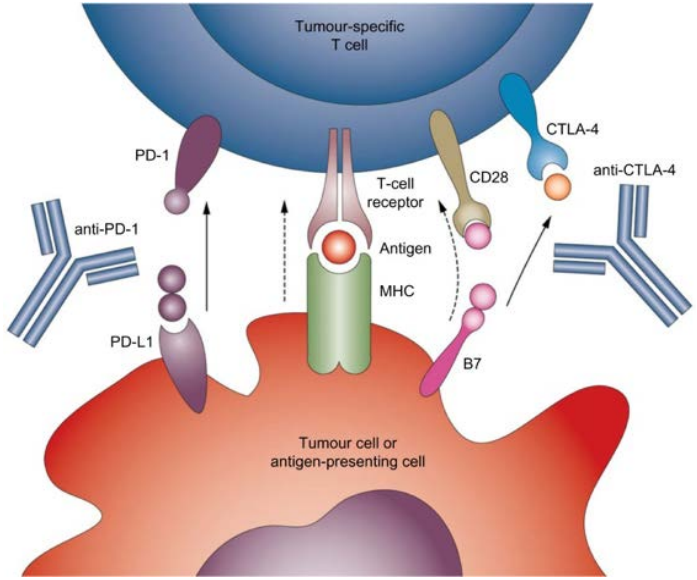
Novel Applications of Immune Checkpoint Inhibitors for Patients with Early TNBC



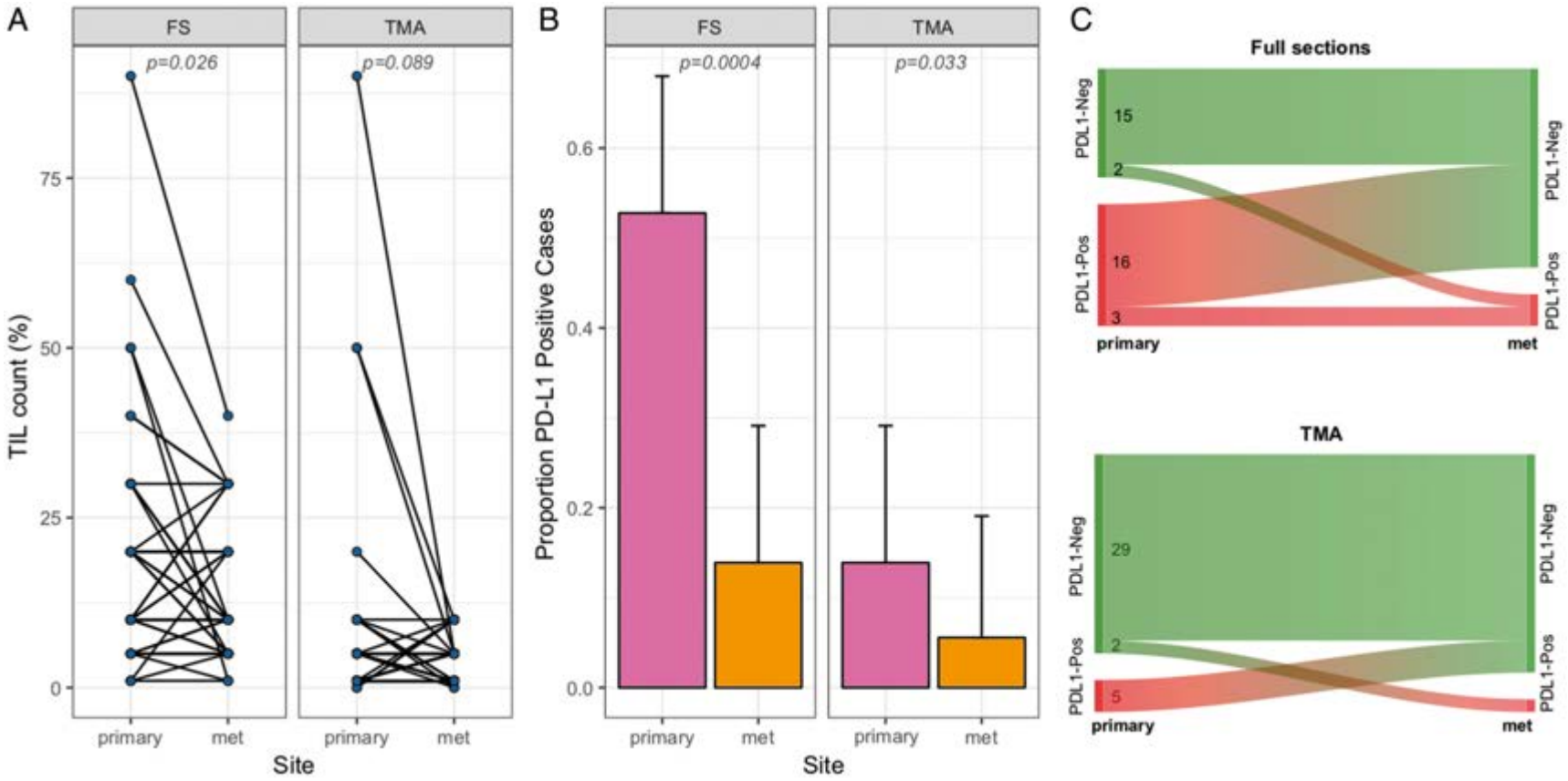
Hope S. Rugo, MD

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



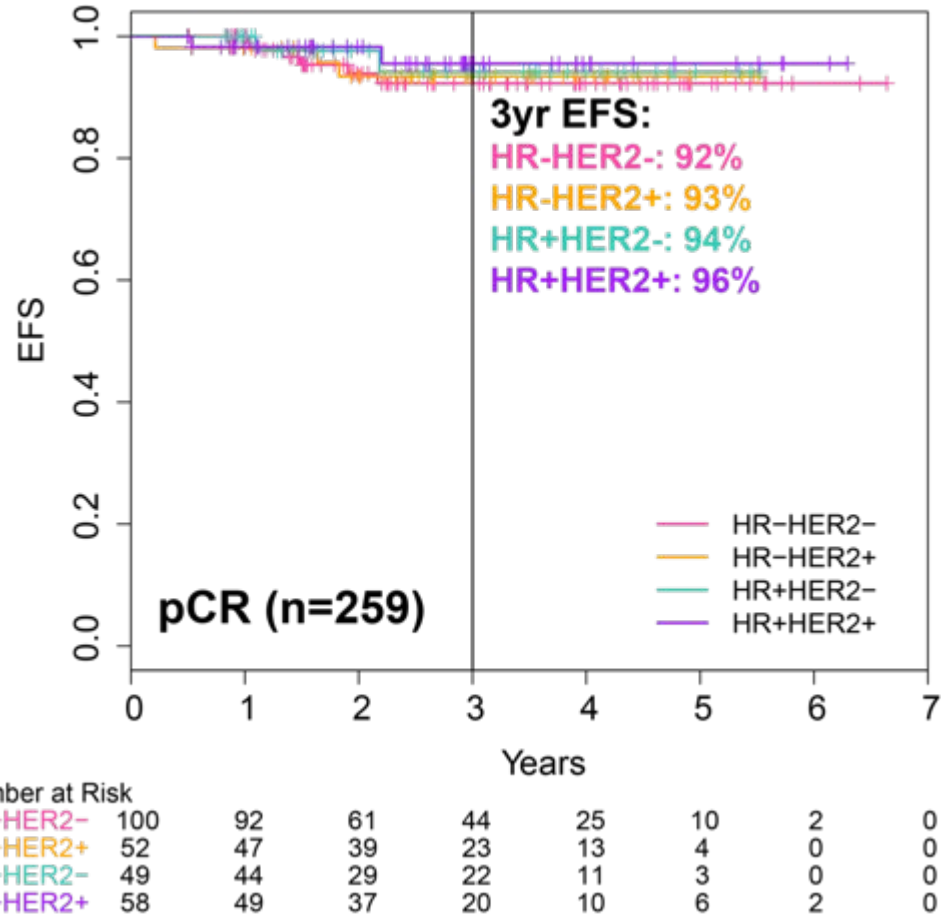
Percent TIL counts in full sections and TMAs.

