sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Breast Cancer

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

- Partner Contracted Research: Institutional Support - Genentech, Seattle Genetics, Novartis, Astra Zeneca, Daiichi, Immunomedics; no personal fees
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy in breast

- Standard-of-care treatment may involve surgery, endocrine therapy, chemotherapy, radiation
- Application of immunotherapy is still in early stages

Est new cases

Female		
Breast	268,600	30%
Lung & bronchus	111,710	13%
Colon & rectum	67,100	7%
Uterine corpus	61,880	7%
Melanoma of the skin	39,260	5%
Thyroid	37,810	4%
Non-Hodgkin lymphoma	33,110	4%
Kidney & renal pelvis	29,700	3%
Pancreas	26,830	3%
Leukemia	25,860	3%
All sites	**891,480**	

Est deaths

Female		
Lung & bronchus	66,020	23%
Breast	41,760	15%
Colon & rectum	23,380	8%
Pancreas	21,950	8%
Ovary	13,980	5%
Uterine corpus	12,160	4%
Liver & intrahepatic bile duct	10,180	4%
Leukemia	9,690	3%
Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	7,850	3%
All sites	**285,210**	

American Cancer Society

Outline

- Overview of current landscape
- Metastatic breast cancer
  - Atezolizumab
  - Pembrolizumab
- Preoperative therapy
- Sacituzumab
- Future directions
- Cases

“Personalizing” Therapy

- Germline testing
  - ***BRCA 1/2-* PARP inhibition**

- Molecular profiling – find mutations that are “actionable”
  - MMR and MSI - pembrolizumab
  - **Immune cell PDL1+ – atezolizumab**
  - NRTK gene fusion - larotrectinib, entrectinib
  - **PI3KC mutation (40% of hormone receptor positive) - alpelisib**
  - **ESR mutation – aromatase inhibitor vs (selective estrogen receptor degrader) SERD**

Current approvals

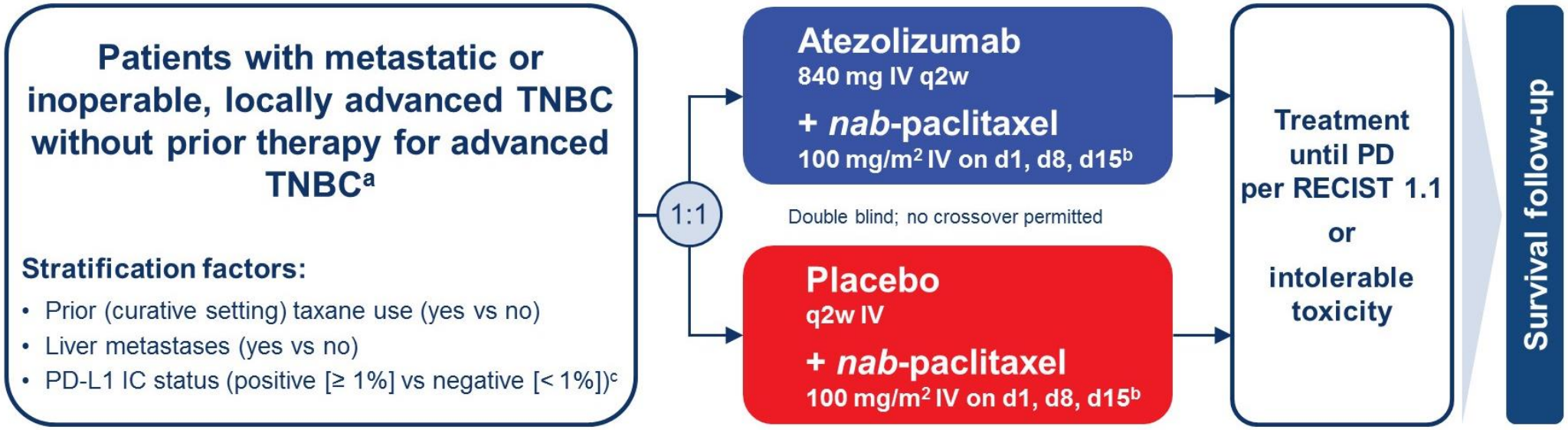
Drug	Approved	Indication	Dose
Pembrolizumab	2017	MSI-H/dMMR **advanced cancer** with progression on previous treatment (includes especially **endometrial**)	200 mg Q3W
Atezolizumab + nab-paclitaxel or paclitaxel protein-bound	2019	Advanced/Metastatic **TNBC** with PD-L1 ≥1%	840 mg atezolizumab + 100 mg/m^2 paclitaxel
Sacituzumab govitecan	2020	Metastatic **TNBC** after two previous therapies	10mg/kg on D1&D8 of 21-day cycle

Checkpoint Inhibitor Monotherapy

Agent	Subtype	N	ORR	ORR (PD-L1+)*
Pembrolizumab				
• Single agent (Keynote-012)	TNBC	32	18.5%	18.5%
• Single agent (Keynote-028)	ER+	25	12.0%	12.0%
• Single agent (Keynote-086-A)	TNBC	170	5.7% (PD-L1+)	5.7%
• Single agent (Keynote-086-B)	TNBC	84	21.4%	21.4%
• Plus trastuzumab (PANACEA)	HER2+	58		15.0%
Atezolizumab				
• Single agent	TNBC	21	19.0%	19.0%
• Single agent (expanded)	TNBC	115	10.0% IL (n=21): 26% ≥2L (n-91): 6%	13.0%
Avelumab				
• Single agent (Javelin)	All	168	4.8%	33.3%
	ER+/HER2-	72	2.8%	NR
	HER2+	38	3.8%	NR
	TNBC	58	8.6%	44.4%

Nanda et al, JCO 2016; Rugo et al, CCR 2018; Dirix et al, BCRT 2017;
Loi et al, SABCS 2017; Emens et al, JAMA Onc 2019; Adams et al, Ann Onc 2019
*Studies used different antibodies and cutoffs for PD-L1 positivity

Clinical Data – IMpassion130 PD-L1+ TNBC

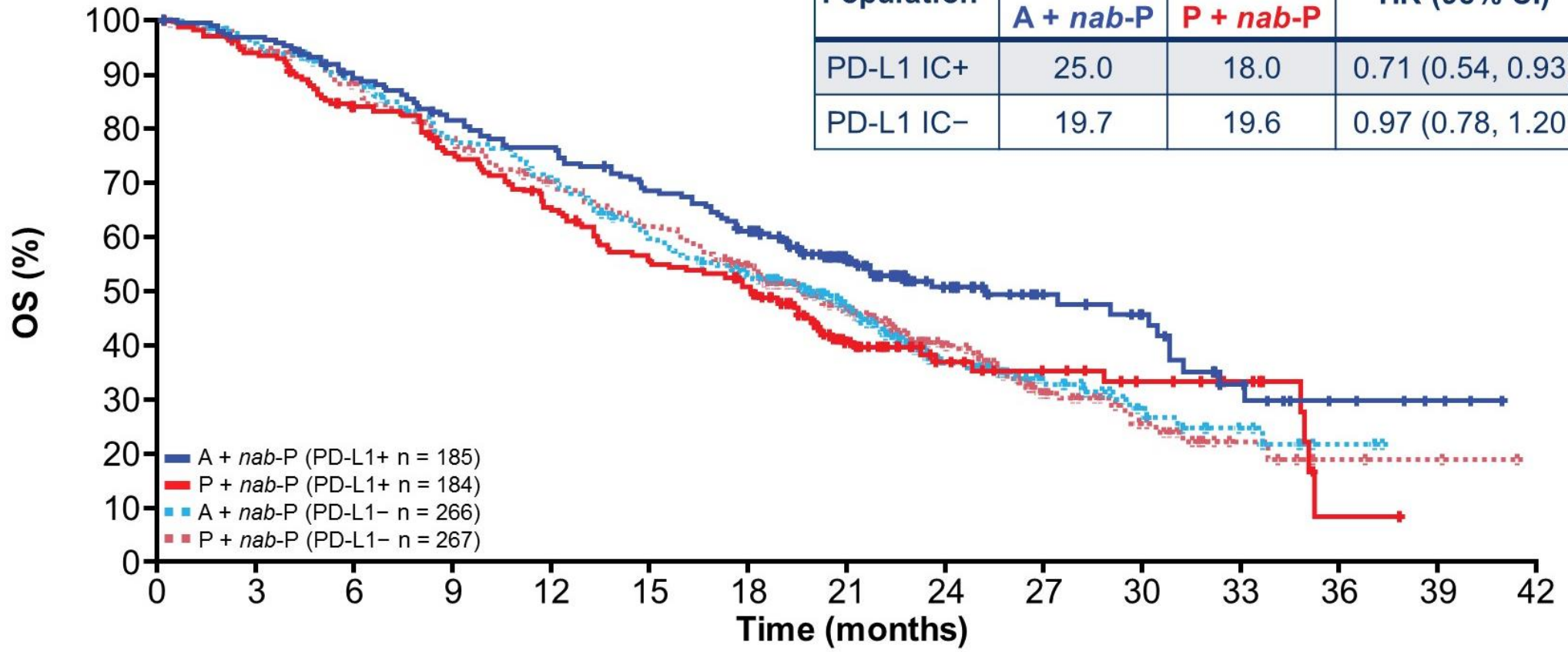


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

Schmid, ASCO 2019.

Clinical Data – IMpassion130 PD-L1+ TNBC

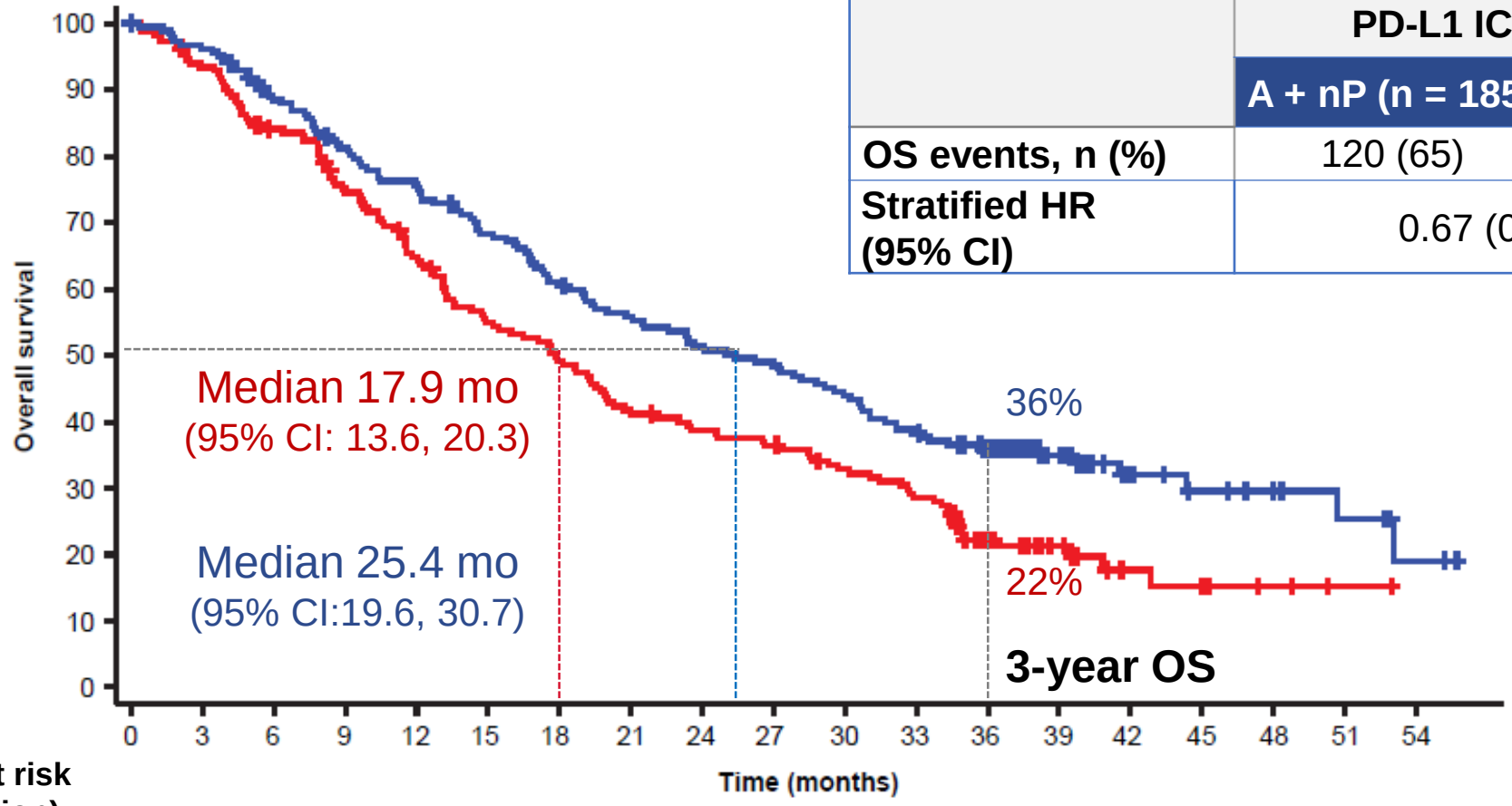
Population	Median OS, mo		HR (95% CI)
	A + *nab*-P	P + *nab*-P	
PD-L1 IC+	25.0	18.0	0.71 (0.54, 0.93)
PD-L1 IC−	19.7	19.6	0.97 (0.78, 1.20)



Schmid, ASCO 2019.

