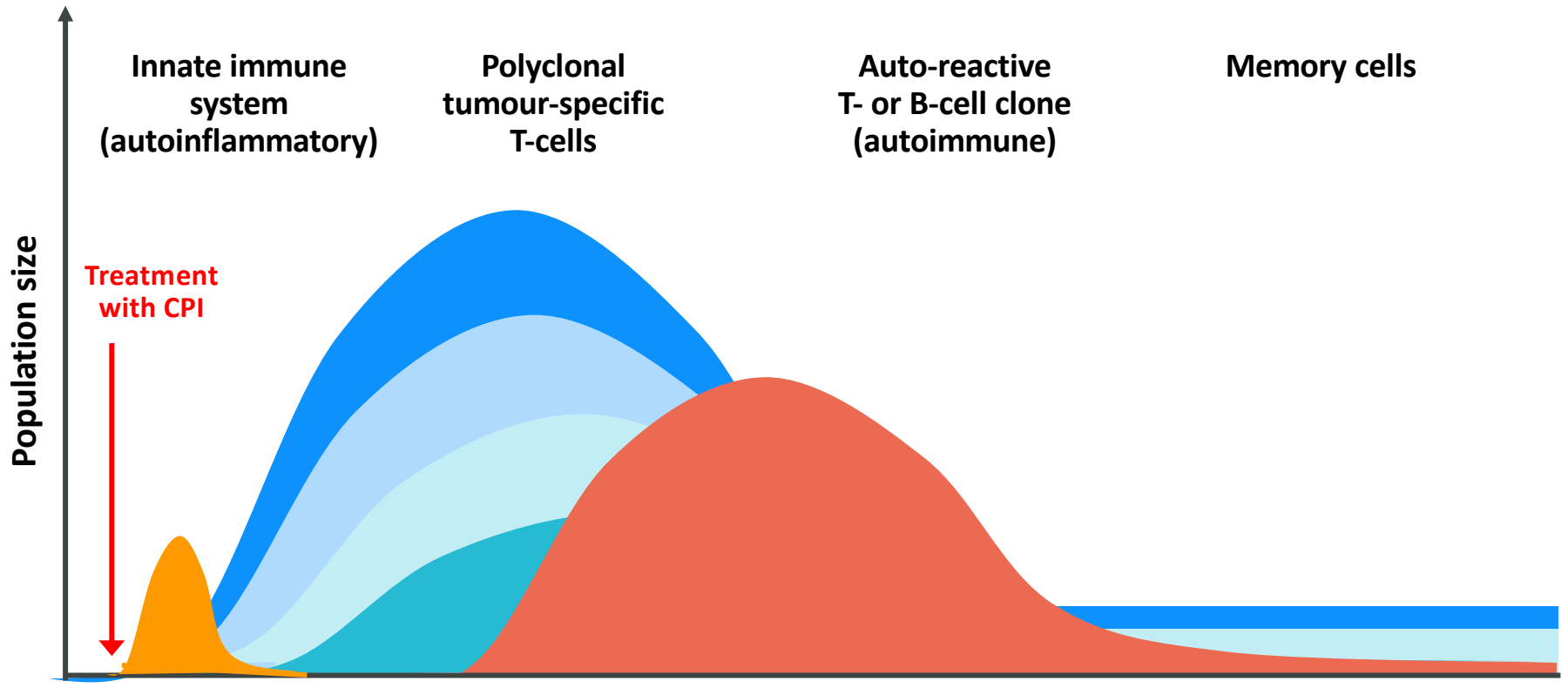
General events
- Fatigue
- Pyrexia, Chills
- Infusion reactions



Courtesy of Professor Peter Schmid, MD, PhD

Schmid P, et al. Personal Communication

Kinetics of anti-tumour and auto-immune response

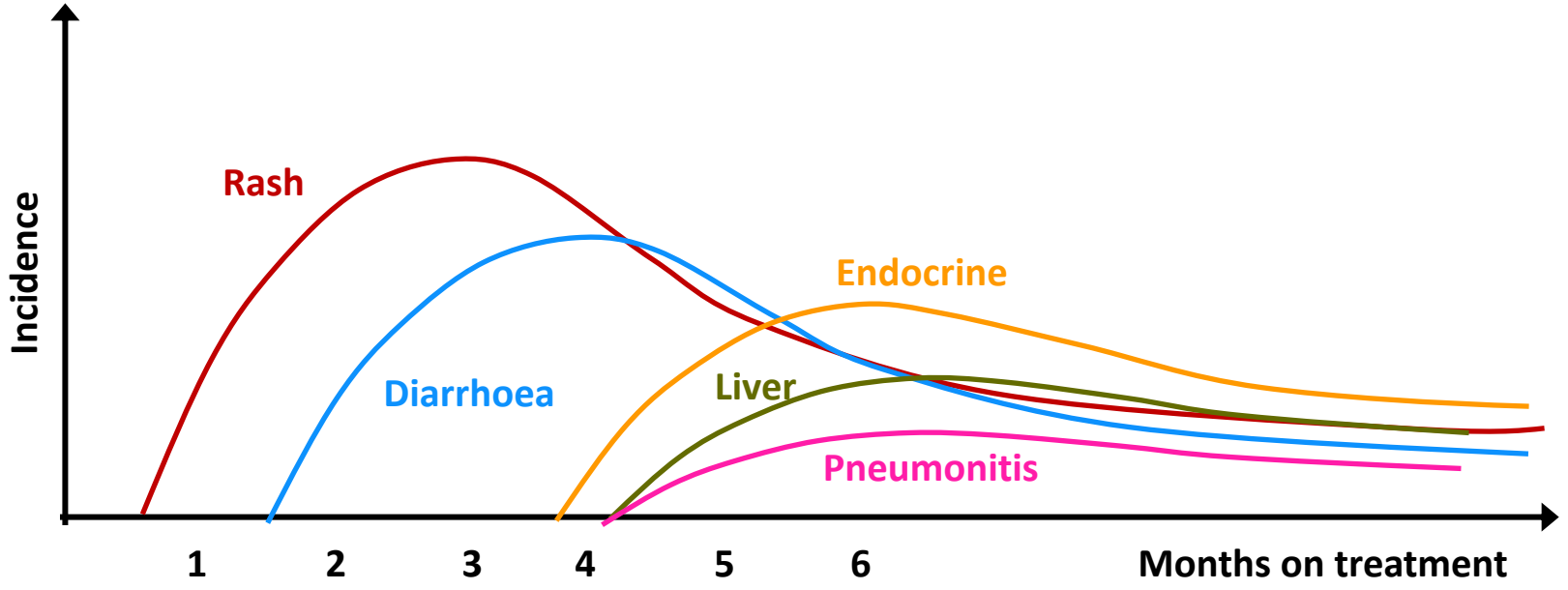


Courtesy of Professor Peter Schmid, MD, PhD

Adapted from Michot, JM. Cancer world 2019

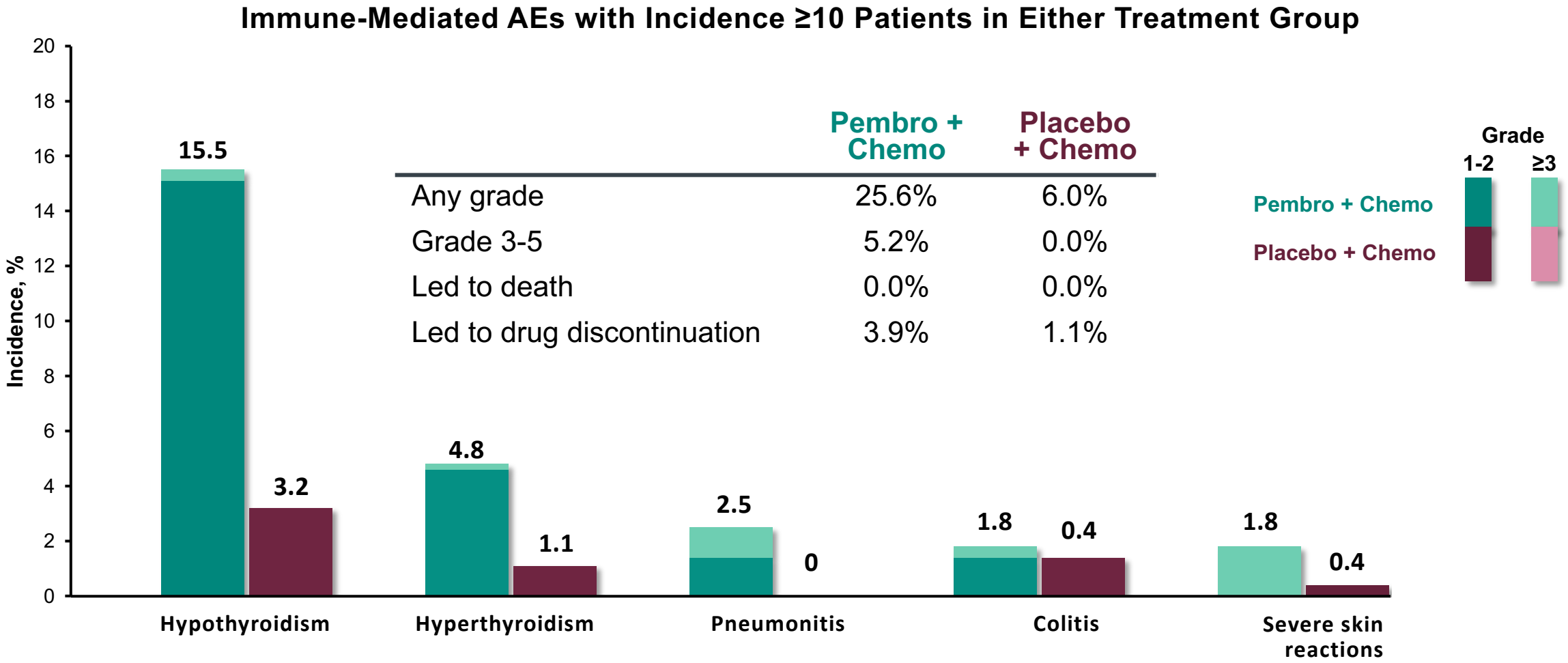
Toxicities with Immune Checkpoint Inhibitors

- Timing can be highly variable
- irAE can occur even months after the end of treatment
- Time course might be even more variable with novel combinations



Courtesy of Professor Peter Schmid, MD, PhD

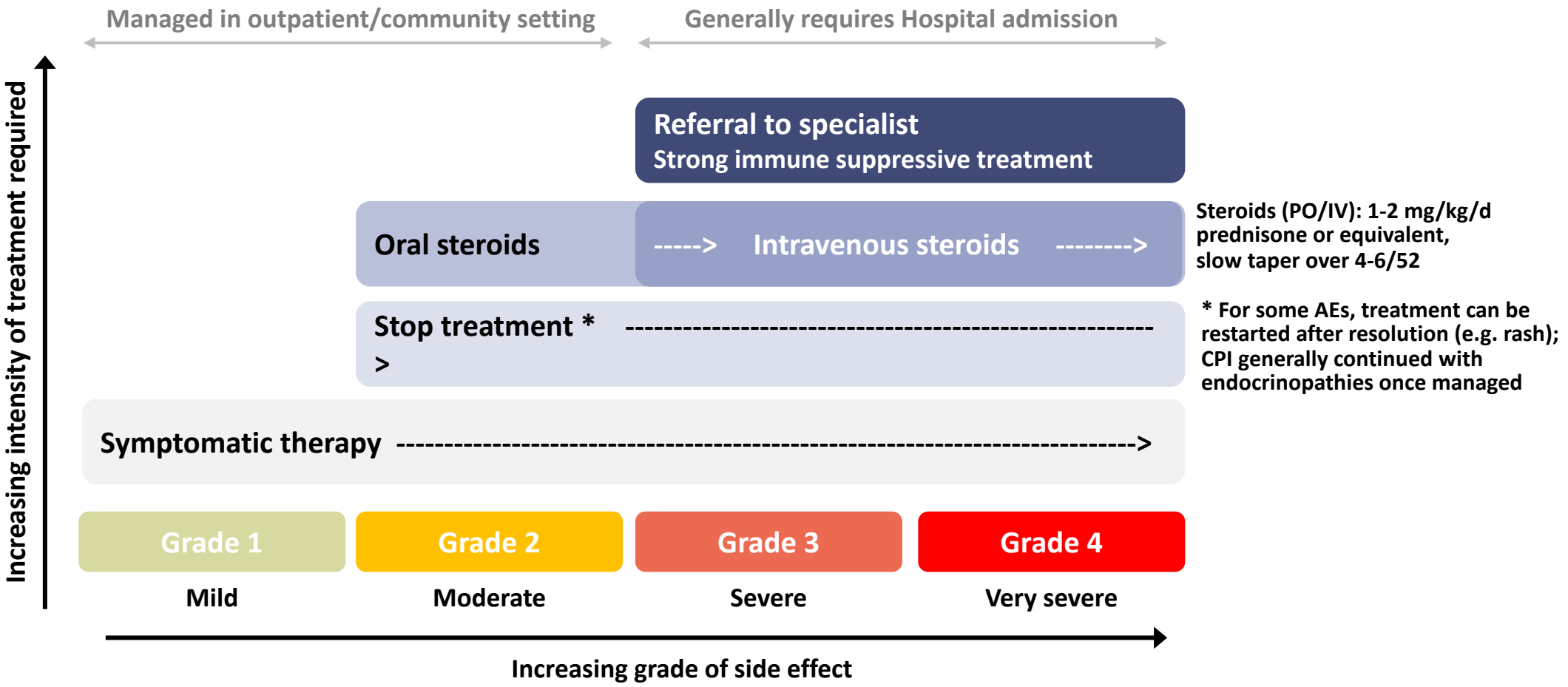
KEYNOTE-355: Immune-Related Adverse Events



Courtesy of Professor Peter Schmid, MD, PhD

Cortes, et al. ASCO 2020

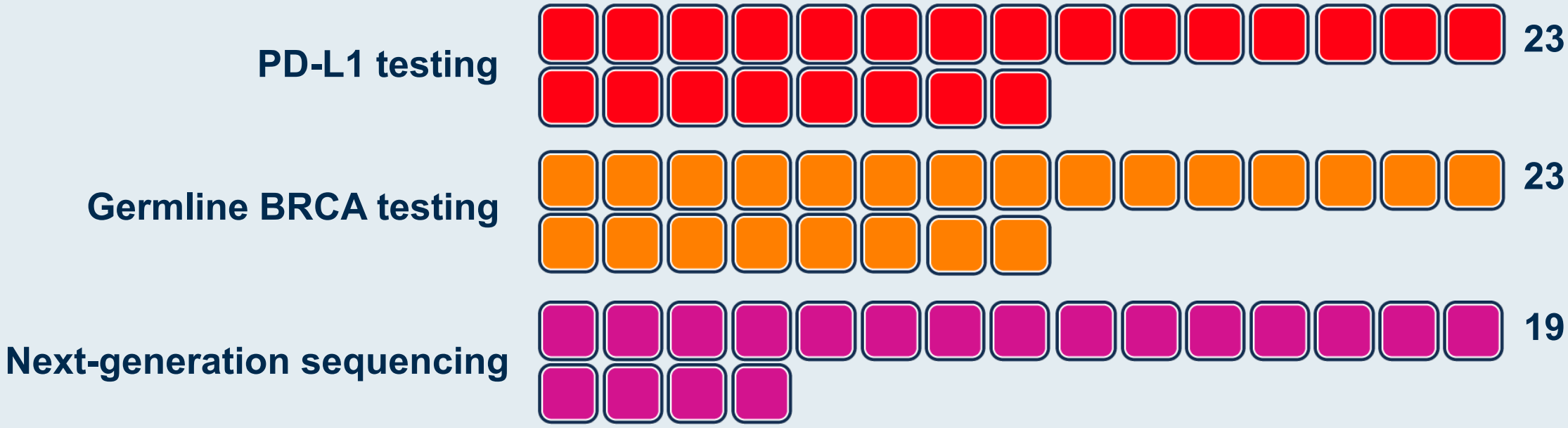
Managing Side Effects from Immune Checkpoint Inhibitors



Courtesy of Professor Peter Schmid, MD, PhD

Adapted from Champiat S. ESMO Patient Guide Series

A 45-year-old woman who completed dd AC-T and radiation therapy 3 years ago for localized TNBC now presents with metastatic disease to the lung and bones. What type of biomarker assessment would you recommend? (Select all that apply.)



Survey of 25 breast cancer clinical investigators

A patient with PD-L1-positive metastatic TNBC experiences a response to pembrolizumab/gemcitabine/carboplatin. How long would you continue the pembrolizumab?

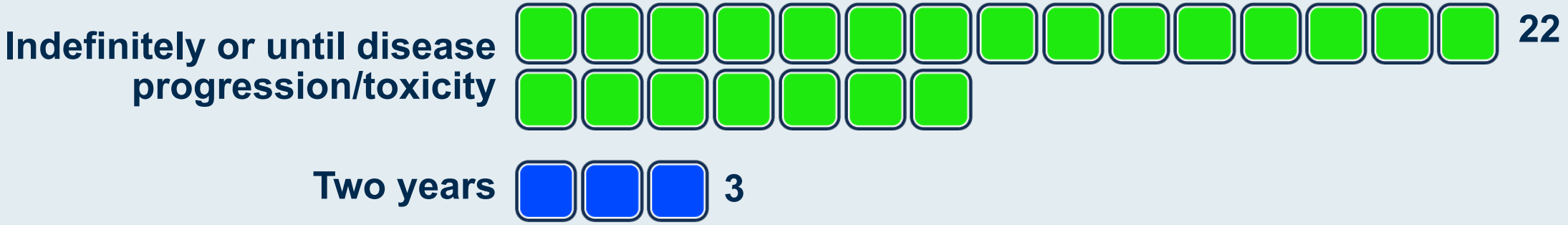
1. 4 cycles
2. 6 cycles
3. 1 year
4. 2 years
5. Indefinitely or until disease progression/toxicity
6. Other

A patient with PD-L1-positive metastatic TNBC experiences a response to pembrolizumab/gemcitabine/carboplatin. How long would you continue the gemcitabine/carboplatin?

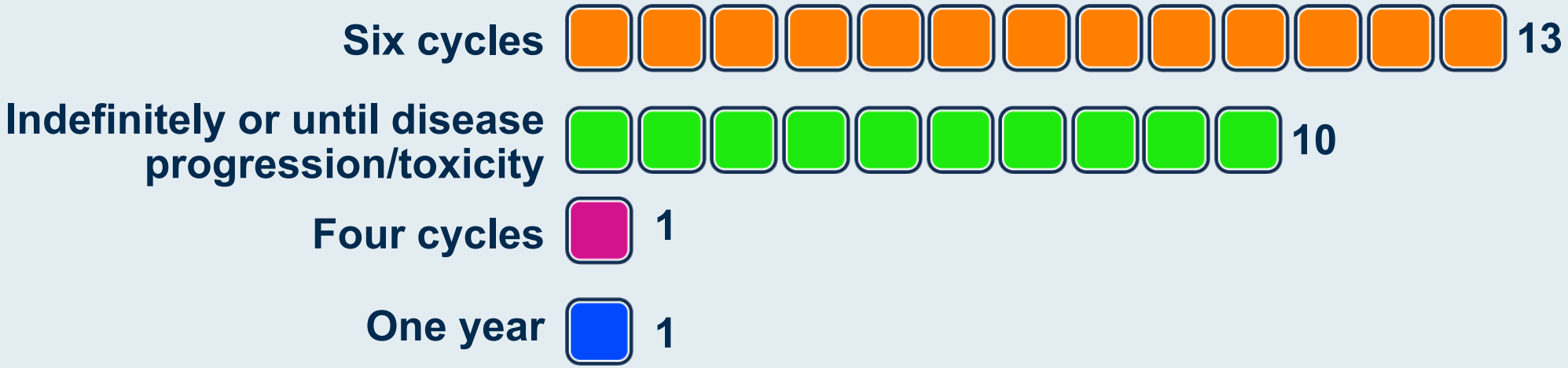
1. 4 cycles
2. 6 cycles
3. 1 year
4. 2 years
5. Indefinitely or until disease progression/toxicity
6. Other

A patient with PD-L1-positive metastatic TNBC experiences a response to pembrolizumab/chemotherapy. How long would you continue…

Pembrolizumab?



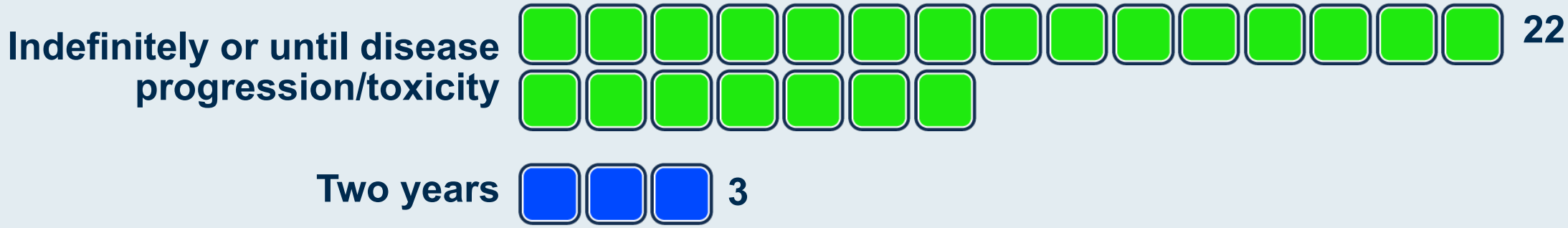
Gemcitabine/carboplatin?



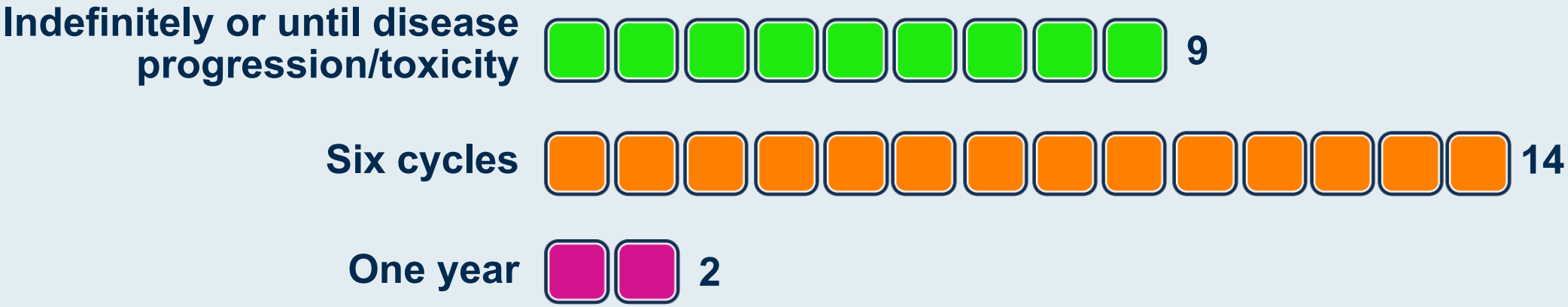
Survey of 25 breast cancer clinical investigators

A patient with PD-L1-positive metastatic TNBC experiences a response to atezolizumab/*nab* paclitaxel. How long would you continue…

Atezolizumab?

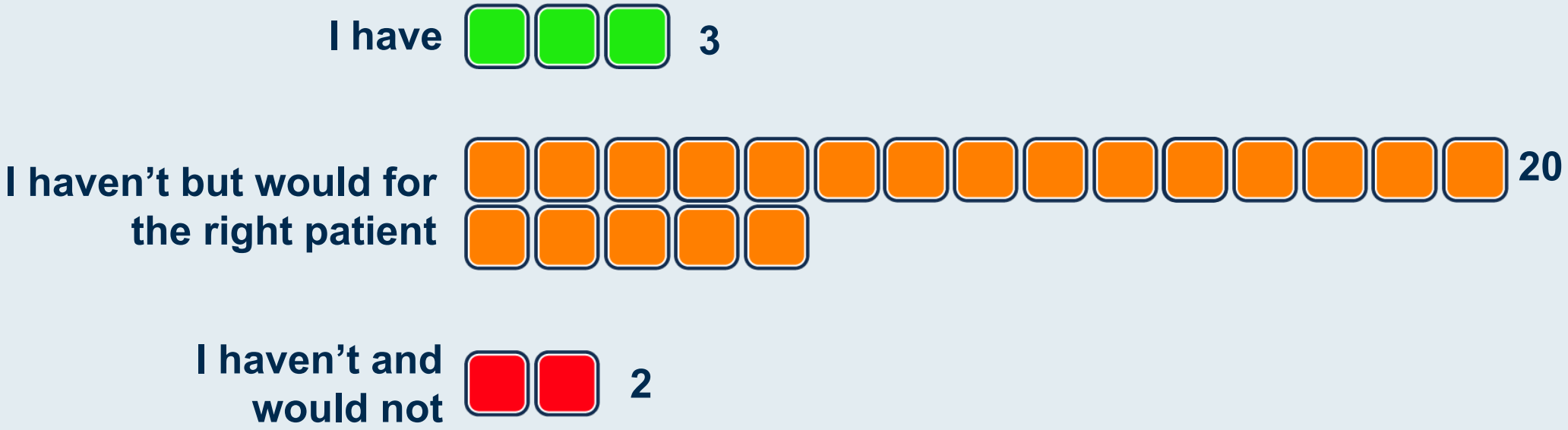


Nab paclitaxel?



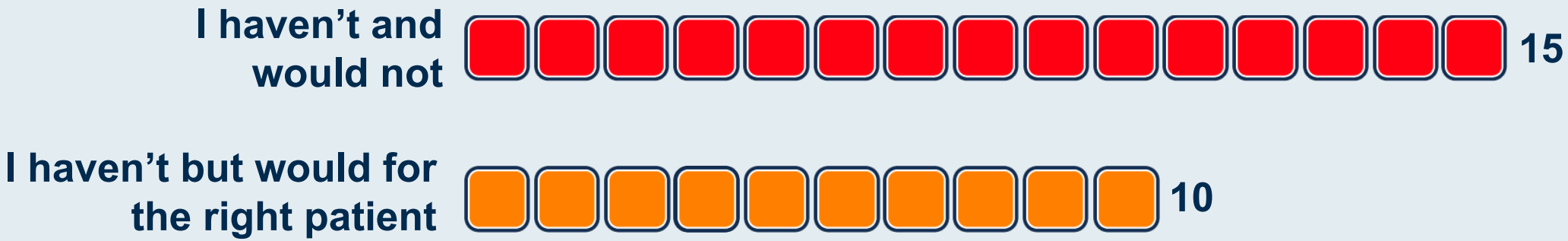
Survey of 25 breast cancer clinical investigators

Have you administered or would you administer an immune checkpoint inhibitor to a patient with metastatic TNBC and psoriasis requiring local therapy?



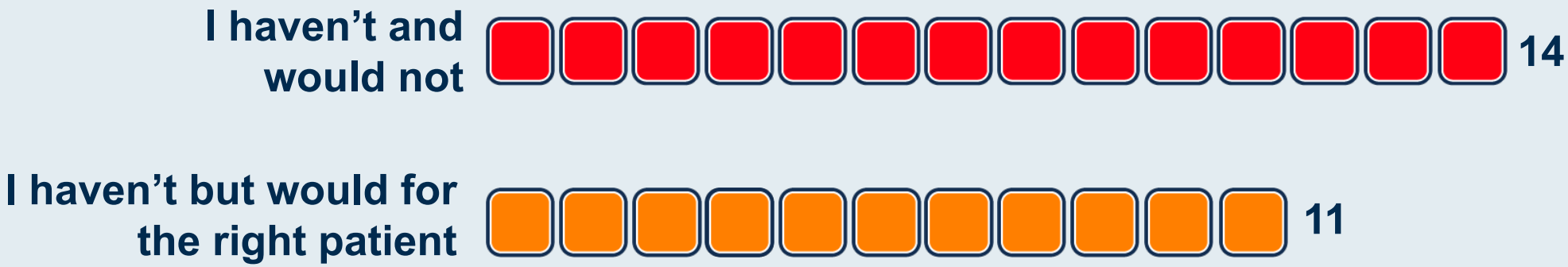
Survey of 25 breast cancer clinical investigators

Have you administered or would you administer an immune checkpoint inhibitor to a patient with metastatic TNBC and multiple sclerosis?



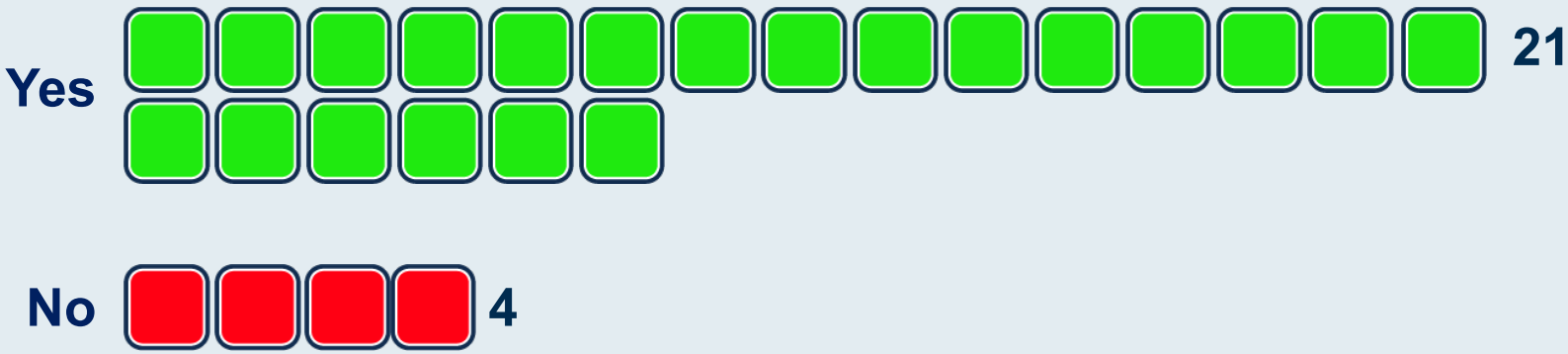
Survey of 25 breast cancer clinical investigators

Have you administered or would you administer an immune checkpoint inhibitor to a patient with metastatic TNBC and a history of kidney transplant?