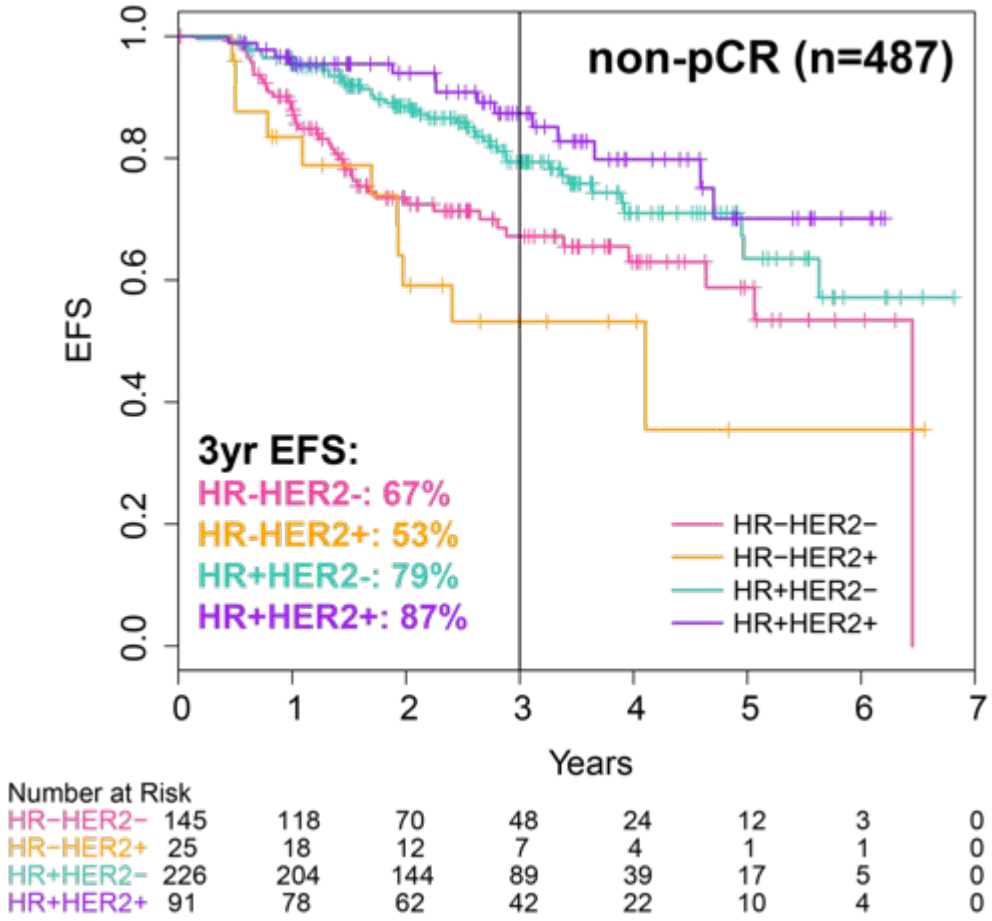
Szekely, et al (Pusztai), Ann Oncol 2018

Courtesy of Hope S Rugo, MD

Event Free Survival by pCR & non-pCR by Subtype

pCR is a great early endpoint

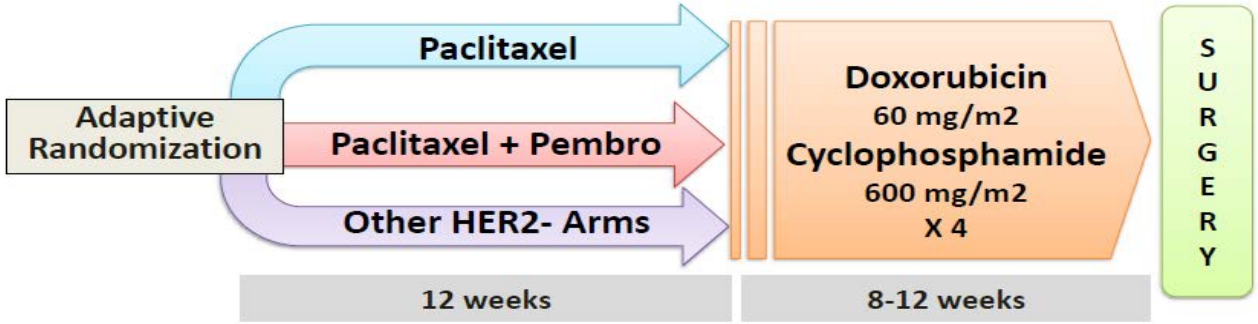




Yee et al., JAMA Onc 2020

Courtesy of Hope S Rugo, MD

I-SPY 2: Pembrolizumab Graduated for Efficacy in HER2 Neg Cohorts



Control
Paclitaxel 80 mg/m2 every wk x 12

Experimental
Paclitaxel 80 mg/m2 every wk x 12
Pembro 200 mg every 3 wks x 4

Final Predictive Probability of Success in Phase III Testing by Signature

Biomarker Signature	Estimated Rate of Pathologic Complete Response (95% Probability Interval)		Probability, %	
	Pembrolizumab (n = 69)	Control (n = 181)	Probability Superior to Control	Predictive Probability of Success in Phase 3 Trial
ERBB2 negative	44 (33-55)	17 (11-23)	>99.9	98.5
HR positive/*ERBB2* negative	30 (17-43)	13 (7-19)	>99.9	99.6
TNBC	60 (44-75)	22 (13-30)	99.6	83.4