OS in the PD-L1 IC+ population

	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]	



Patients at risk (PD-L1 IC+ 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

Emens LA. IMpassion130 Final OS. ESMO 2020. https://bit.ly/34BtGfV

FDA Accelerated Approval

- Atezolizumab (Tecentriq®) in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 stained **tumor-infiltrating immune cells** [IC] of any intensity covering ≥ 1% of the tumor area)

- FDA also approved the VENTANA PD-L1 (SP142) assay as a companion diagnostic device for selecting TNBC patients for atezolizumab.

IMpassion131 trial design

Double-blind placebo-controlled randomised phase 3 trial

- Metastatic or unresectable locally advanced TNBC
- No prior chemotherapy or targeted therapy for advanced TNBC
- Previous eBC treatment completed ≥12 months before randomisation
- Taxane eligible
- Measurable disease
- ECOG PS 0/1

R
2:1

Atezolizumab 840 mg d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

8–10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

Placebo d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

Stratification:
- Prior taxane (yes vs no)
- Tumour PD-L1 status (IC <1% vs ≥1%)[a]
- Liver metastases (yes vs no)
- Geographical region (N America vs W Europe/Australia vs E Europe/Asia Pacific vs S America)

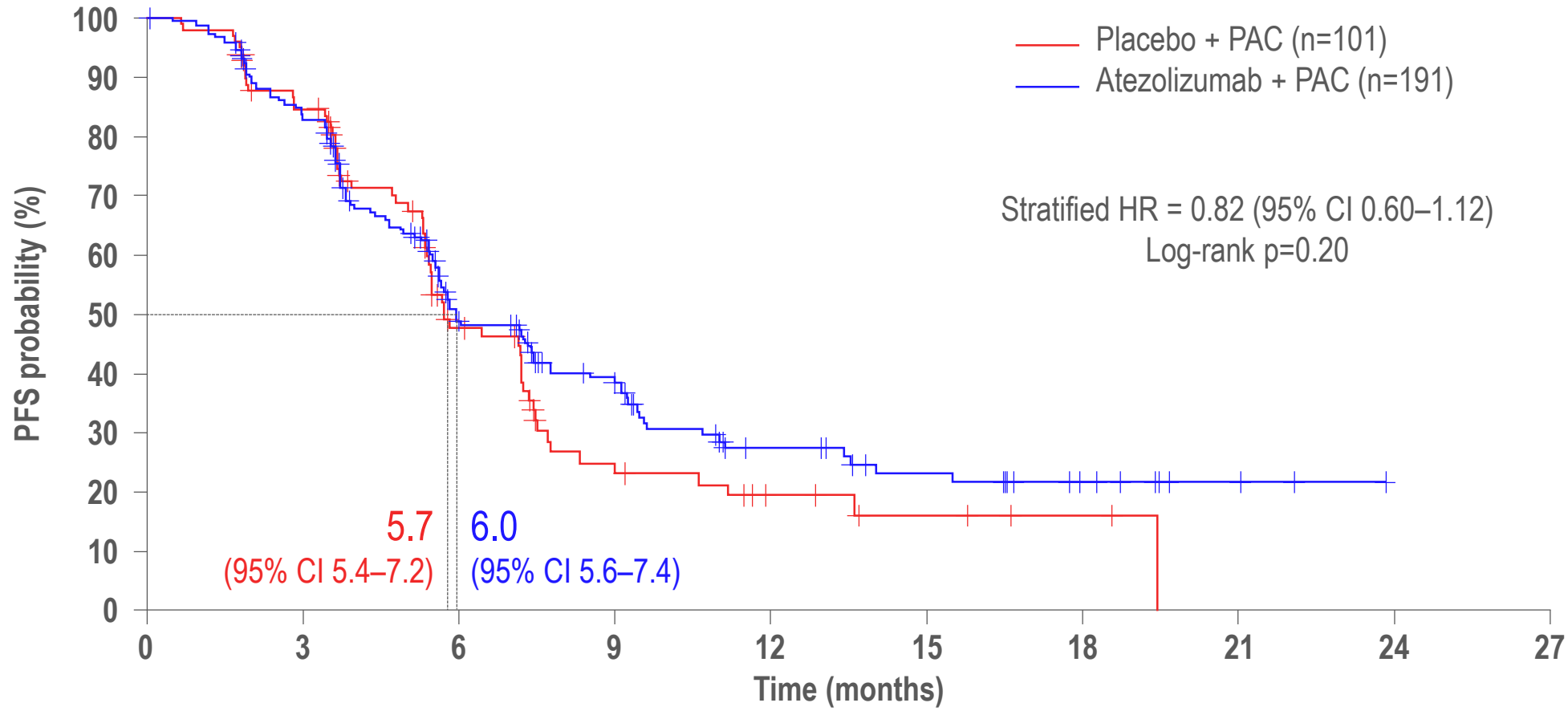
Primary endpoint: PFS (investigator assessed)
Secondary endpoints include:
- OS, ORR, PFS (IRC assessed)
- PROs
- Safety
- Translational research

[a]PD-L1 IC: area of PD-L1-stained tumour-infiltrating ICs as a percentage of tumour area by VENTANA SP142 immunohistochemistry assay. eBC = early breast cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; IC = immune cell; IRC = independent review committee; ORR = objective response rate; PRO = patient-reported outcome; q28d = every 28 days; R = randomisation

Miles et al., ESMO Congress 2020

Primary analysis: PFS in the PD-L1+ population

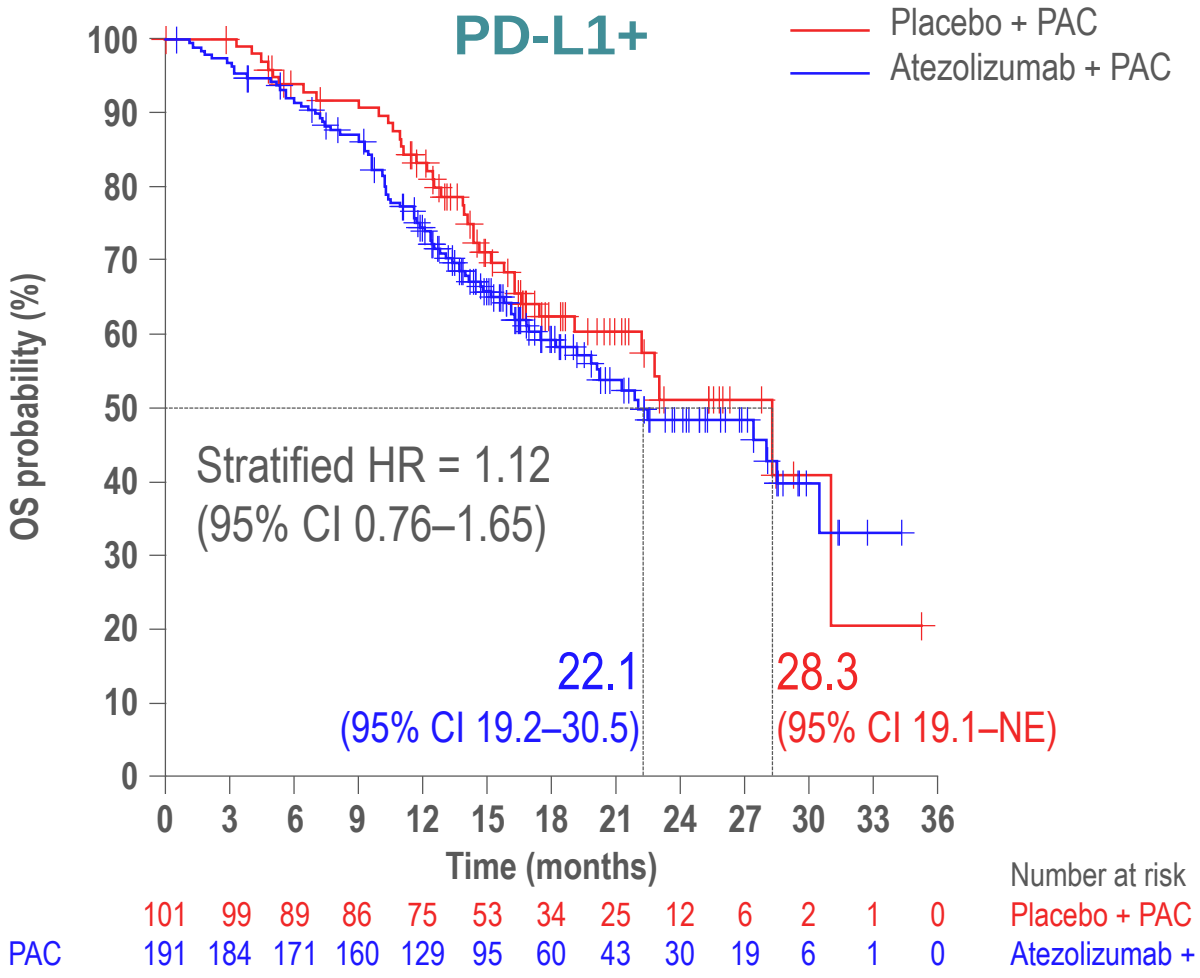
Events in 61% of patients (data cut-off: 15 Nov 2019)

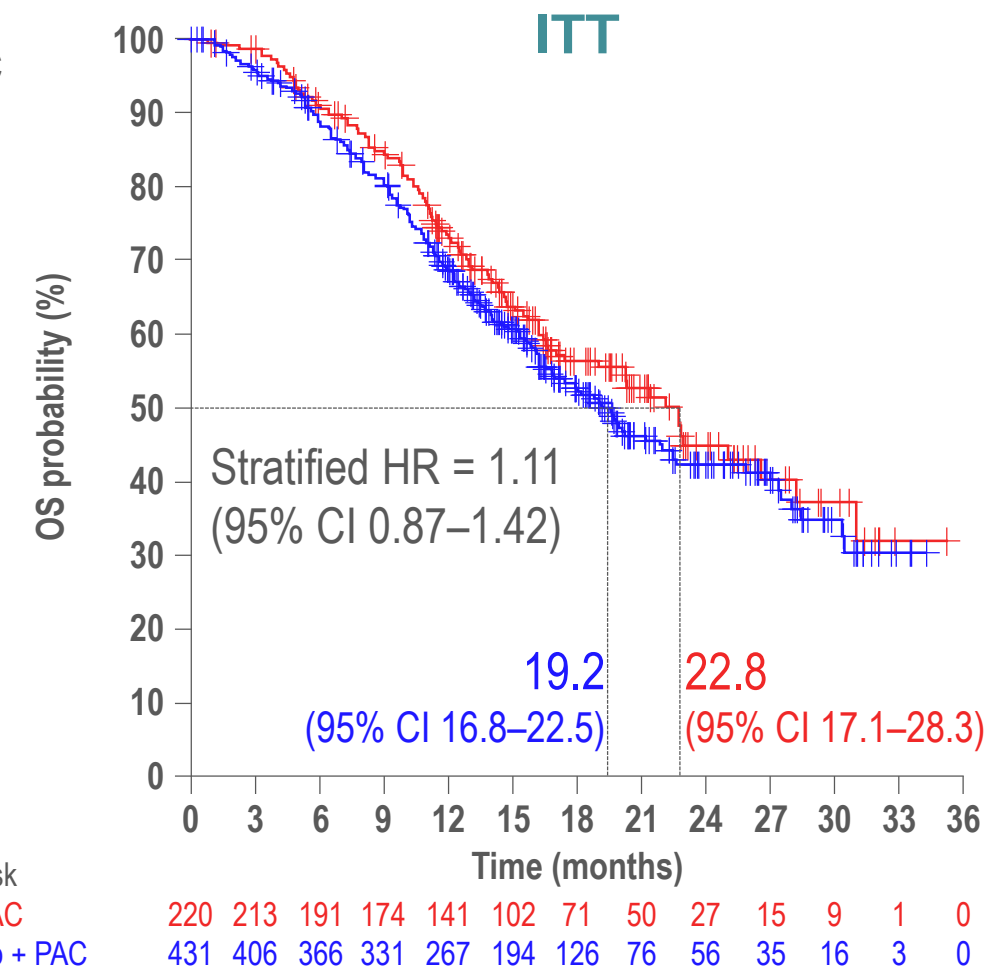


Number at risk										
Placebo + PAC	101	81	33	14	7	4	2	0	0	0
Atezolizumab + PAC	191	152	69	44	22	15	8	3	0	0

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

Updated Overall Survival





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

What Accounts for Difference Between Different Outcomes?