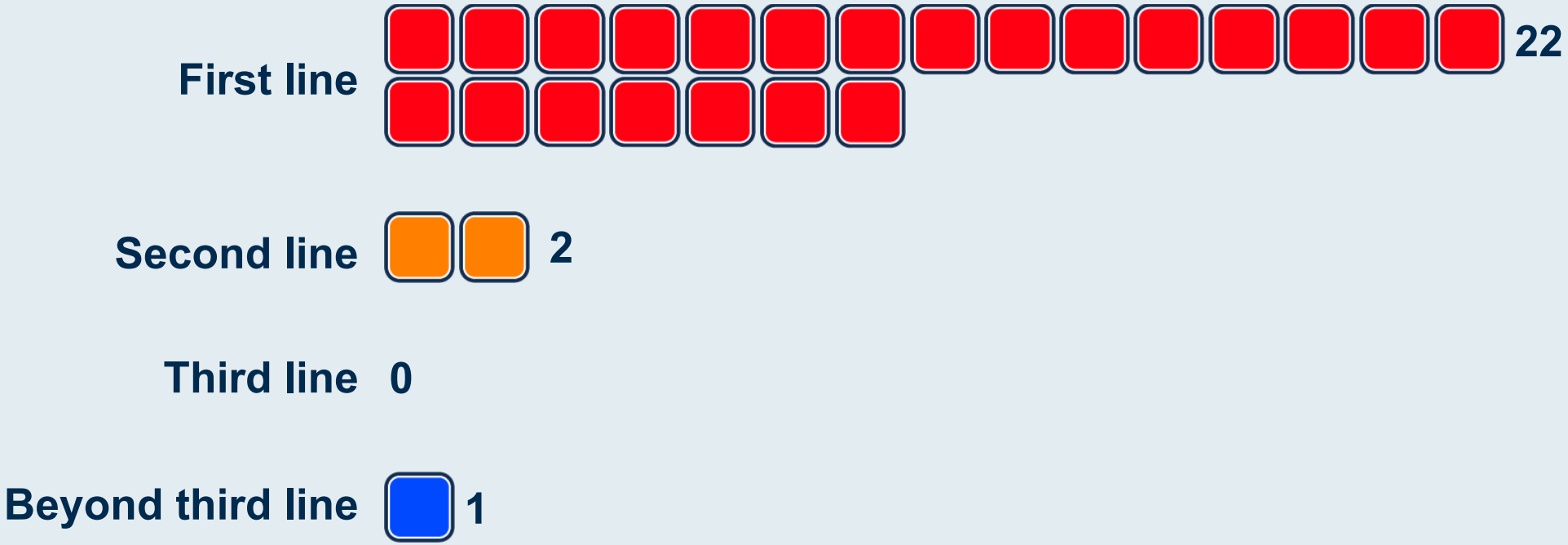
Survey of 25 breast cancer clinical investigators

Do you generally test for microsatellite instability (MSI) in your patients with metastatic TNBC?



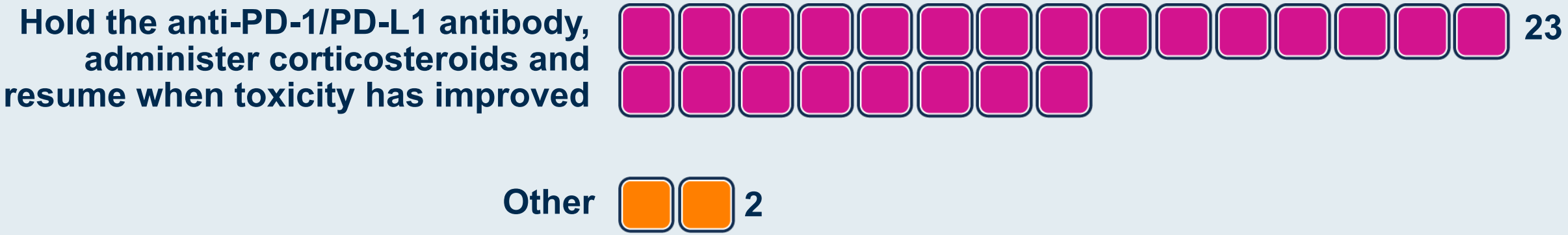
Survey of 25 breast cancer clinical investigators

Reimbursement and regulatory issues aside, in general, in which line of therapy would you generally administer an anti-PD-1/PD-L1 antibody to a patient with MSI-high TNBC?



Survey of 25 breast cancer clinical investigators

A 49-year-old woman who is experiencing a good response to an anti-PD-1/PD-L1 antibody for metastatic TNBC presents with cough and dyspnea and is found to have Grade 2 pneumonitis. What would you recommend?

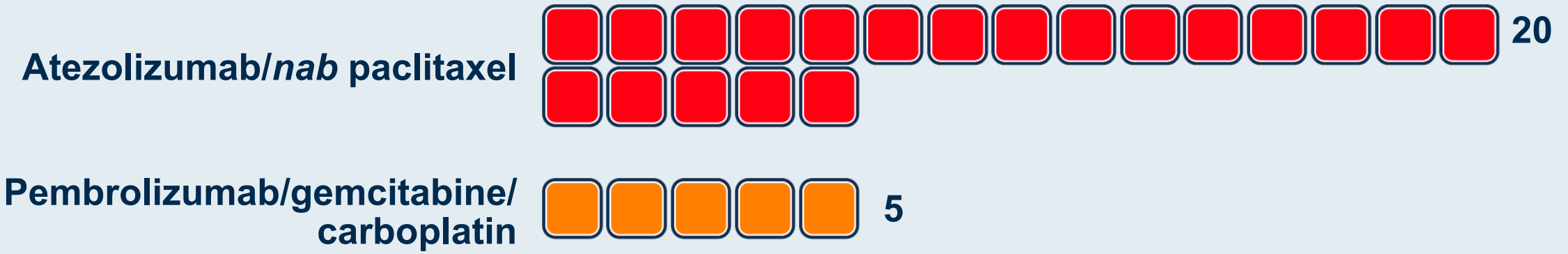


Survey of 25 breast cancer clinical investigators

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

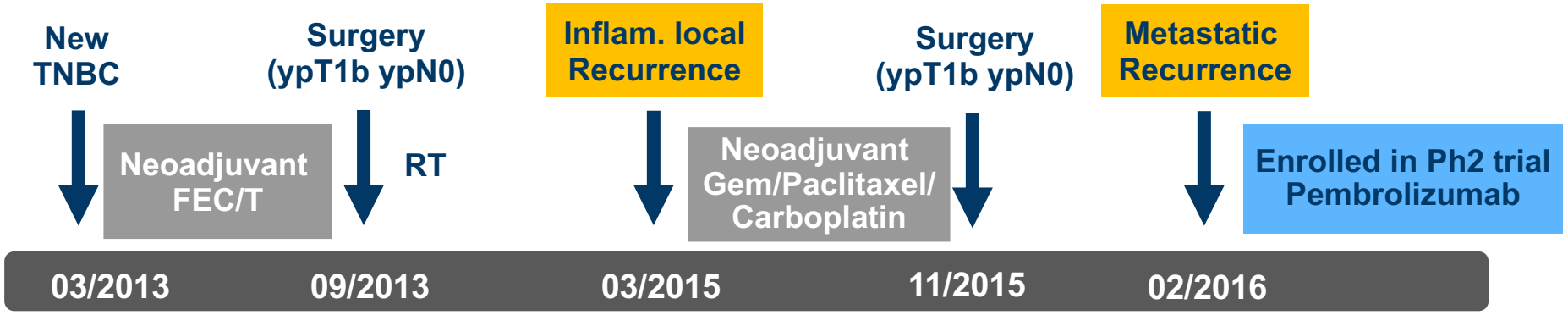
A 32-year-old woman who completed neoadjuvant FEC/T and radiation therapy 21 months ago for localized TNBC now presents with liver and nodal metastases. Biomarker assessment reveals BRCA WT, PD-L1-positive disease. What therapy would you recommend?



Survey of 25 breast cancer clinical investigators

Case Presentation – Prof Schmid: A 32-Year-Old Woman with mTNBC

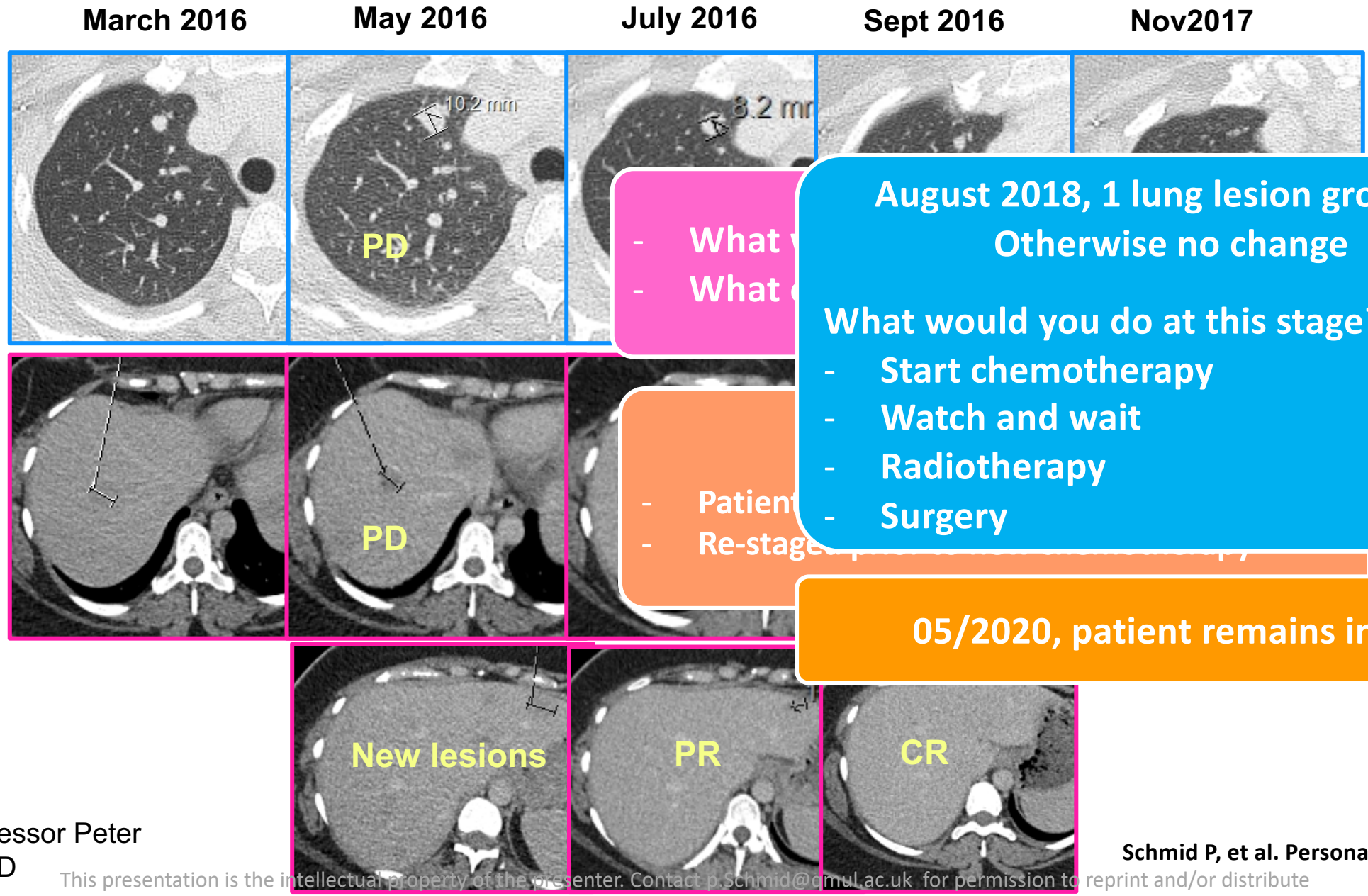
32 y/o woman



Courtesy of Professor Peter Schmid, MD, PhD

Schmid P, et al. Personal Communication

Case Presentation – Prof Schmid: A 32-Year-Old Woman with mTNBC (continued)



- What
- What

- Patient
- Re-stage

August 2018, 1 lung lesion growing.
Otherwise no change

What would you do at this stage?

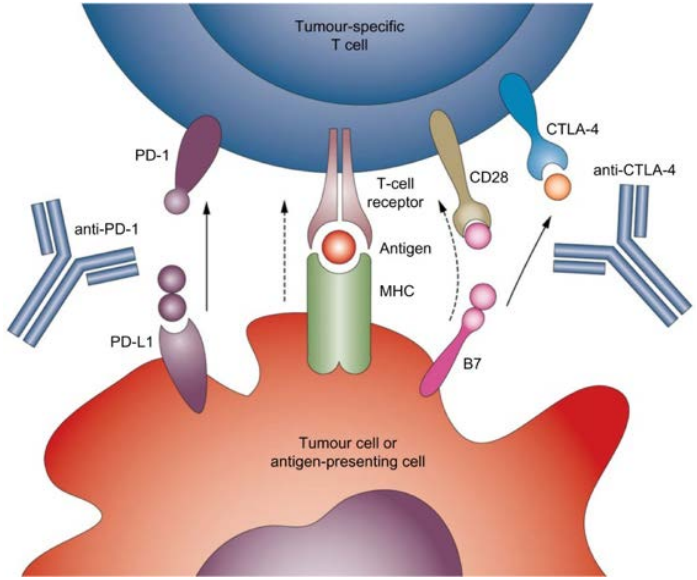
- Start chemotherapy
- Watch and wait
- Radiotherapy
- Surgery

05/2020, patient remains in CR

Courtesy of Professor Peter Schmid, MD, PhD

Schmid P, et al. Personal Communication

Novel Applications of Immune Checkpoint Inhibitors for Patients with Early TNBC



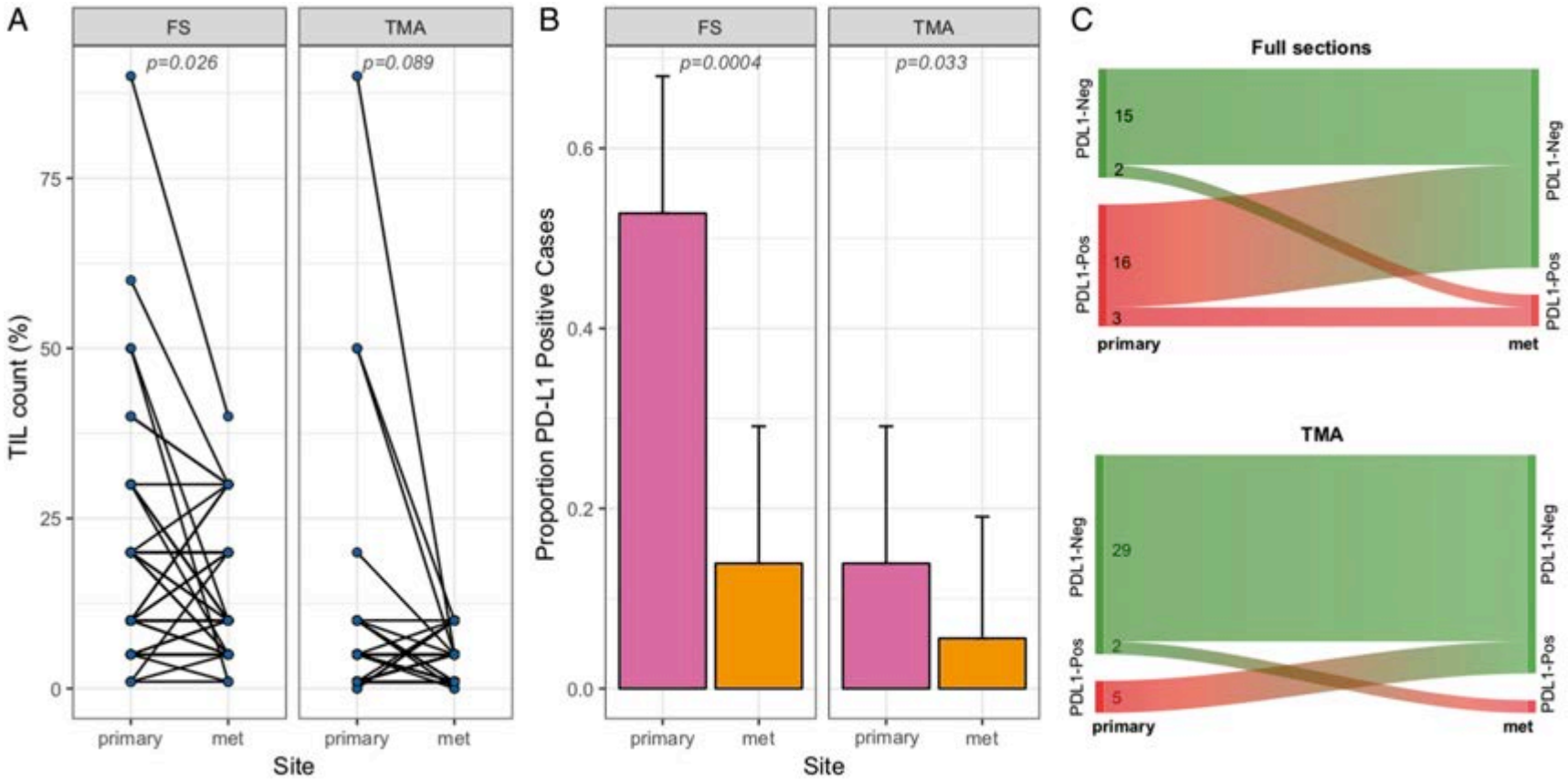
Hope S. Rugo, MD

Professor of Medicine

Director, Breast Oncology and Clinical Trials Education

University of California San Francisco Comprehensive Cancer Center

Immunologic Differences Between Primary and Metastatic Tumor Samples

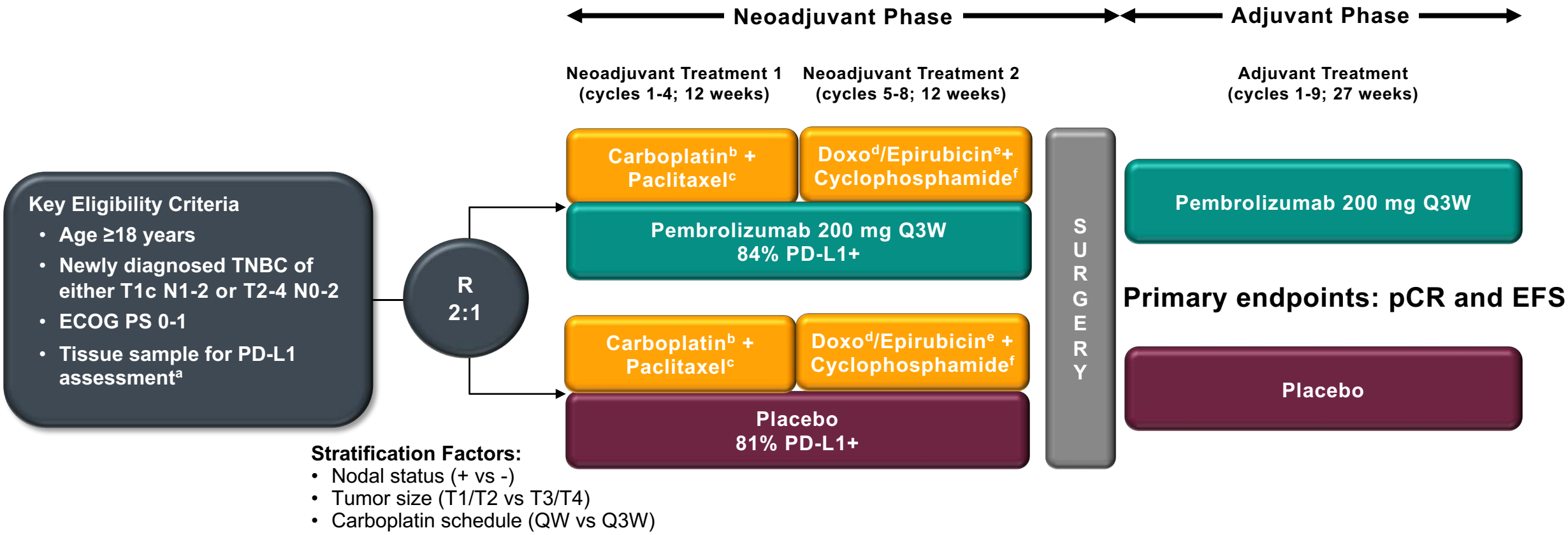


Percent TIL counts in full sections and TMAs.

Szekely, et al (Pusztai), Ann Oncol 2018

Courtesy of Hope S Rugo, MD

KEYNOTE-522 Study Design (NCT03036488)



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

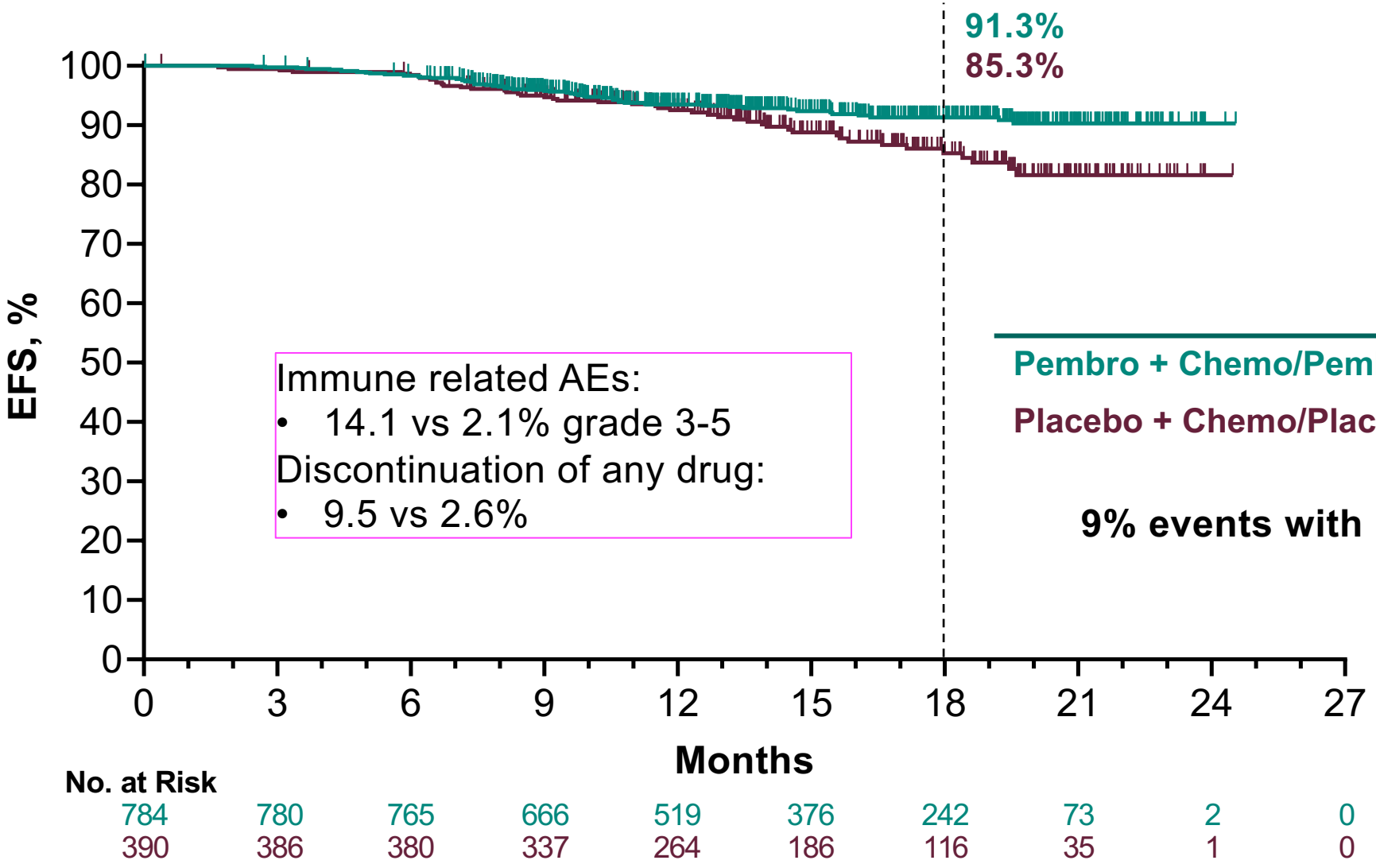
PD-L1 + defined by CPS ≥1

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m^2 QW.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Courtesy of Hope S Rugo, MD
Schmid et al, NEJM 2020

Event-Free Survival at IA2: 1st Interim Analysis

P value boundary for significance 0.000051 (HR<0.4)



Immune related AEs:
- 14.1 vs 2.1% grade 3-5

Discontinuation of any drug:
- 9.5 vs 2.6%

	Events	HR (95% CI)
Pembro + Chemo/Pembro	7.4%	0.63[a] (0.43-0.93)
Placebo + Chemo/Placebo	11.8%	

9% events with median FU 15.5 months

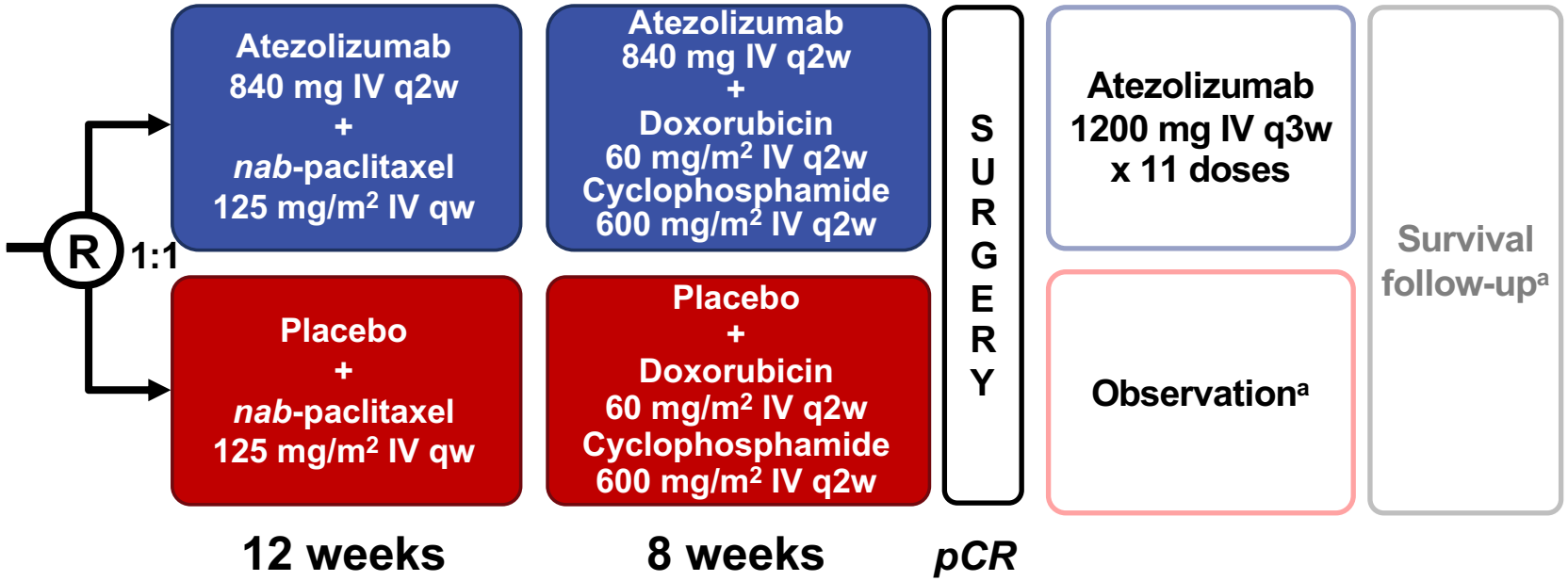
Courtesy of Hope S Rugo, MD

[a]Prespecified *P* value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS). IA2: If pCR hypothesis successful at IA1, pCR will not be formally tested at IA2

HR (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by randomization stratification factors. **Data cutoff April 24, 2019; 24 mo after last pt enrolled**

IMpassion031: Randomized Phase III Trial

- 333 patients with TNBC, T>2cm
- Co-primary endpoints: pCR in ITT and PD-L1+ (SP142)