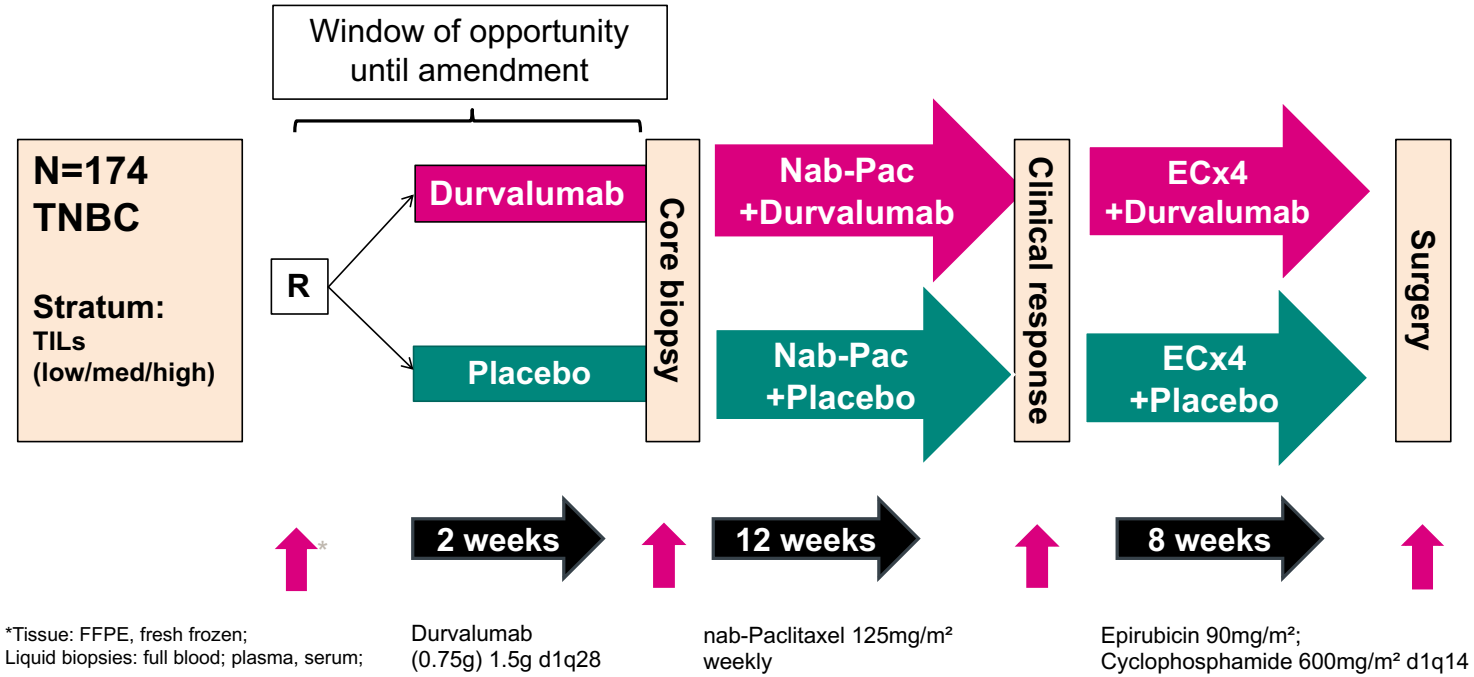
Nanda et al, JAMA Oncol 2020

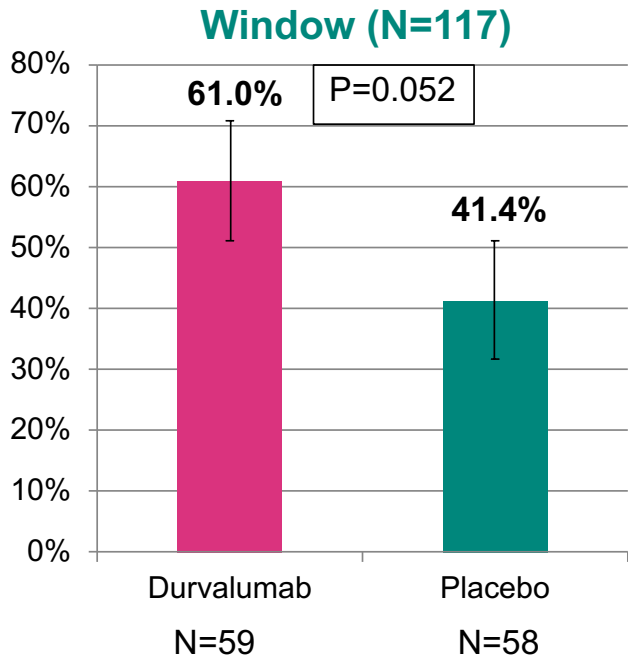
Courtesy of Hope S Rugo, MD

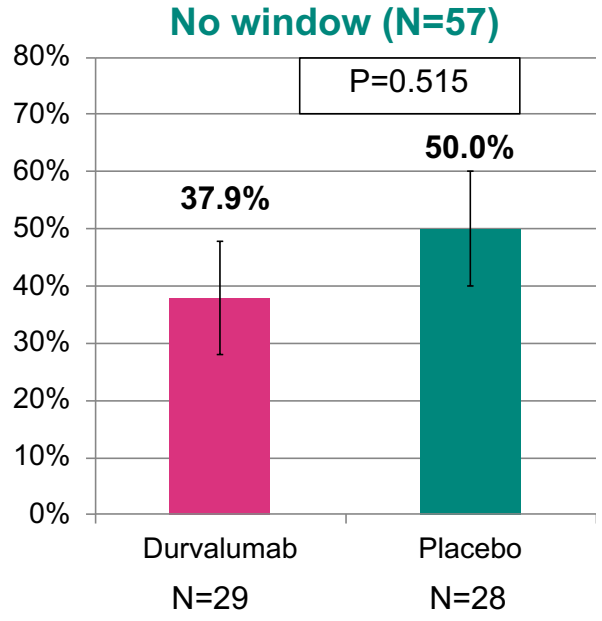
GeparNUEVO Study

Subgroup Analysis of the Window Cohort

(Overall pCR 52.4% vs 44.2%; Adjusted OR 1.53, p 0.182)







Courtesy of Hope S Rugo, MD

Loibl et al, Ann Oncol 2019

NeoTRIP Trial

280 randomized patients

*HER-2 negative, ER and PgR negative early high-risk **(T1cN1; T2N1; T3N0)** or locally advanced unilateral breast cancer

R

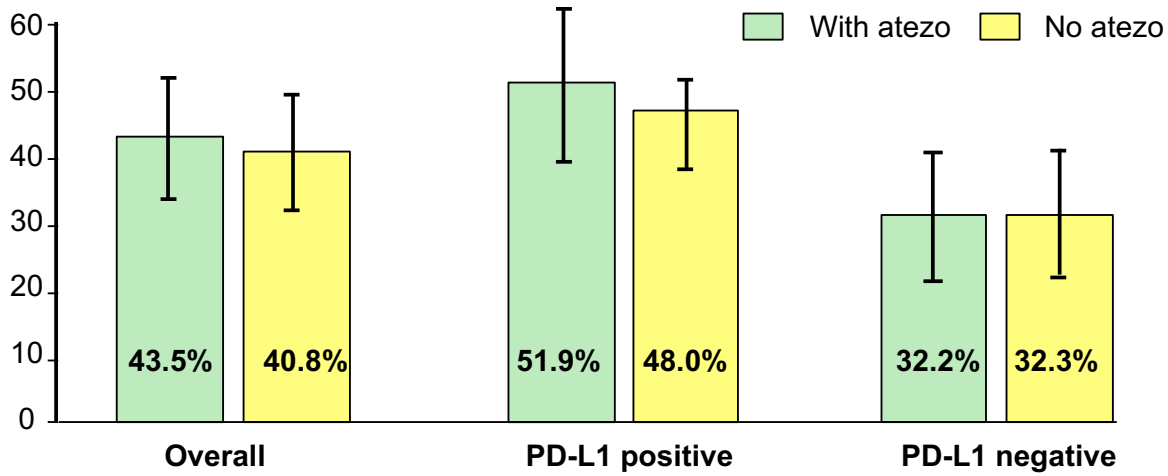
Carboplatin (AUC2) + *nab*-paclitaxel (125 mg/m²) weekly for 2 wks every 3; 8 cy → S

Carboplatin (AUC2) + *nab*-paclitaxel (125 mg/m²) weekly for 2 wks every 3; 8 cy **+ Atezolizumab (1200 mg)** day 1 every 3 wks for 8 cycles → S

- ***All patients received AC/ED/FEC x 4 after surgery***
- ***Primary aim*:*** 5 year EFS after randomization of last patient
- ***Key secondary aim:*** **pCR**

*Estrogen receptor, progesterone receptor, HER2 and PD-L1 were centrally assessed before randomization **56% PD-L1+**

Tumour & Blood banked for correlative studies

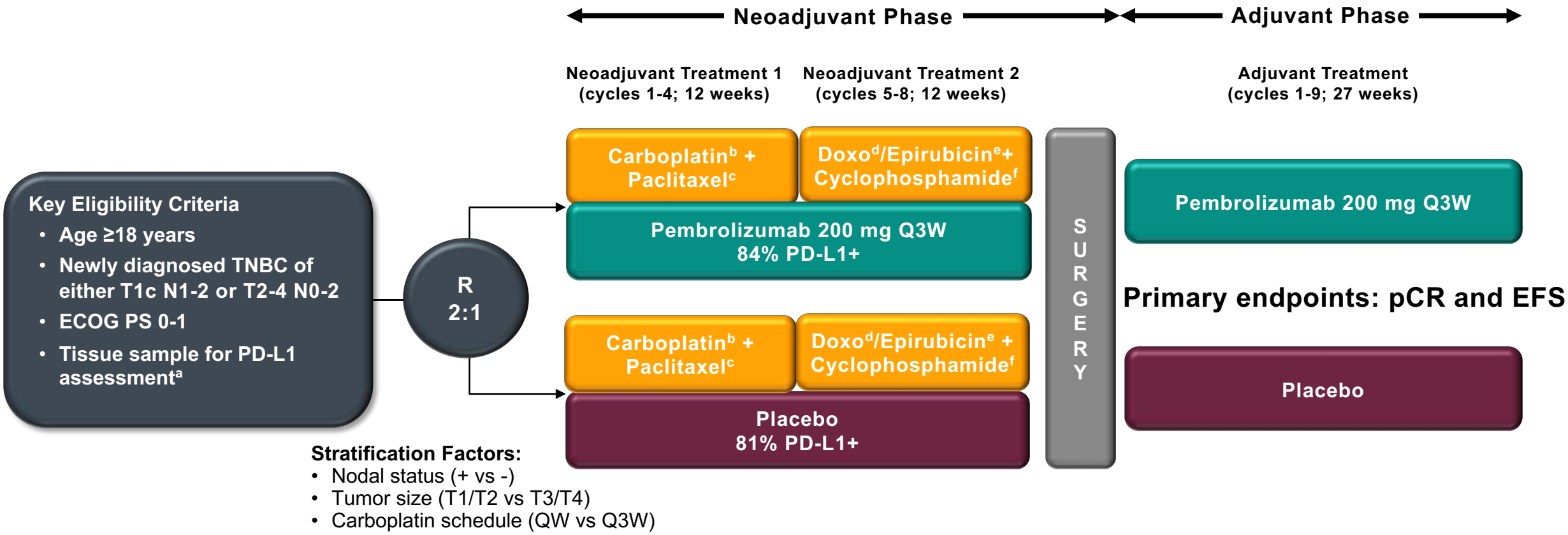


- No difference based on disease stage
- Only variable with impact PD-L1 status: HR 2.08 (1.64-2.65), P<0.0001

Courtesy of Hope S Rugo, MD

Gianni et al, SABCS 2019

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

Patients and Statistics

Characteristic, n (%)	All Subjects, N = 1174	
	Pembro + Chemo N = 784	Placebo + Chemo N = 390
Age, median (range), yrs	49 (22-80)	48 (24-79)
PD-L1–positive (using 22C3 assay/CPS)	656 (83.7)	317 (81.3)
Tumor size		
T1/T2	580 (74.0)	290 (74.4)
Nodal involvement		
Negative	379 (48.3)	190 (48.7)

- **IA1:** Performed after last patient enrolled (9/18)
  - Primary pCR analysis to test primary hypothesis of pCR based on prespecified first 602 subjects (pre-calculated *P* value boundary for significance of 0.003)
- **IA2:** Performed ~24 months after first patient enrolled (4/19)
  - If pCR hypothesis successful at IA1 (thus definitive), pCR will not be formally tested at IA2
- EFS at IA2 (1st interim EFS): precalculated *P* value boundary for significance of 0.000051 (HR <0.4)