STEROID PREMEDICATION

Most patients took steroids over the entire time they were on chemotherapy (also less immune-toxicity in this trial which maybe related to steroids)

PATIENT POPULATION

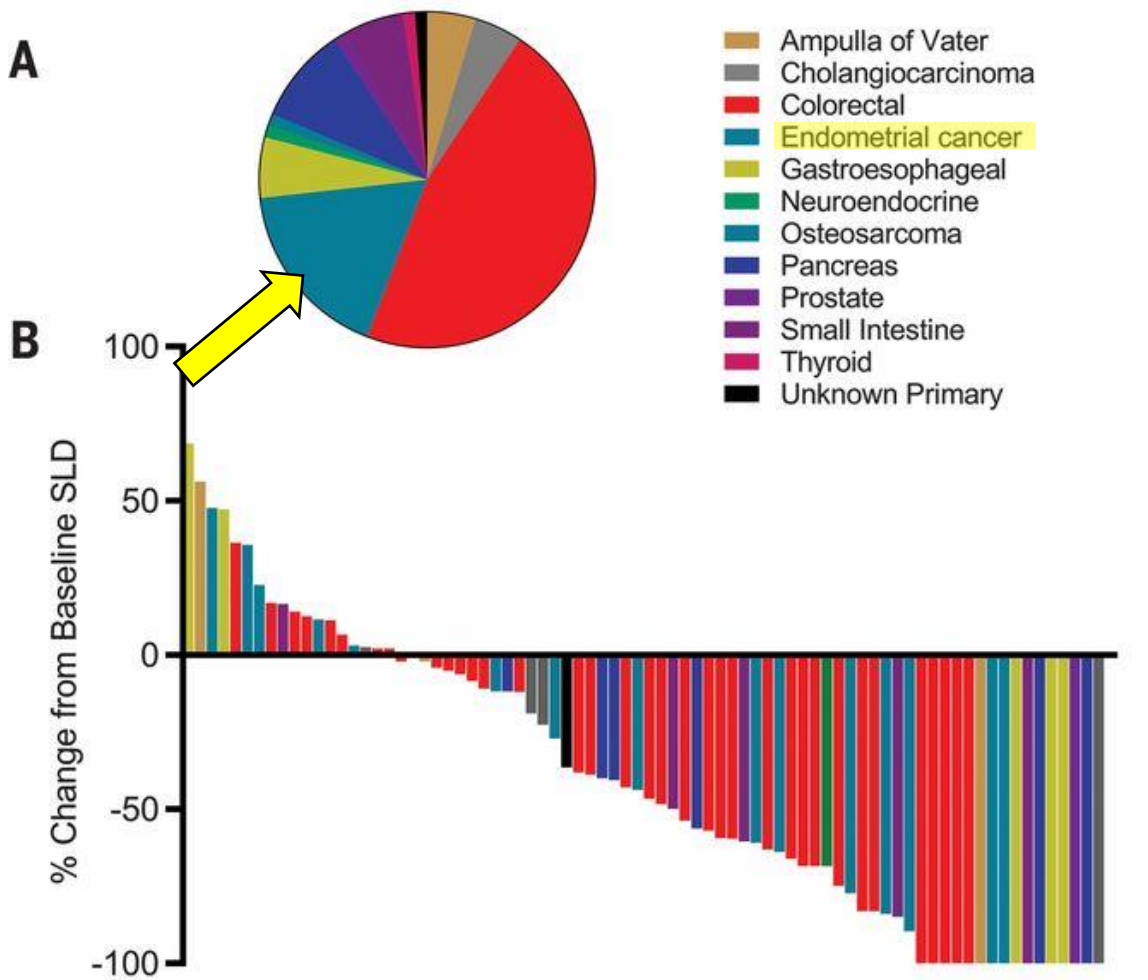
Fewer de novo metastatic patients (30% c/w 40% in IMP130)
Equal number of patients with prior adjuvant taxane (but maybe differences in DFI since taxane)
More Asians who seem to benefit less

SAMPLE SIZE/TRIAL DESIGN

2:1 randomization with small #s in PDL1+ control arm
Control arm outperforming what we would expect from single agent taxane (~28mo OS)

DIFFERENCES IN CHEMOTHERAPY AND SYNERGY WITH IO

Clinical Data – pembrolizumab in MSI-high cancers

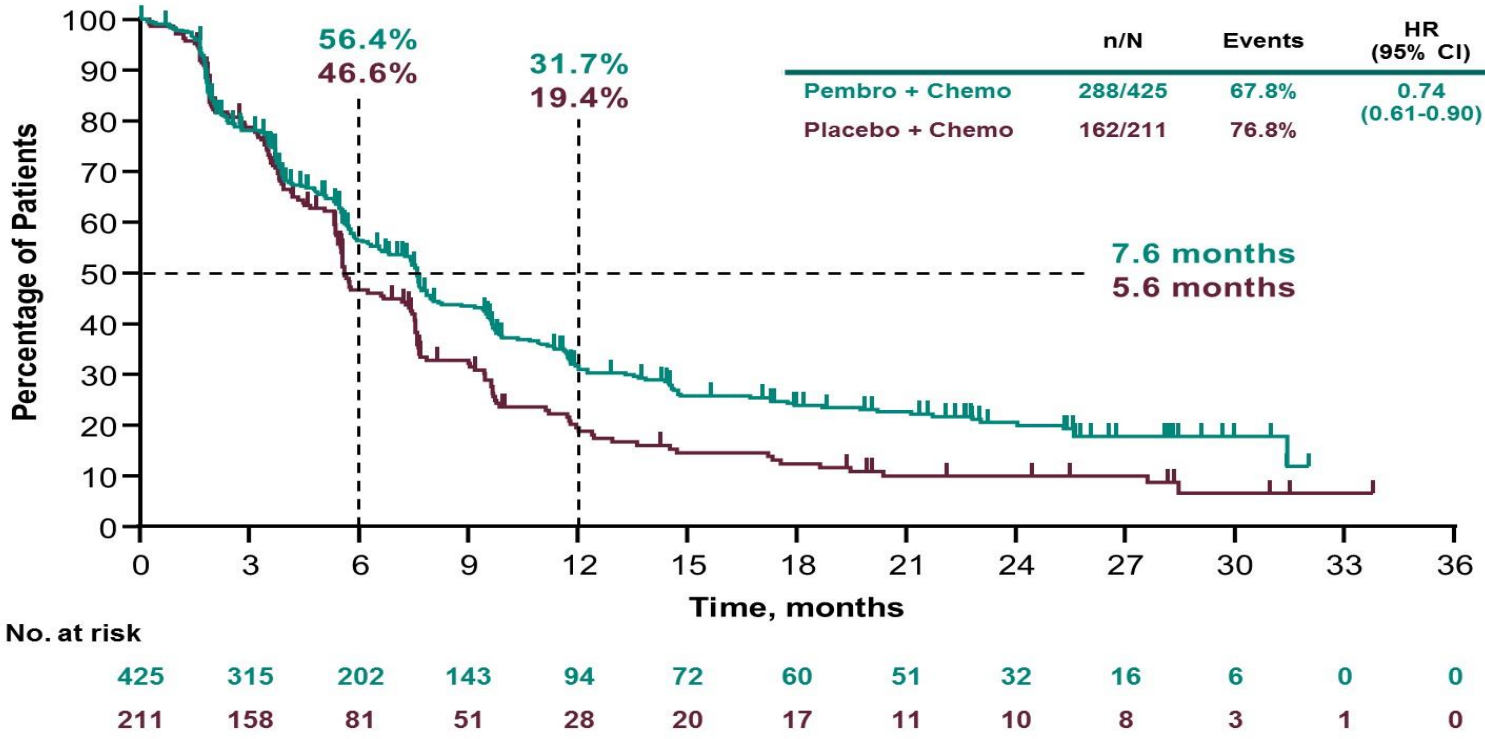


- NCT01876511
- 12 cancer types with dMMR
- ORR: 53%
- CR: 21%

Le, Science 2017.

KEYNOTE-355

Progression-Free Survival: PD-L1 CPS ≥1



	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	288/425	67.8%	0.74 (0.61-0.90)	0.0014[a]
Placebo + Chemo	162/211	76.8%		

No. at risk

425	315	202	143	94	72	60	51	32	16	6	0	0
211	158	81	51	28	20	17	11	10	8	3	1	0

[a]Prespecified *P* value boundary of 0.00111 not met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff December 11, 2019.

Chemo: nab-paclitaxel, paclitaxel or gemcitabine/carboplatin

Cortes et al., J Clin Oncol 38: 2020 (suppl; abstr 1000)

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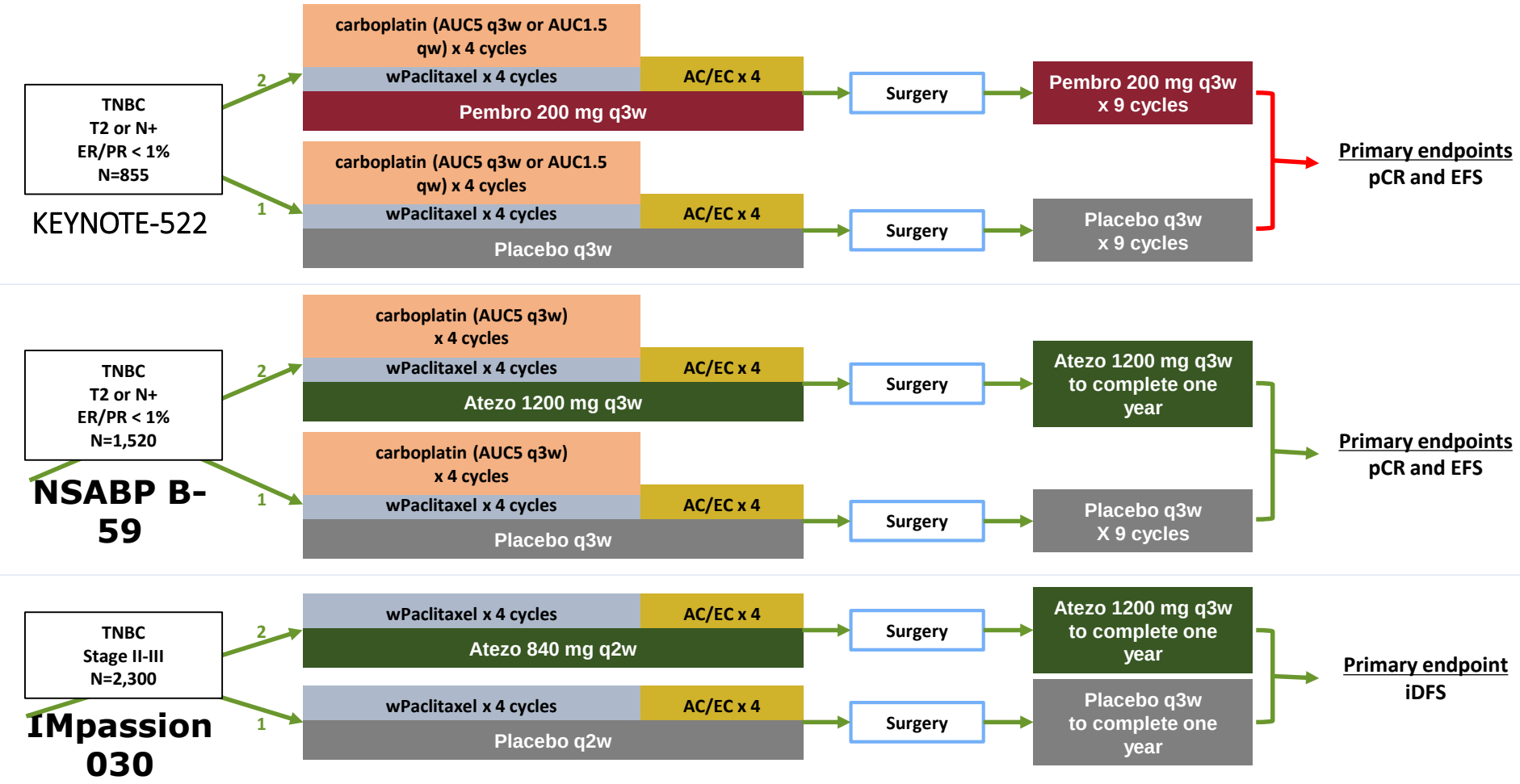
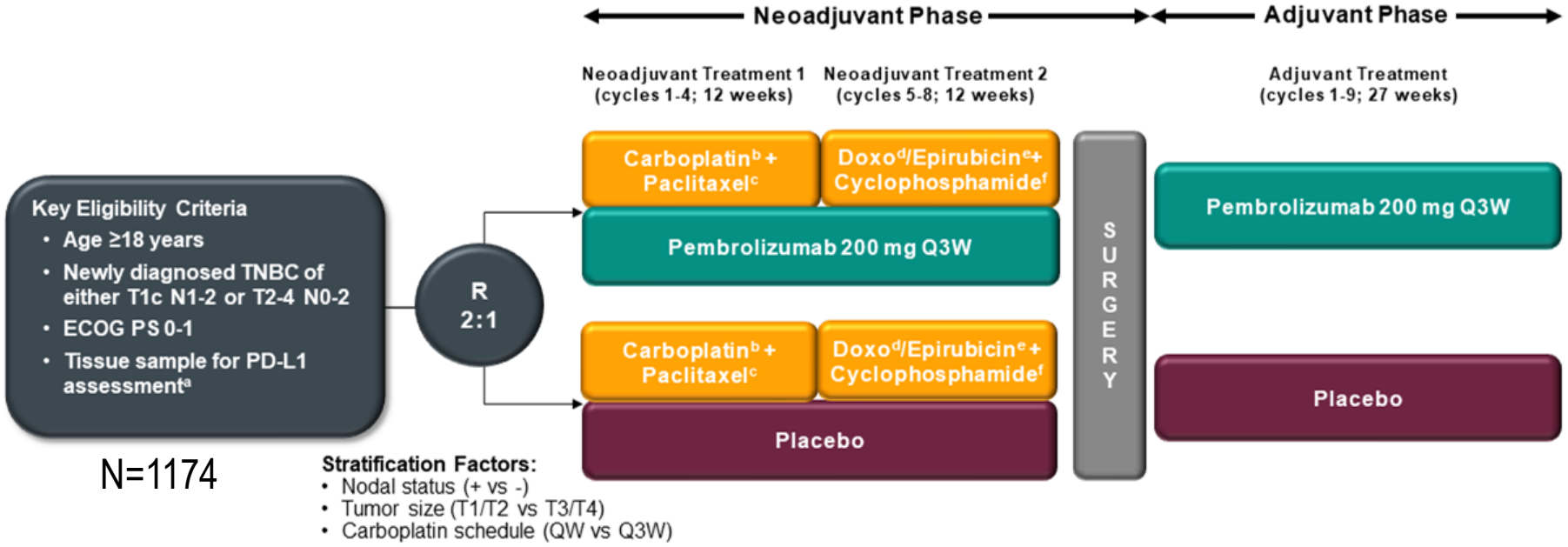
Ongoing neo/adjuvant trials with PD1/PDL1 inhibitors