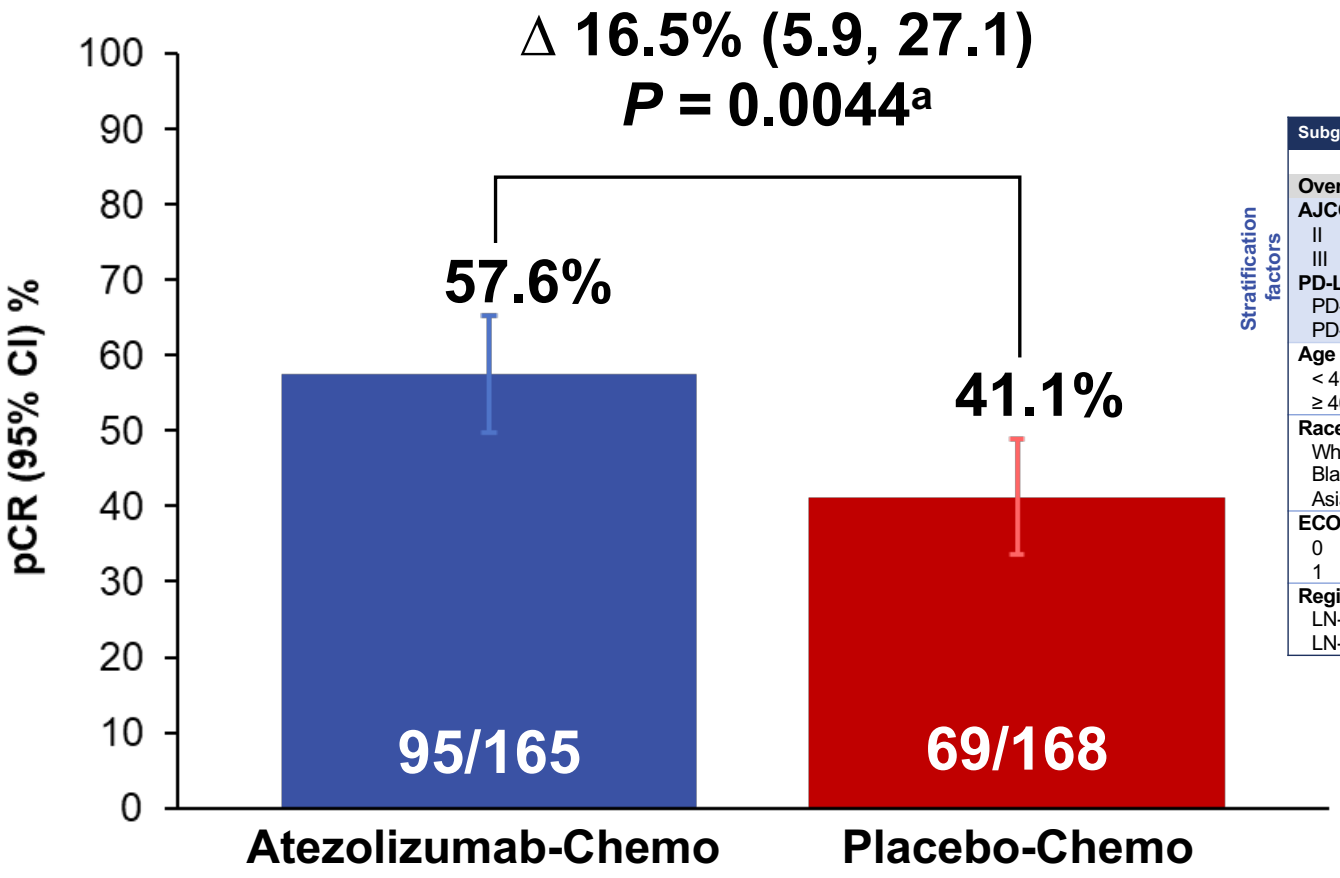


45-47% PD-L1+
76% stage II; 23% stage III
Median FU ~20 months

Courtesy of Hope S Rugo, MD

Harbeck et al, ESMO 2020 and Mittendorf et al, Lancet 2020

Primary Endpoint: pCR



Subgroup	Atezolizumab-Chemo		Placebo-Chemo			
	pCR (%)	n/n	pCR (%)	n/n	Difference in pCR (95% CI)	Δ (%) 95% CI
Overall	57.6	95/165	41.1	69/168		16.5 5.9, 27.1
AJCC BC Stage						
II	61.9	78/126	46.5	60/129		15.4 3.3, 27.5
III	44.7	17/38	23.1	9/39		21.7 1.1, 42.3
PD-L1 status[a]						
PD-L1-positive	68.8	53/77	49.3	37/75		19.5 4.2, 34.8
PD-L1-negative	47.7	42/88	34.4	32/93		13.3 −0.9, 27.5
Age group						
< 40 years	58.8	20/34	35.7	15/42		23.1 1.1, 45.1
≥ 40 years	57.3	75/131	42.9	54/126		14.4 2.3, 26.5
Race						
White	57.8	59/102	44.4	48/108		13.4 0, 26.8
Black	44.4	4/9	26.7	4/15		17.8 −21.7, 57.2
Asian	57.4	24/47	34.1	14/41		23.3 3.0, 43.6
ECOG PS						
0	57.7	90/156	43.1	66/153		14.6 3.5, 25.6
1	62.5	5/8	21.4	3/14		41 1.2, 80.9
Regional lymph node						
LN-negative	57.8	63/109	49	47/96		8.8 −4.8, 22.5
LN-positive	57.1	32/56	30.6	22/72		26.6 9.8, 43.4

Stratification factors

-30 -20 -10 0 10 20 30 40 50 60 70 80 90

Placebo better | Atezolizumab better

DFS and OS too early

AEs leading to discontinuation of any drug: 22.6 v 19.8%

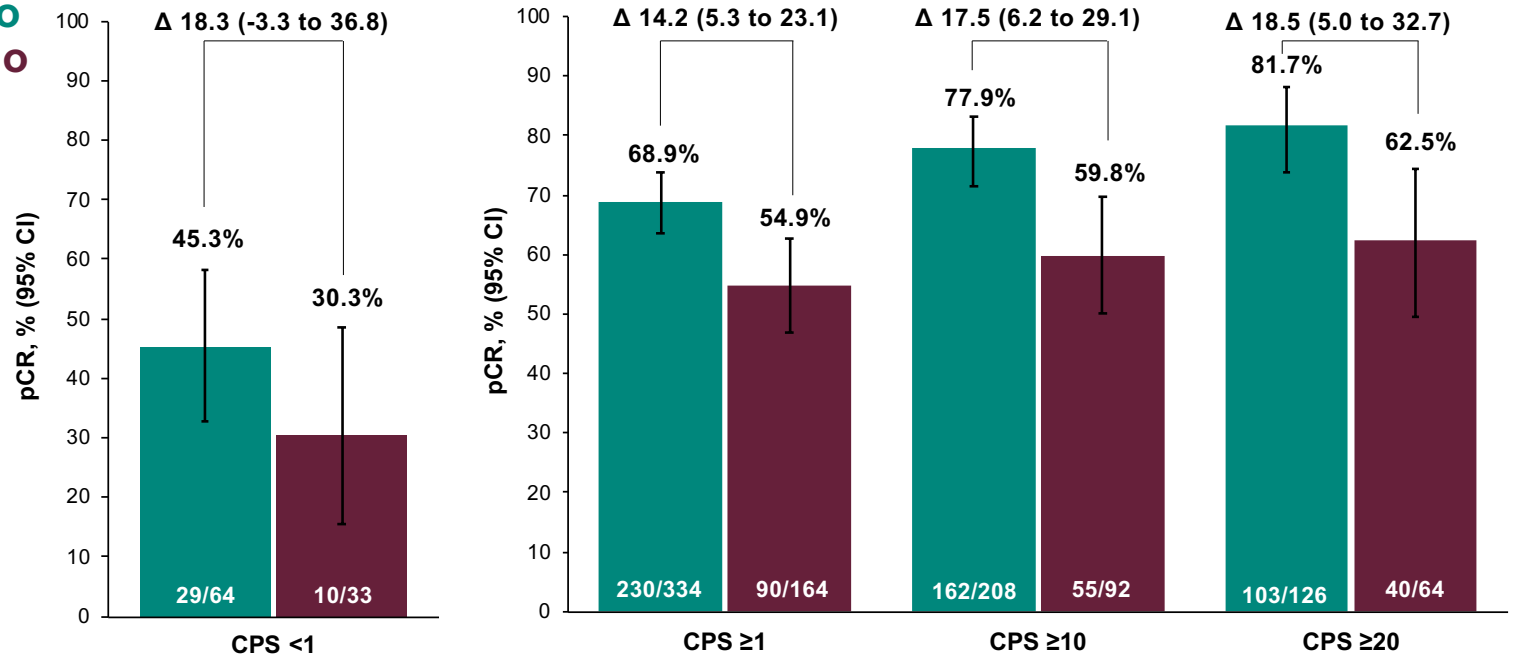
AEs requiring corticosteroids: 12.8 v 9.6%

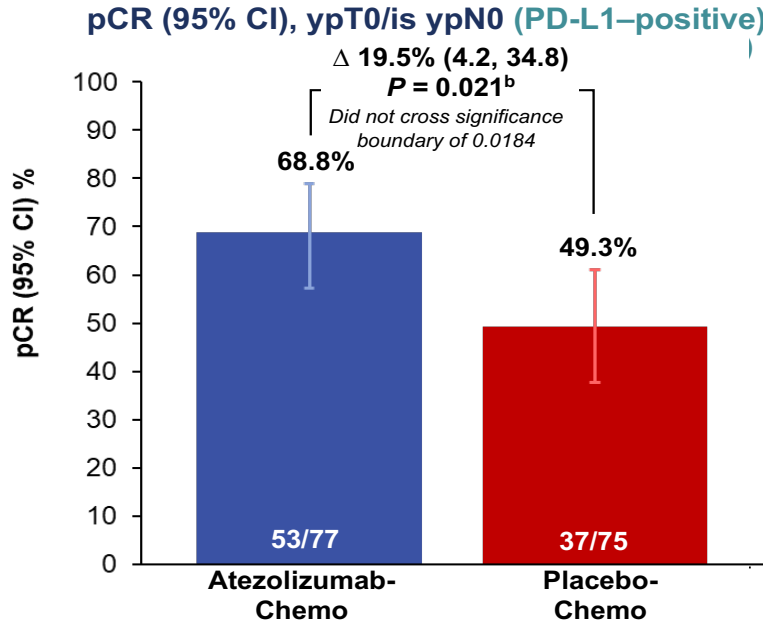
Harbeck et al, ESMO 2020 and Mittendorf et al, Lancet 2020

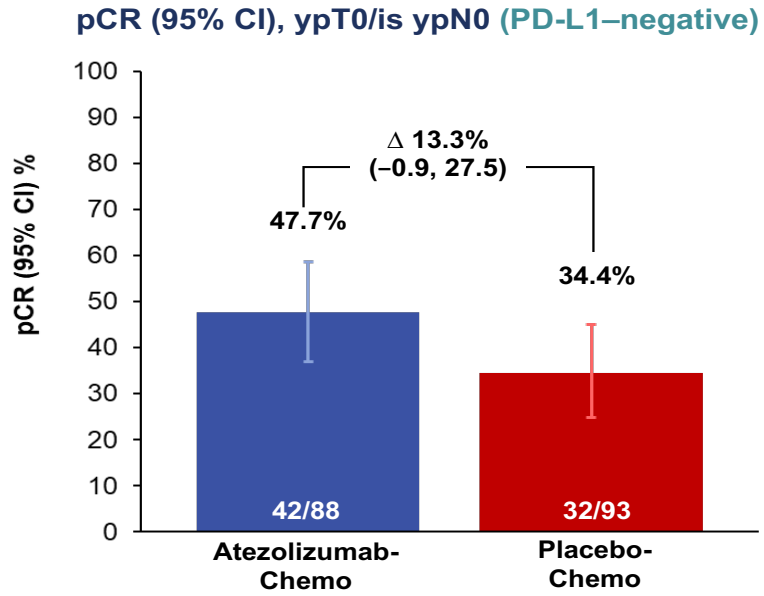
Courtesy of Hope S Rugo, MD

Benefit from Immunotherapy is Independent of PD-L1 status

Is PD-L1 Predictive of Response to Chemotherapy?





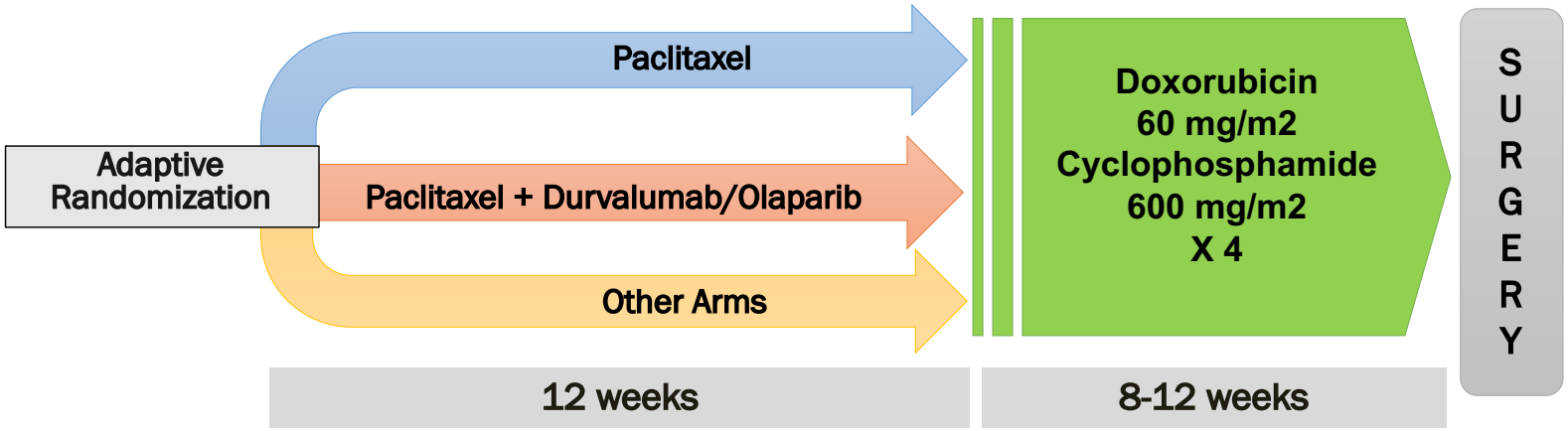


Schmidt et al, SABCS 2019, Harbeck et al, ESMO 2020, Mittendorf et al, Lancet 2020

Courtesy of Hope S Rugo, MD

New Approaches: Durvalumab/Olaparib in I-SPY 2

- Rationale for combining PARPi/checkpoint inhibitor
  - Impaired nucleotide and base excision repair increase mutation and neoantigen load[1]
    - DNA fragments activate intracellular STING (Stimulator of Interferon Genes) pathway
    - PARP inhibition upregulates PD-L1 expression in breast cell lines



Control Arm
Paclitaxel 80 mg/m2 every wk x 12

Experimental Arm
Paclitaxel 80 mg/m2 every wk x 12
Durvalumab 1500 mg every 4 wks x 3
Olaparib 100 mg twice daily wks 1-11

Courtesy of Hope S Rugo, MD

Pusztai et al, AACR 2020

[1]Lancet Oncology. 2019 Mar 1;20(3):e175-86

Ongoing Phase III Trials with IO in TNBC

Neoadjuvant/adjuvant	Adjuvant

• Atezolizumab
  • NSABP B59/GeparDouze (n=1520)
  • Pac/carbo → AC/EC
  • EFS NeoTRIPaPDL1 (n=272)
  • EFS IMpassion031 (n=333)
• Pembrolizumab
  • EFS KEYNOTE-522 (n=1174)
  • NeoPACT (n=100)
  • Docetaxel/carbo/pembro x 6
	• Atezolizumab
	  • IMpassion030 (n=2300)
	  • Pac → AC/EC
	• Avelumab
	  • A-Brave (n=335)
	  • Adjuvant and post NAC high risk: avelumab alone
	• Pembrolizumab
	  • SWOG S1418/NRG-BR006 (n=1000)
	  • Post NAC: Pembro vs Obs x 1 yr

Courtesy of Hope S Rugo, MD

Conclusions

- The role of immunotherapy in the neoadjuvant setting
  - KEYNOTE-522 and IMpassion031: success in treating early TNBC independent of PD-L1 positivity
    - Await EFS results
    - Role of node status?
    - Best backbone chemotherapy?
    - The impetus to improve outcome is strong now…..
  - Discordance between studies
    - Role of anthracyclines, disease stage, differences between CPIs?
  - Balancing cost and toxicity: who needs immunotherapy?
  - Novel combination strategies offer great promise

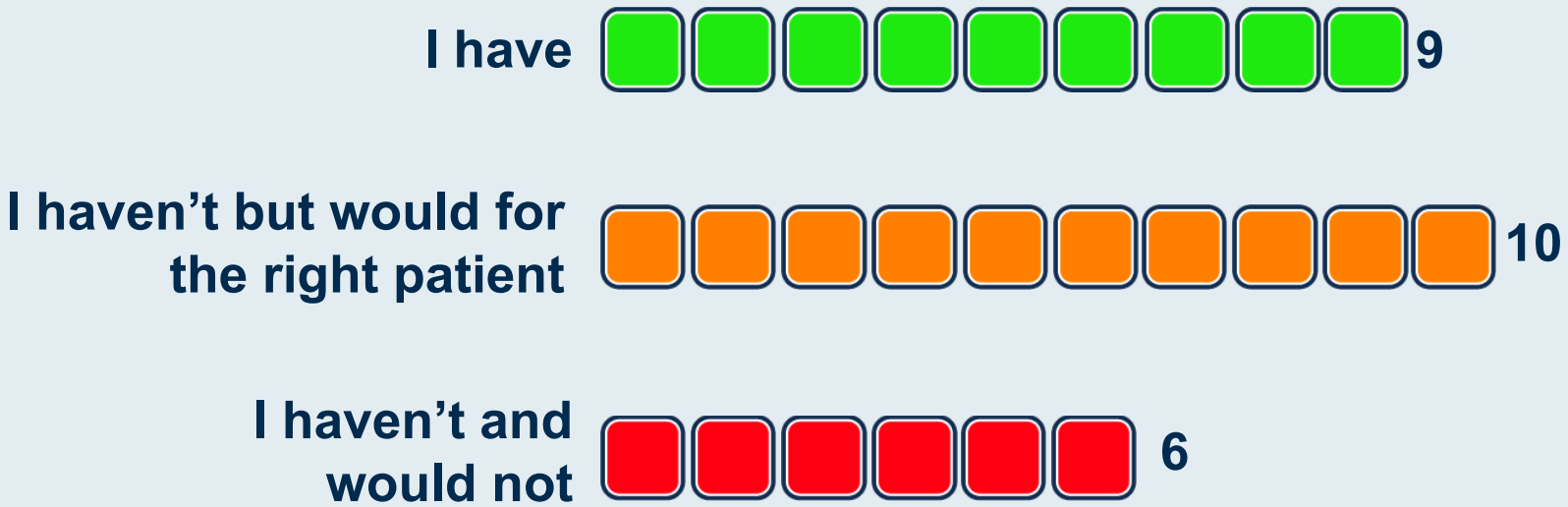
Courtesy of Hope S Rugo, MD

Regulatory and reimbursement issues aside, have you 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 a 6-cm TNBC with 3 positive axillary nodes on biopsy (PD-L1 60%)?

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

Regulatory and reimbursement issues aside, have you or would you attempt to access an anti-PD-1/PD-L1 antibody as part of neoadjuvant therapy off protocol for a 60-year-old patient with TNBC with the following characteristics?

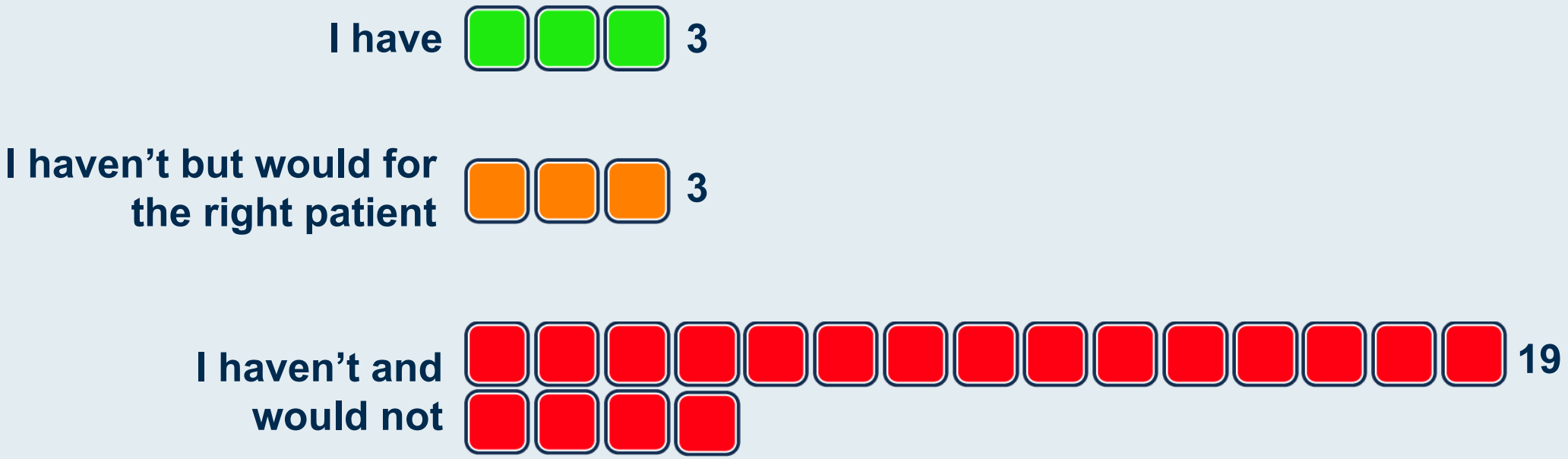
Tumor size: 6 cm, Nodal status: 3 positive nodes, PD-L1: 60%



Survey of 25 breast cancer clinical investigators

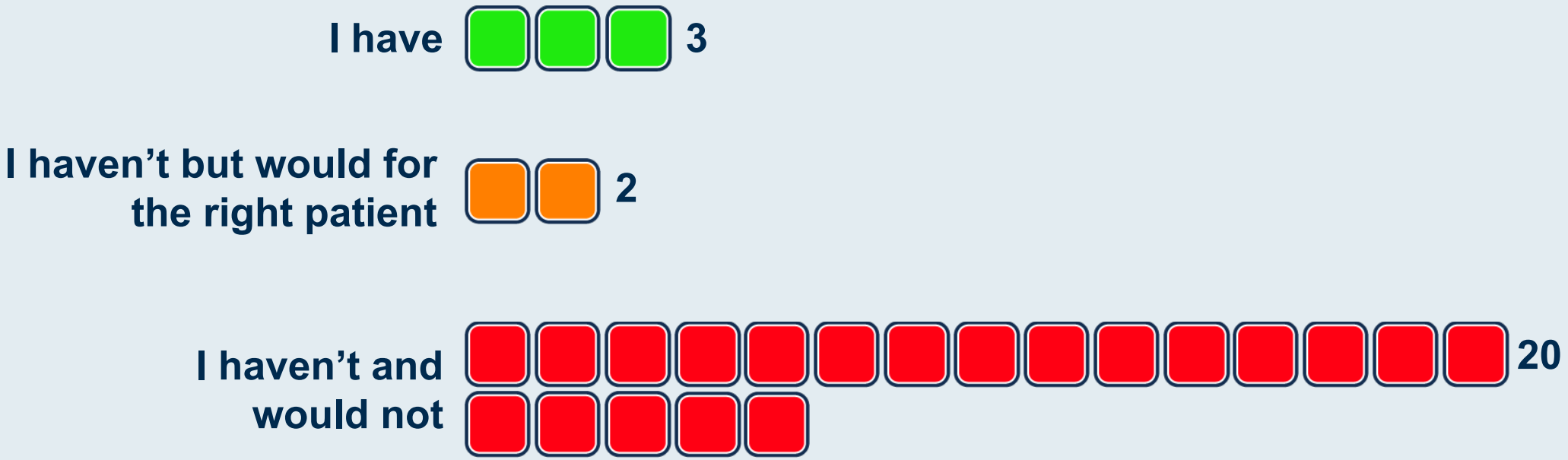
Regulatory and reimbursement issues aside, have you or would you attempt to access an anti-PD-1/PD-L1 antibody as part of neoadjuvant therapy off protocol for a 60-year-old patient with TNBC with the following characteristics?

Tumor size: 6 cm, Nodal status: node-negative, PD-L1: 10%



Survey of 25 breast cancer clinical investigators

Regulatory and reimbursement issues aside, have you or would you attempt to access an anti-PD-1/PD-L1 antibody as part of adjuvant therapy for a patient with TNBC outside of a clinical trial?



Survey of 25 breast cancer clinical investigators

Case Presentation – Dr Rugo: A 42-year-old woman with localized TNBC, node-positive

42 year old woman presented with a right breast mass & palpable axillary nodes

- US guided core biopsy: high grade ER/PR and HER2-negative IDC; an FNA of axillary node was also positive for carcinoma
- Genetic testing revealed no pathologic mutations
- By MRI, the total extent of disease was 6.7 cm
- She was treated with neoadjuvant chemotherapy on a clinical trial including:
  - Weekly paclitaxel x 12 with pembrolizumab every 3 weeks x 4 followed by AC x 4
- She had an excellent response by imaging and clinical examination
- Several days before her planned surgery she presented with dizziness, nausea, diarrhea, abdominal cramps, dyspnea on exertion
  - She was orthostatic and her sodium level was 119
  - Cortisol was 0, ACTH was within normal limits

Courtesy of Hope S Rugo, MD

Case Presentation – Dr Rugo: A 42-year-old woman with localized TNBC, node-positive (continued)

- She was diagnosed with secondary adrenal insufficiency and was started on steroids
- She underwent bilateral mastectomy and right axillary node sampling
  - There was no evidence of invasive disease in breast and 6 axillary nodes
- She is now almost 4 years from surgery and remains NED

Courtesy of Hope S Rugo, MD

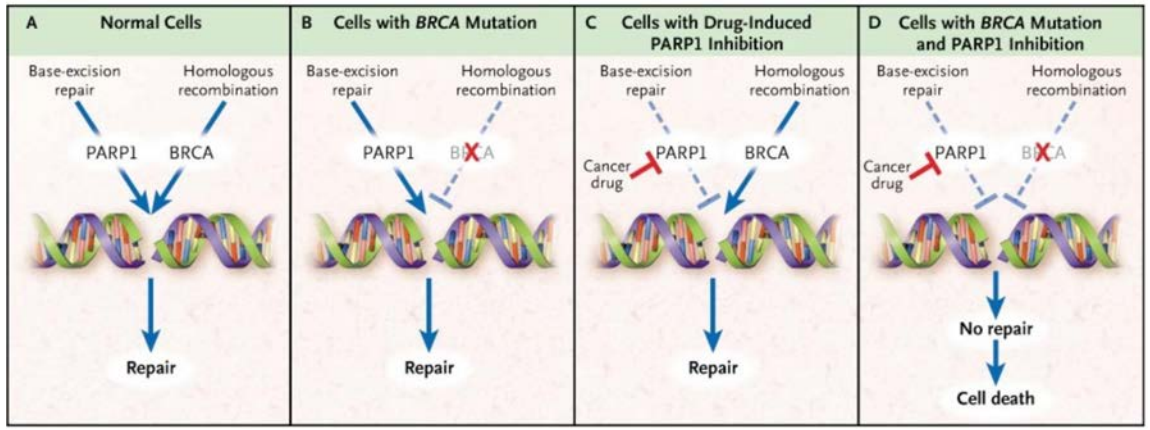
DUKE CANCER INSTITUTE
A National Cancer Institute-designated Comprehensive Cancer Center

Current and Future Role of PARP Inhibitors for Patients with TNBC and a BRCA Mutation

P. Kelly Marcom, MD
Duke Cancer Institute
Breast Oncology Program Director
Professor of Medicine
Duke University Hospital

DukeMedicine

PARPi MOA Trapping vs. Not and Potency



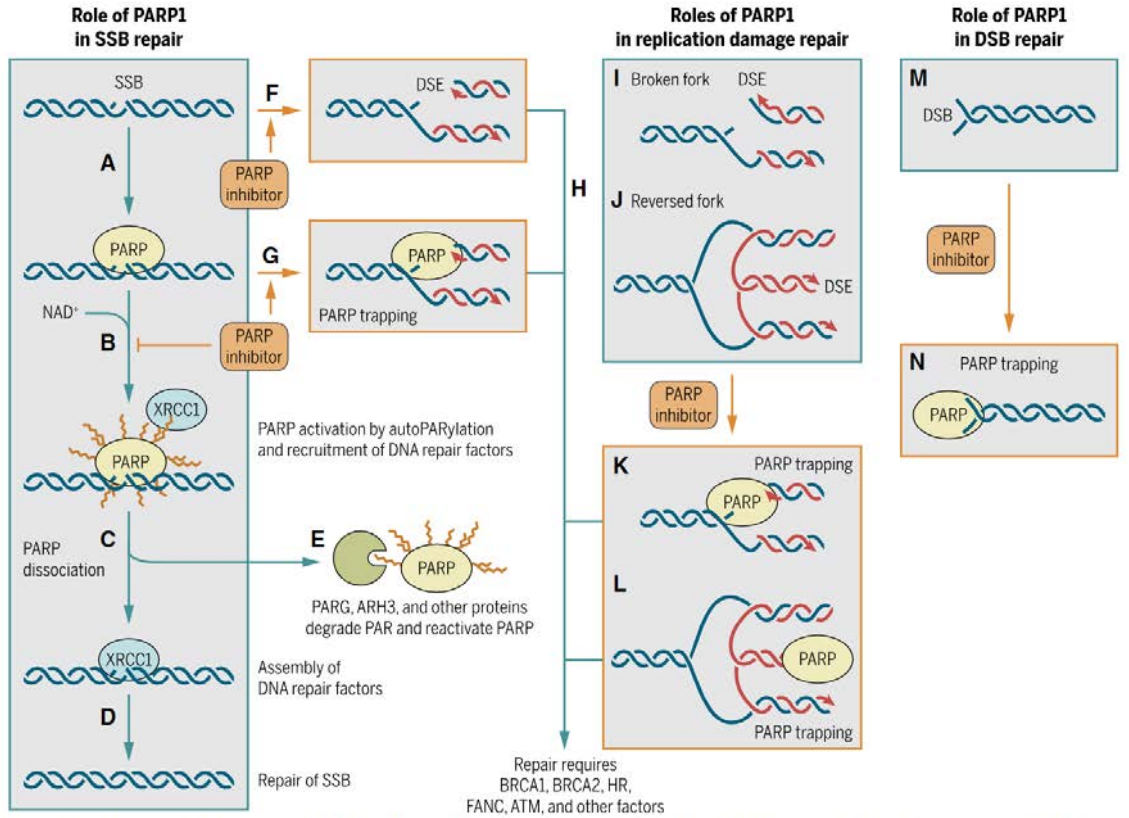


Fig. 1. DNA repair by PARP1 and the effects of PARP inhibitors. Upon the generation of an SSB, PARP1 binds to the break (**A**) and uses NAD^+ (**B**) to generate PAR polymers on itself (auto-PARylation), as well as on histones and chromatin-associated proteins. This serves the purpose of relaxing chromatin and recruiting repair proteins. Cumulative auto-PARylation causes the dissociation of PARP1 from DNA (**C**), allowing access to other repair factors scaffolded by XRCC1 (**D**). PARylation is removed by PARG (**E**), a glycohydrolase, which allows PARP1 reactivation. PARP inhibitors block NAD^+ binding and PARylation for as long as the inhibitor is bound to the NAD^+ site (B), thereby preventing PARP dissociation from the SSB, resulting in both accumulation of unrepaired SSBs (**F**) and PARP trapping (**G**). Repairing the ensuing DSB and PARP trapping will require BRCA1, BRCA2, and other HRR factors, as well as ATM, Fanconi, and replication bypass pathways for cell survival (**H**). PARP1 is also involved in the repair of "collapsed forks" with DSEs (**I**), in the retraction and restart of stalled replication forks (**J**), and in the repair of DSBs (**M**). PARP inhibitors trap PARP at DSEs (**K** and **L**) and DSBs (**N**).