Courtesy of Hope S Rugo, MD

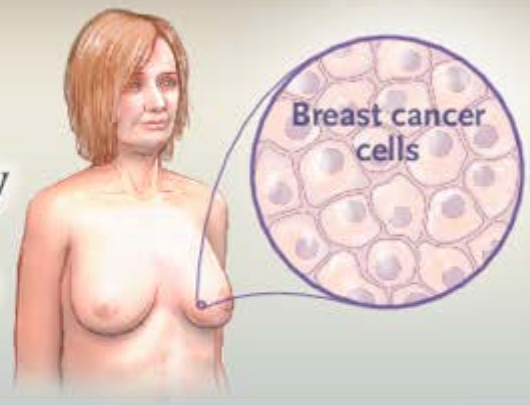
KEYNOTE 522

The NEW ENGLAND JOURNAL of MEDICINE

Pembrolizumab for Triple-Negative Breast Cancer

RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

1174 Patients with previously untreated triple-negative breast cancer



	Neoadjuvant Pembrolizumab + chemotherapy, followed by surgery and adjuvant pembrolizumab + chemotherapy (N=784)	Neoadjuvant Placebo + chemotherapy, followed by surgery and adjuvant placebo + chemotherapy (N=390)
Pathological complete response at time of surgery (n=602)	64.8%	51.2%
	Difference, 13.6 percentage points; 95% CI, 5.4–21.8; P<0.001	
Event-free survival	91.3% (95% CI, 88.8–93.3)	85.3% (95% CI, 80.3–89.1)
	HR for an event or death, 0.63; 95% CI, 0.43–0.93	
Grade ≥3 adverse events	76.8%	72.2%

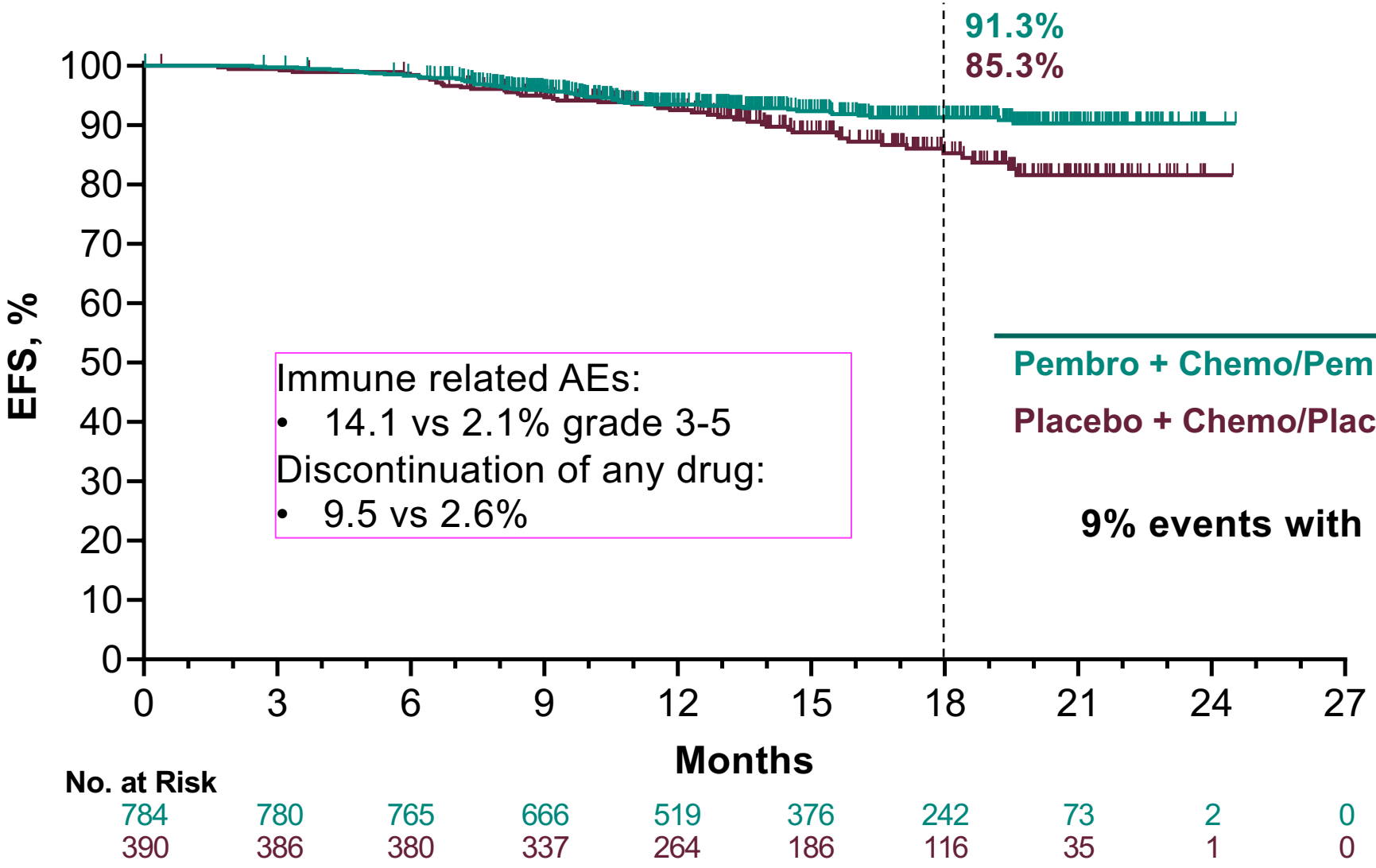
Highest pCR rate reported for TNBC!

P. Schmid et al. 10.1056/NEJMoa1910549 2020

Courtesy of Hope S Rugo, MD

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

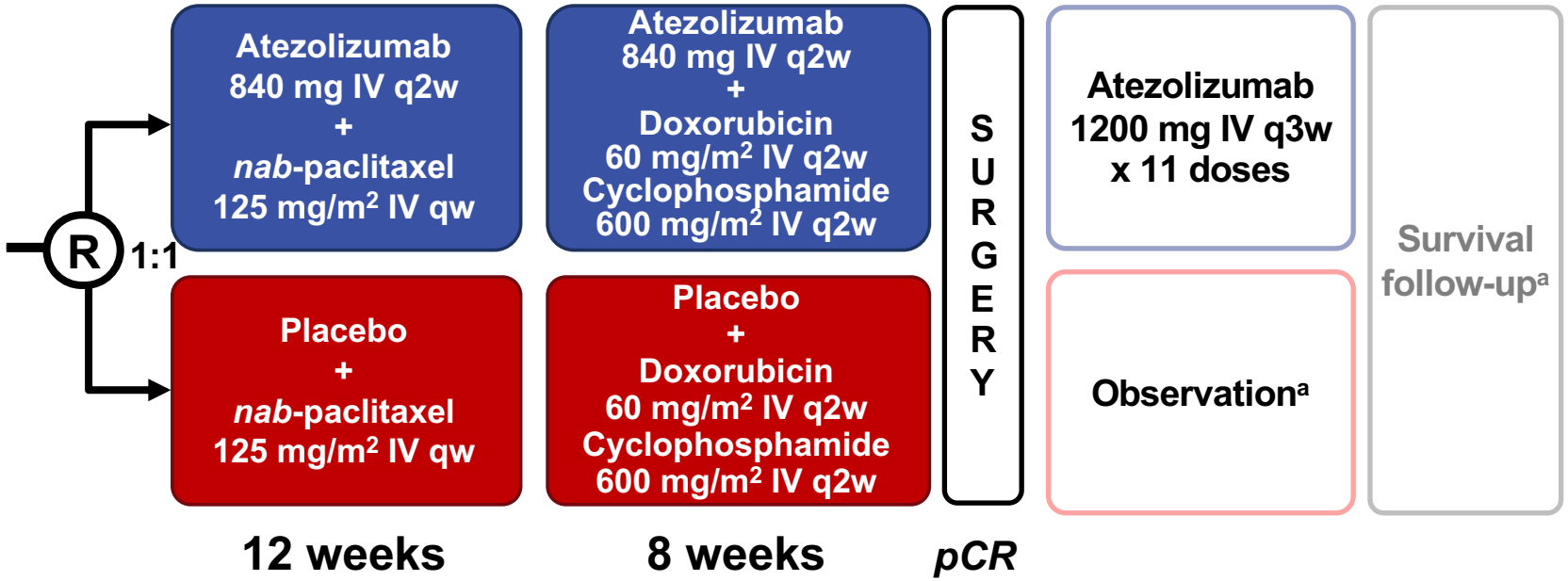
Courtesy of Hope S Rugo, MD

[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)