KEYNOTE 522: Preoperative pembrolizumab



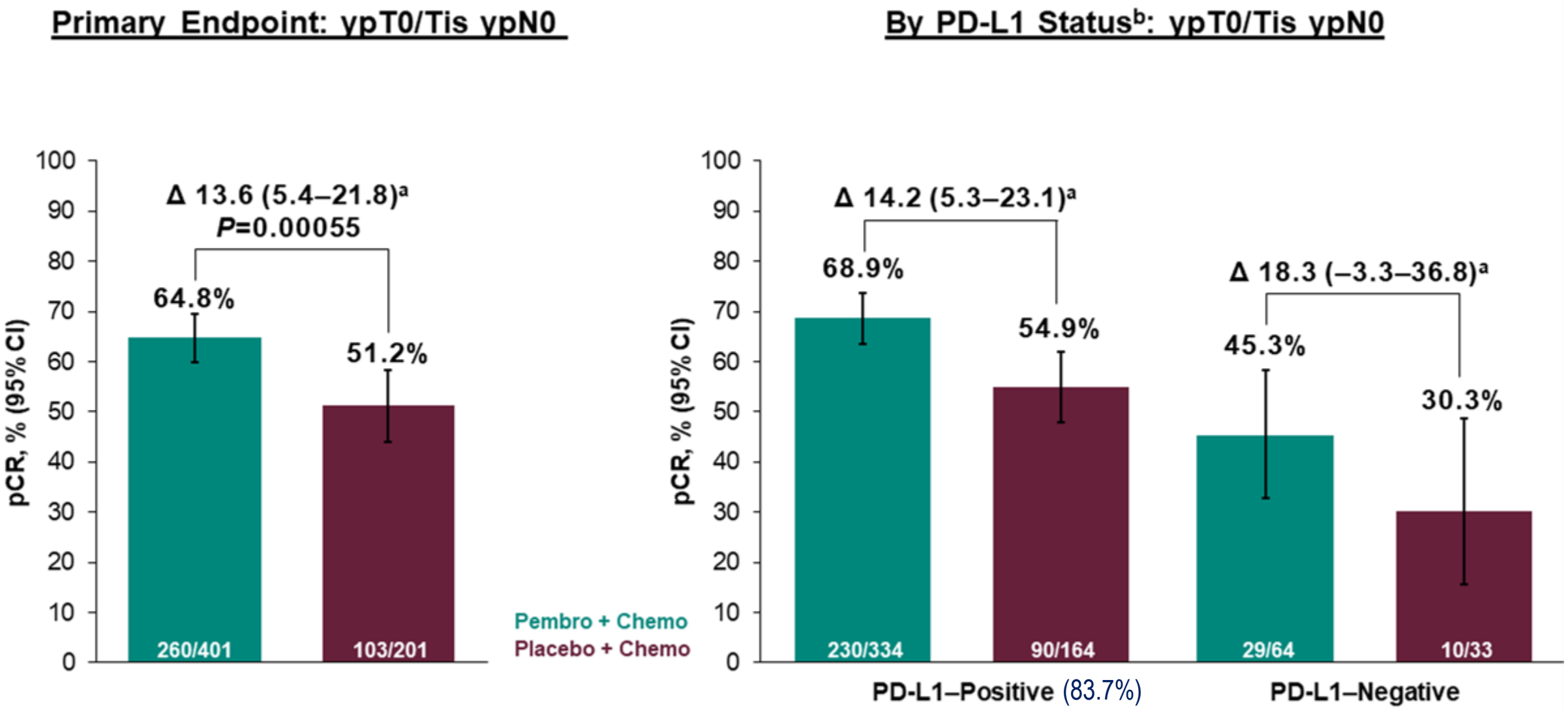
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

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

[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/m² QW.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

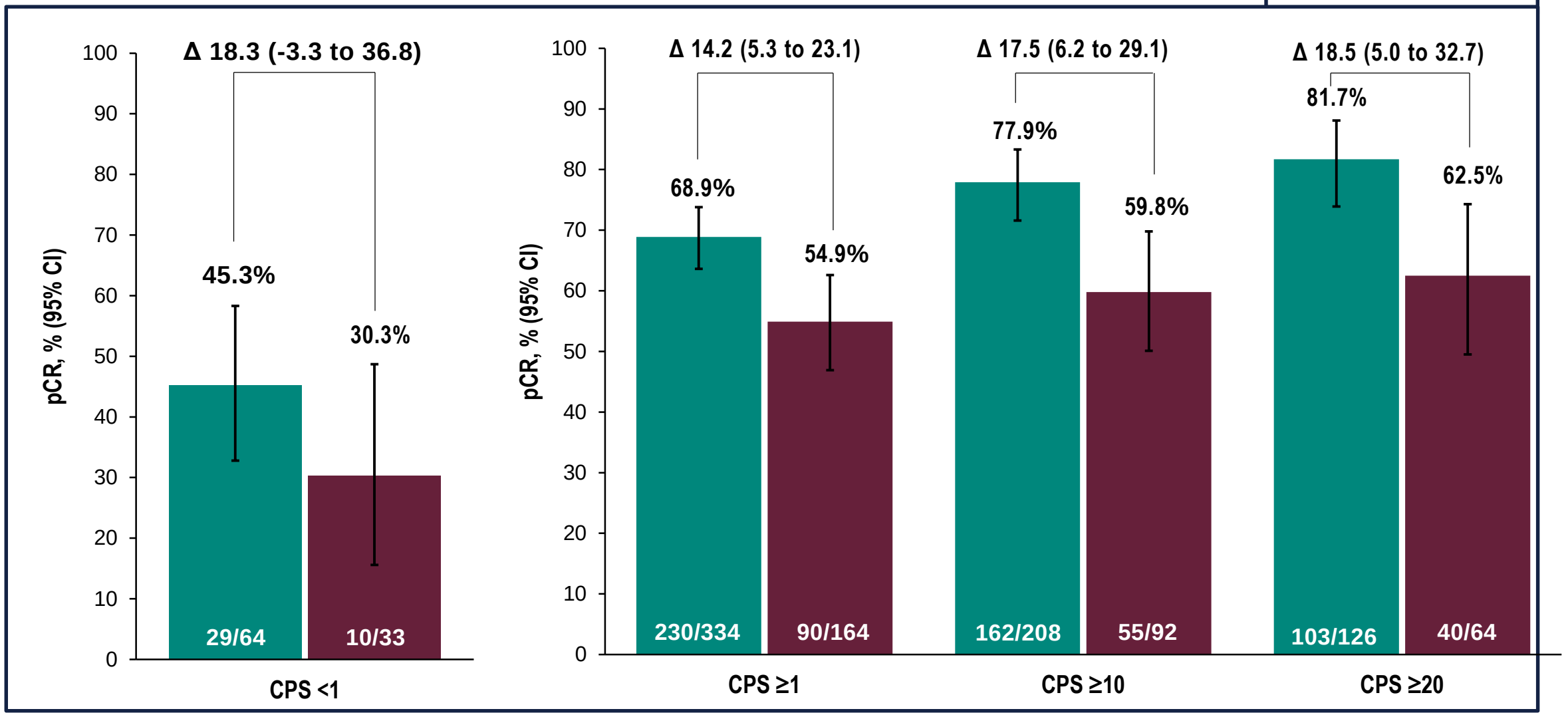
Harbeck et al. IMpassion031 Primary Analysishttps://bit.ly/3ji97cn

KEYNOTE 522: Pathologic Complete Response (pCR)



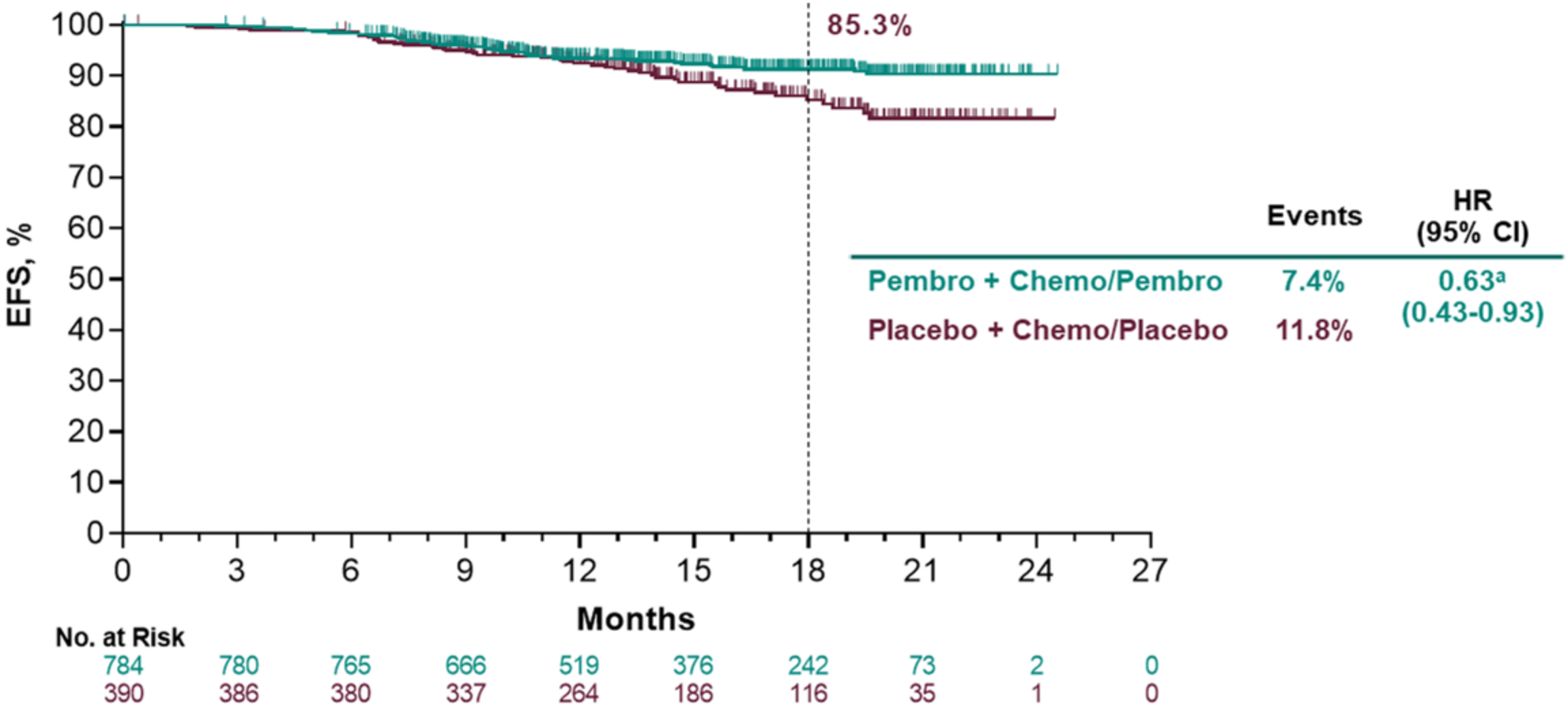
Harbeck et al. IMpassion031 Primary Analysishttps://bit.ly/3ji97cn

pCR by PD-L1 Expression Level



Harbeck et al. IMpassion031 Primary Analysishttps://bit.ly/3ji97cn

KEYNOTE 522: Event Free Survival (Interim Analysis)



Harbeck et al. IMpassion031 Primary Analysishttps://bit.ly/3ji97cn

IMpassion031: Phase III atezolizumab neoadjuvant study in eTNBC[1,2]

A randomised, multicentre, international, double-blind, placebo-controlled trial

N = 333

TNBC, with primary tumour > 2 cm

cT2-cT4, cN0-cN3, cM0

Known PD-L1 status (IHC)

No prior therapy for treatment or prevention of BC

ECOG PS 0 or 1

Stratification Factors:
- Stage II vs Stage III
- PD-L1 IC < 1% vs IC ≥ 1%

R 1:1

12 weeks	8 weeks	pCR	≤ 1 year from start
Atezolizumab 840 mg IV q2w + *nab*-paclitaxel 125 mg/m² IV qw	Atezolizumab 840 mg IV q2w + Doxorubicin 60 mg/m² IV q2w Cyclophosphamide 600 mg/m² IV q2w	SURGERY	Atezolizumab 1200 mg IV q3w x 11 doses
Placebo + *nab*-paclitaxel 125 mg/m² IV qw	Placebo + Doxorubicin 60 mg/m² IV q2w Cyclophosphamide 600 mg/m² IV q2w		Observation[a]

Survival follow-up[a]

Co-primary endpoints: pathologic complete response (pCR, ypT0/is ypN0) in ITT and PD-L1–positive (IC ≥ 1%) subpopulation