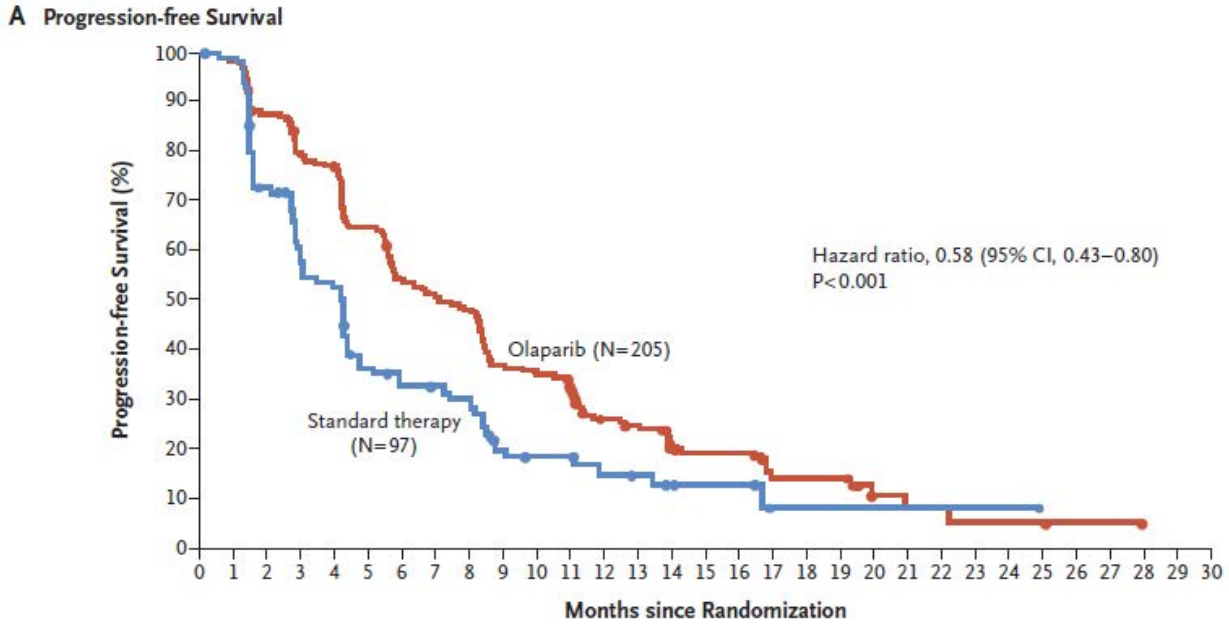
Iglehart, J.D., Silver, D.P., 2009. Synthetic Lethality — A New Direction in Cancer-Drug Development. New England Journal of Medicine.. doi:10.1056/nejme0903044

Courtesy of P Kelly Marcom, MD

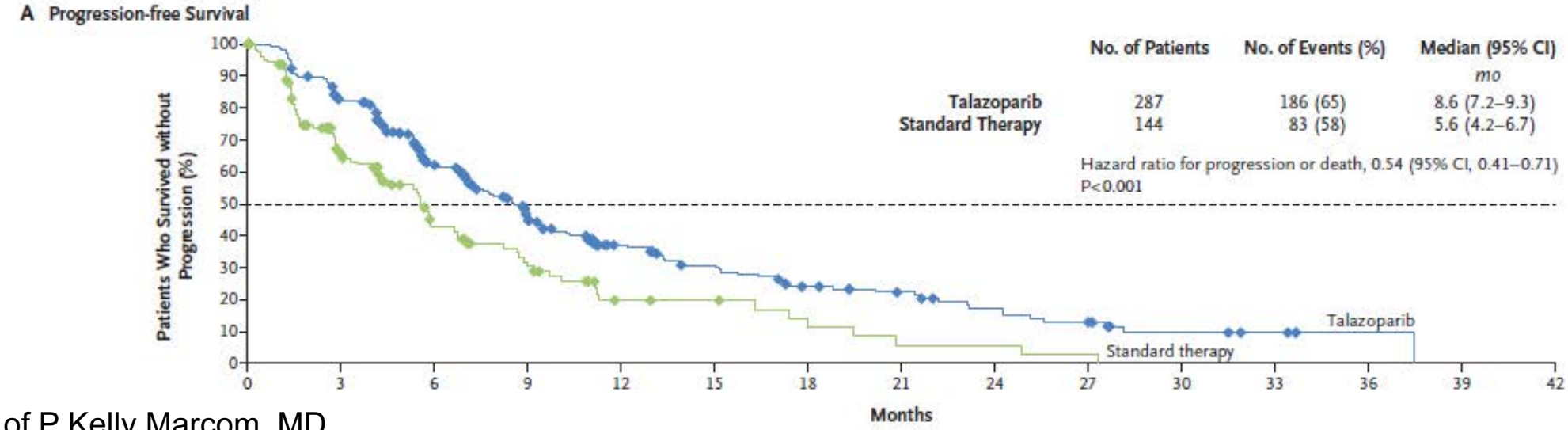
Pommier, O'Connor, de Bono, Sci. Transl. Med. 8, 362ps17 (2016) 26 October 2016

Phase III Trials: Progression-Free Survival

OlympiAD



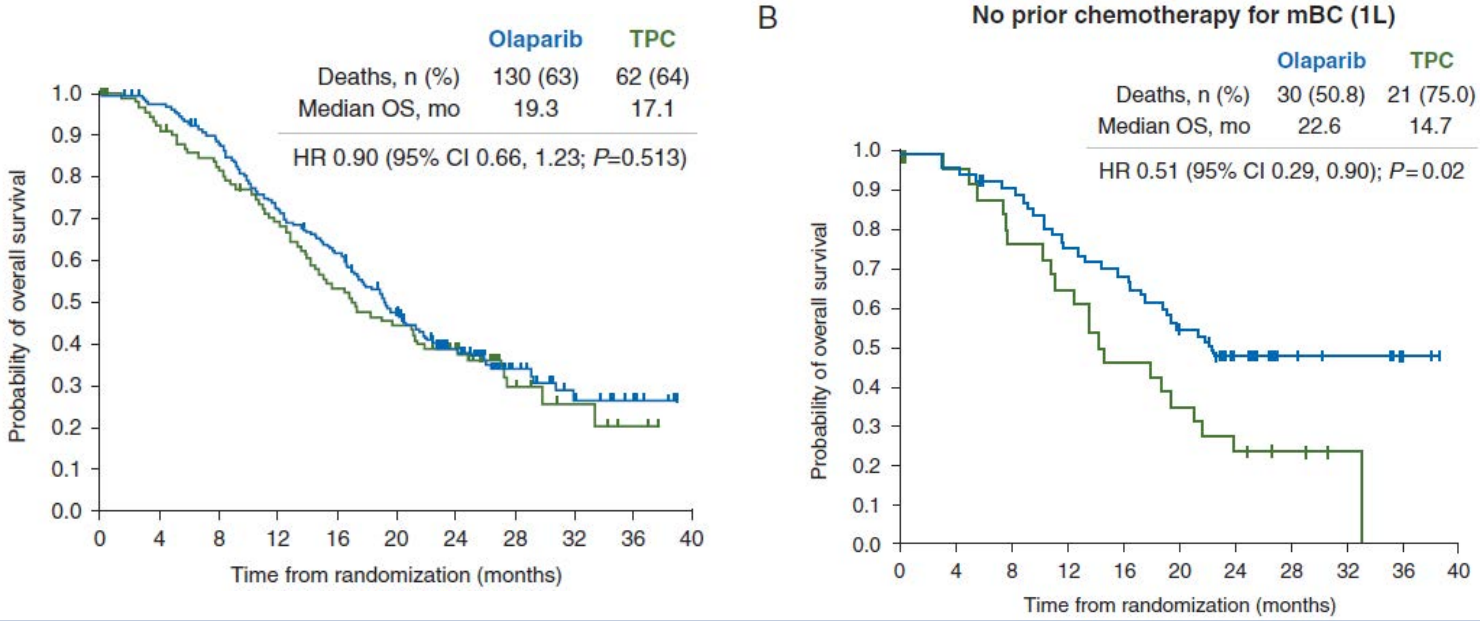
EMBRACA



Courtesy of P Kelly Marcom, MD

Phase III Trials: Final Overall Survival Data

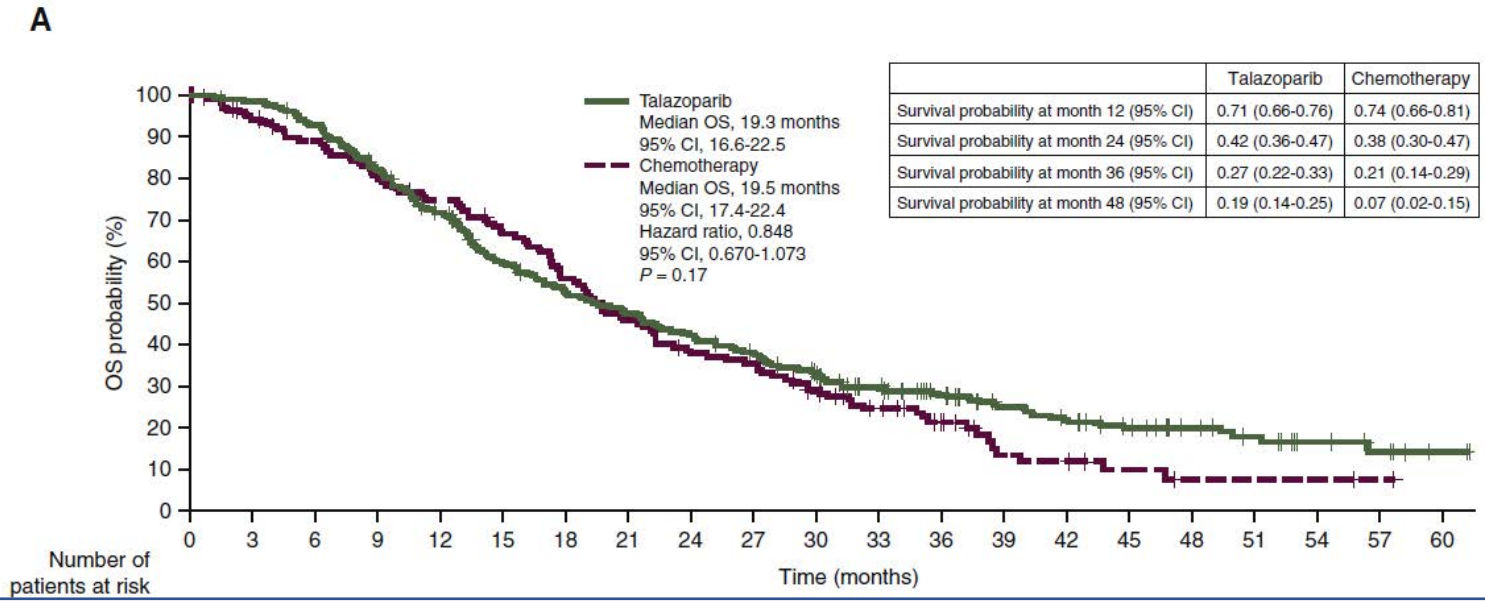
OlympiAD



- No crossover
- No approved PARPi available at progression.

Robson, Annals of Oncology 30: 558–566, 2019

EMBRACA



	Talazoparib	Chemotherapy
Survival probability at month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)
Survival probability at month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)
Survival probability at month 36 (95% CI)	0.27 (0.22-0.33)	0.21 (0.14-0.29)
Survival probability at month 48 (95% CI)	0.19 (0.14-0.25)	0.07 (0.02-0.15)

- 25% of chemo received olaparib in subsequent lines v. 2.8% of talazoparib.
- CDK4/6i: 13.6% talazoparib v. 10.4% chemotherapy

Litton, Annals of Oncology, 31: 1526-1535, 2020

Courtesy of P Kelly Marcom, MD

Veliparib

- A different PARP inhibitor; Inhibits PARP1 and PARP2
- No “PARP trapping”. More limited MOA allows combining with chemotherapy
- Results of I-SPY2 indicated high probability of improving pCR in TNBC (not genetically selected)
- In the BrighTNess preoperative trial, the addition of veliparib did NOT increase pCR rate, although was tolerated.
- The BROCADE2 Phase II trial investigated addition of veliparib to carboplatin/paclitaxel in gBRCA mutated metastatic breast cancer; a statistically non-significant improvement in PFS was seen.

Courtesy of P Kelly Marcom, MD

Loibl, BrighTNess, Lancet Oncol 2018; 19: 497–509

Han, BROCADE2, Annals of Oncology 29: 154–161, 2018

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

2:1 Randomization
N=513

Veliparib + Carboplatin/paclitaxel

Placebo + Carboplatin/paclitaxel

Treat to progression:
If carboplatin and paclitaxel were discontinued prior to progression, dosing of veliparib/placebo increased to 300mg BID continuous, and then 400mg BID if tolerated

Optional open-label crossover to veliparib

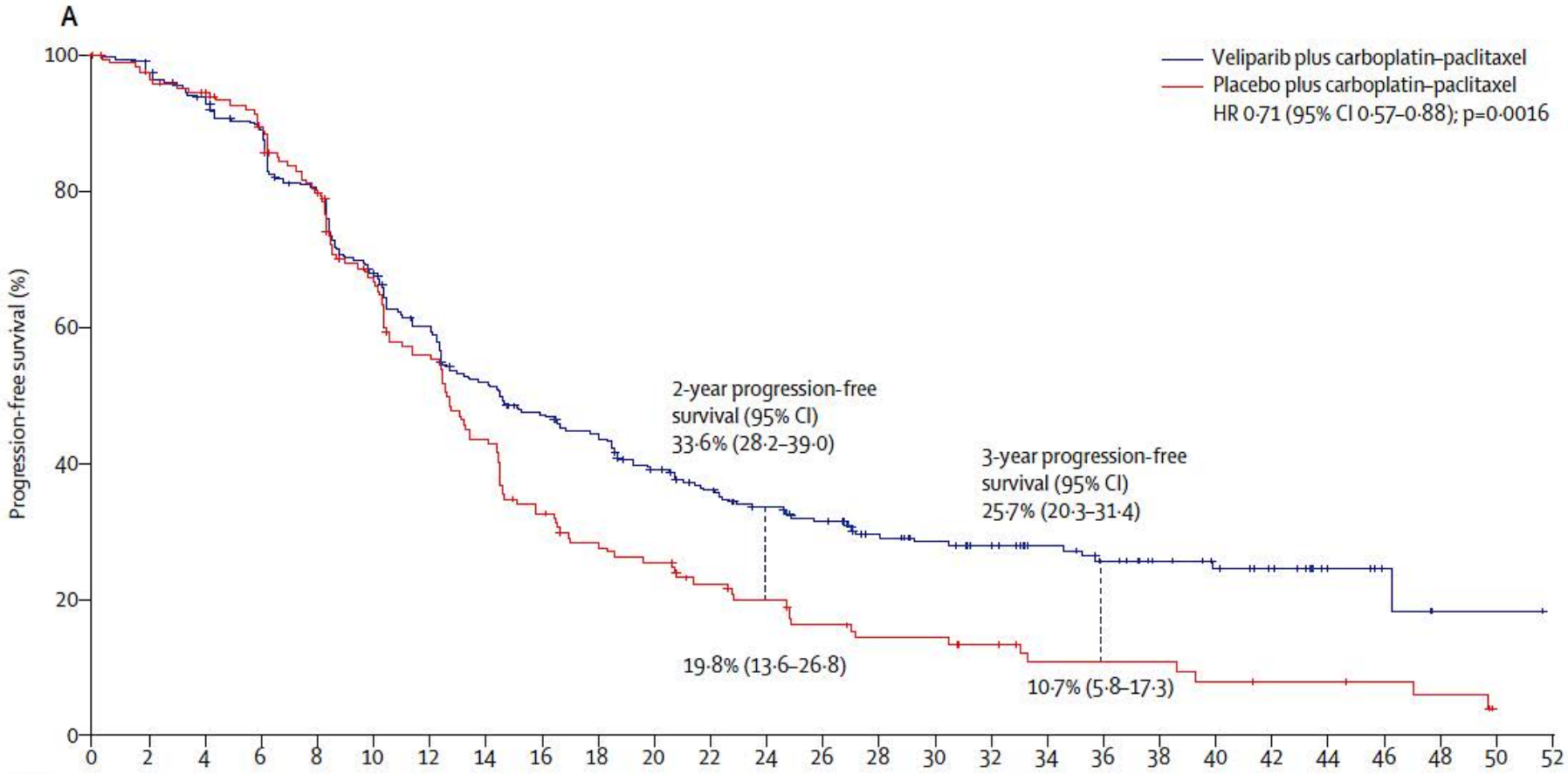
Primary Endpoint:
Investigator-assessed PFS per RECIST 1.1

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

BARCELONA 2019 ESMO congress

Courtesy of P Kelly Marcom, MD

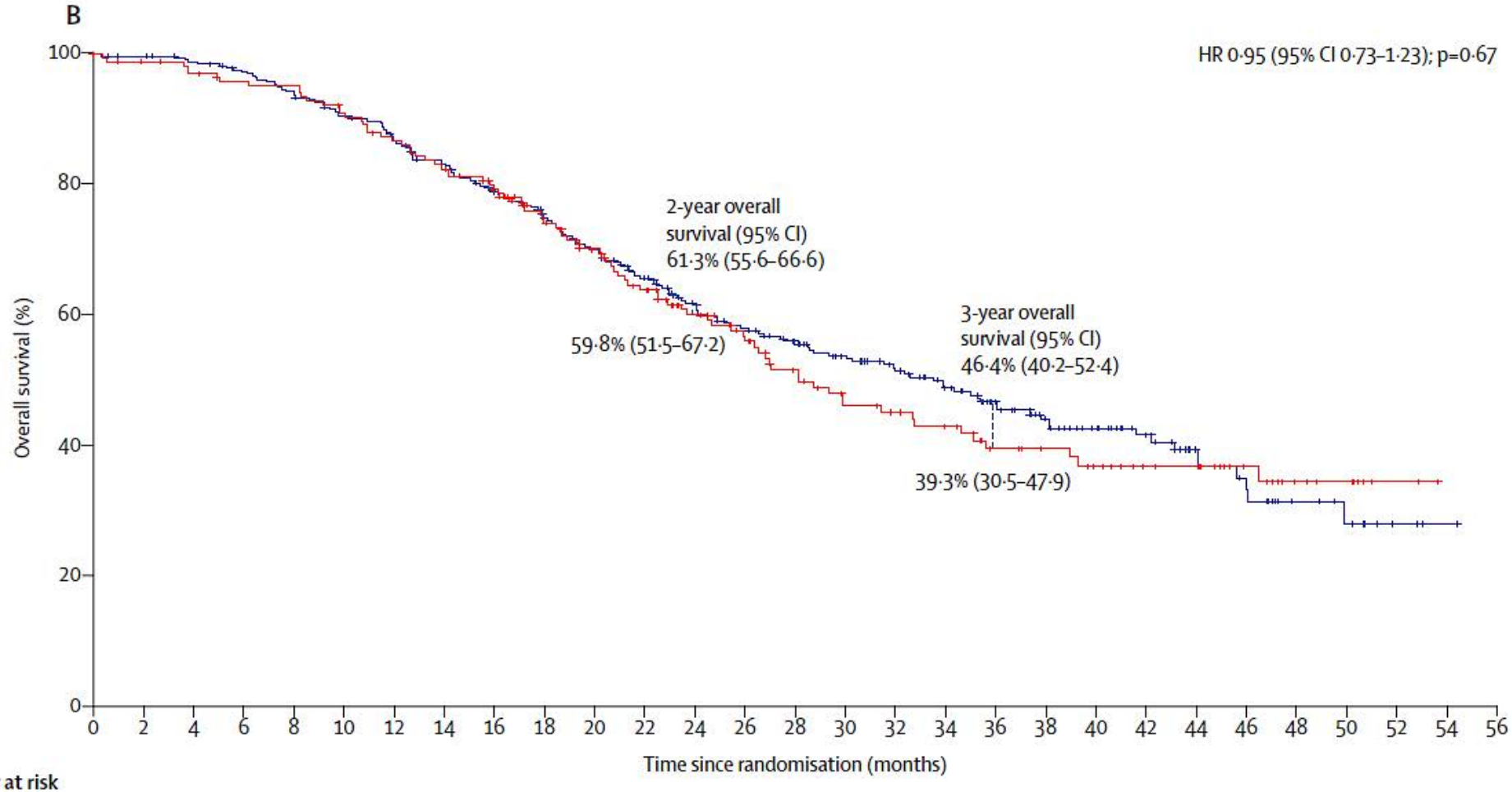
BROCADE3: Progression-Free Survival



Number at risk (number censored)																											
Veliparib plus carboplatin–paclitaxel	337 (0)	316 (13)	301 (16)	282 (21)	250 (24)	207 (29)	181 (32)	154 (43)	137 (37)	126 (40)	107 (44)	92 (51)	81 (56)	72 (60)	60 (68)	51 (75)	45 (80)	38 (87)	32 (90)	25 (97)	20 (101)	16 (105)	8 (113)	4 (117)	1 (119)	1 (119)	0 (120)
Placebo plus carboplatin–paclitaxel	172 (0)	160 (8)	153 (10)	140 (15)	123 (17)	99 (21)	82 (22)	64 (22)	47 (23)	39 (25)	35 (25)	27 (29)	23 (30)	18 (31)	15 (32)	15 (32)	12 (34)	8 (36)	8 (36)	8 (36)	6 (36)	5 (37)	5 (37)	4 (38)	3 (38)	0 (40)	.. ..

Courtesy of P Kelly Marcom, MD

BROCADE3: Overall Survival



Number at risk (number censored)																													
Veliparib plus carboplatin–paclitaxel	337 (0)	332 (4)	326 (7)	318 (10)	307 (10)	294 (12)	281 (14)	265 (17)	247 (22)	223 (34)	203 (39)	185 (44)	161 (57)	145 (64)	132 (72)	117 (82)	106 (89)	90 (99)	76 (109)	62 (119)	50 (129)	41 (137)	30 (146)	18 (154)	11 (160)	8 (162)	3 (167)	1 (169)	0 (170)
Placebo plus carboplatin–paclitaxel	172 (0)	166 (4)	162 (5)	158 (7)	157 (7)	149 (8)	141 (9)	134 (9)	125 (14)	111 (19)	102 (22)	90 (25)	75 (35)	68 (38)	57 (43)	47 (47)	44 (49)	40 (51)	32 (56)	29 (59)	25 (61)	19 (67)	18 (68)	15 (71)	9 (76)	7 (78)	2 (83)	0 (85)	.. ..

Courtesy of P Kelly Marcom, MD

Safety and Toxicity: PARPi Associated ≥ Grade 3

PARPi	Any ≥ Gr3	Hematologic	Gastrointestinal	General	Treatment Change for Any AE	Alopecia (Any)
Olaparib	37%	Anemia: 16% Neutropenia: 9%	N/V: 0% Diarrhea: 1% LFTs: 3%	Fatigue: 3% Headache: 1%	Dose Reduction: 25% Delay: 35% Stop: 5%	3.4%
Talazoparib	26%	Anemia: 39% Neutropenia: 21%	N/V: 3% Diarrhea: 0.7%	Fatigue: 2% Headache: 2% Pleural Eff: 1.7%	Dose Reduction: 33% Dose interruption: 37% (At 7-12 months) Stop: 6%	25%
Veliparib+Chemo (BROCADE3)	95%	Anemia: 42% Neutropenia: 82% Thrombocytopenia: 40%	N/V: 7% Diarrhea: 5%	Fatigue: 4% Headache: 2%		54%

- Transfusions in OlympiAD were high at 20% but driven per protocol for Gr1/2 anemia. No leukemias or MDS.
- Transfusions in EMBRACA (at least one) were 39%. One leukemia case.

Courtesy of P Kelly Marcom, MD

TBCRC 048 Study: 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, PI)

Hypothesis: Olaparib will have an overall response rate ≥ 20% in breast cancer patients with a germline or somatic mutation in DNA damage response (DDR) pathway genes associated with HR other than BRCA1/2 or with a somatic BRCA1/2 mutation.

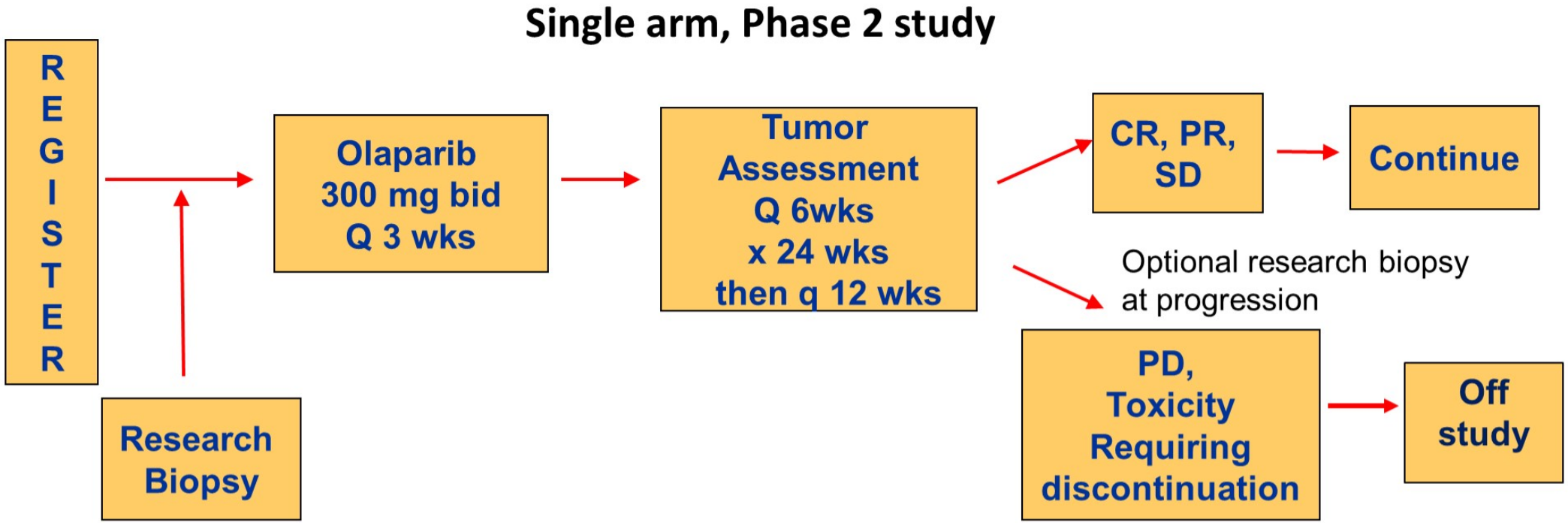
- Primary Aim: ORR (CR + PR by RECIST 1.1)
- Secondary Aim: CBR (CR + PR + SD ≥ 18 weeks), Duration of Response, Progression-Free Survival, Toxicity.

Eligibility: Measurable metastatic disease; no prior PARPi; No more than 2 prior chemotherapy regimens; Not platinum refractory.