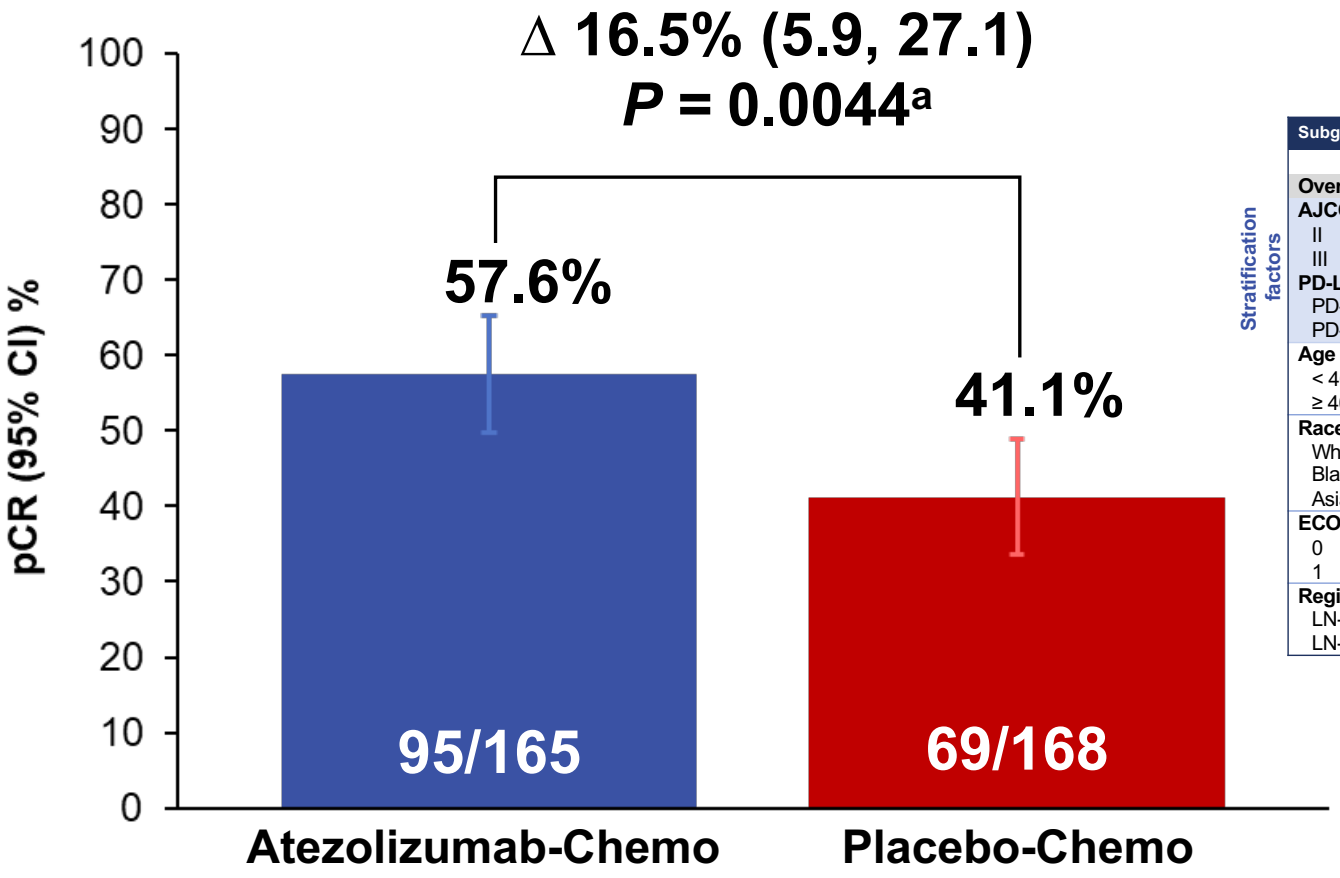


45-47% PD-L1+
76% stage II; 23% stage III
Median FU ~20 months

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%

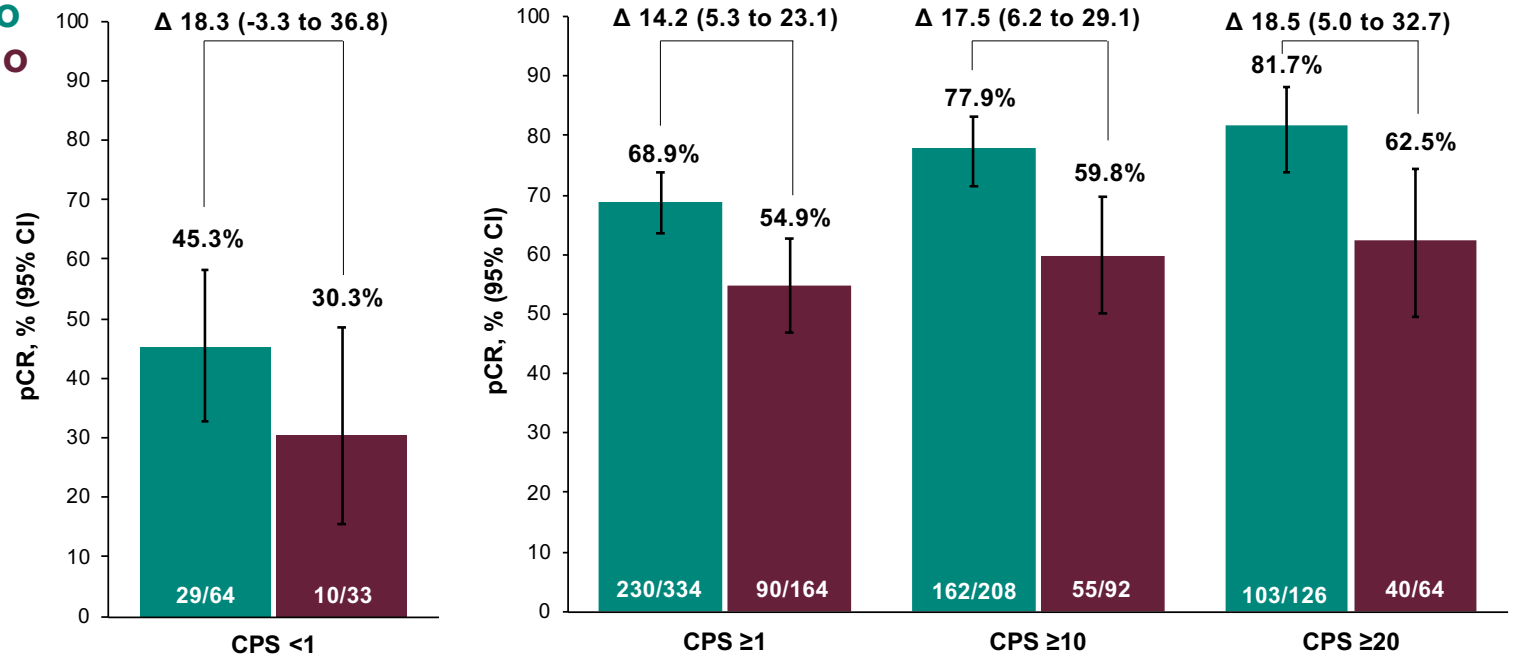
AEs requiring corticosteroids: 12.8 v 9.6%

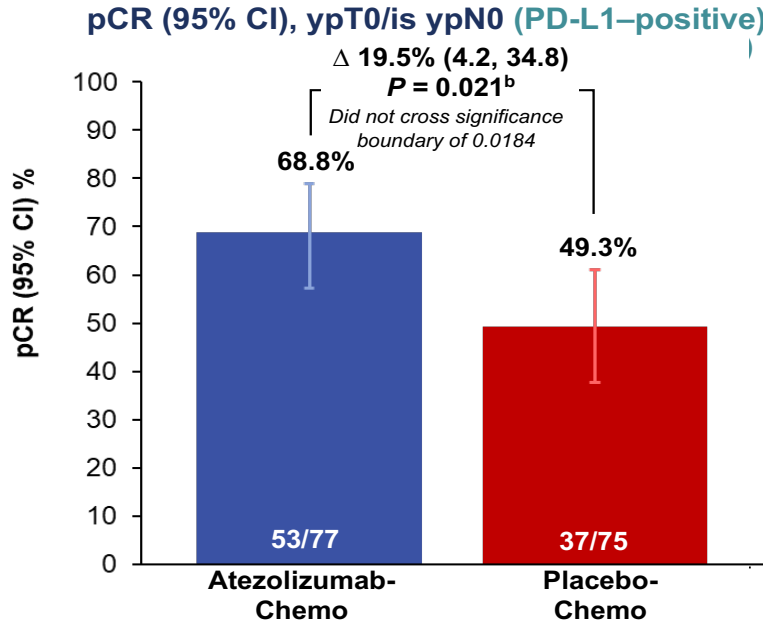
Harbeck et al, ESMO 2020 and Mittendorf et al, Lancet 2020

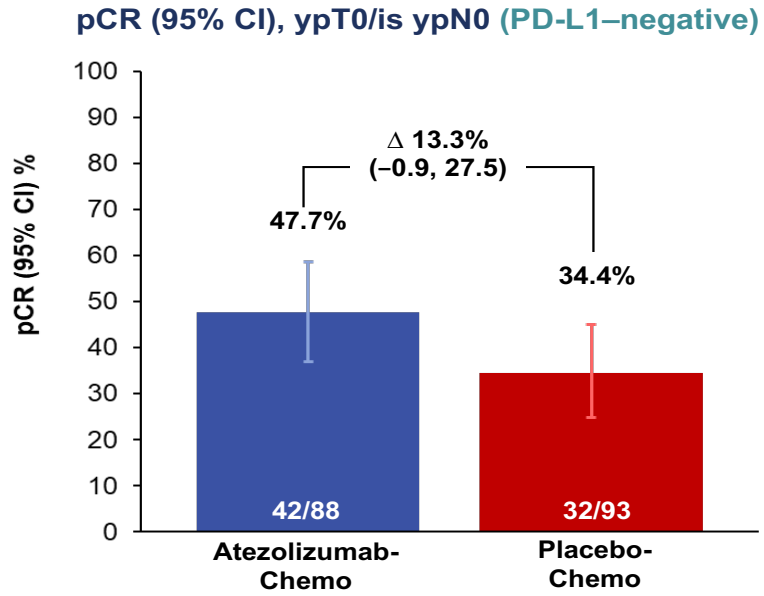
Courtesy of Hope S Rugo, MD

Benefit from Immunotherapy is Independent of PD-L1 status

Is PD-L1 Predictive of Response to Chemotherapy?