Secondary endpoints: EFS, DFS, and OS in ITT and in PD-L1–positive subpopulation, safety, PROs

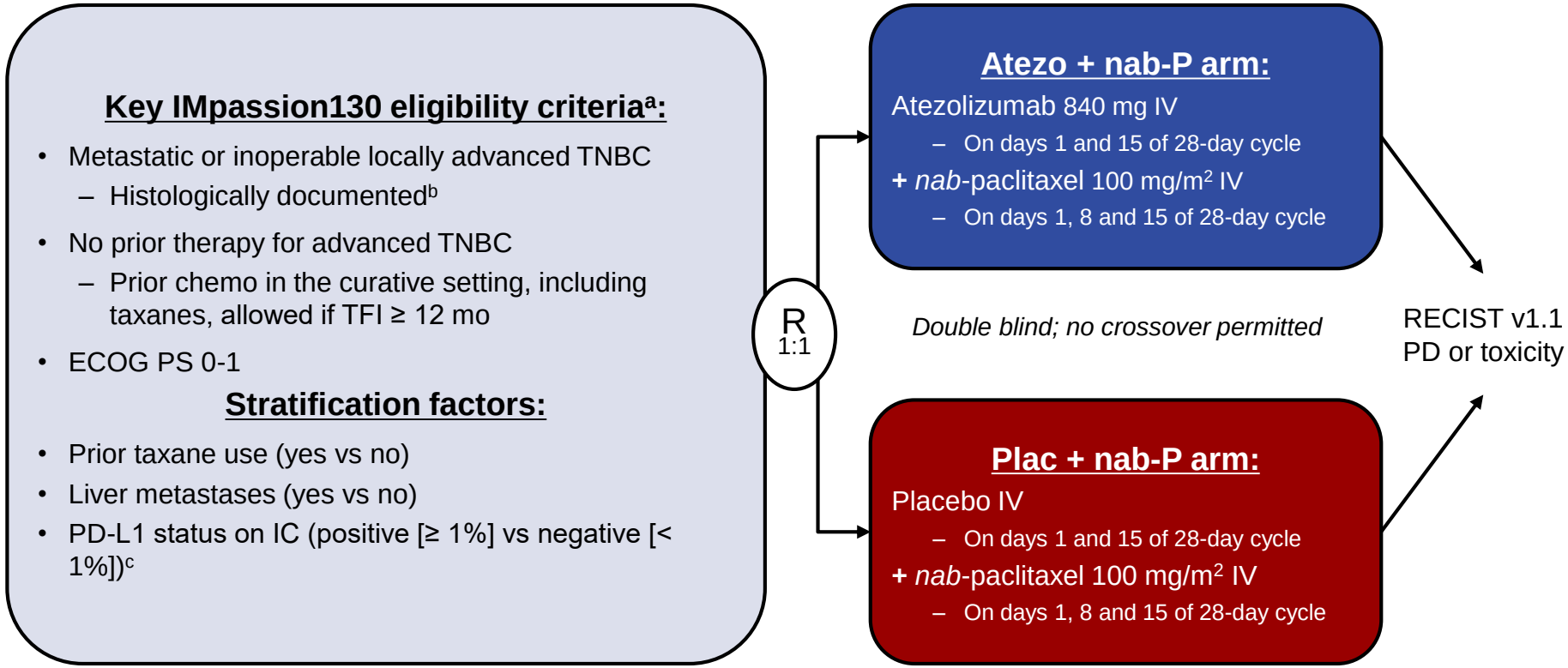
[a] Postsurgical management of patients was at the discretion of the treating investigator and based on local practice guidelines.

pCR, pathologic complete response; PD-L1 IC, PD-L1–expressing tumor-infiltrating immune cells as percentage of tumor area using the VENTANA SP142 assay; PRO, patient-reported outcome; q2w, every 2 weeks, q3w, every 3 weeks, qw, every week.

1. Mittendorf E, et al. SABCS 2017 [abstract 17-OT2-07-03]. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT03197935. Accessed 11 August 2020.

Mittendorf et al., Lancet 2020 Harbeck et al. IMpassion031 Primary Analysishttps://bit.ly/3247cn

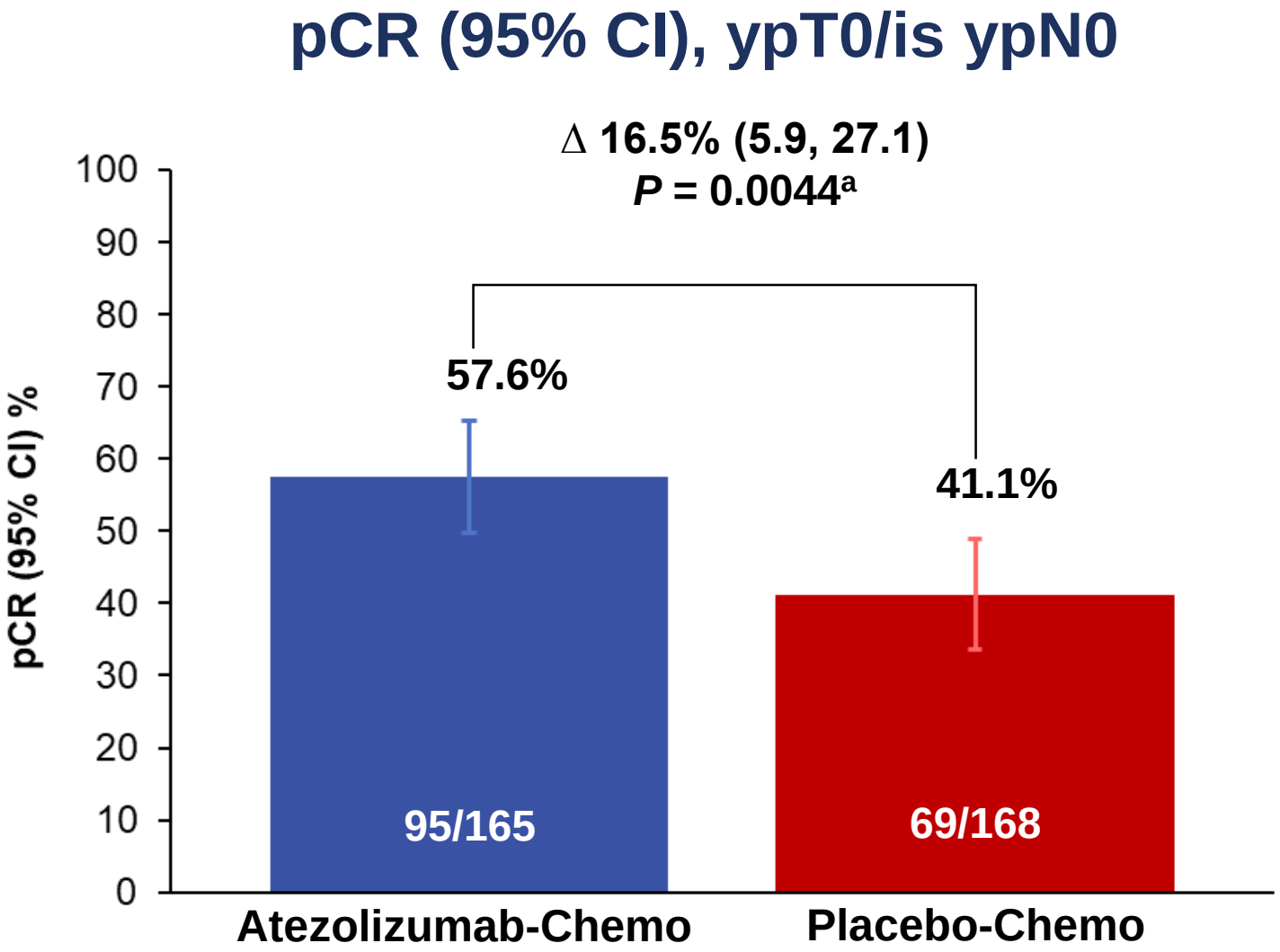
IMpassion130: Adding checkpoint inhibition to chemotherapy to enhance activity



- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

Harbeck et al. IMpassion031 Primary Analysishttps://bit.ly/3ji97cn

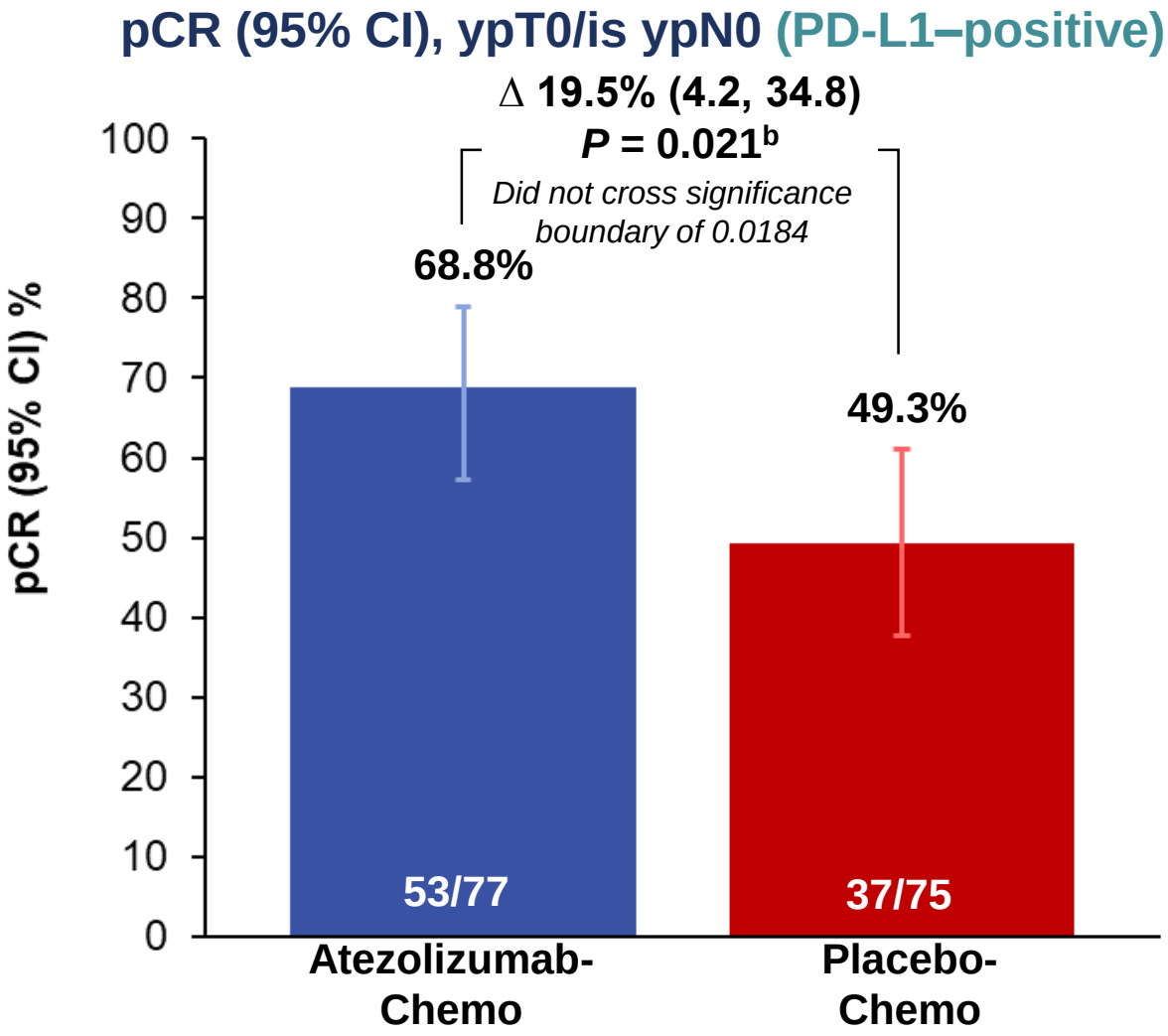
IMpassion031: Co-primary endpoint pathologic complete response (ITT)