Courtesy of P Kelly Marcom, MD

Tung, Journal of Clinical Oncology, Oct 29, 2020 https://dx.doi.org/10.1200/jco.20.02151

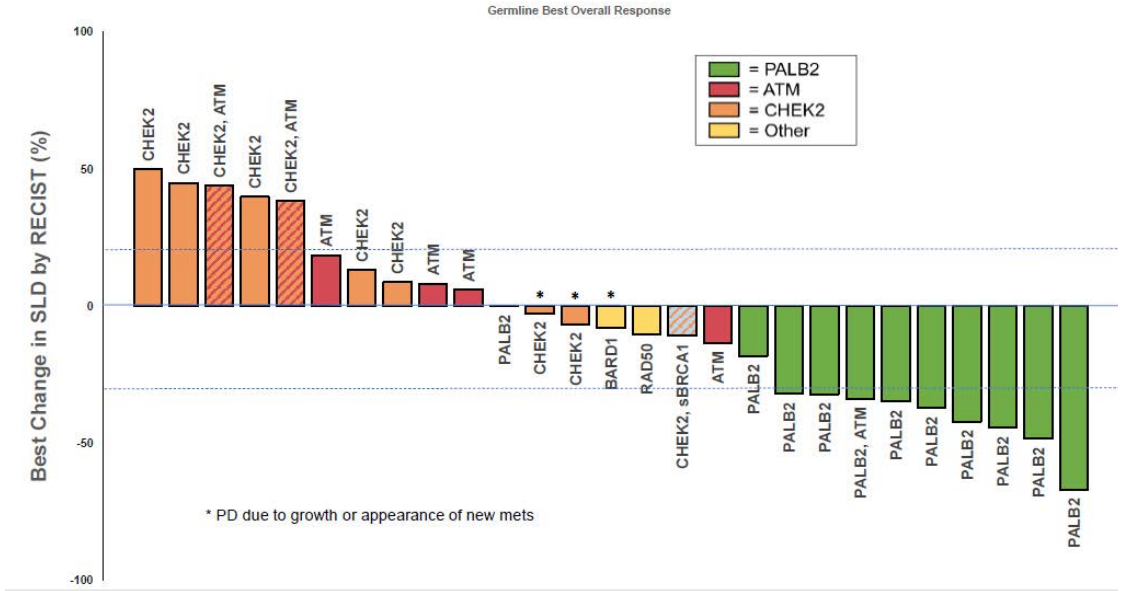
TBCRC 048 Trial Schema: Olaparib Expanded

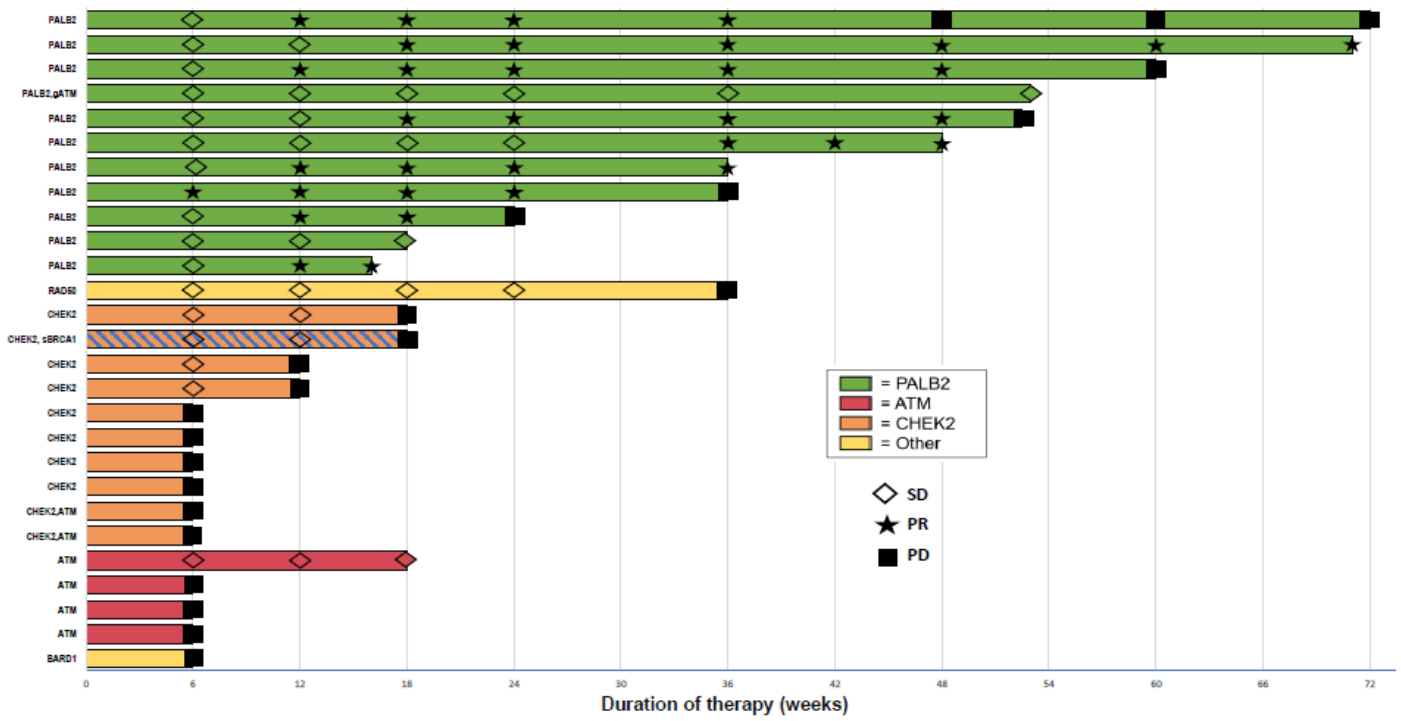


Tung NM et al. ASCO 2020;Abstract 1002.

Courtesy of P Kelly Marcom, MD

TBCRC 048 Trial Germline Cohort: Best Response and DOR

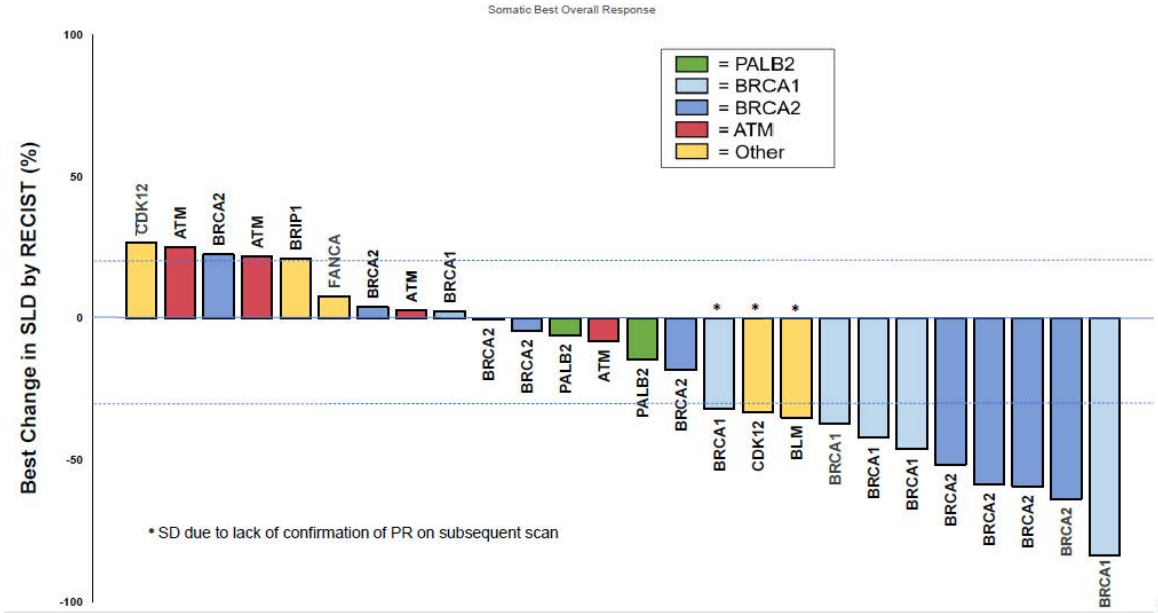


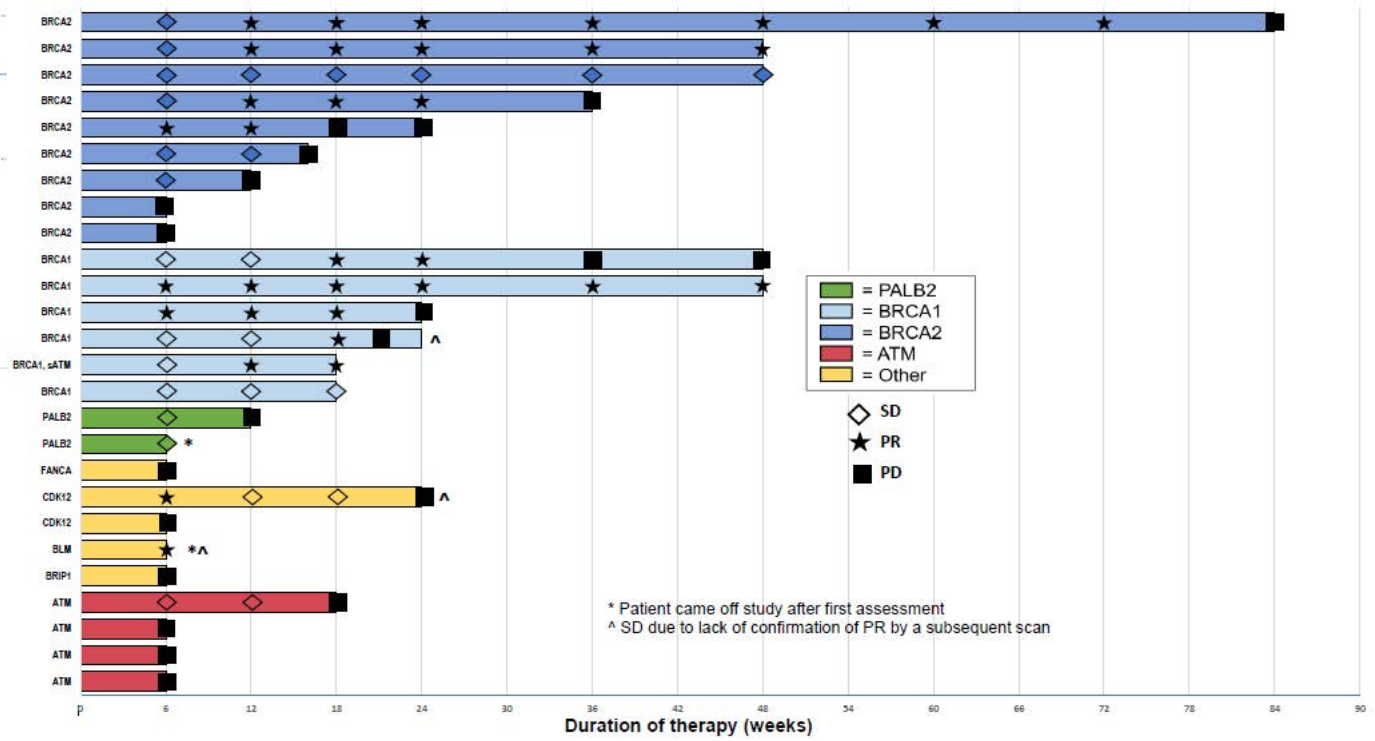


Tung NM et al. ASCO 2020;Abstract 1002.

Courtesy of P Kelly Marcom, MD

TBCRC 048 Trial Somatic Cohort: Best Response and DOR





Tung NM et al. ASCO 2020;Abstract 1002.

Courtesy of P Kelly Marcom, MD

PARPi (Neo) Adjuvant Trials

Preoperative Talazoparib Study:
Single Agent for 6 months gBRCA+

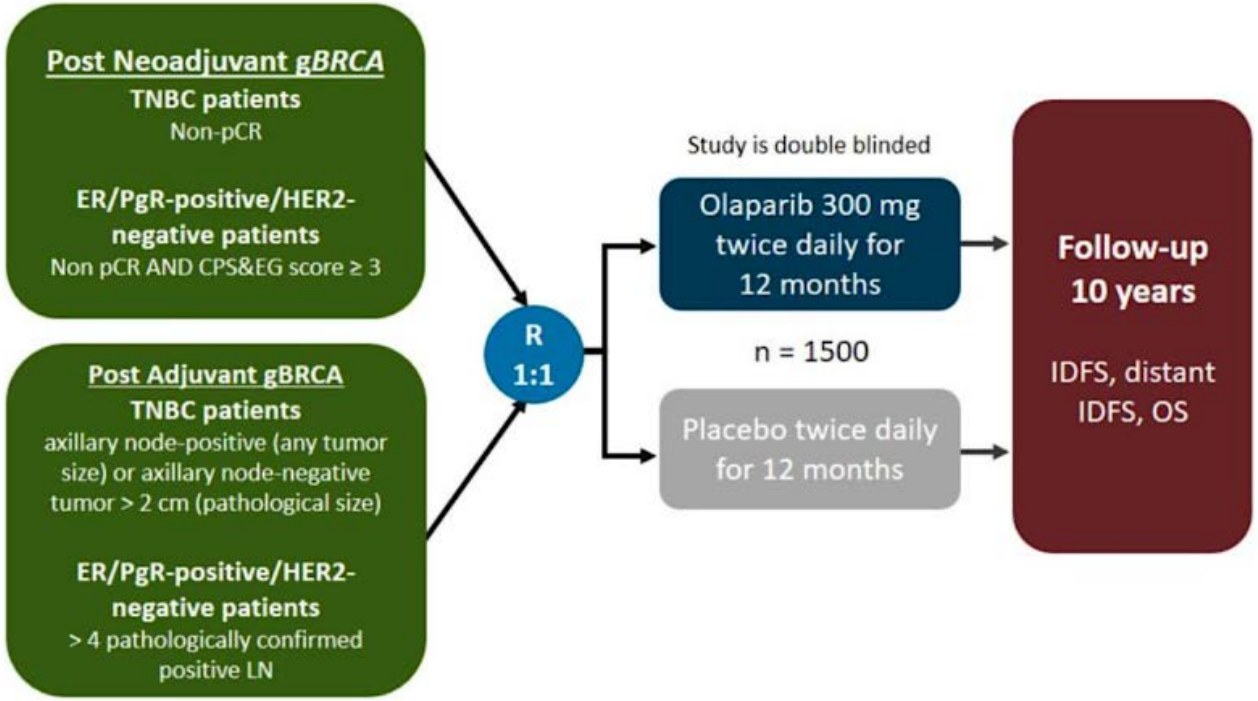
TABLE 1. Patient Characteristics

Characteristic	No. of Patients
Age, years	20
Median (range)	38 (23-58)
Race	
White	7
Black	5
Hispanic	5
Asian	3
BRCA	
1	16
2	4
Clinical stage	
I	5
II	12
III	3
Histology	
Ductal	18
Lobular	1
Metaplastic chondrosarcomatous	1
Tissue receptor subtype	
TNBC (ER and PR < 10%)	15
Hormone receptor positive (≥ 10%)	5

pCR 53%

OlympiA: Adjuvant Olaparib gBRCA+/HER2-

(NSABP B55/BIG 6-13)



Estimated primary completion date: November 18, 2020

Courtesy of P Kelly Marcom, MD

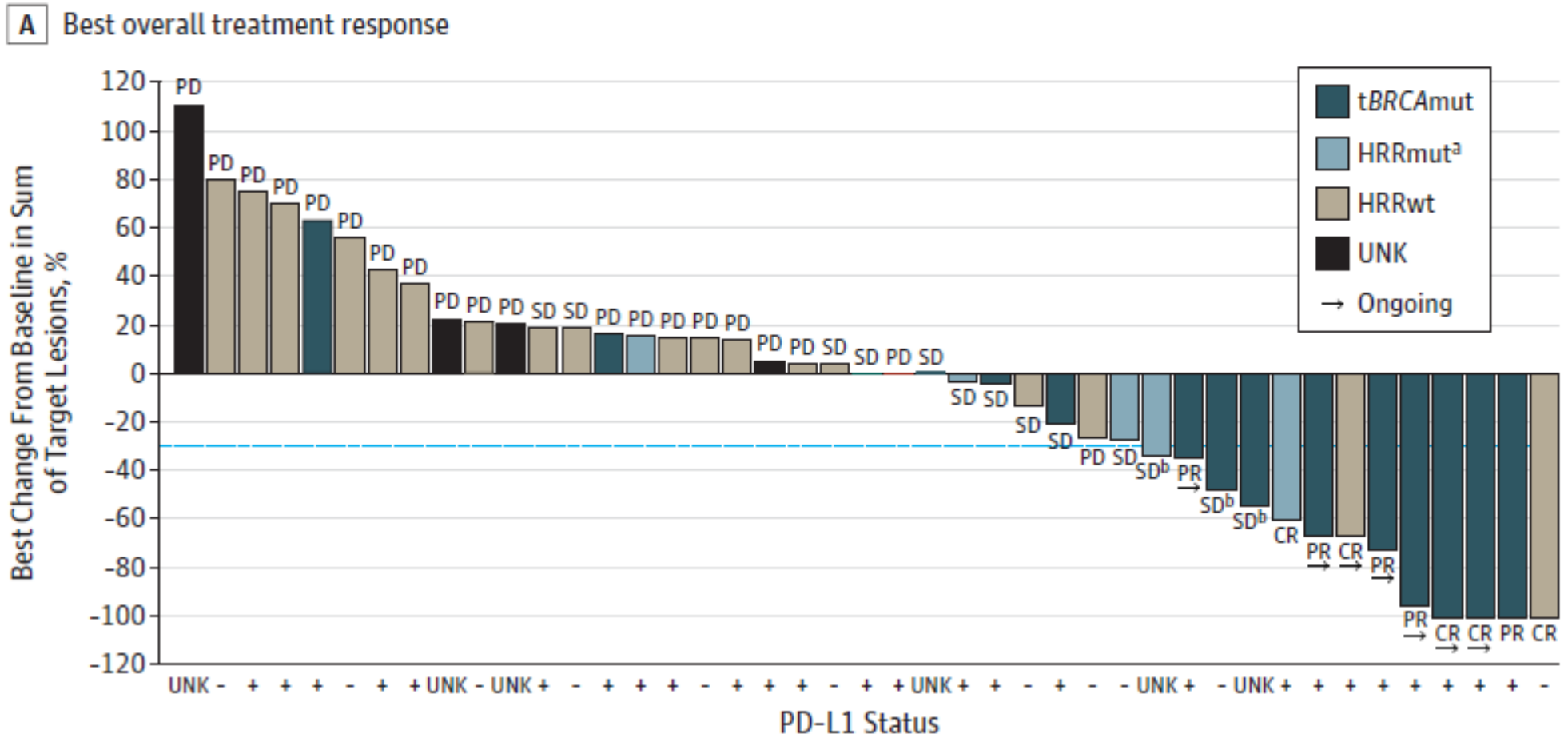
Novel Combinations: PARPi and Immune Checkpoints

- RATIONALE: PARPi activates intratumoral STING/c-GAS pathway causing CD8+ T-cell recruitment. IC might act synergistically with this activation.(Pantelidou, Cancer Discovery, 9: 722, 2019)

Trial	BRCA1/2 Status	Drugs	Eligibility	Cohort Size	Overall Response Rate
TOPACIO	Any BRCA or PD-L1 status	Niraparib Pembrolizumab	≤ 2 chemo	55	21%
MEDIOLA	gBRCA	Olaparib Durvalumab	≤ 2 chemo	30	63%

Courtesy of P Kelly Marcom, MD

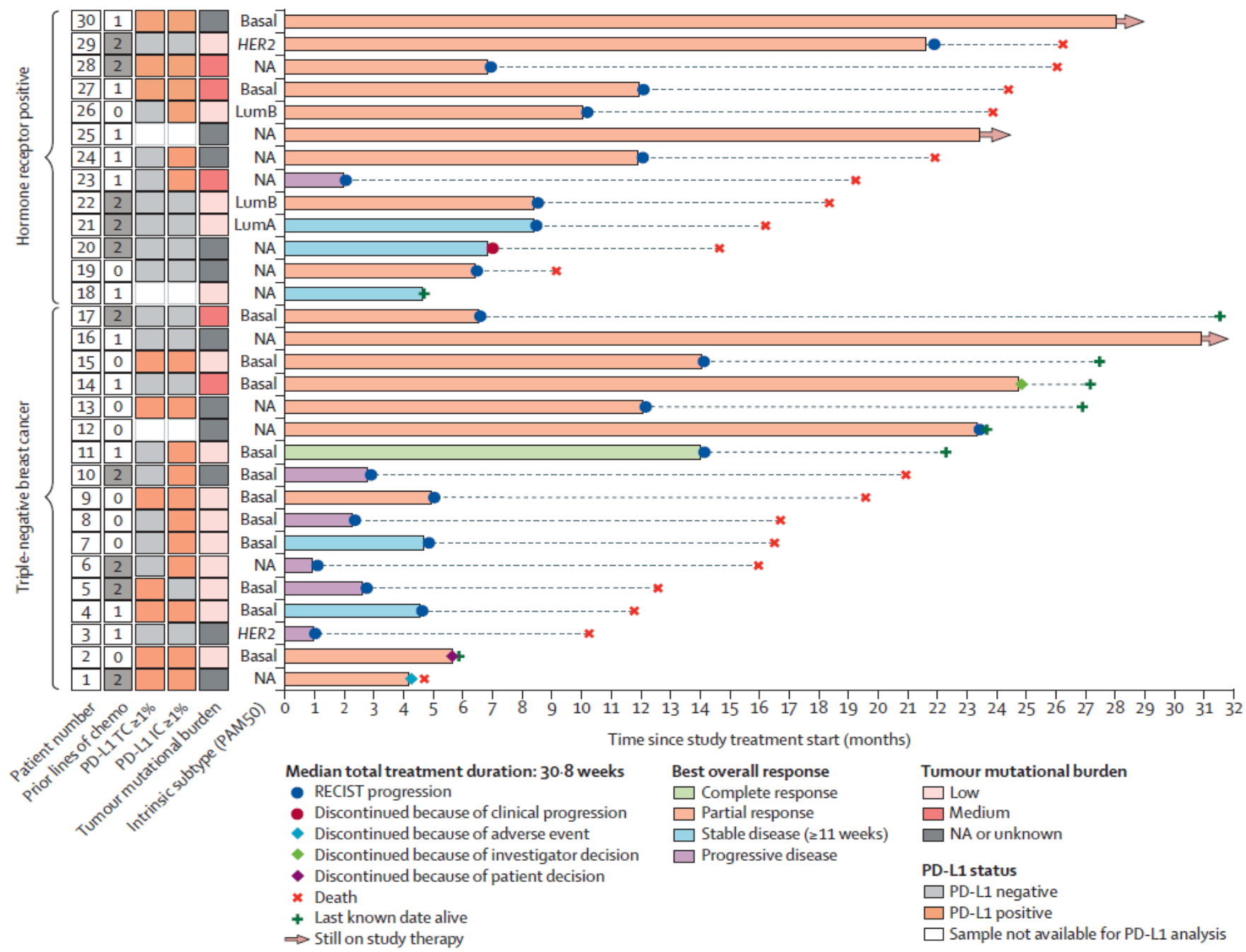
TOPACIO: Best Overall Response



Courtesy of P Kelly Marcom, MD

Vinayak, JAMA Oncol. 2019;5(8):1132-1140

MEDIOLA Trial



Courtesy of P Kelly Marcom, MD

Domchek, Lancet Oncol 2020; 21: 1155–64

Open PARPi/IO Trials

Olaparib:

- DORA- Durvalumab (consolidation of platinum responsive TNBC)
- OHSU-Durvalumab with multi-omics analysis
- KEYLYNK-009-Consolidation with olaparib/pembro v. chemo/pembro after chemo/pembro induction

Talazoparib:

- Avelumab

Niraparib:

- Dostarlimab (TSR042) - PD-1i (early-stage preop)
- HX008 (PD-1i)

Courtesy of P Kelly Marcom, MD

ClinicalTrials.gov Active/Recruiting November 2020

Novel Combinations: PARPi/Other Therapies

Olaparib:

- Radiation (IBC),
- Sapacitabine (nucleoside analogue)
- trastuzumab in BRCA+/HER2+ disease
- ceralasertib (ATRi) or adavosertib (WEE1i)
- hyperthermia
- palbociclib/fulvestrant in BRCA+/ER+
- Selumetinib (MEKi)
- CYH33 (alpha-PIK3CAi)

Talazoparib:

- Sacituzumab
- Decitabine & cedazuridine (ASTX727) - DNMTi
- ZEN003694 (BETi)
- Gedatolisib (PI3K/mTORi)

Niraparib:

- Radiation (TNBC post-op)
- AI in ER+/HRD+
- Everolimus

Veliparib:

- Radiation (Preop)

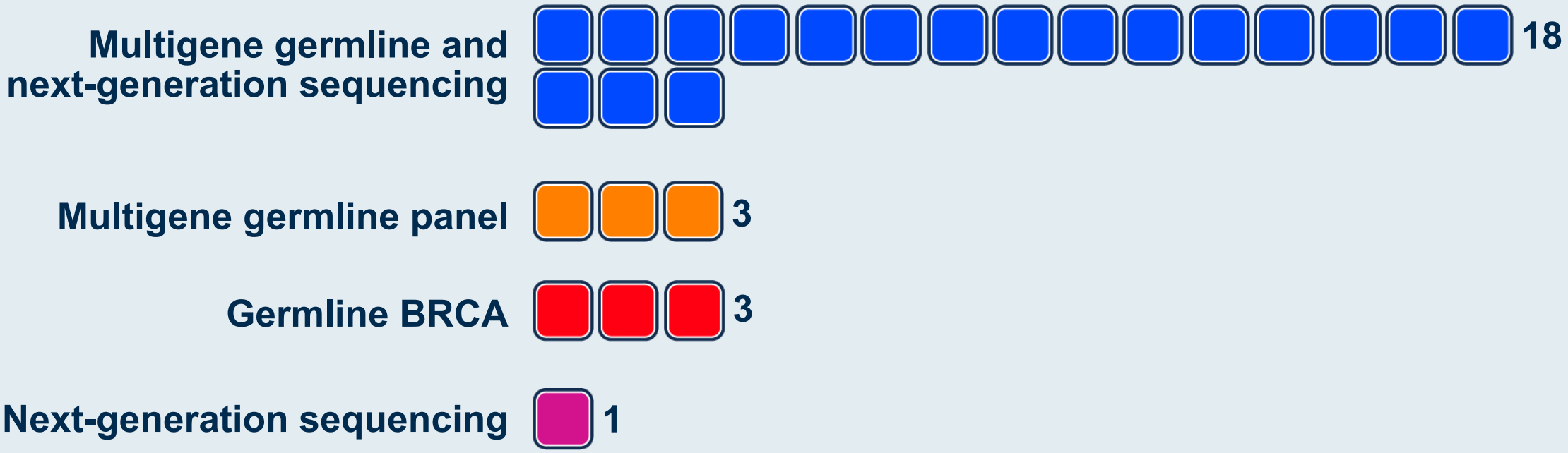
Courtesy of P Kelly Marcom, MD

ClinicalTrials.gov Active/Recruiting November 2020

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

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

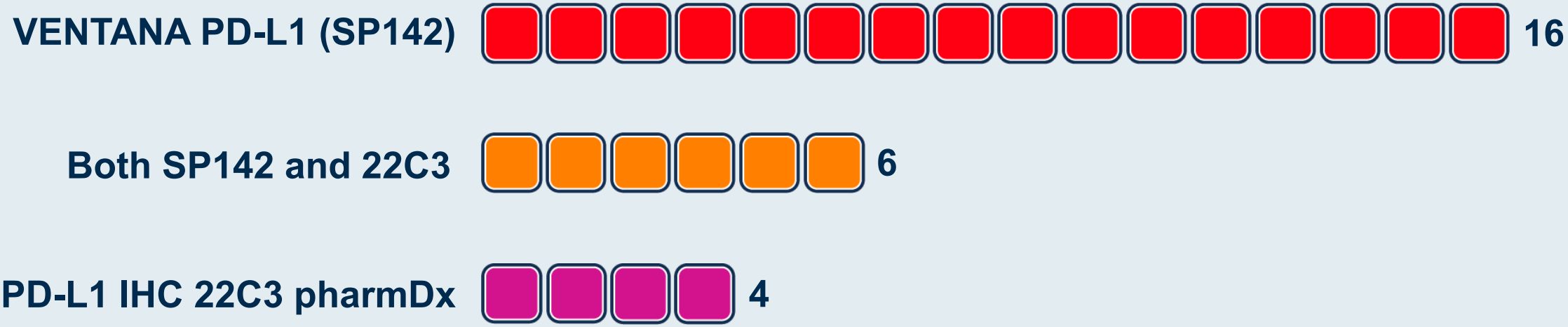


Survey of 25 breast cancer clinical investigators

A 41-year-old woman with a germline BRCA mutation who completed neoadjuvant AC/docetaxel and postoperative radiation therapy 21 months ago for localized TNBC now presents with liver, lung and nodal metastases. Which assay would you use to evaluate PD-L1 status?

1. VENTANA PD-L1 (SP142)
2. PD-L1 IHC 22C3 pharmDx
3. PD-L1 IHC 28-8 pharmDx
4. VENTANA PD-L1 (SP263)
5. Other

A 41-year-old woman with a germline BRCA mutation who completed neoadjuvant AC/docetaxel and postoperative radiation therapy 21 months ago for localized TNBC now presents with liver, lung and nodal metastases. Which assay would you use to evaluate PD-L1 status?

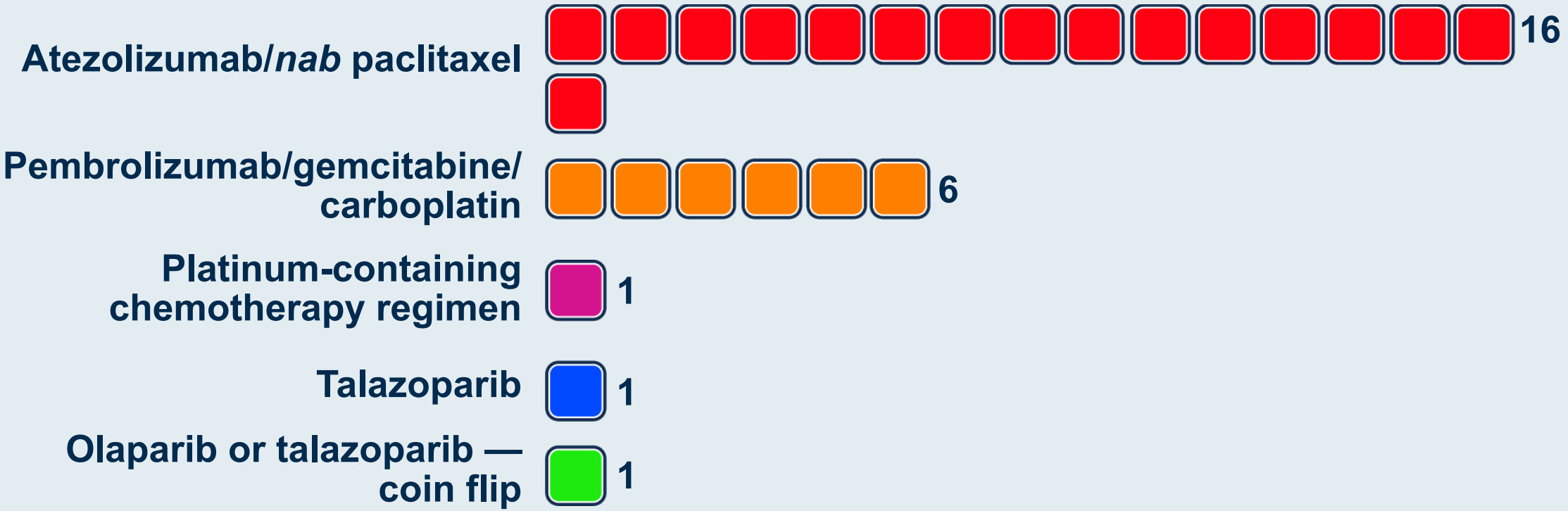


Survey of 25 breast cancer clinical investigators

What therapy would you most likely recommend if the patient's tumor is found to be PD-L1-positive?