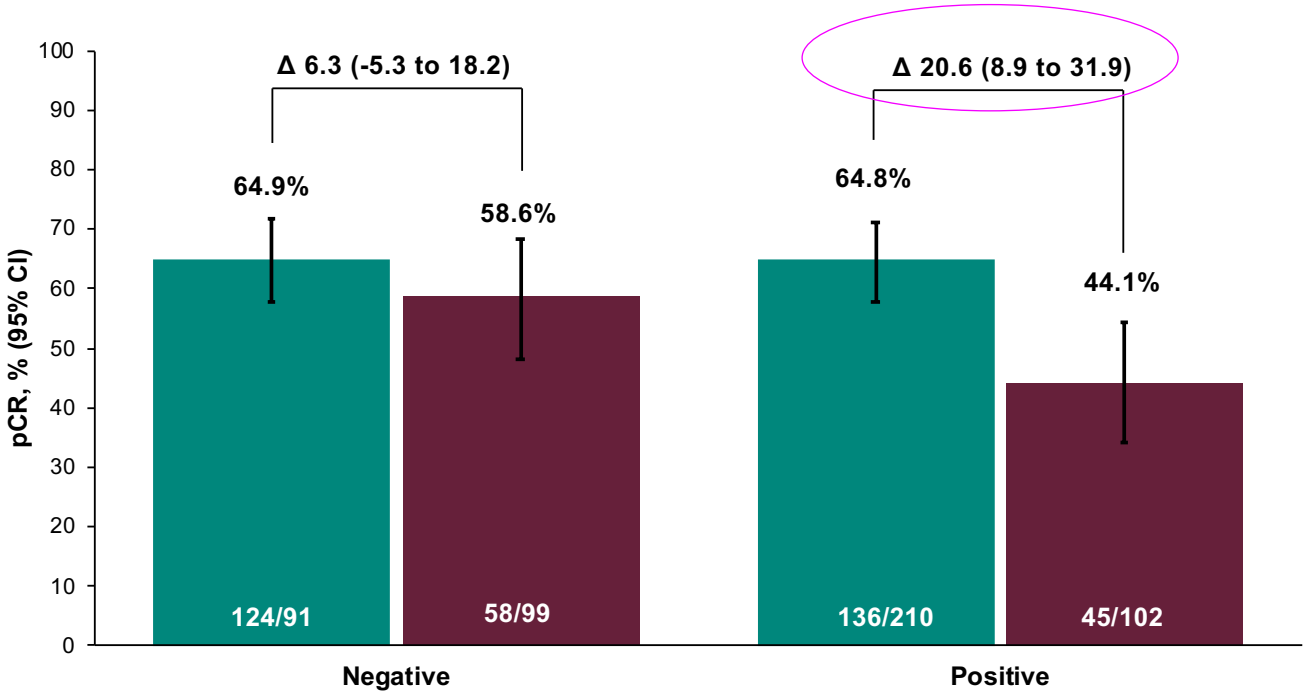




Schmidt et al, SABCS 2019, Harbeck et al, ESMO 2020, Mittendorf et al, Lancet 2020

Courtesy of Hope S Rugo, MD

Greater Benefit in Node Positive Disease
Inflamed Tumors or Greater Tumor Burden?



Subgroup	Atezolizumab-Chemo		Placebo-Chemo		Difference in pCR (95% CI)		
	pCR (%)	n/n	pCR (%)	n/n		Δ (%)	95% CI
Overall	57.6	95/165	41.1	69/168		16.5	5.9, 27.1
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

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

Courtesy of Hope S Rugo, MD

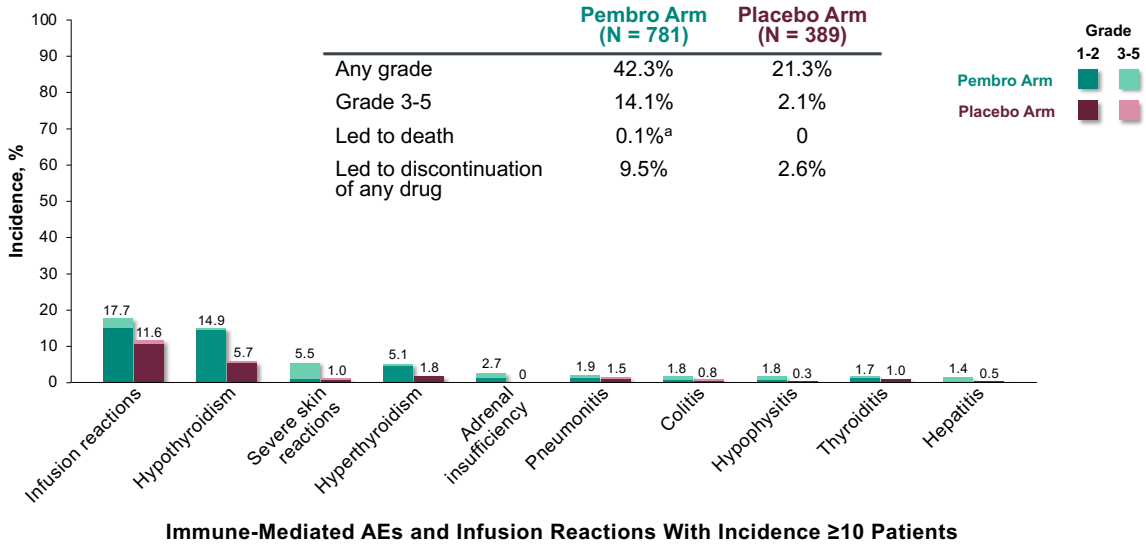
Immune Related AEs

IMpassion031: Adverse events of special interest (AESI) in the neoadjuvant phase[a]

Summary, n (%)	Atezolizumab-Chemo (n = 164)		Placebo-Chemo (n = 167)	
All AESIs	115 (70.1)		101 (60.5)	
Grade 3-4 AESI	24 (14.6)		20 (12.0)	
Serious AESI	11 (6.7)		5 (3.0)	
AESI requiring systemic corticosteroids	21 (12.8)		16 (9.6)	
Specific AESIs, n (%)	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Hepatitis	2 (1.2)	0	1 (0.6)	0
Hypothyroidism	11 (6.7)	0	2 (1.2)	0
Hyperthyroidism	5 (3.0)	0	0	0
Adrenal insufficiency	0	0	1 (0.6)	0
Pneumonitis	2 (1.2)	1 (0.6)	2 (1.2)	0
Colitis	1 (0.6)	1 (0.6)	1 (0.6)	0
Guillain-Barré syndrome	0	0	2 (1.2)	1 (0.6)
Diabetes	1 (0.6)	0	1 (0.6)	0
Encephalitis[b]	1 (0.6)	1 (0.6)	0	0
Myositis	1 (0.6)	1 (0.6)	0	0
Rash	80 (48.8)	6 (3.7)	82 (49.1)	6 (3.6)
Infusion-related reactions	17 (10.4)	1 (0.6)	11 (6.6)	1 (0.6)
Ocular inflammatory toxicity	2 (1.2)	0	0	0
Severe cutaneous reactions	0	0	1 (0.6)	0

[a]AESI as medical concepts (grouped by MedDRA preferred terms) as defined by the sponsor.
[b]One additional case of photophobia in each arm not included.

Immune-Mediated AEs and Infusion Reactions in Combined Phases: IA2



Immune-Mediated AEs and Infusion Reactions With Incidence ≥10 Patients

[a]1 patient from pneumonitis.
Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: April 24, 2019.