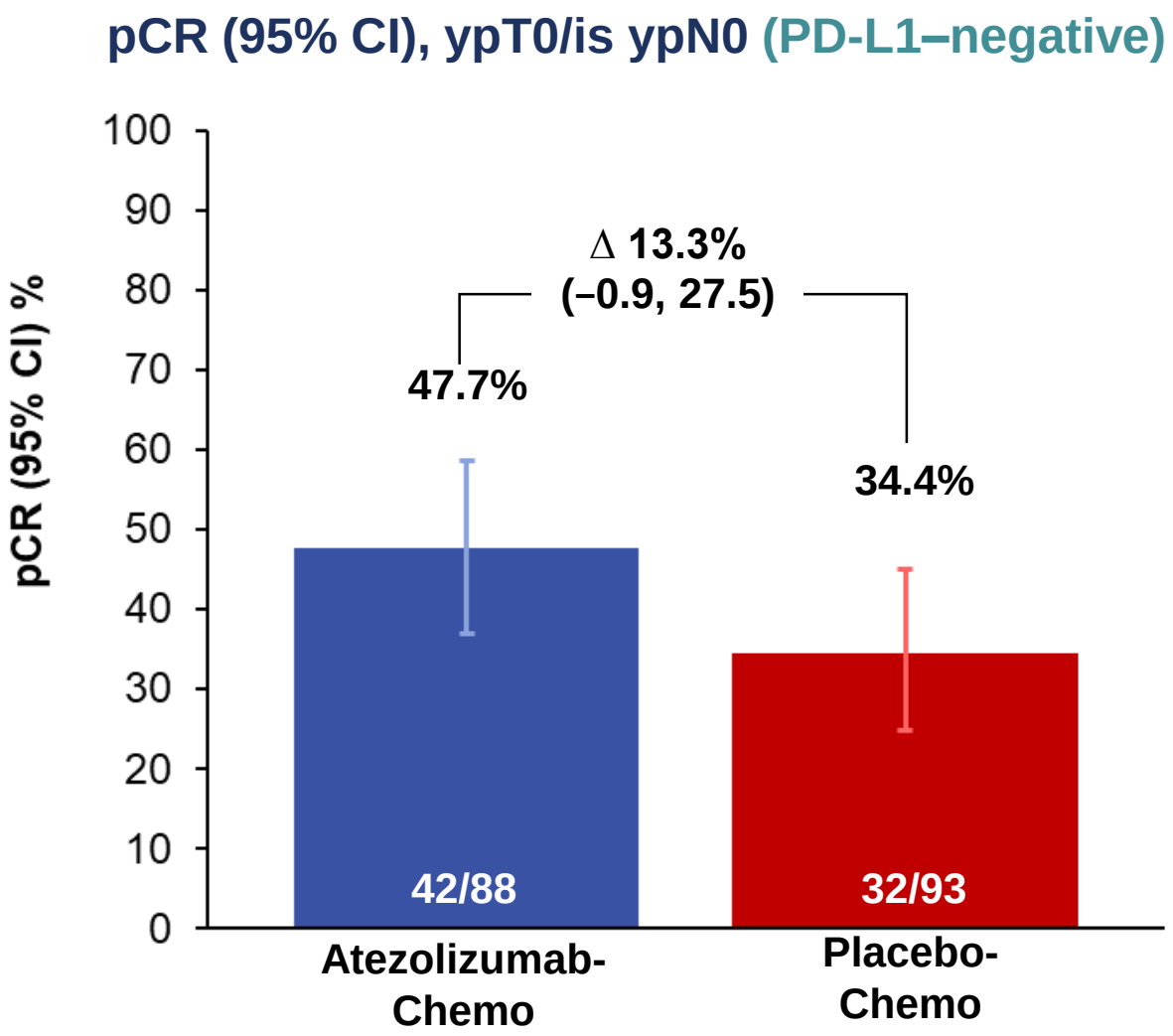


[a] One-sided significance boundary *P* = 0.0184 (accounting for the adaptive enrichment design). *P* = 0.0085 for the intersection hypothesis of pCR in the ITT and PD-L1–positive population.

Harbeck et al. IMpassion031 Primary Analysishttps://bit.ly/3ji97cn

IMpassion031: Co-primary endpoint pathologic complete response in PD-L1 positive tumours[a]





[a] PD-L1+, PD-L1 IC ≥ 1%; PD-L1–, PD-L1 IC < 1%.
[b] One-sided significance boundary *P* = 0.0184 (accounting for the adaptive enrichment design). *P* = 0.0085 for the intersection hypothesis of pCR in the ITT and PD-L1–positive population.

IMpassion031: Secondary time-to-event endpoints (ITT)[a]

		Atezolizumab-Chemo	Placebo-Chemo
EFS	Events, n/N (%)	17/165 (10.3%)	22/168 (13.1%)
	Median (95% CI)	NE (NE, NE)	NE (NE, NE)
	Stratified HR (95% CI)	**0.76** (0.40, 1.44)	
DFS	Events, n/N (%)	10/154[b] (6.5%)	13/153[b] (8.5%)
	Median (95% CI)	NE (NE, NE)	NE (NE, NE)
	Stratified HR (95% CI)	**0.74** (0.32, 1.70)	
OS	Events, n/N (%)	7/165 (4.2%)	9/168 (5.4%)
	Median (95% CI)	NE (27.40, NE)	NE (NE, NE)
	Stratified HR (95% CI)	**0.69** (0.25, 1.87)	

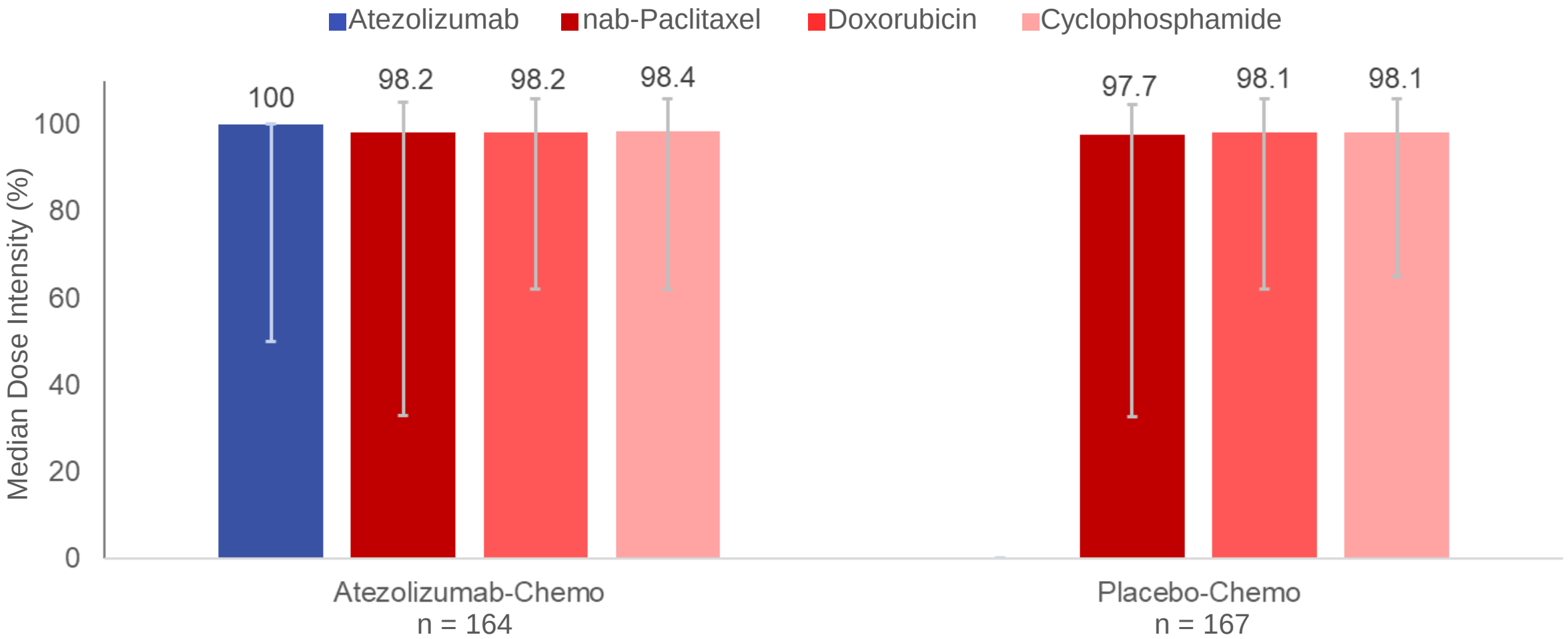
- EFS, DFS and OS trends support the pCR benefit seen for atezolizumab-chemo
- EFS, DFS and OS are immature and will continue to be collected until the final analysis per protocol

NE, not estimable.
[a] This study was not formally powered for long-term secondary efficacy time-to-event endpoints.
[b] Only patients having surgery are included.

Harbeck et al. IMpassion031 Primary Analysishttps://bit.ly/3ji97cn

IMpassion031: Treatment exposure in the neoadjuvant phase

Median dose intensity[a]



Dose intensity for a patient is defined as the total dose received over all planned cycles divided by the total planned dose.

[a] Error bars indicate range.

Harbeck et al. IMpassion031 Primary Analysishttps://bit.ly/3ji97cn

IMpassion031: Overall safety profile in the neoadjuvant phase

	Atezolizumab-Chemo (n = 164)	Placebo-Chemo (n = 167)
Number of patients ≥ 1 AE, n (%)	163 (99.4)	167 (100)
Grade 3-4, n (%)	103 (62.8)	101 (60.5)
Treatment-related Grade 3-4 AE	93 (56.7)	89 (53.3)
Grade 5, n (%)[a]	1 (0.6)	1 (0.6)
Serious AE, n (%)	50 (30.5)	30 (18.0)
Treatment-related SAE	37 (22.6)	26 (15.6)
AE leading to any treatment discontinuation, n (%)	37 (22.6)	33 (19.8)
Of atezolizumab/placebo	21 (12.8)	19 (11.4)
Of nab-paclitaxel	27 (16.5)	23 (13.8)
Of doxorubicin	8 (4.9)	10 (6.0)
Of cyclophosphamide	8 (4.9)	10 (6.0)

- Rates of treatment-related serious AEs were higher in the atezolizumab-chemo arm
- Grade 3-4 AEs and discontinuation rates were well balanced

[a] One unrelated Grade 5 AE each occurred in the atezolizumab-chemo arm (road traffic accident) and the placebo-chemo arm (pneumonia).

Harbeck et al. IMpassion031 Primary Analysishttps://bit.ly/3ji97cn

IMpassion031: Summary

- Atezolizumab + chemotherapy resulted in a statistically significant and clinically meaningful +16.5% increase in pCR rate vs placebo + chemotherapy (57.6% vs 41.1%) in the ITT population (*P* = 0.0044)
  - Benefit was observed regardless of PD-L1 status and across clinical subgroups
- Although the data are immature, trends for EFS, DFS, and OS support the pCR benefit seen with atezolizumab + chemotherapy
- The safety profile of atezolizumab + chemotherapy (nab-paclitaxel/AC) was consistent with the known risks of the individual study drugs
  - Commonly reported AEs were relatively similar between arms and mostly driven by chemotherapy
- The combination of atezolizumab with neoadjuvant chemotherapy for stage II-III TNBC provides clinically meaningful pCR benefit with an acceptable safety profile independent of PD-L1 status

Lessons Learned From Neoadjuvant Studies of Immunotherapy

	I-SPY2[1] Pembrolizumab	KEYNOTE-522[2] Pembrolizumab	NEOTRIP[3] Atezolizumab	IMpassion 031 Atezolizumab	GEPARNUEVO[4] Durvalumab
Total patients	69/181	602/1174	280	333	174
Target	PD-1	PD-1	PD-L1	PD-L1	PD-L1
Stage	II/III	II/III	Included N3	II/III	35% stage I
Anthracyclines	Yes	Yes	No	Yes	Yes
Carboplatin	No	Yes	Yes	No	No
pCR rate	60% vs 22% (graduated)	65% vs 51% (p=0.00055)	44% vs 41% (p=0.66)	58% vs 41% P=0.0044	53% vs 44% (p=0.287)

- Anthracyclines and stage are key factors determining benefit from neoadjuvant immunotherapy
- PD-L1 status does not matter when immune system is intact
- Other variables may play role, such as tumor-infiltrating lymphocytes

Slide courtesy of Sara Tolaney MD

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VIRTUAL 2020 ESMO congress

ASCENT:

A Randomized Phase 3 Study of Sacituzumab Govitecan vs Treatment of Physician's Choice in Patients With Previously Treated Metastatic Triple-Negative Breast Cancer

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ClinicalTrials.gov Number: NCT02574455.

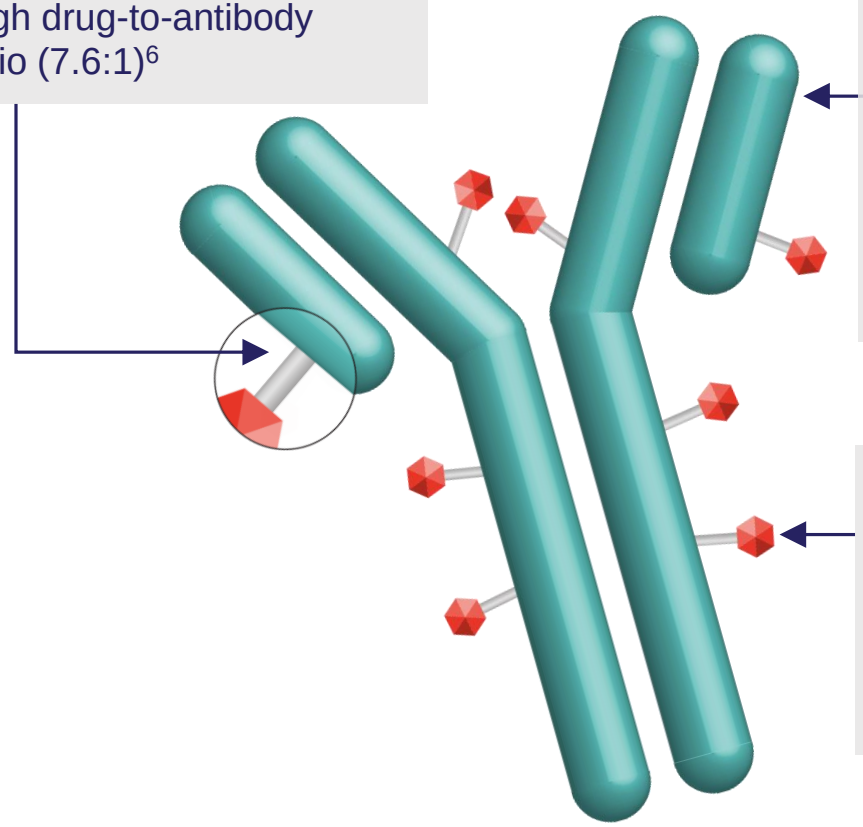
To obtain presentation, bit.ly/immu_ascent