1. Olaparib
2. Talazoparib
3. Olaparib or talazoparib — coin flip
4. Atezolizumab/*nab* paclitaxel
5. Pembrolizumab/chemotherapy
6. Chemotherapy
7. Chemotherapy followed by maintenance PARP inhibitor
8. Other

What therapy would you most likely recommend if the patient's tumor were found to be PD-L1-positive?

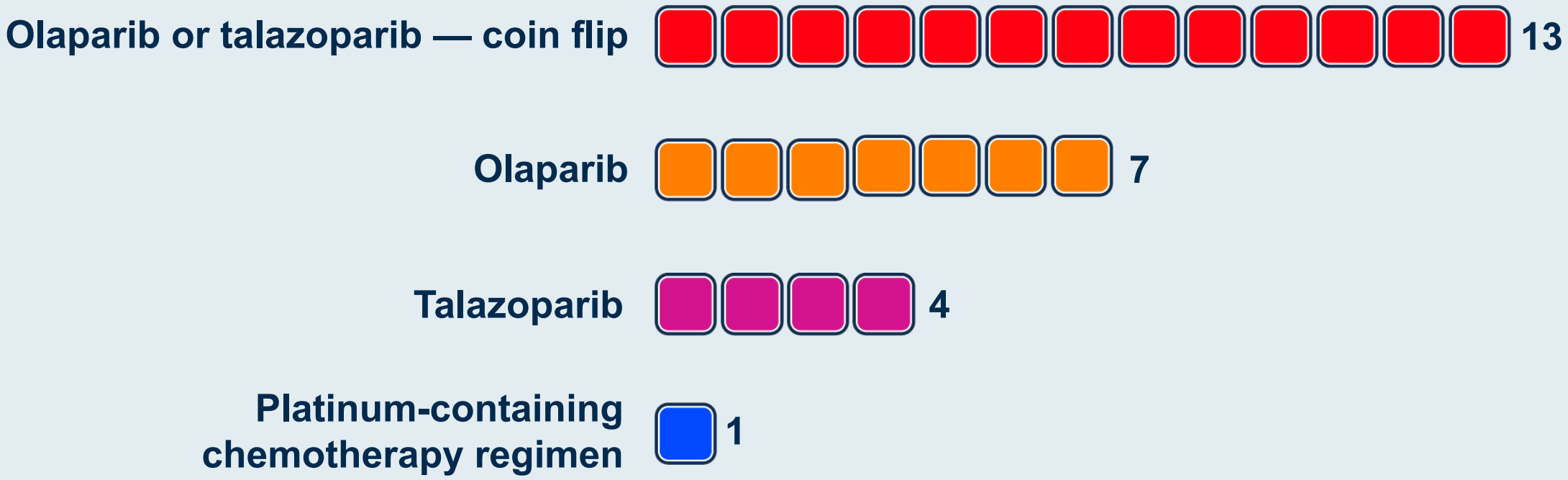


Survey of 25 breast cancer clinical investigators

The patient in the previous scenario receives first-line atezolizumab/*nab* paclitaxel but experiences disease progression after 29 months. What would you recommend next?

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

The patient in the previous scenario receives first-line atezolizumab/*nab* paclitaxel but experiences disease progression after 29 months. What would you recommend next?

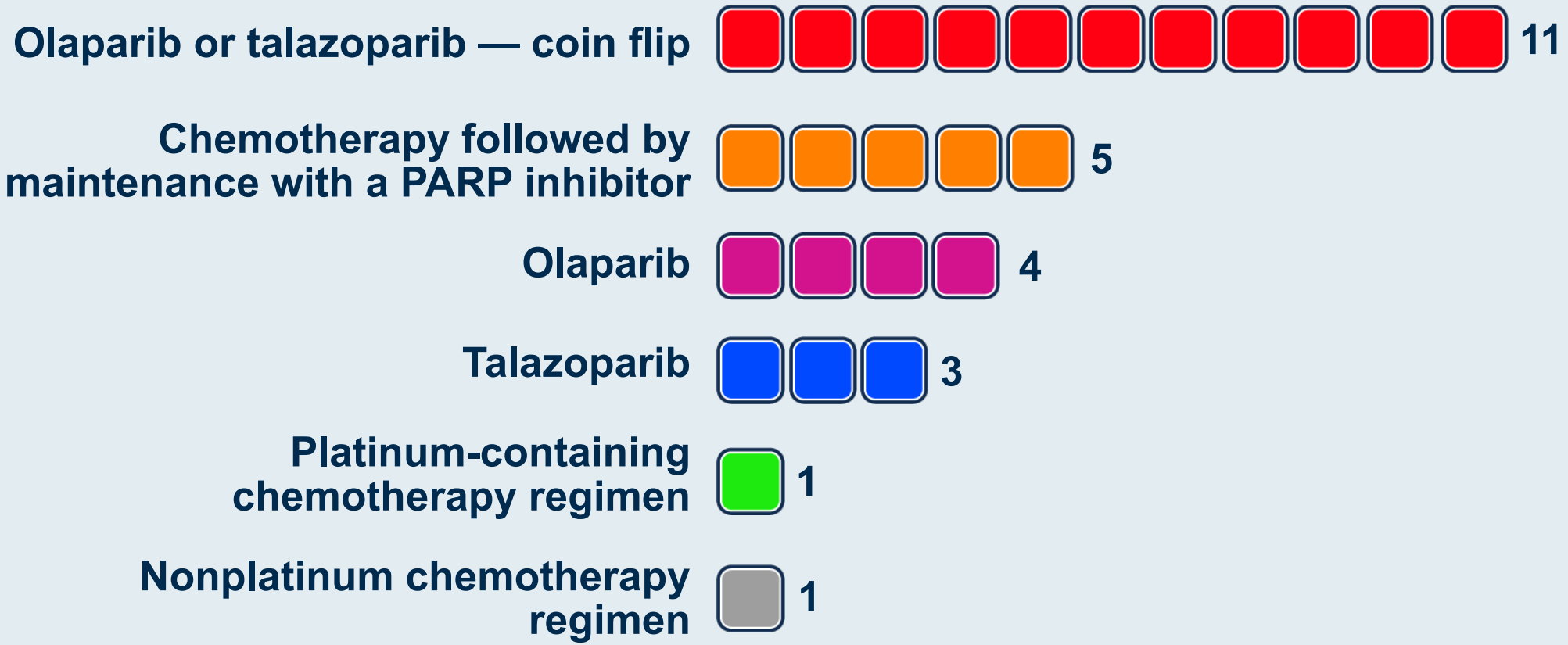


Survey of 25 breast cancer clinical investigators

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?

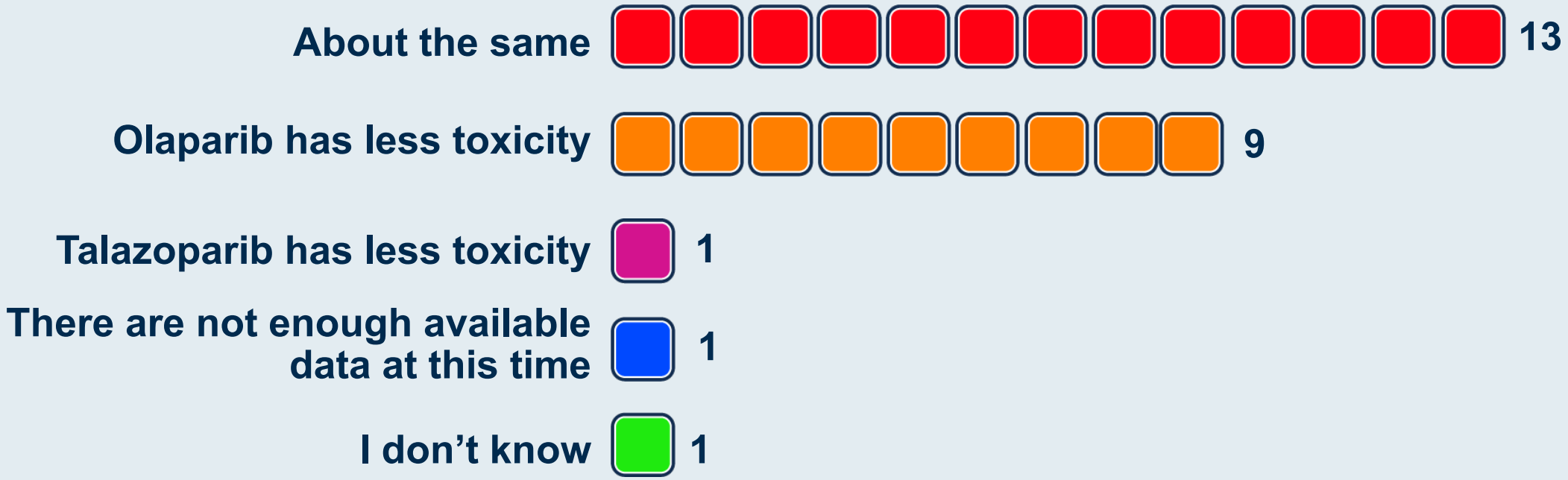
1. Olaparib
2. Talazoparib
3. Olaparib or talazoparib — coin flip
4. Nonplatinum chemotherapy
5. Platinum-containing chemotherapy
6. Chemotherapy followed by maintenance PARP inhibitor
7. Chemotherapy combined with a PARP inhibitor
8. Other

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?



Survey of 25 breast cancer clinical investigators

Based on current clinical trial data and your personal experience, how would you compare the global tolerability/ toxicity of olaparib to that of talazoparib when used as treatment for metastatic breast cancer?

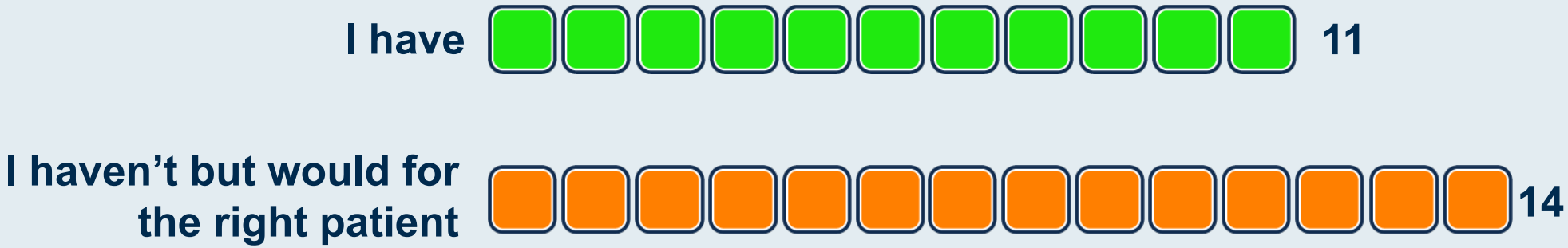


Survey of 25 breast cancer clinical investigators

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

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

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

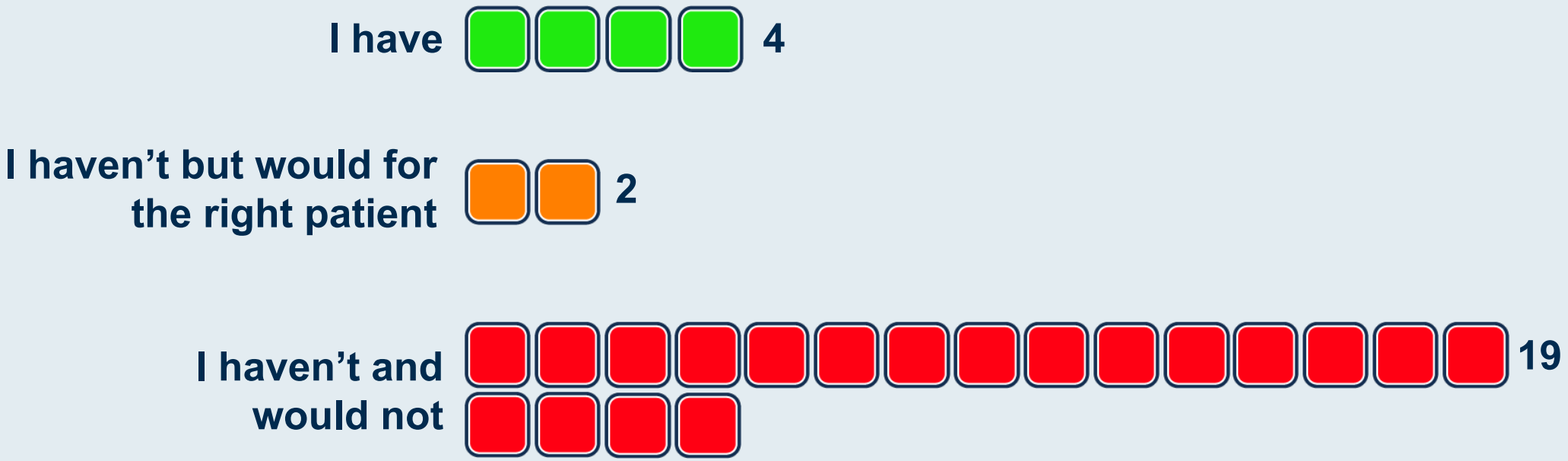


Survey of 25 breast cancer clinical investigators

Regulatory and reimbursement issues aside, have you or would you attempt to access a PARP inhibitor for a patient with metastatic TNBC and a germline ATM mutation?

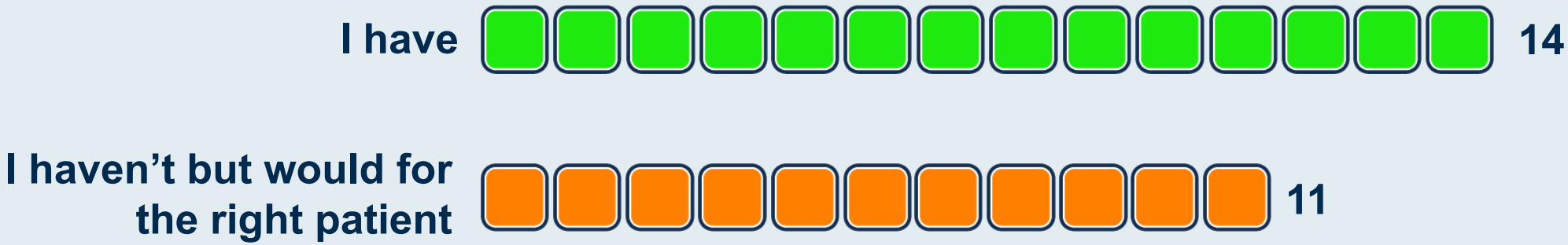
1. I have
2. I haven't but would for the right patient
3. I haven't and would not

Regulatory and reimbursement issues aside, have you attempted or would you attempt to access a PARP inhibitor for a patient with metastatic TNBC and a germline ATM mutation?



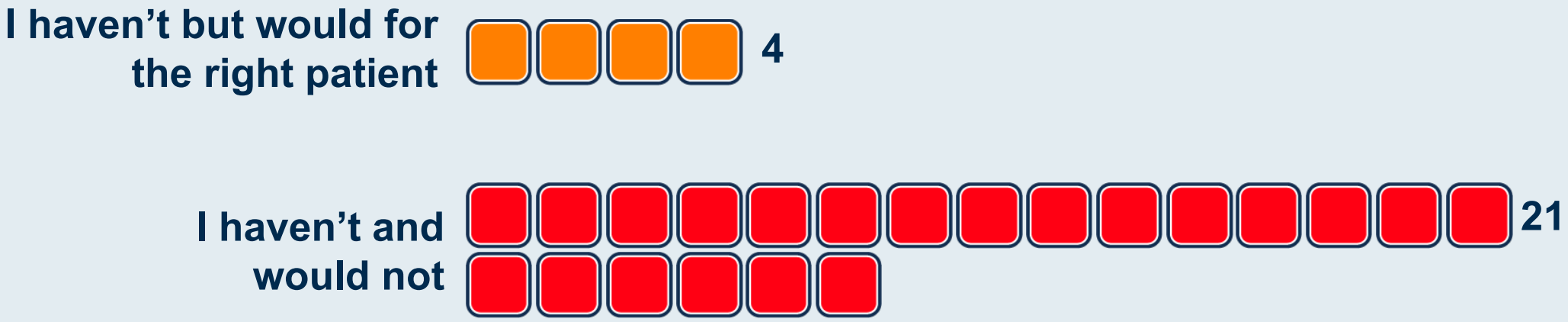
Survey of 25 breast cancer clinical investigators

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



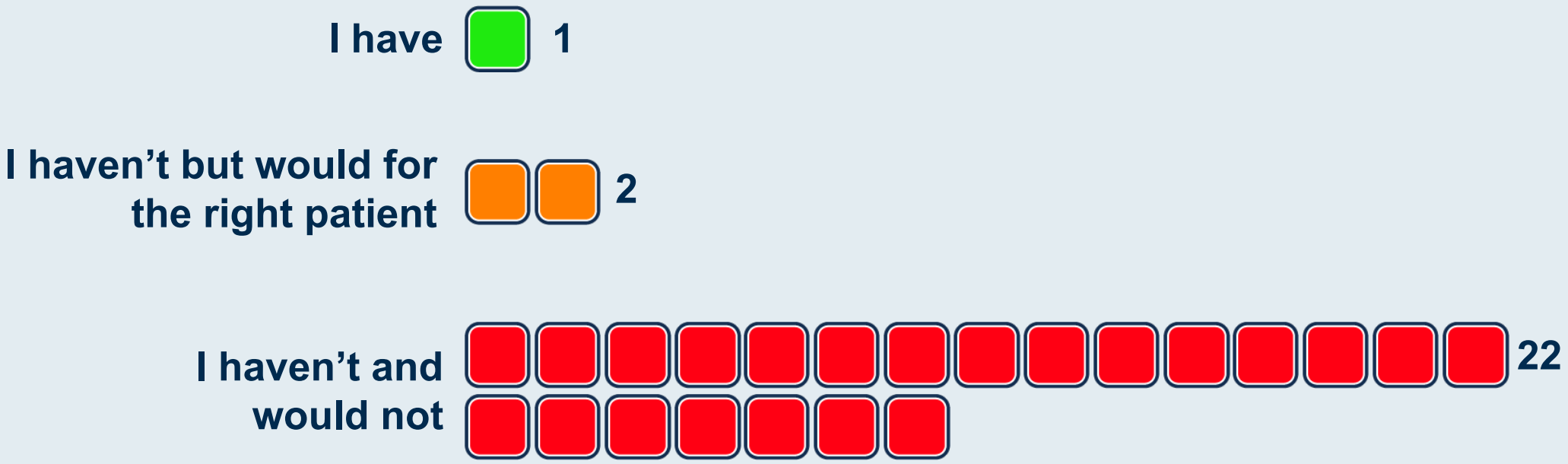
Survey of 25 breast cancer clinical investigators

Regulatory and reimbursement issues aside, have you attempted or would you attempt to access a PARP inhibitor as part of neoadjuvant therapy for a patient with TNBC outside of a clinical trial?



Survey of 25 breast cancer clinical investigators

Regulatory and reimbursement issues aside, have you attempted or would you attempt to access a PARP inhibitor as part of adjuvant therapy for a patient with TNBC outside of a clinical trial?



Survey of 25 breast cancer clinical investigators

Case Presentation – Dr Marcom: A 63-year-old woman with mTNBC and a somatic BRCA1 mutation

The patient is a 63-year-old white woman initially diagnosed with right breast cancer in February, 2018. She underwent a right lumpectomy and sentinel node mapping for a grade 3 2.6cm invasive ductal breast cancer. The sentinel node had a 3mm metastasis. The cancer was estrogen, progesterone, and HER2 receptor negative.

On staging PET scan done following surgery, she had multiple pulmonary nodules. Biopsy confirmed metastatic breast cancer.

She was started on weekly paclitaxel in June 2018. Germline genetic testing with a 28 gene panel was done given the metastatic TNBC; the family history showed minimal cancer (father with bladder cancer at a young age and a paternal cousin with breast cancer at 50). Only an incidental MUTYH mutation was found.

On Next-Generation Sequencing of her tumor in July 2018, however, somatic mutations in BRCA1 (p.K739*; c. 2215A>T; estimated variant allele frequency 43%) and TP53 (p.E298*; c.892G>T; estimated variant allele frequency 43%) were found.

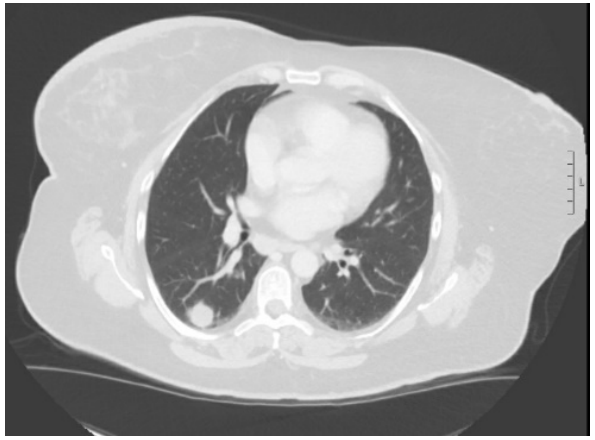


Figure 1: Baseline lung nodule

Courtesy of P Kelly Marcom, MD

Case Presentation – Dr Marcom: A 63-year-old woman with mTNBC and a somatic BRCA1 mutation (continued)

Restaging PET scan in October 2018 showed improvement in the lung lesions. However, a new lesion in the right cerebellum was noted; a brain MRI confirmed a 1.4 cm cerebellar lesion and a 4 mm left inferior temporal lobe lesion. Both lesions were treated by CyberKnife radiation to 18 Gy and 20 Gy, respectively. Paclitaxel was continued.

In February 2019, staging showed progression in the lung nodules.
She was treated with capecitabine, but it was discontinued for side effects.
Restaging in April 2019 showed progression in the lung lesions again and a new brain lesion in the left parietal cortex. The brain lesion was treated with stereotactic radiosurgery and systemic treatment was changed to weekly carboplatin.

She received weekly carboplatin through July, with continued response in the lungs and no brain progression; however, she developed carboplatin hypersensitivity requiring treatment change.

Given the somatic BRCA1 mutation, she was enrolled in a clinical trial evaluating olaparib activity in mutations in homologous repair deficiency genes other than BRCA1/2 as well as somatic BRCA1/2 mutations.

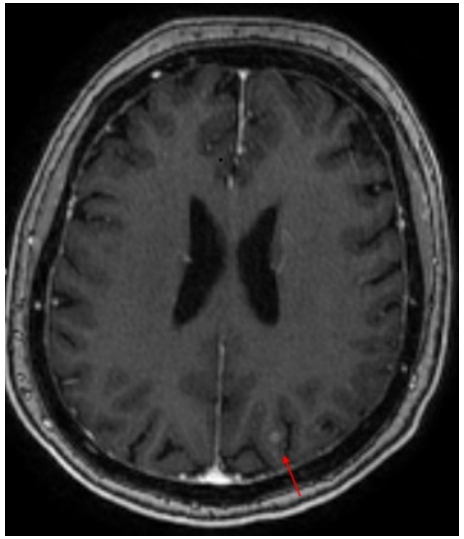


Figure 2: Recurrent left parietal lesion April 2019

Courtesy of P Kelly Marcom, MD

Case Presentation – Dr Marcom: A 63-year-old woman with mTNBC and a somatic BRCA1 mutation (continued)

She initiated single-agent olaparib at 300 mg PO BID in August 2019. She had resection of the cerebellar area for progression concerns in August 2020 that showed only radiation necrosis. She required one transfusion after 15 months of treatment at full dose olaparib, but has otherwise tolerated treatment well and remains in a complete clinical remission.

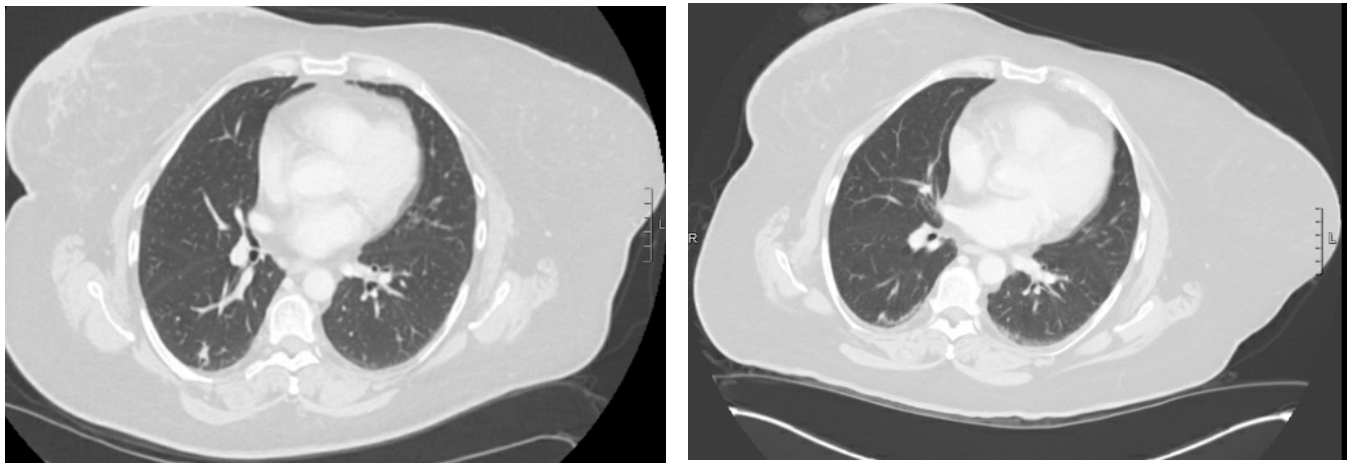


Figure 3 Lung lesion at baseline and 15 months on olaparib

Courtesy of P Kelly Marcom, MD

Current and Future Management of PD-L1-Negative Metastatic Triple Negative Breast Cancer

Joyce O'Shaughnessy, MD
Baylor University Medical Center
Texas Oncology
US Oncology

Therapeutics for PD-L1 Negative metTNBC

- Cytotoxic therapy is the mainstay of treatment for PD-L1-negative metastatic TNBC
- Median OS is about 18 mos
- Eribulin improves OS in pretreated metastatic TNBC with neutropenia and neuropathy as treatment-limiting toxicities
- Sacituzumab govitecan improves OS in pretreated metastatic TNBC with neutropenia and diarrhea as treatment-limiting toxicities
- Other ADCs ladiratuzumab vedotin and trastuzumab deruxtecan have promising activity in metastatic TNBC patients
- Trials targeting AKT, DNA damage repair, AR, AURKA, FGFR1/2, CDK4/6, STAT3 in metastatic TNBC are underway

Courtesy of Joyce O'Shaughnessy, MD

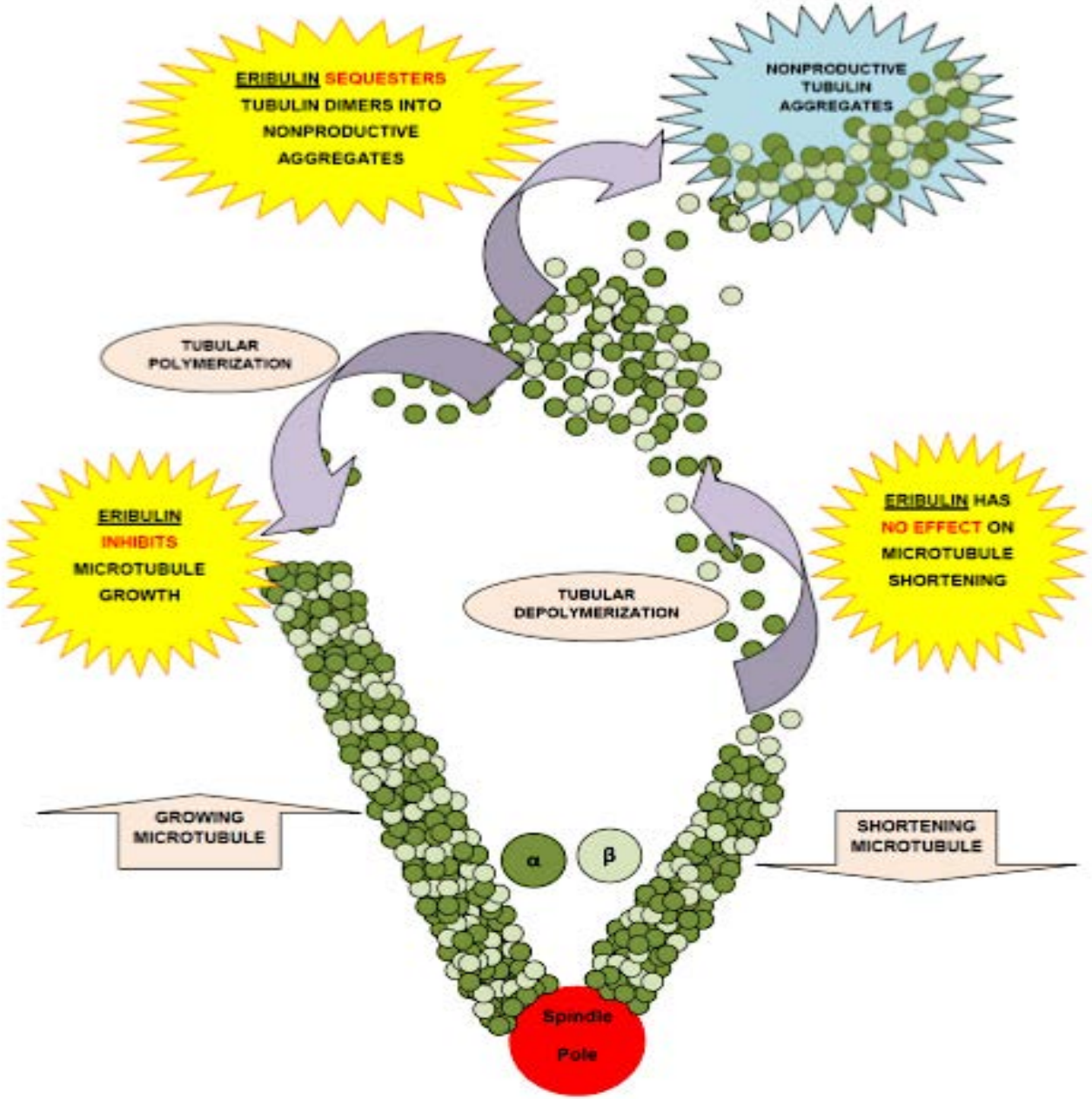
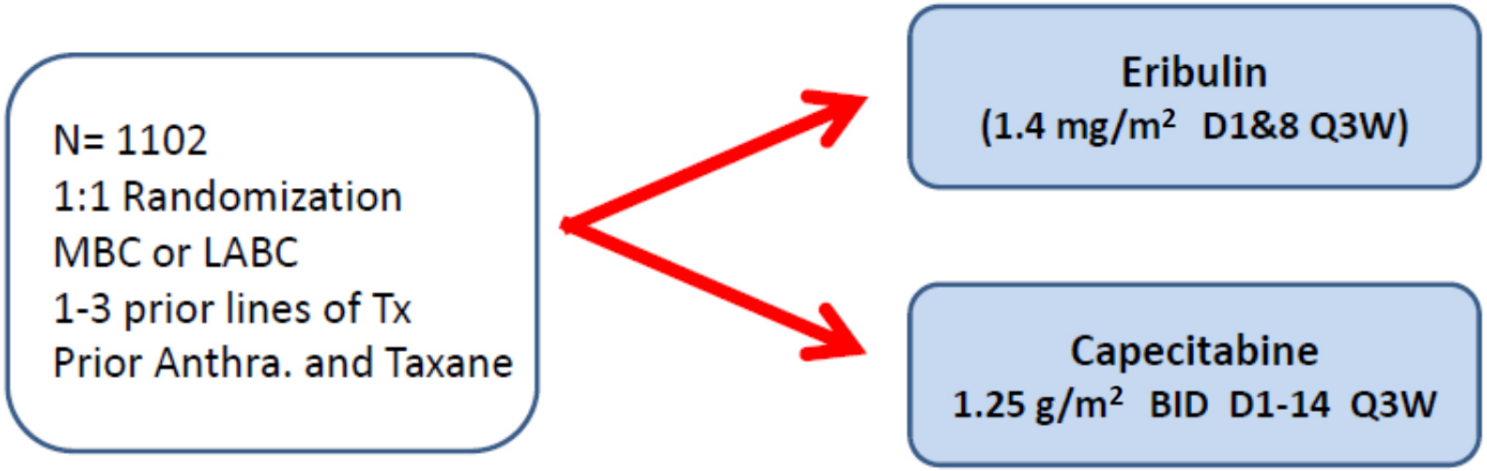


Figure 2. Mechanism of action of eribulin mesylate.