Courtesy of Hope S Rugo, MD

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

Making Sense of Discordant Data

Variable	I-SPY	KEYNOTE-522	IMpassion031	NeoTRIP	GeparNUEVO
Total patients	69/180	1174 (602)	333	280	174
Type of CPi	PD1	PD1	PD-L1	PD-L1	PD-L1
Stage	Stage II/III	Stage II/III	Stage II/III	Included N3 disease	35% stage I
Anthracycline pre-op	yes	yes	yes	no	yes
Included carboplatin	no	yes	No (nab-pac)	Yes (nab-pac)	no

My take:

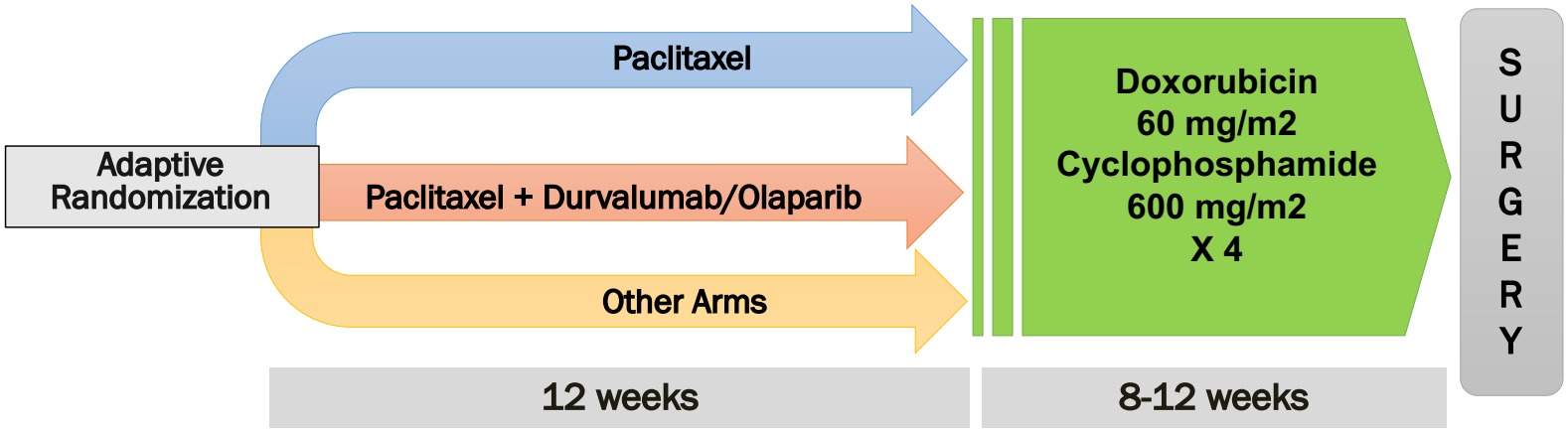
- **Anthracyclines** and **stage** are key factors determining benefit from neoadjuvant CPI therapy
  - KEYNOTE-522 is the largest trial to date evaluating IO NAC in TNBC
  - Confirmatory data with IMpassion031
- PD-L1 status in tumor/IC doesn't matter when the immune system is intact
- Other variables may also play a role (TILs?)
  - Role of TILS and TIL/PD-L1 dynamics on outcome – who needs immunotherapy?

Courtesy of Hope S Rugo, MD

Nanda et al, JAMA Onc 2020; Schmid et al, NEJM 2020; Mittendorf et al Lancet Oncol 2020; Gianni et al, SABCS 2019; Loibl et al, Ann Oncol 2019

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

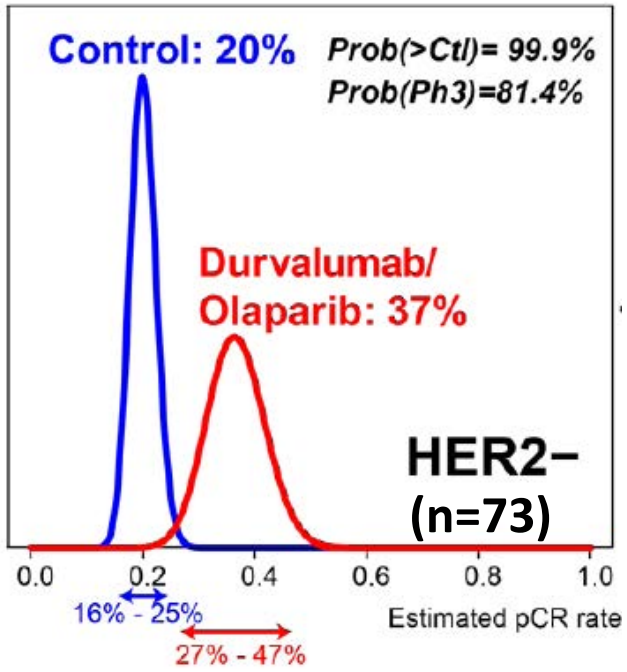
Experimental Arm
Paclitaxel 80 mg/m2 every wk x 12
Durvalumab 1500 mg every 4 wks x 3
Olaparib 100 mg twice daily wks 1-11

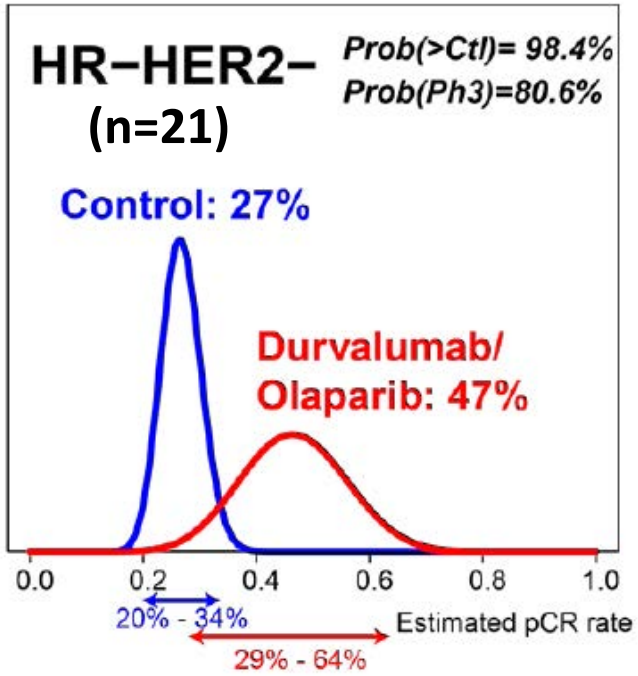
Courtesy of Hope S Rugo, MD

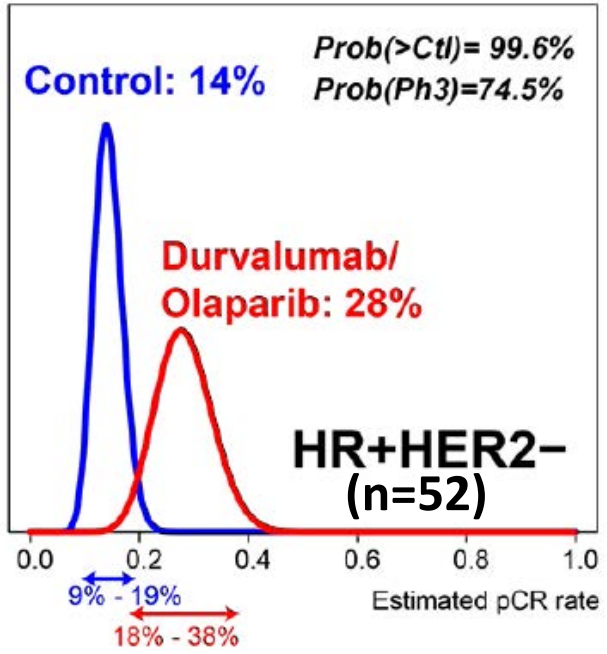
Pusztai et al, AACR 2020

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

Results: pCR Probability by Signature







Signature	Estimated pCR Rate (95% Probability Interval)		Probability that superior to control	Predicted probability of success in 300 patient randomized trial
	Durvalumab/Olaparib	Control		
HER2-	0.367 (0.27-0.47)	0.201 (0.16-0.25)	0.999	0.814
TNBC	0.466 (0.29-0.64)	0.267 (0.20-0.34)	0.984	0.806
HR+ HER2-	0.282 (0.18-0.38)	0.143 (0.09-0.19)	0.996	0.745

Duravalumab + Olaparib graduated in all 3 eligible biomarker signatures by demonstrating increased pCR

Overall, the percent* of patients with any grade 3-4 adverse event were 58% in the experimental and 41% in the control arm; 19% immune related grade 3 AEs

Courtesy of Hope S Rugo, MD

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

Case 1

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 1 (cont)

- 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

Case 2

- 40-year-old woman presents with a right breast mass that is a 2 cm solid mass on US
  - US guided core biopsy: grade 3 IDC, ER/PR/HER2 negative
  - Breast MRI: up to 3.3 cm mass in the right breast
  - Genetic testing: pathogenic mutation in BRCA1
- Treated on a clinical trial with neoadjuvant weekly paclitaxel and cemiplimab followed by dose dense AC x 4
  - Initial slow response, improved by cycle 6 of paclitaxel
  - Continued response by exam and imaging through AC
- Bilateral mastectomy and right SLNBx
  - No residual carcinoma, 3 negative sentinel nodes