ASCENT Clinical Trial

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

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC and fast-track designation in metastatic urothelial cancer[7]

Linker for SN-38
- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7.6:1)[6]



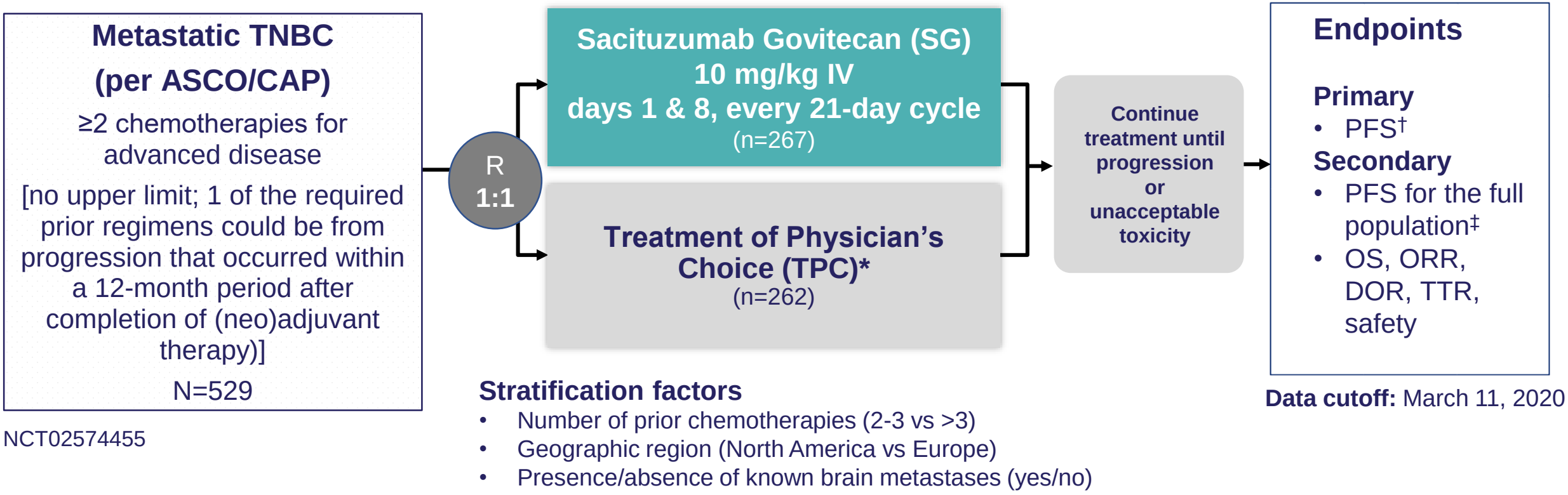
Humanized anti–Trop-2 antibody
- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

SN-38 payload
- SN-38 more potent than parent compound, irinotecan

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

1. Vidula N et al. *J Clin Oncol.* 2017;35:15(suppl):Abstract 1075. 2. Ambrogi et al. *PLoS One.* 2014;9(5):e96993. 3. Goldenberg DM et al. *Expert Opin Biol Ther*. 2020 Aug;20(8):871-885. 4. Nagayama A et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 5. Cardillo TM et al. *Bioconjugate Chem.* 2015;26:919-931. 6. Goldenberg DM et al. *Oncotarget.* 2015;6:22496-224512. 7. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020.

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



NCT02574455

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

Data cutoff: March 11, 2020

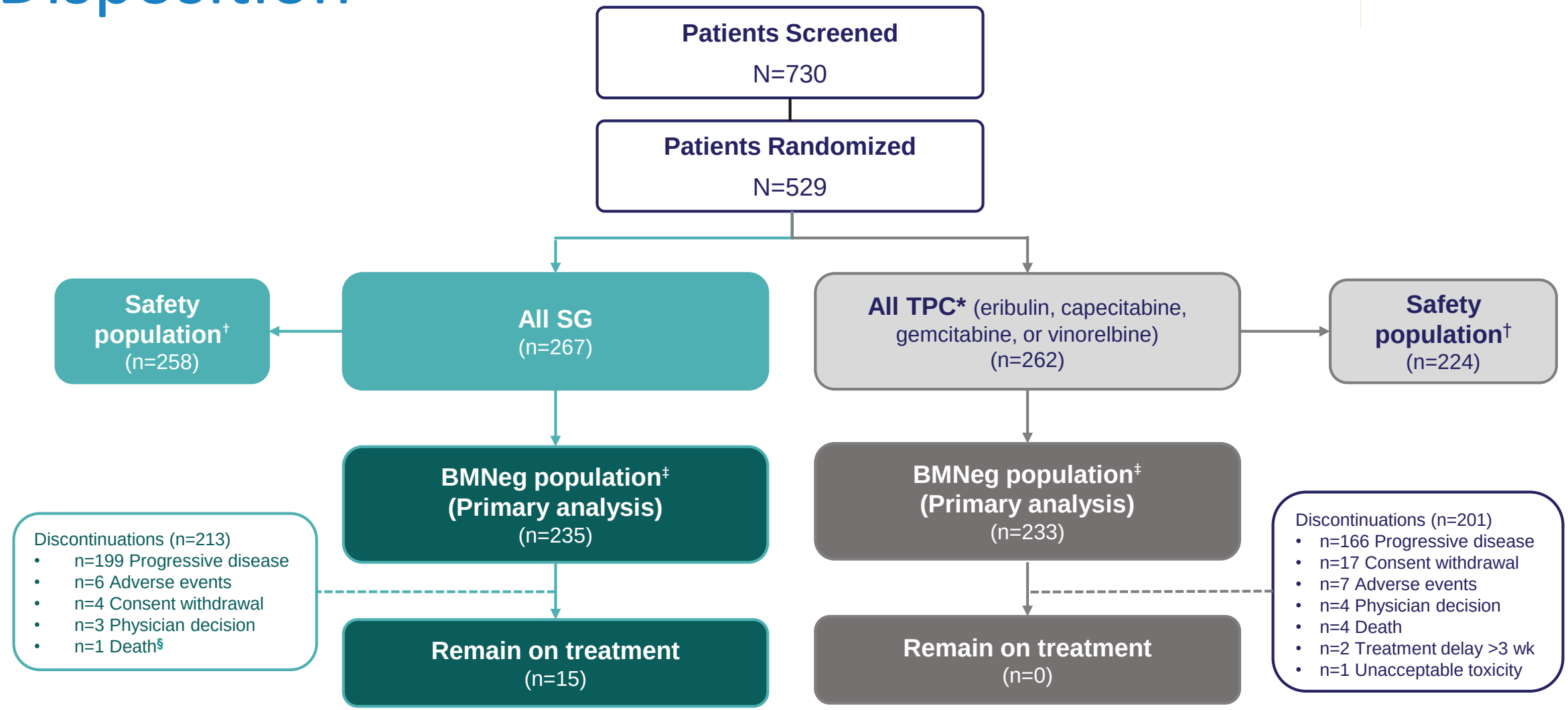
ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation. Here, we report the primary results from ASCENT, including PFS and OS.

*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.

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

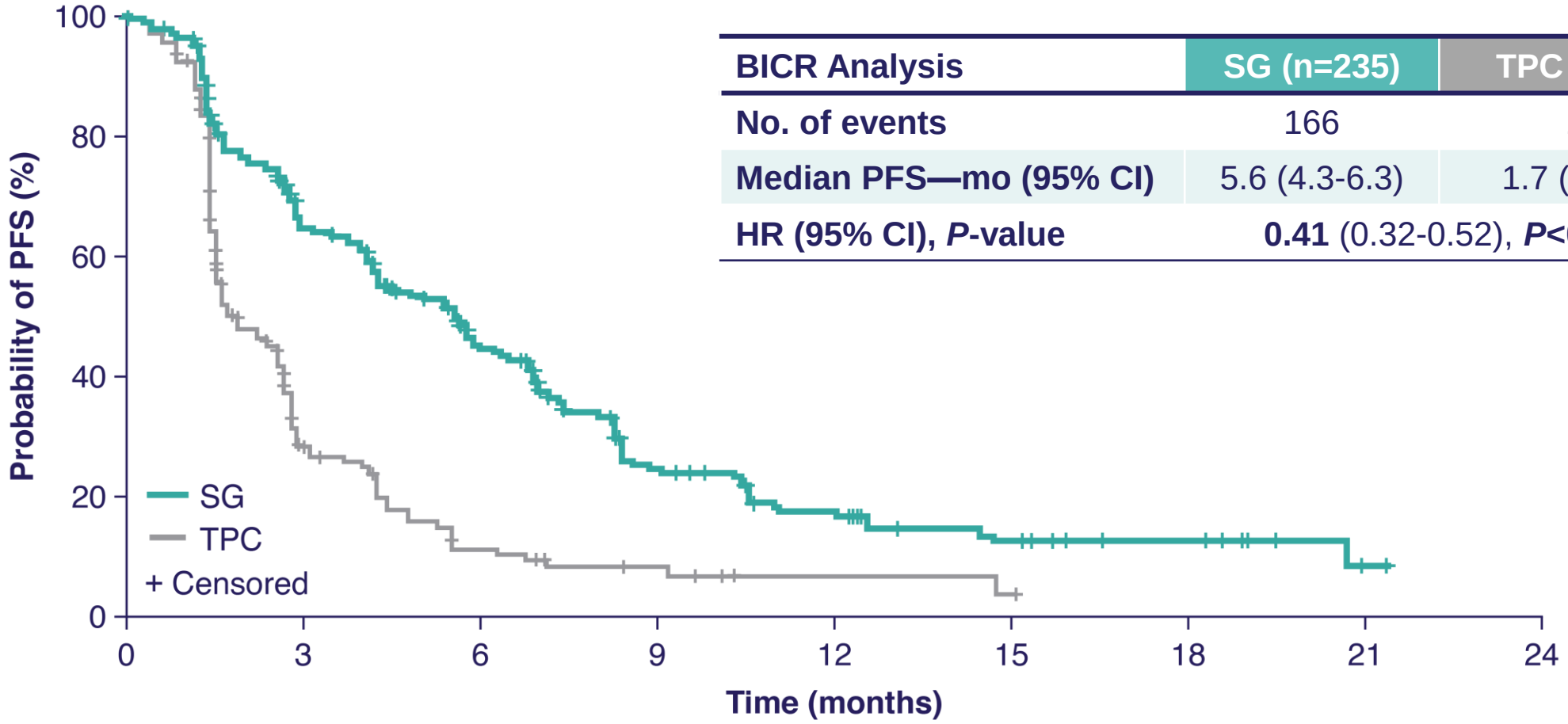
Disposition



*Patients in the TPC arm were randomized to: eribulin (n=139); vinorelbine (n=52); gemcitabine (n=38); capecitabine (n=33).

†All patients who received ≥1 dose of study treatment. ‡Seven pts in the SG arm and 32 pts in the TPC arm were randomized but not treated in the brain metastases-negative population.
§This was considered unlikely to be related to SG treatment.
BMNeg, brain metastases-negative; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Progression-Free Survival (BICR Analysis)



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

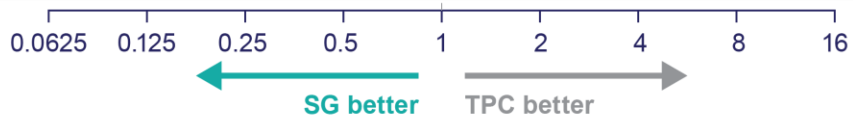
Number of patients at risk

SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

Primary endpoint (PFS) assessed by independent central review in the brain metastases-negative population, as pre-defined in the study protocol.
Secondary endpoint (PFS) assessed in the full population (brain metastases-positive and -negative) and PFS benefit was consistent (HR=0.43 [0.35-0.54], *P*<0.0001).
BICR, blind independent central review; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Progression-Free Survival by Subgroup