Swami U et al Marine Drugs 13:5016, 2017

Courtesy of Joyce O'Shaughnessy, MD



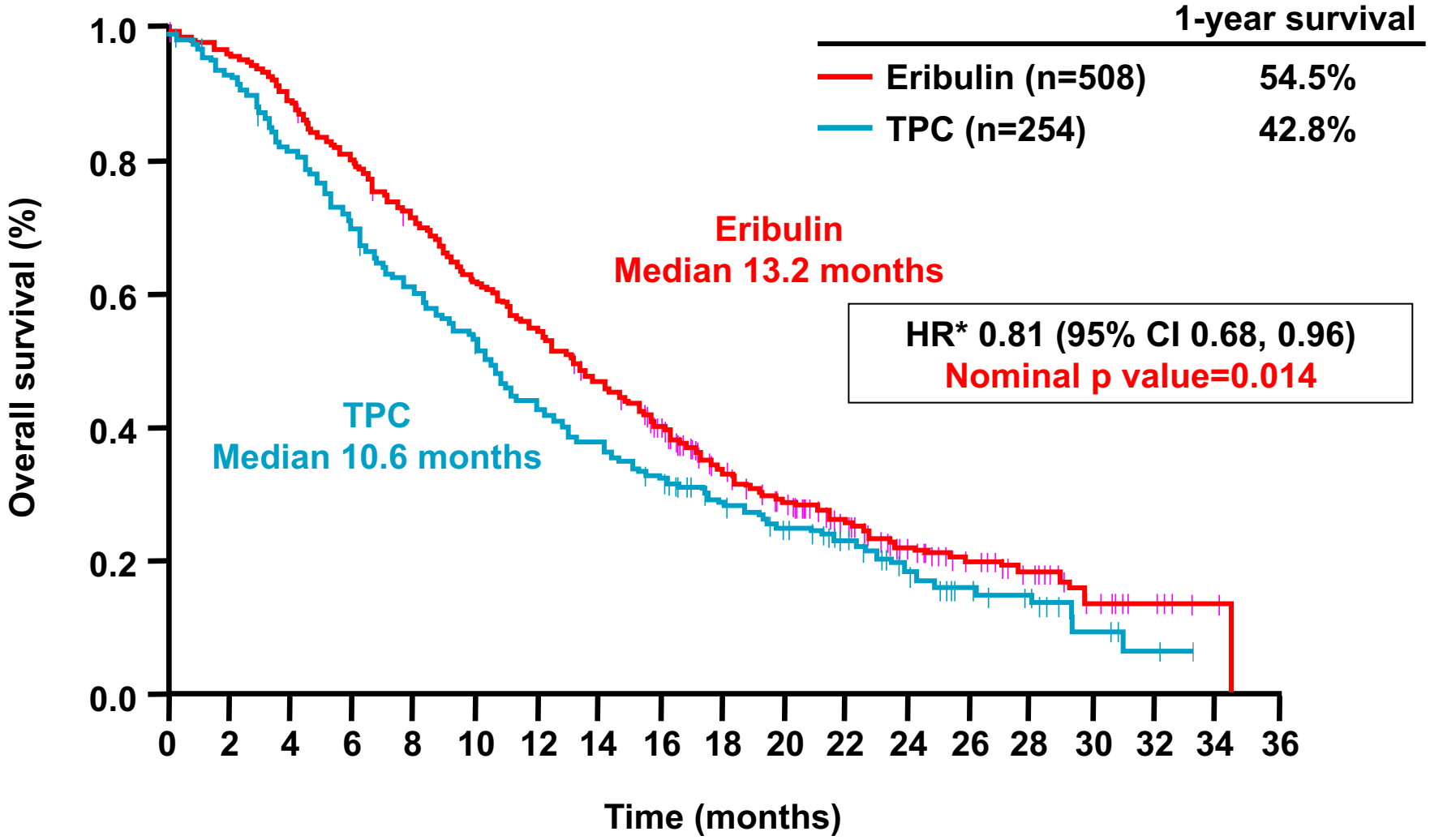
Study 301: eribulin vs capecitabine 2L MBC

Median OS	Eribulin	Cape	Hazard ratio
HER2 status			
Positive	14.3 mo	17.1 mo	0.965
Negative	15.9 mo	13.5 mo	0.838
ER status			
Positive	18.2 mo	16.8 mo	0.897
Negative	14.4 mo	10.5 mo	0.779
Triple-negative BC (TNBC)			
Yes	14.4 mo	9.4 mo	0.702
No	17.5 mo	16.6 mo	0.927
Overall	**15.9 mo**	**14.5 mo**	**0.879**

Courtesy of Joyce O'Shaughnessy, MD

Kaufman PA et al. J Clin Oncol 2015

EMBRACE: OS (ITT Population)
Eribulin vs Treatment of Physician's Choice



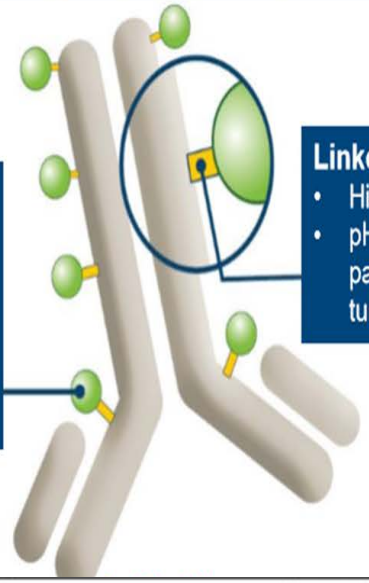
Courtesy of Joyce O'Shaughnessy, MD

Cortes J, et al. Lancet 2011;377:914-923.

Phase II Trial Sacituzumab Govitecan

Sacituzumab Antibody-Drug Conjugate (ADC)

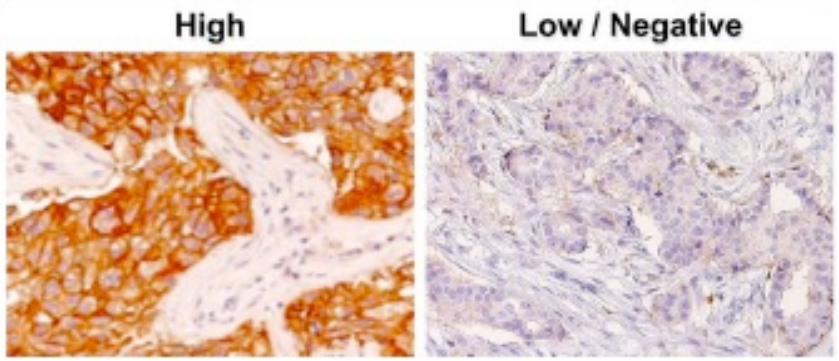
Humanized RS7 antibody
- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC



SN-38 payload
- Targets 136-fold more SN-38 than the parent compound, irinotecan (topoisomerase I inhibitor)
- ADCs unique chemistry avoids low solubility and selectively delivers SN-38 to the tumor

Linker for SN-38
- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid payload release at or inside the tumor

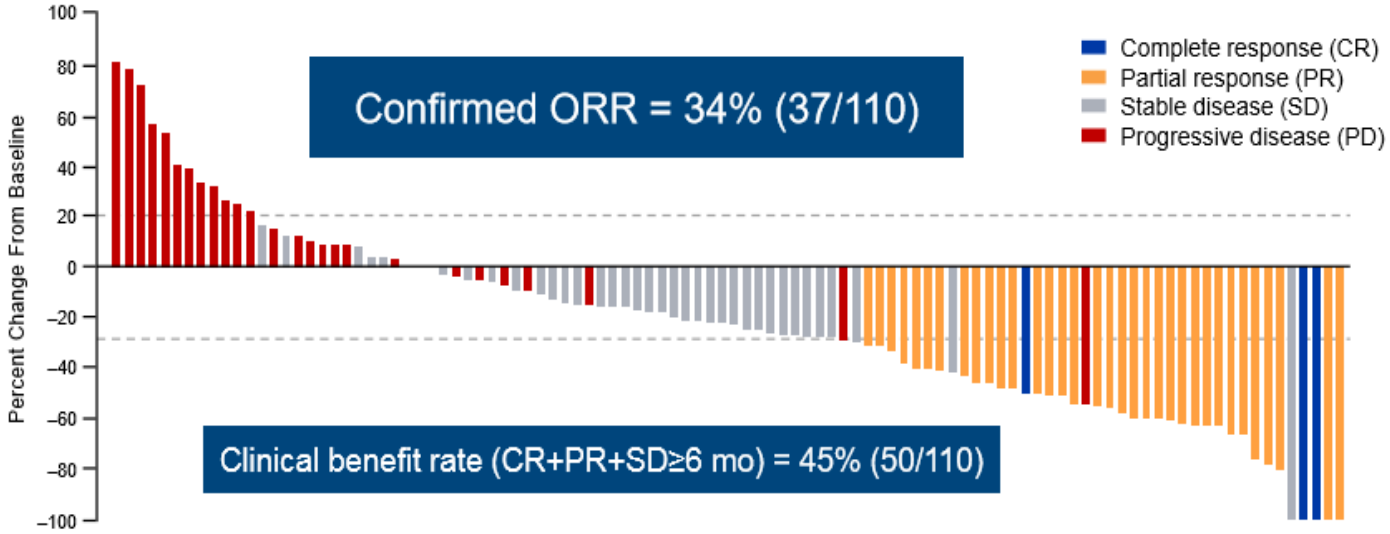
5



> 90% TNBCs express Trop-2

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)

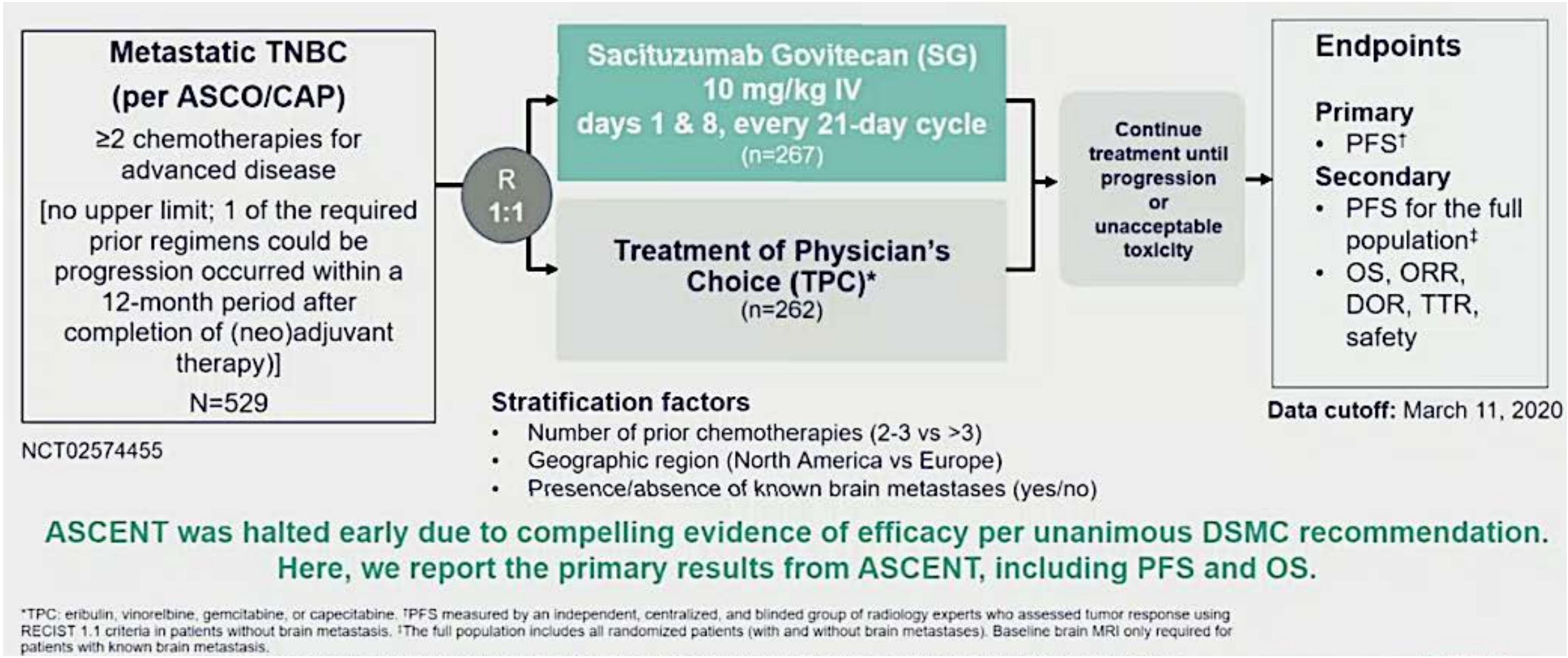
11

Median DoR 7.6 mos
Med PFS 5.5 mos

Bardia A et al. SABCS 2017

Courtesy of Joyce O'Shaughnessy, MD

ASCENT (Phase III): Sacituzumab Govitecan (SG) vs Treatment of Physician´s Choice (TPC) in pretreated mTNBC (N=529) – *Study Design*



ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation. Here, we report the primary results from ASCENT, including PFS and OS.

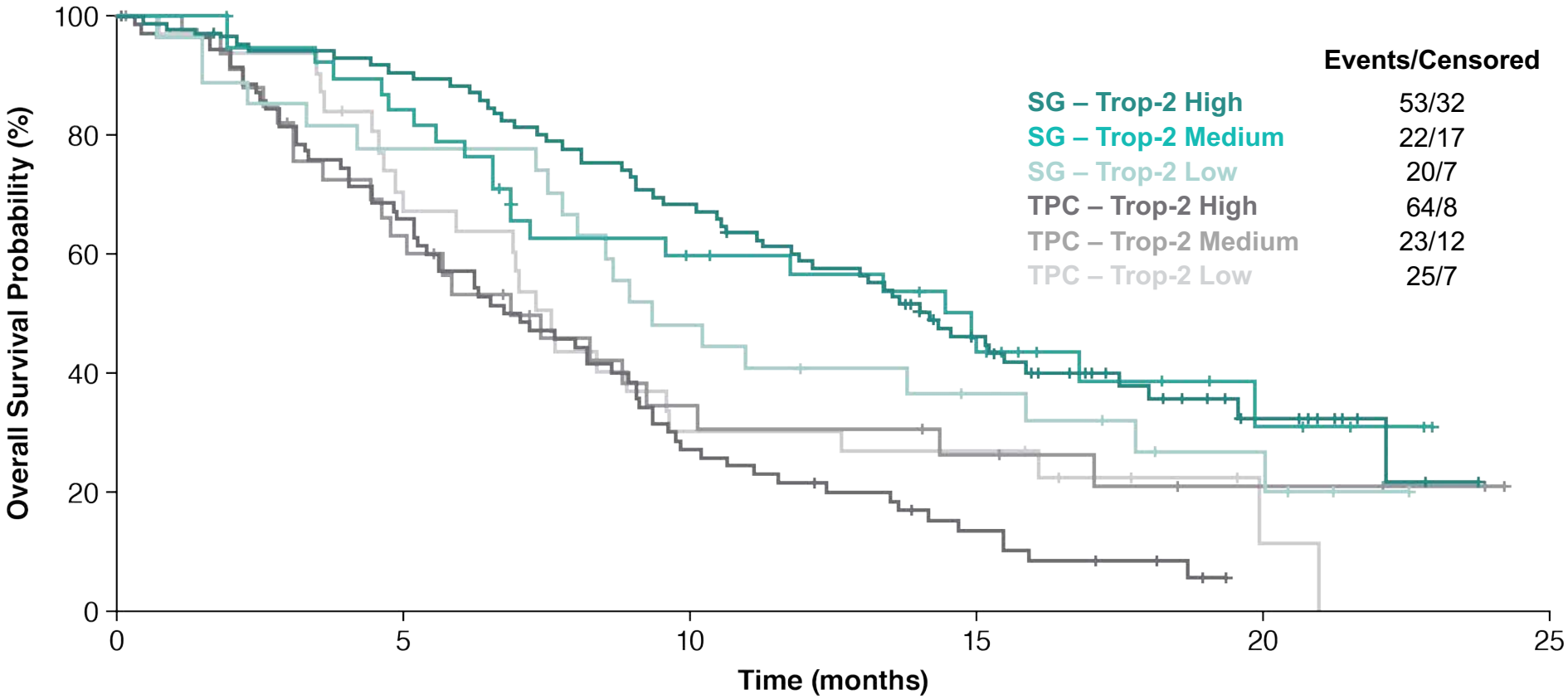
*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.

Bardia A, et al. ESMO 2020 (LBA17)

Courtesy of Joyce O'Shaughnessy, MD

ASCENT Clinical Trial

Overall Survival by Trop-2 Expression

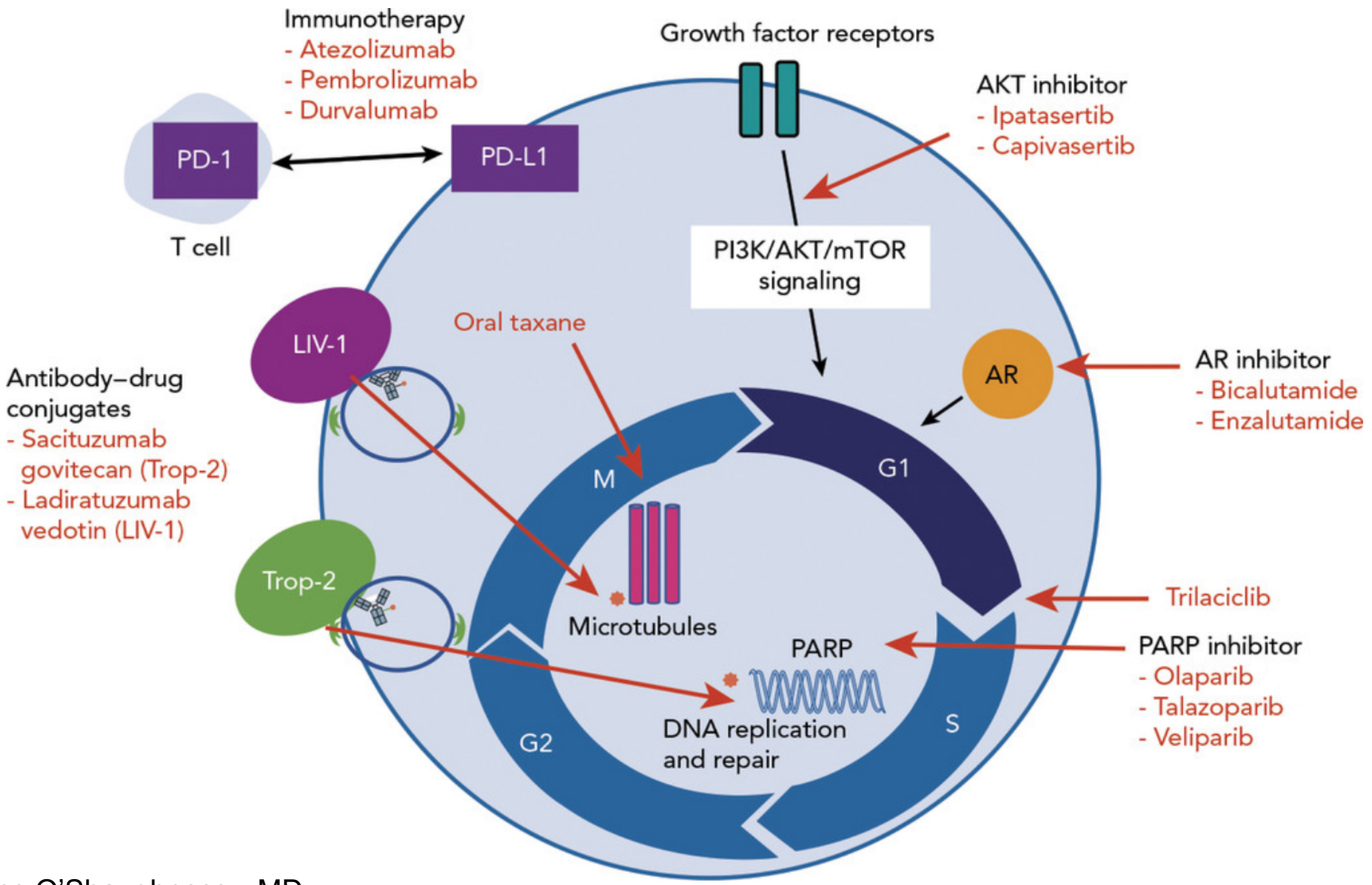


	Trop-2 High | H-score: 200-300		Trop-2 Medium | H-score: 100-200		Trop-2 Low | H-score: <100	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
Median OS—mo (95% CI)	14.2 (11.3-17.5)	6.9 (5.3-8.9)	14.9 (6.9-NE)	6.9 (4.6-10.1)	9.3 (7.5-17.8)	7.6 (5.0-9.6)

Assessed in brain metastases-negative population. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring.
H-score, histochemical-score; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen-2.

Courtesy of Joyce O'Shaughnessy, MD

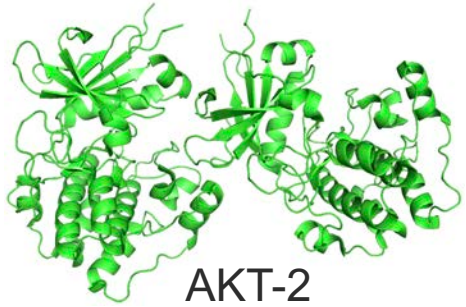
Novel Targets in Triple Negative Breast Cancer

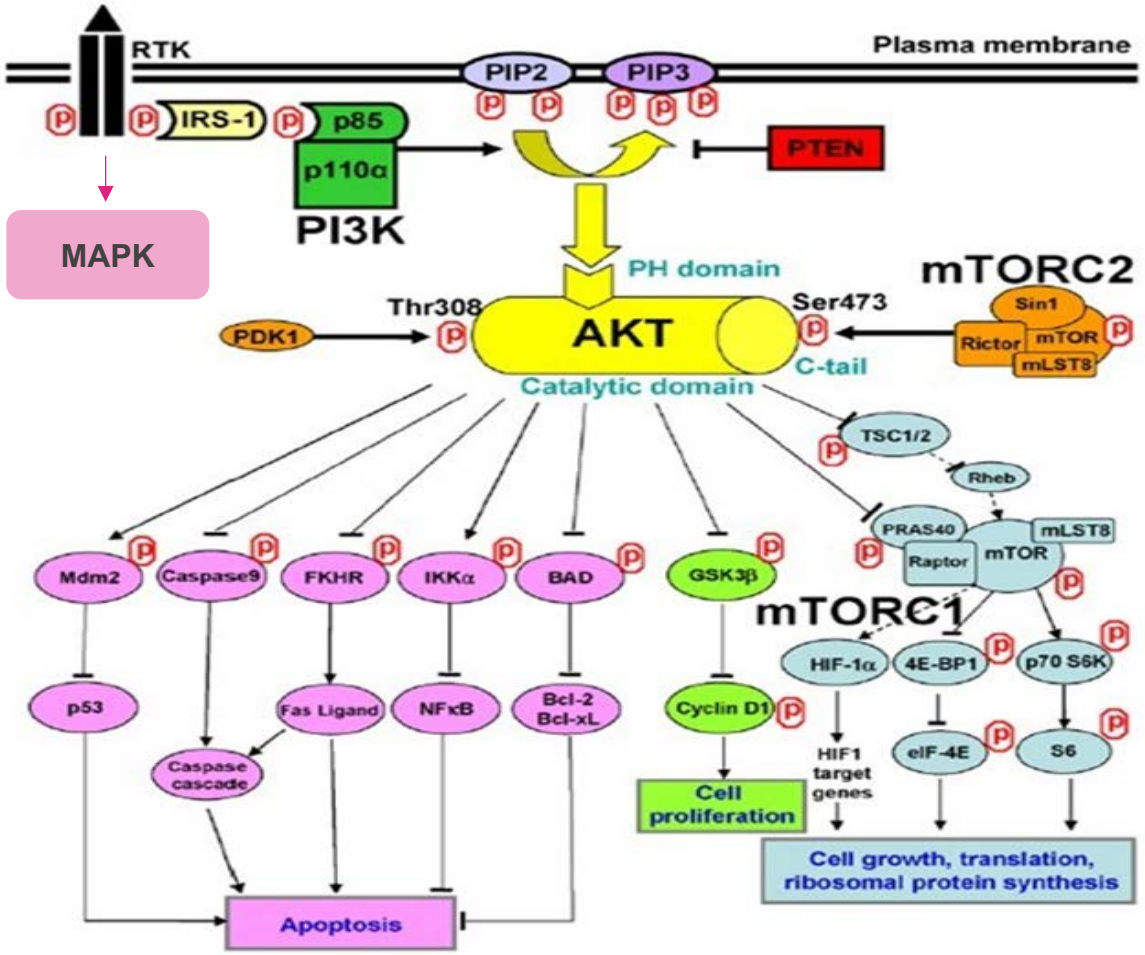


Courtesy of Joyce O'Shaughnessy, MD

Breast cancer and PI3K/AKT pathway

The PI3K/AKT pathway is one of the most frequently altered pathways in breast cancer and is key for survival and growth of tumors



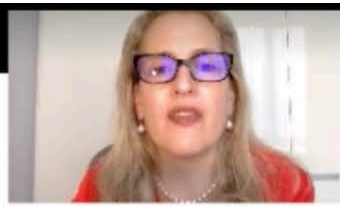


Courtesy of Joyce O'Shaughnessy, MD

AKT can be activated by:

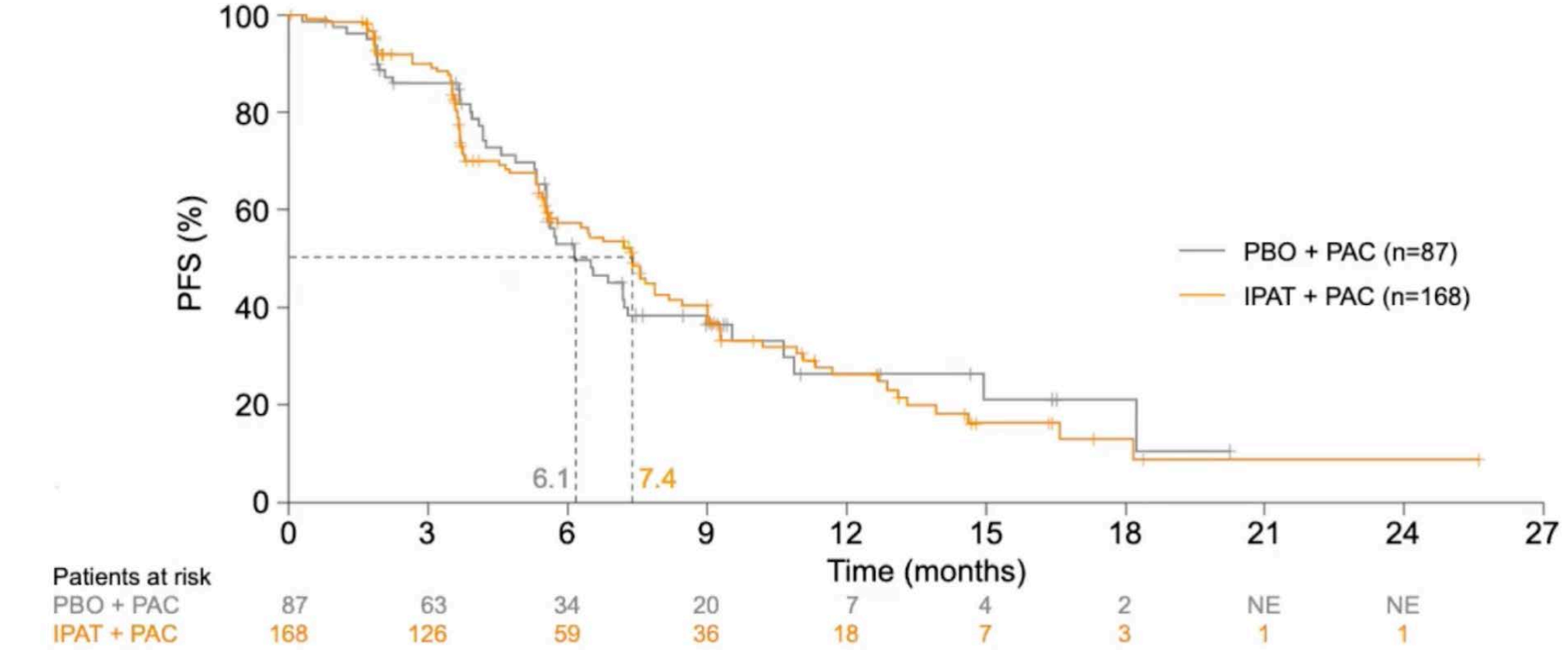
- Gain of function of positive regulators
  - PI3K
  - AKT
  - Receptor tyrosine kinases (HER2)
- Loss of function of negative regulators
  - PTEN
  - INPP4B
  - PHLPP
  - PP2A
- Therapy-induced survival response
  - Chemotherapy
  - Hormone therapy

IPATunity130 Phase III Trial of Paclitaxel + Ipatasertib in AKT Pathway-Altered First-Line Metastatic TNBC



San Antonio Breast Cancer Symposium®, December 8–11, 2020

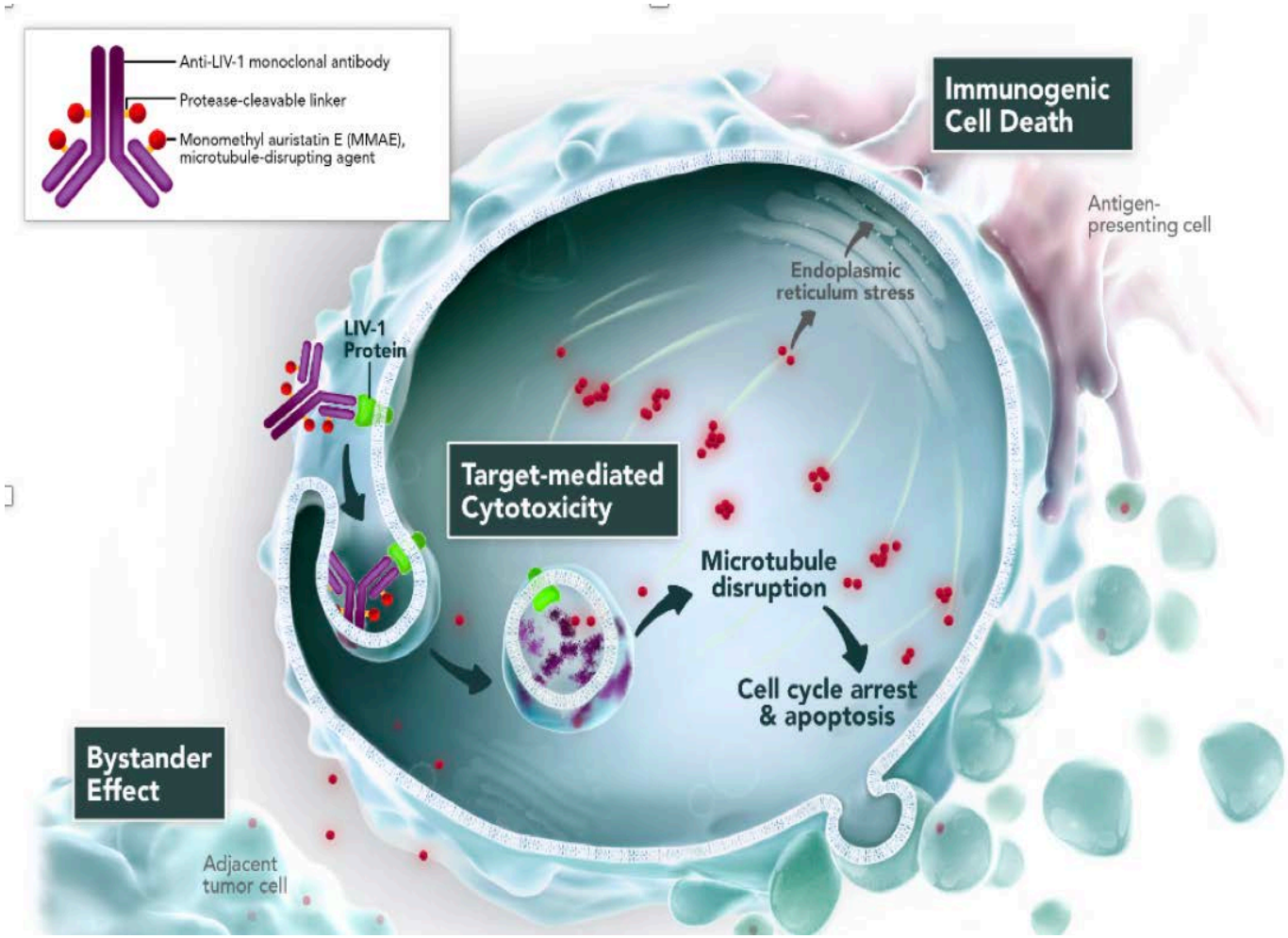
Primary endpoint: Investigator-assessed PFS
Data cut-off: May 7, 2020 (median follow-up: 8.3 months)



Courtesy of Joyce O'Shaughnessy, MD

Ladiratuzumab Vedotin (LV) Novel Antibody Drug Conjugate

- LV
  - Humanized IgG1 ADC
  - Selectively binds to cells expressing LIV-1 (90%+ MBCs)
    - Conjugated to monomethyl auristatin E (MMAE)
- LV-mediated delivery of MMAE drives antitumor activity through
  - Cytotoxic cell killing
  - Inducing Immunogenic Cell Death



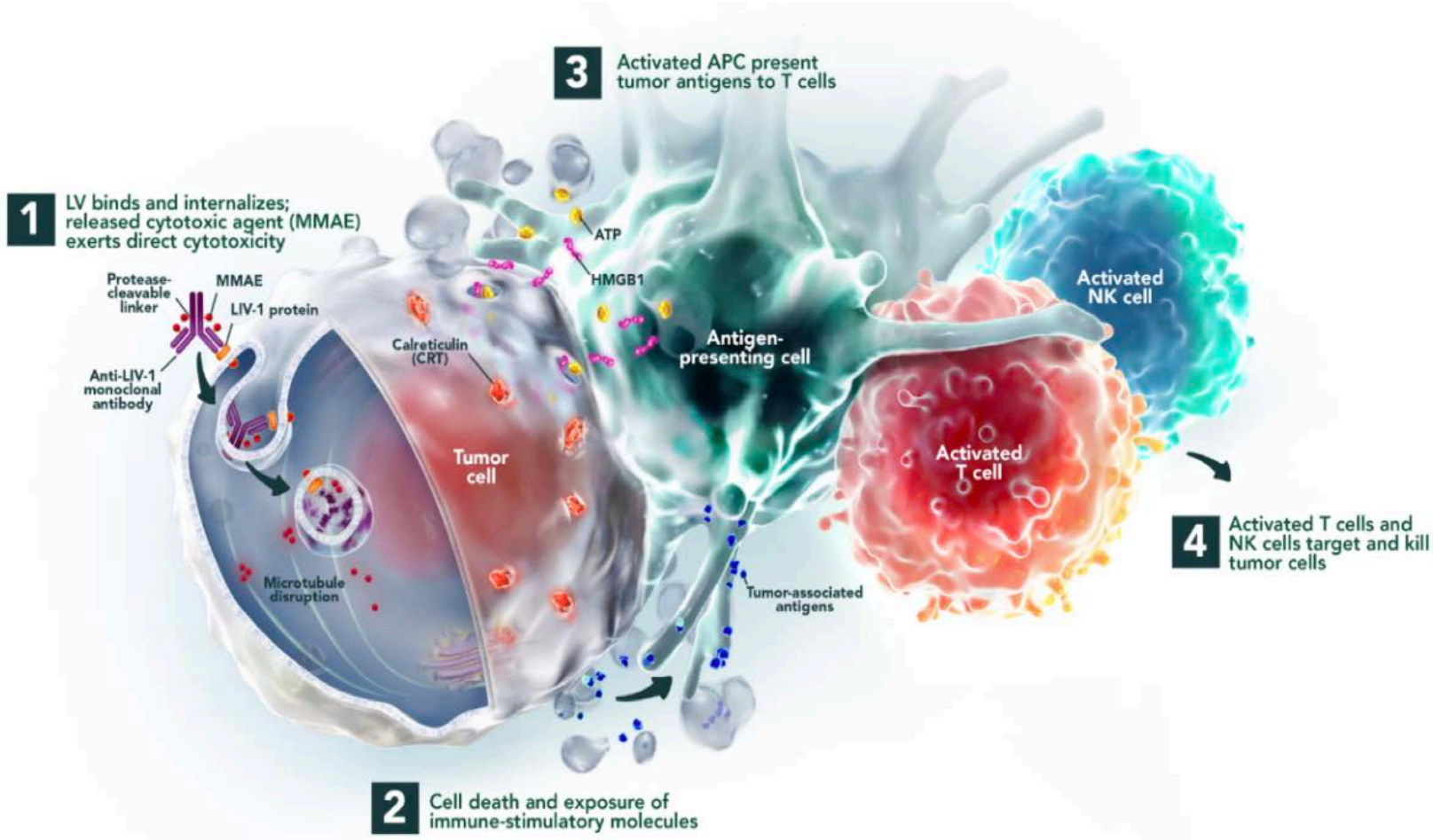
Courtesy of Joyce O'Shaughnessy, MD

Rationale for Combining LV with Pembrolizumab

- LV and pembrolizumab act through distinct and complementary mechanisms

- LV-induced ICD elicits an inflammatory response
  - Increases tumor immune cell infiltration[14]

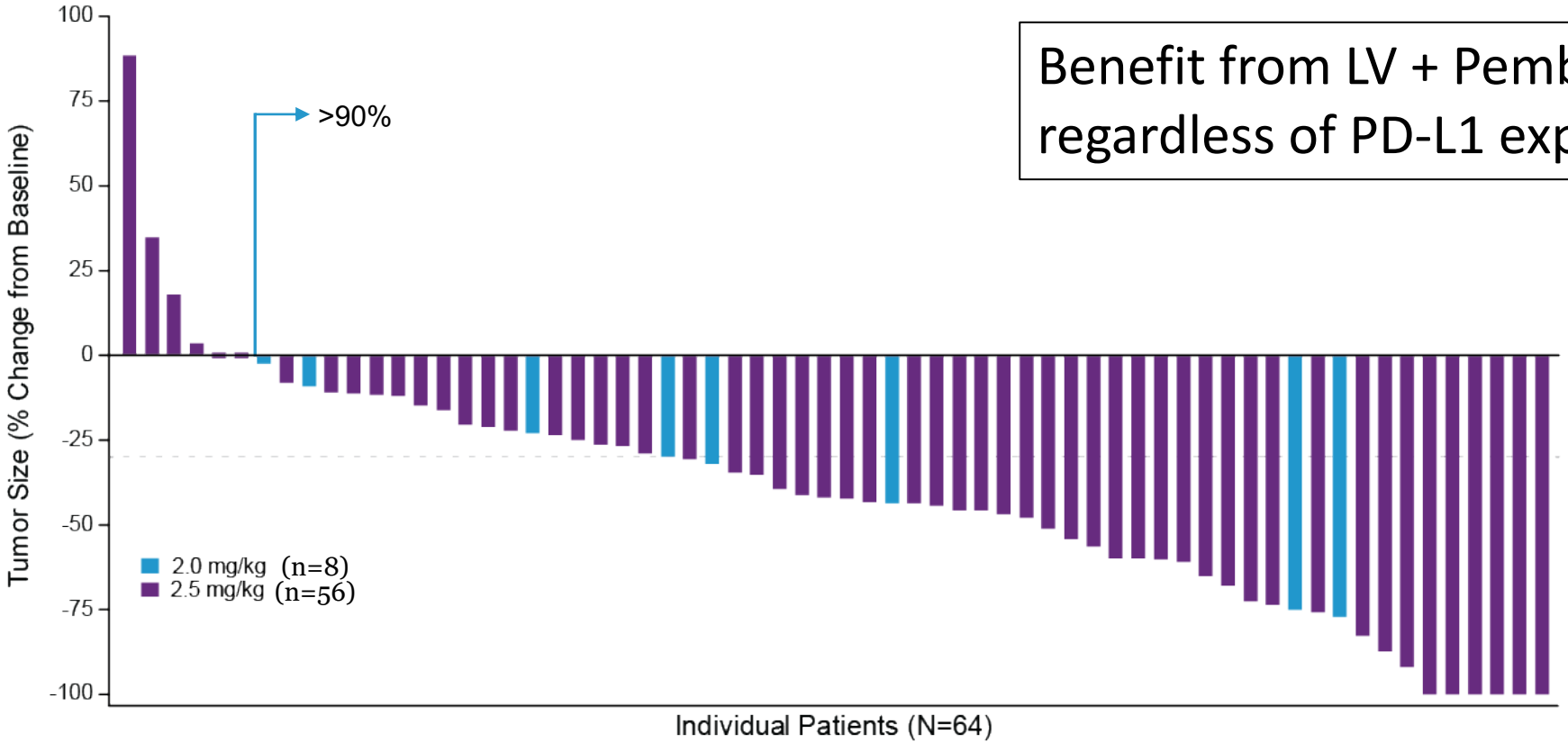
- LV-induced ICD creates a microenvironment favorable for enhanced pembrolizumab activity



Courtesy of Joyce O'Shaughnessy, MD

LV + Pembrolizumab Maximum Change in Tumor Burden in 1L metTNBC

- >90% of subjects achieved tumor reduction



Benefit from LV + Pembrolizumab regardless of PD-L1 expression

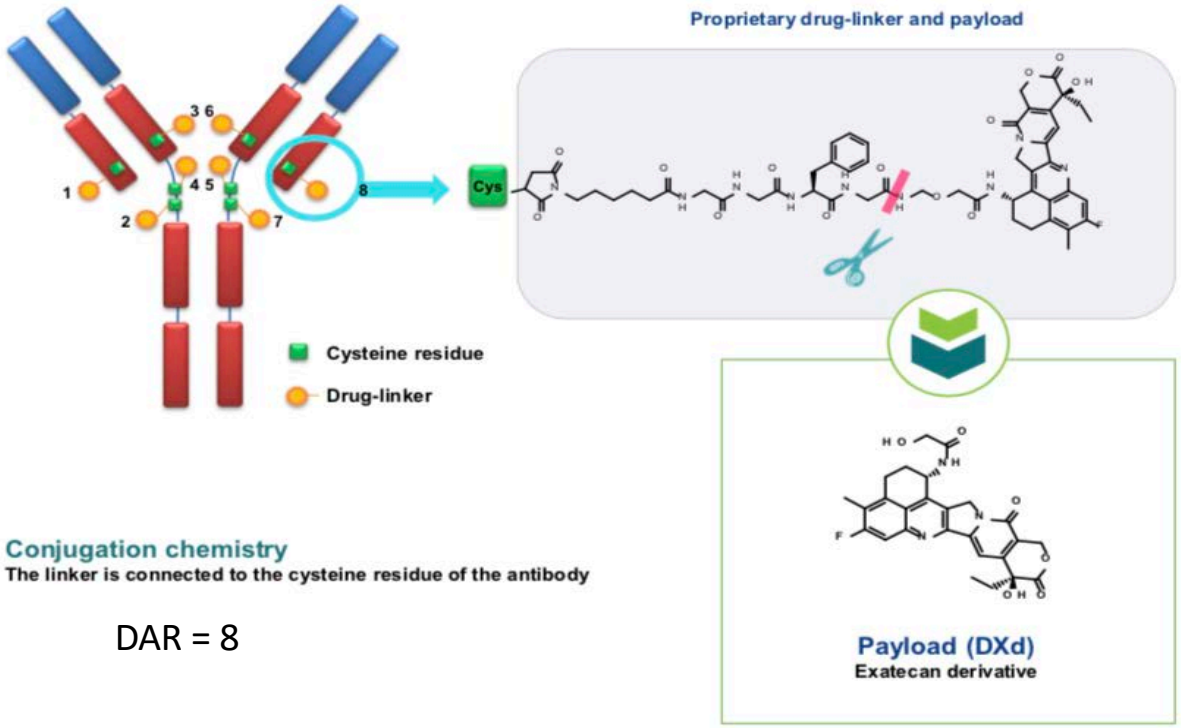
- The efficacy evaluable population includes all treated subjects with at least one evaluable post-baseline assessment according to RECIST v1.1 or who had discontinued from the study (N=69).
- Of the efficacy evaluable population, 5 subjects did not have evaluable response assessments before study discontinuation.

SABCS 2019, San Antonio, TX, Dec 10-14, 2019, Abstract No. 151

Courtesy of Joyce O'Shaughnessy, MD

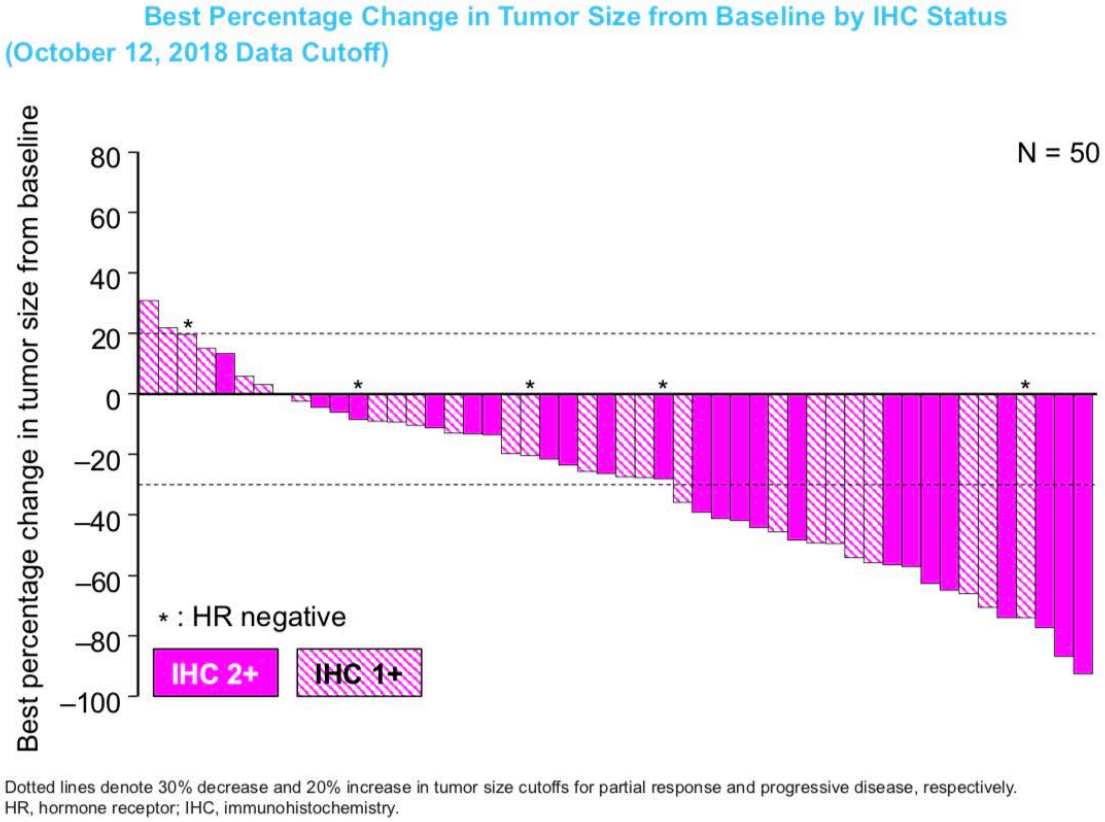
Other ADCs in TNBC…
trastuzumab deruxtecan

Trastuzumab deruxtecan
DS-8201a



DAR = 8

HER2 "low"



Poster # P6-17-02 – San Antonio Breast Cancer Symposium® – December 4–8, 2018

Courtesy of Joyce O'Shaughnessy, MD

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

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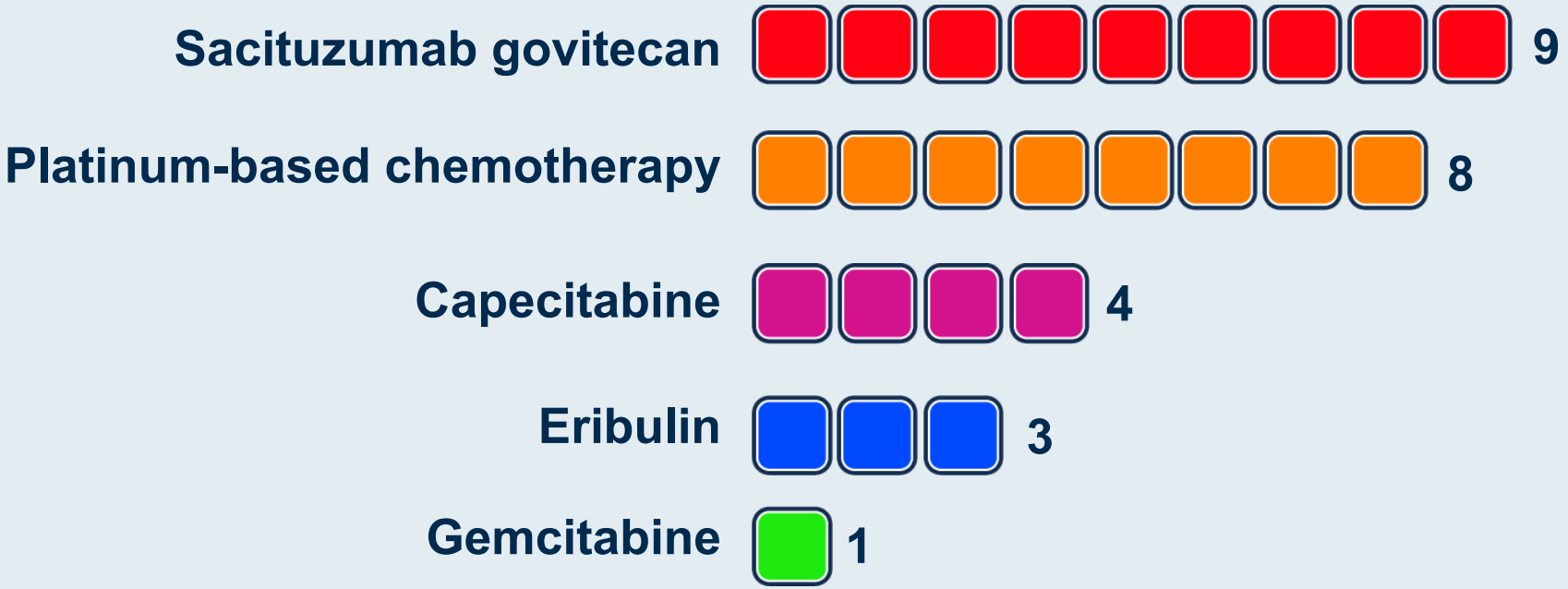
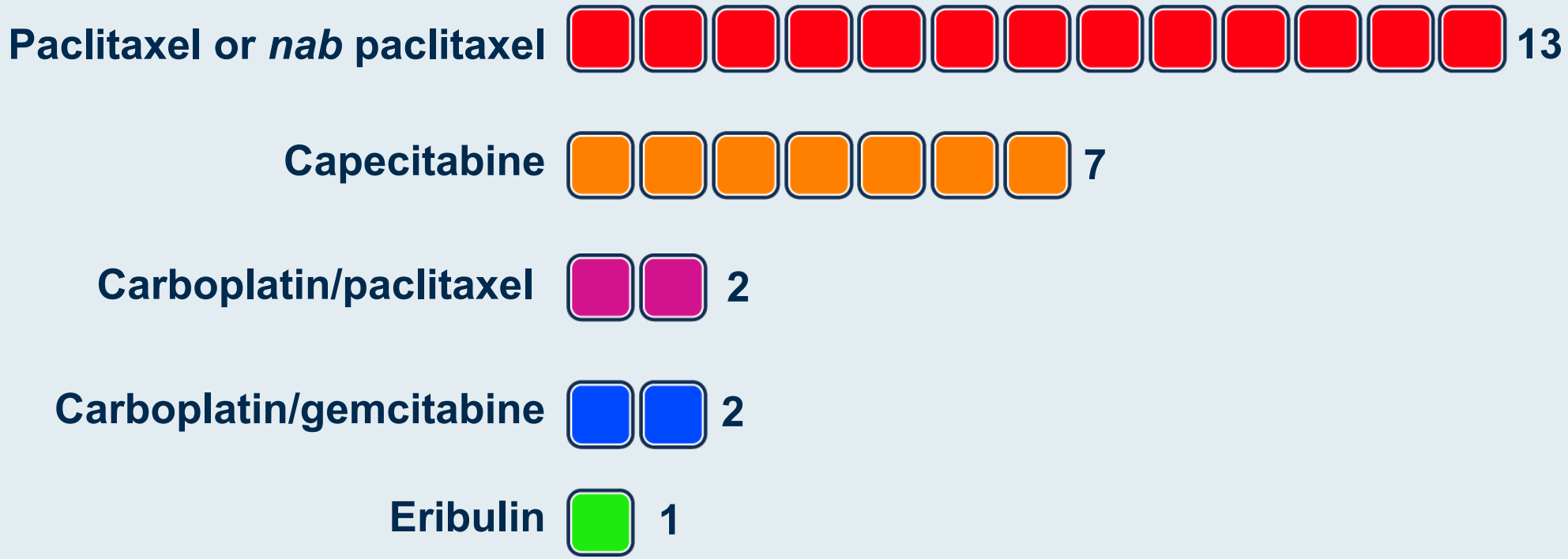
TO PRACTICE

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



Survey of 25 breast cancer clinical investigators

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



Survey of 25 breast cancer clinical investigators

Case Presentation – Dr O'Shaughnessy: A 30-year-old woman with mTNBC

- A 30 yo G1P1 Latina woman presented with a T3N0 TNBC and was treated with preoperative AC then paclitaxel carboplatin. BRCA1/2 testing was negative
- At mastectomy there was 3cm residual disease with sarcomatous metaplastic features, node negative
- 9 mos later she presented to ER with abdominal pain and had a 7 cm liver metastasis and questionable second small lesion; biopsy showed TNBC

Courtesy of Joyce O'Shaughnessy, MD

Case Presentation – Dr O'Shaughnessy: A 30-year-old woman with mTNBC (continued)

- She was treated with eribulin 1.4 mg/m^2 days 1, 8 plus capecitabine 1650 mg/m^2 d1-14 q 21 d and had no toxicity including no alopecia, no disruption of menses, no neuropathy and no HFS
- The liver metastasis responded nearly completely and resection of residual disease showed 3-4 mm of TNBC. NSG showed multiple activating alterations in the AKT pathway

Courtesy of Joyce O'Shaughnessy, MD

Case Presentation – Dr O'Shaughnessy: A 30-year-old woman with mTNBC (continued)

- She remained on combined eribulin plus capecitabine for 4 additional years without toxicity
- She stopped therapy 2 years ago to have a second child, successfully, and she has remained NED

Courtesy of Joyce O'Shaughnessy, MD

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

Hepatobiliary and Pancreatic Cancers

Tuesday, December 15, 2020
5:00 PM – 6:00 PM ET

Faculty

Tanios Bekaii-Saab, MD
Lipika Goyal, MD, MPhil

Moderator

Neil Love, MD

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Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.

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