Courtesy of Hope S Rugo, MD

Case 3

- A 33 year old woman presents with a large left breast mass
- Imaging confirms a solid mass up to 4.4 cm
- US guided core biopsy: grade 3 triple negative IDC; FNA axillary nodes benign
- Genetic testing negative for pathogenic mutations
- MRI: 5.1 cm largely necrotic mass and 3.3 cm mass just medial to the main mass in the left breast.
- Treated on a clinical trial with neoadjuvant weekly paclitaxel, durvalumab and Olaparib
  - Changed to nab-paclitaxel at cycle 3 due to hives
  - By cycle 5 had developed diarrhea, nausea and vomiting
  - Durvalumab and Olaparib held
  - Endoscopy and colonoscopy: extensive gastritis and colitis
  - Treated with steroids with immediate improvement in symptoms

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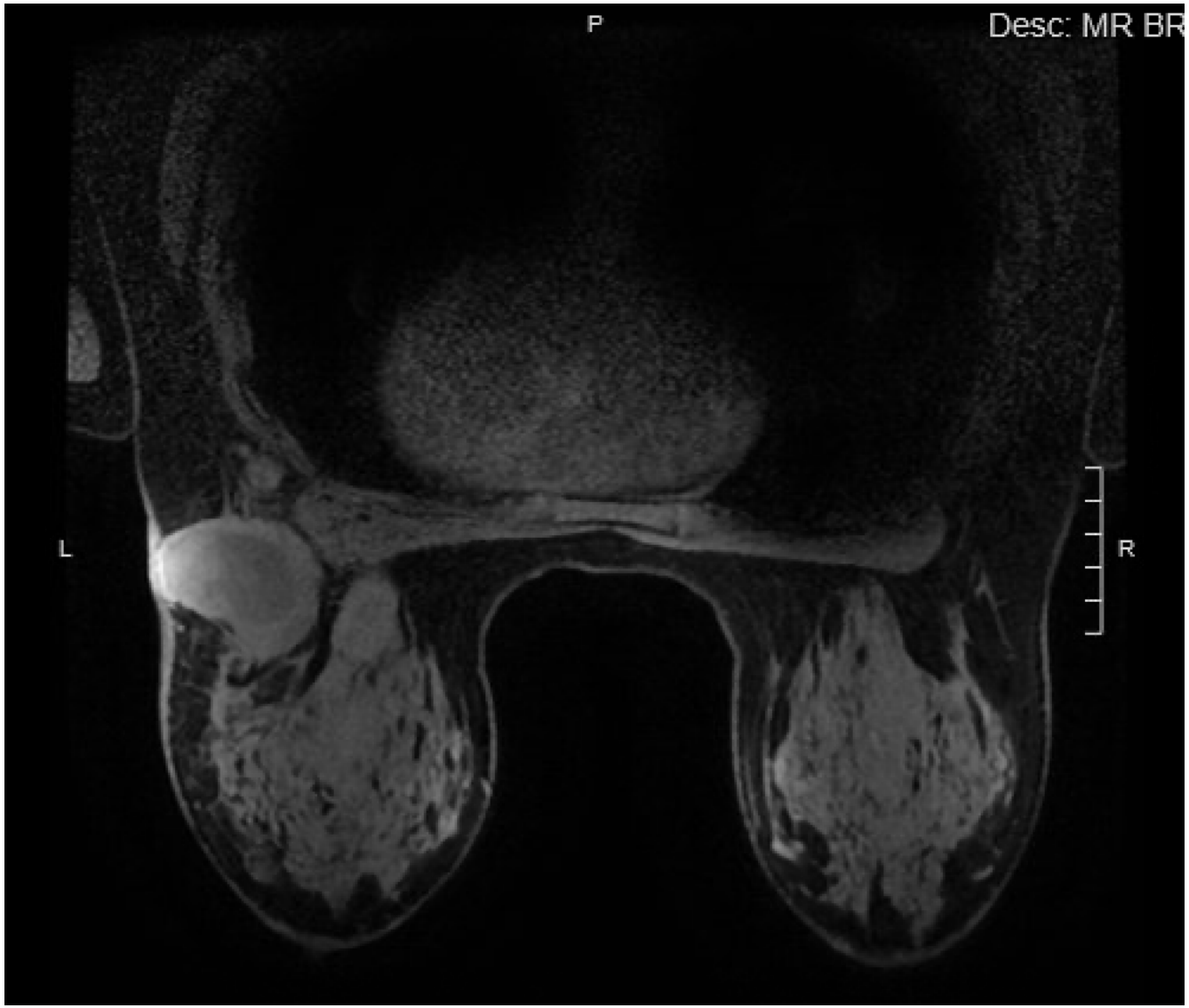
Case 3 (cont)

- Completed 12 weekly doses of taxane and then dose dense AC x 4
  - Carboplatin added to nab-paclitaxel after cycle 7 due to sluggish response
- Left breast lumpectomy and SLNBx: 3 foci of residual invasive cancer and 3 negative nodes
  - 1 cm grade 3 IDC with 70% cellularity
    - ER/PR/HER2 negative, Ki67 80%
  - 0.1 cm with 30% cellularity
  - 0.07 cm with 20% cellularity
- Treated with radiation therapy and capecitabine x 8 cycles, completed 6/2020

Courtesy of Hope S Rugo, MD

Case 3 Breast MRI pre-treatment



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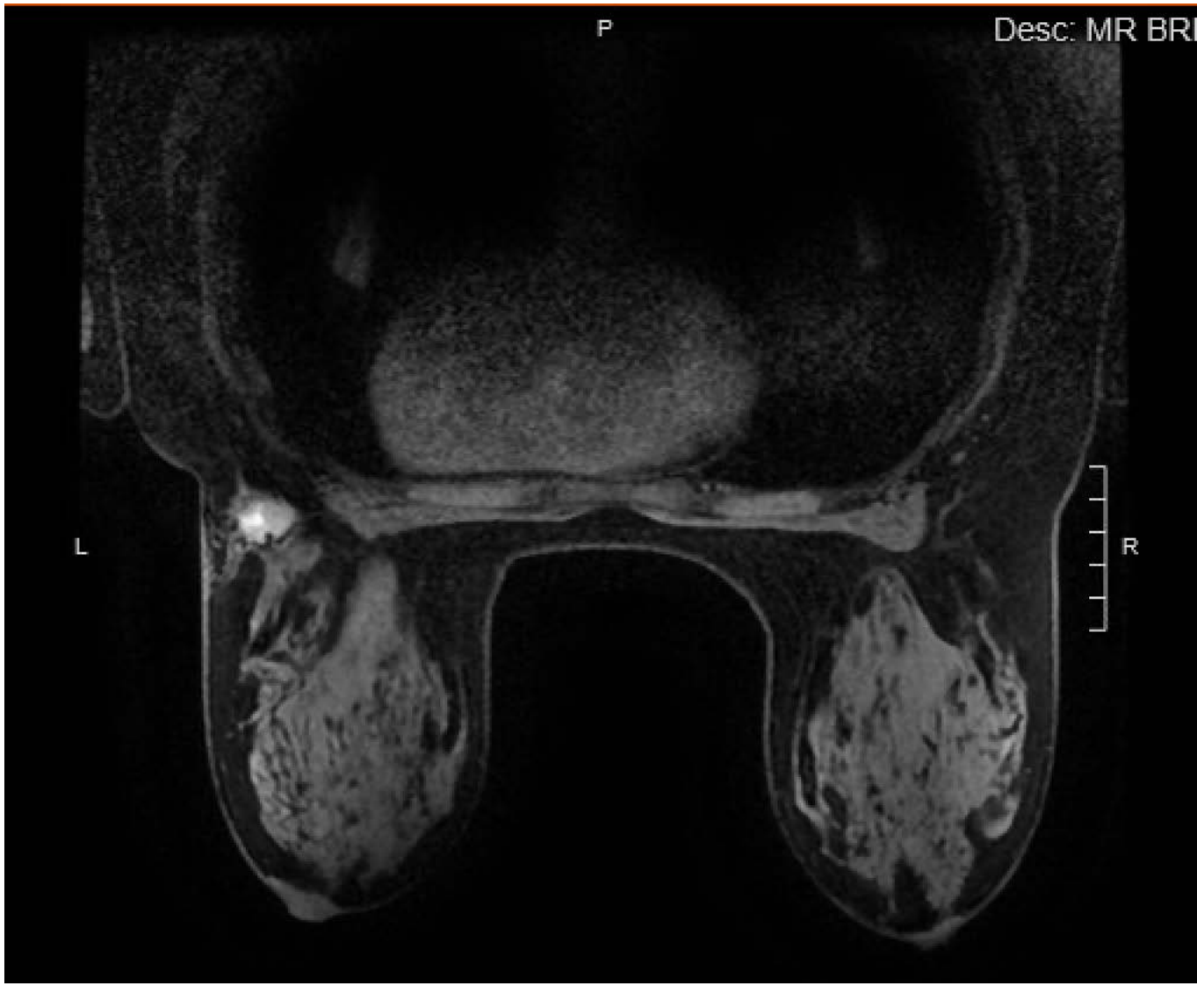
Case 3 Breast MRI at end of therapy



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