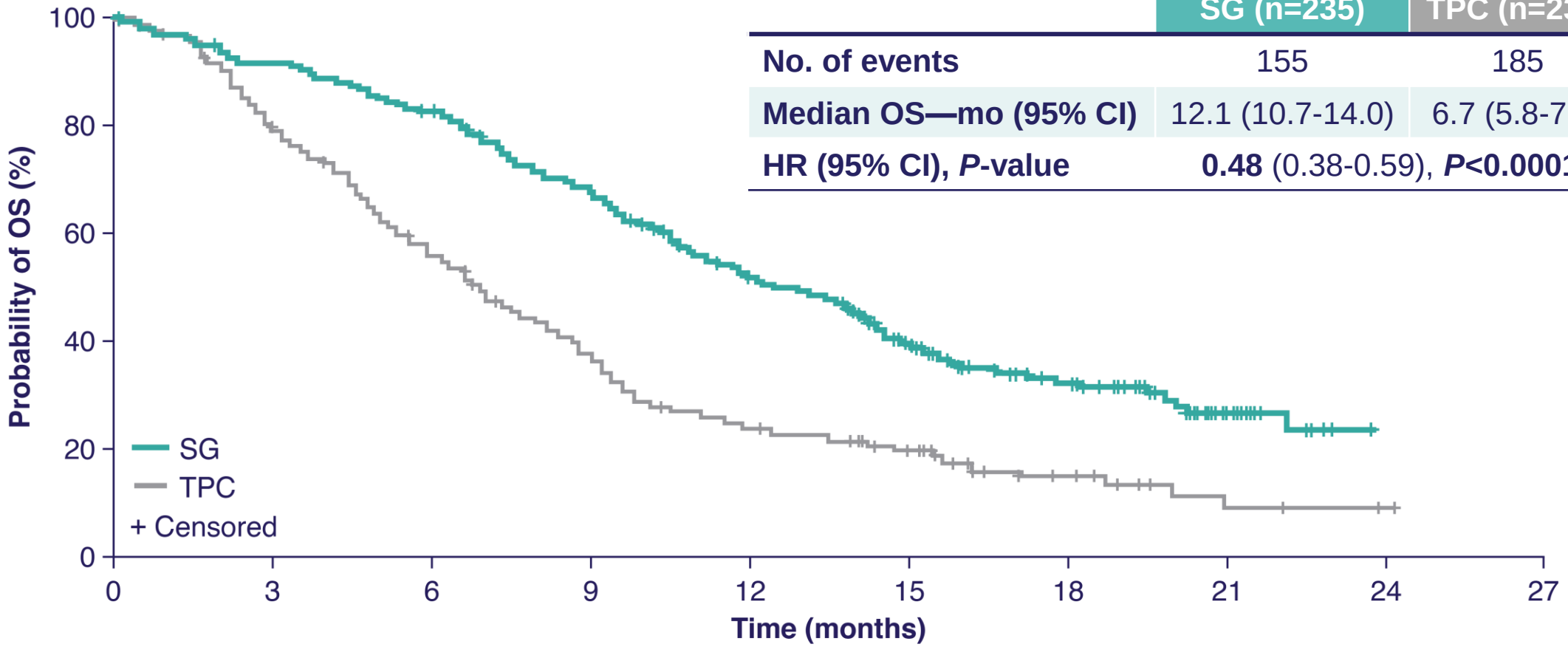
Subgroup	Median PFS, Months (95% CI) SG	TPC	HR (95% CI)	P value
Overall (n=468)	5.6 (4.3–6.3)	1.7 (1.5–2.6)	0.41 (0.33–0.52)	<0.0001
Age Group				
<65 (n=378)	4.6 (3.7–5.7)	1.7 (1.5–2.5)	0.46 (0.35–0.59)	<0.0001
≥65 (n=90)	7.1 (5.8–8.9)	2.4 (1.4–2.9)	0.22 (0.12–0.40)	<0.0001
Race				
White (n=369)	5.7 (4.3–6.8)	1.7 (1.5–2.6)	0.39 (0.30–0.51)	<0.0001
Black (n=56)	5.4 (2.8–7.4)	2.2 (1.5–2.9)	0.45 (0.24–0.86)	0.0152
Asian (n=18)	NE (1.3–NE)	1.5 (1.2–NE)	0.40 (0.08–2.08)	0.2781
Prior Therapies				
2-3 (n=330)	5.8 (4.2–7.1)	1.6 (1.5–2.5)	0.39 (0.29–0.52)	<0.0001
>3 (n=138)	5.6 (3.0–6.5)	2.5 (1.5–2.8)	0.48 (0.32–0.72)	0.0004
Region				
North America (n=298)	4.9 (4.0–6.3)	2.0 (1.5–2.6)	0.44 (0.33–0.60)	<0.0001
Rest of World (n=170)	5.9 (4.2–6.9)	1.6 (1.4–2.7)	0.36 (0.24–0.53)	<0.0001
Prior PD-L1/PD-1 use				
Yes (n=127)	4.2 (3.2–5.6)	1.6 (1.4–2.3)	0.37 (0.24–0.57)	<0.0001
No (n=341)	6.2 (4.9–7.1)	2.1 (1.5–2.7)	0.42 (0.32–0.56)	<0.0001
Liver Metastases				
Yes (n=199)	4.2 (2.8–5.8)	1.5 (1.4–2.4)	0.48 (0.34–0.67)	<0.0001
No (n=269)	6.8 (4.6–8.0)	2.3 (1.6–2.7)	0.36 (0.26–0.50)	<0.0001
Initial Diagnosis TNBC				
Yes (n=322)	5.7 (4.3–6.9)	1.6 (1.5–2.6)	0.38 (0.29–0.51)	<0.0001
No (n=146)	4.6 (3.7–6.9)	2.3 (1.5–2.8)	0.48 (0.32–0.72)	0.0004



Assessed by independent central review in brain metastases-negative population.
HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Overall Survival

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



Number of patients at risk

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

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

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

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

- Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%)
  - G-CSF usage was 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)
- No severe cardiovascular toxicity, no grade >2 neuropathy or grade >3 interstitial lung disease with SG
- No treatment-related deaths with SG; 1 treatment-related death (neutropenic sepsis) with TPC
- AEs leading to treatment discontinuation were low for SG and TPC: 4.7% and 5.4%
- Patients received a median of 7 treatment cycles of SG, with a median treatment duration of 4.4 months (range, 0.03-22.9)

*Patients may report more than 1 event per preferred term. AEs were classified according to the MedDRA systems of preferred terms and system organ class and according to severity by NCI CTCAE v4.03. †Combined preferred terms of 'neutropenia' and 'decreased neutrophil count'. ‡Combined preferred terms of 'anemia' and 'decreased hemoglobin'. §Combined preferred terms of 'leukopenia' and 'decreased white blood cell count'.
G-CSF, granulocyte-colony stimulating factor; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related AE.

Conclusions

- ASCENT is the first phase 3 study with Trop-2–directed ADC (sacituzumab govitecan [SG]) in pretreated mTNBC to demonstrate a significant improvement over standard single-agent chemotherapy:
  - Median PFS of 5.6 vs 1.7 months (**HR 0.41**, ***P*<0.0001)**
  - Median OS of 12.1 vs 6.7 months (**HR 0.48**, ***P*<0.0001)**
  - ORR of 35% vs 5%
  - ORR, PFS, and OS benefit across all subgroups

- SG was well tolerated, with a manageable safety profile consistent with previous reports[1]
  - AE leading to treatment discontinuation was low (4.7%)
  - No severe cardiovascular toxicity, no grade >2 neuropathy or >3 interstitial lung disease
  - No treatment-related deaths reported

- The randomized phase 3 study results confirm that SG should be considered as a new standard of care in patients with pretreated mTNBC

- Ongoing studies are evaluating SG in earlier lines of therapy including neoadjuvant and adjuvant setting, in combination with other targeted agents, and in patients with HR+ MBC (phase 3, TROPiCS-02)

ADC, antibody-drug conjugate; AE, adverse event; HR+, hormone receptor-positive; MBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan.

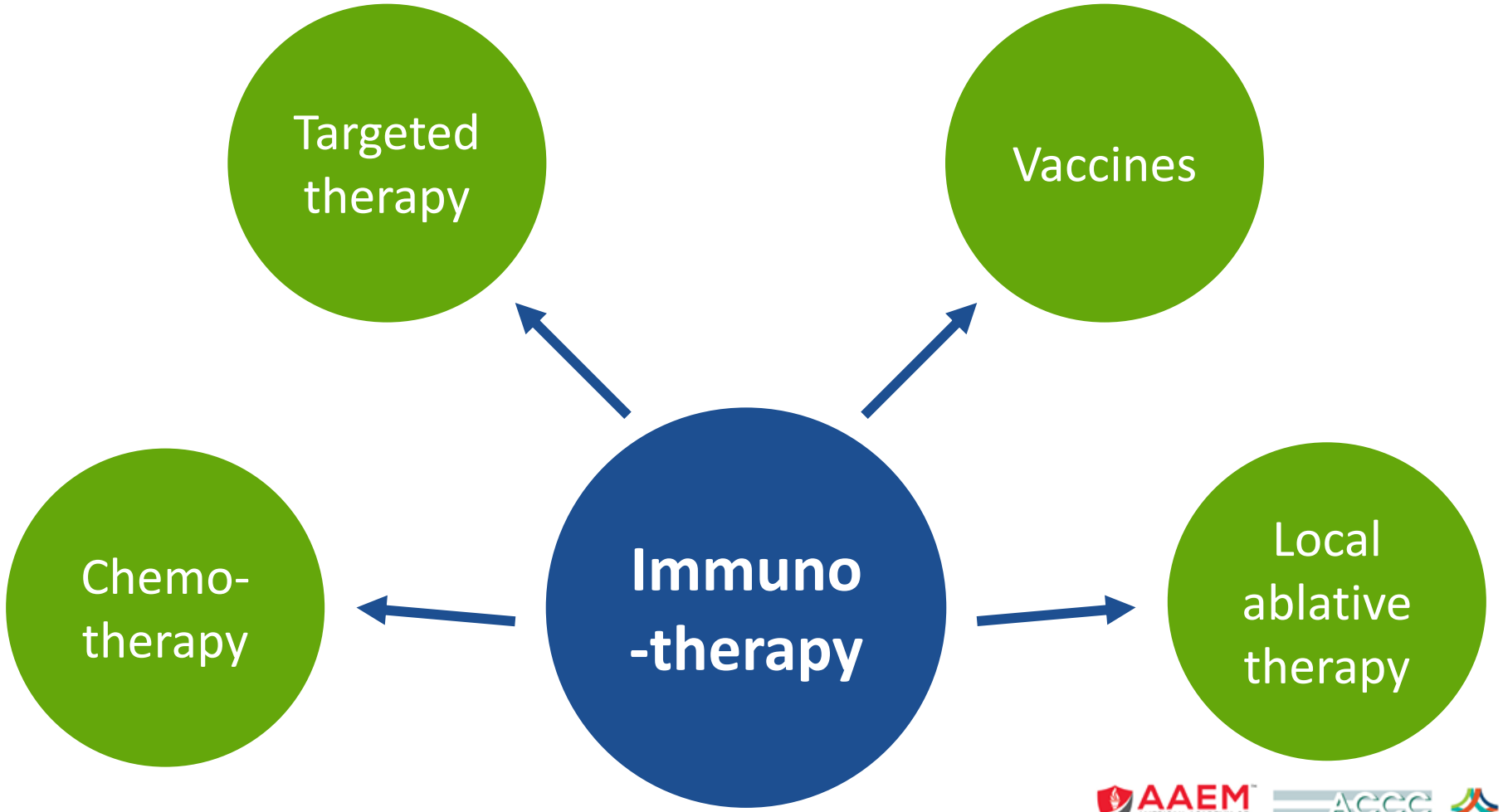
1. Bardia A et al. *N Engl J Med*. 2019;380:741-751.

Outline

- Overview of current landscape
- Metastatic breast cancer
  - Atezolizumab
  - Pembrolizumab
- Preoperative therapy
- Sacituzumab
- Future directions
- Cases

Future Directions

In development: Breast cancer immunotherapy



Adams, JAMA Oncol 2019.

In development: Breast cancer immunotherapy outside of TNBC

Trial	Population	Arms	Status
NCT03199885	1st line HER2+ metastatic breast cancer	• Pertuzumab + trastuzumab + paclitaxel + atezolizumab • Pertuzumab + trastuzumab + paclitaxel + placebo	Recruiting
KEYNOTE-756	Neoadjuvant ER+/HER2- breast cancer	• Pembrolizumab + chemo → pembrolizumab + endocrine therapy • Placebo + chemo → placebo + endocrine therapy	Recruiting
And many more			

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Case Studies

Case Study 1

- 43 year old female presents with new breast mass, shortness of breath. Further work-up reveals a 4cm breast mass; CT scan revealed 4 pulmonary nodules, largest measuring 3cm. Biopsy of lung nodule was consistent with triple negative breast cancer. PDL1 in immune cells is positive. Germline mutation testing is negative for pathogenic mutations. What would be your treatment recommendation?

1. Capecitabine
2. Nab-paclitaxel
3. Nab-paclitaxel with atezolizumab
4. Gemcitabine with carboplatin
5. Halaven

Although each of these agents is active in triple negative breast cancer, nab-paclitaxel with atezolizumab has shown improvement in overall survival compared with nab-paclitaxel alone for PDL-1 positive triple negative breast cancer. Reference: Schmid et al., Engl J Med. 2018 Nov 29;379(22):2108

Case Study 2

- 60 year old female was diagnosed with a T2N1M0 triple negative invasive ductal carcinoma of the left breast 3 years ago. Germline mutation testing revealed a germline *BRCA1* mutation. She underwent preoperative therapy with dose-dense doxorubicin and cyclophosphamide with paclitaxel followed by left axillary lymph node dissection and bilateral mastectomies. Pathology revealed no residual disease in the breast, but 1 lymph node was consistent with macrometastasis. She received 8 cycles of adjuvant capecitabine. She presented with right upper quadrant pain after 18 months and was found to have recurrent triple negative breast cancer. PDL1 testing was negative, and CPS score was 0. MSI stabie. She underwent therapy with talazoparib followed by halaven. What would be next therapeutic choice?

1. Paclitaxel and pembrolizumab
2. Nab-paclitaxel and atezolizumab
3. sacituzumab govitecan
4. Capecitabine

Pembrolizumab and atezolizumab are not indicated due to no improvement in outcomes in this clinical situation. Immunotherapy is most active when given earlier in the disease course with appropriate biomarkers. Sacituzumab improves overall survival when compared with physician's choice chemotherapy.

Bardia et al., Engl J Med. 2019 Feb 21;380(8):741-751; Bardia et al., ESMO Proceedings 2020

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Thank You!