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Immunotherapy for the Treatment of Triple Negative 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

- I have nothing to disclose.
- I will be discussing non-FDA approved indications during my presentation.

Triple negative breast cancer (TNBC)

- Standard-of-care treatment usually involves surgery, chemotherapy, radiation.
- TNBC accounts for 10-20%.
- Overall survival 12-18 months.
- Application of immunotherapy is still in early stages.

Estimated new cases

Female

Breast	281,550	30%
Lung & bronchus	116,660	13%
Colon & rectum	69,980	8%
Uterine corpus	66,570	7%
Melanoma of the skin	43,850	5%
Non-Hodgkin lymphoma	35,930	4%
Thyroid	32,130	3%
Pancreas	28,480	3%
Kidney & renal pelvis	27,300	3%
Leukemia	25,560	3%
All sites	**927,910**	

Estimated deaths

Female

Lung & bronchus	62,470	22%
Breast	43,600	15%
Colon & rectum	24,460	8%
Pancreas	22,950	8%
Ovary	13,770	5%
Uterine corpus	12,940	4%
Liver & intrahepatic bile duct	9,930	3%
Leukemia	9,760	3%
Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	8,100	3%
All sites	**289,150**	

American Cancer Society 2021.

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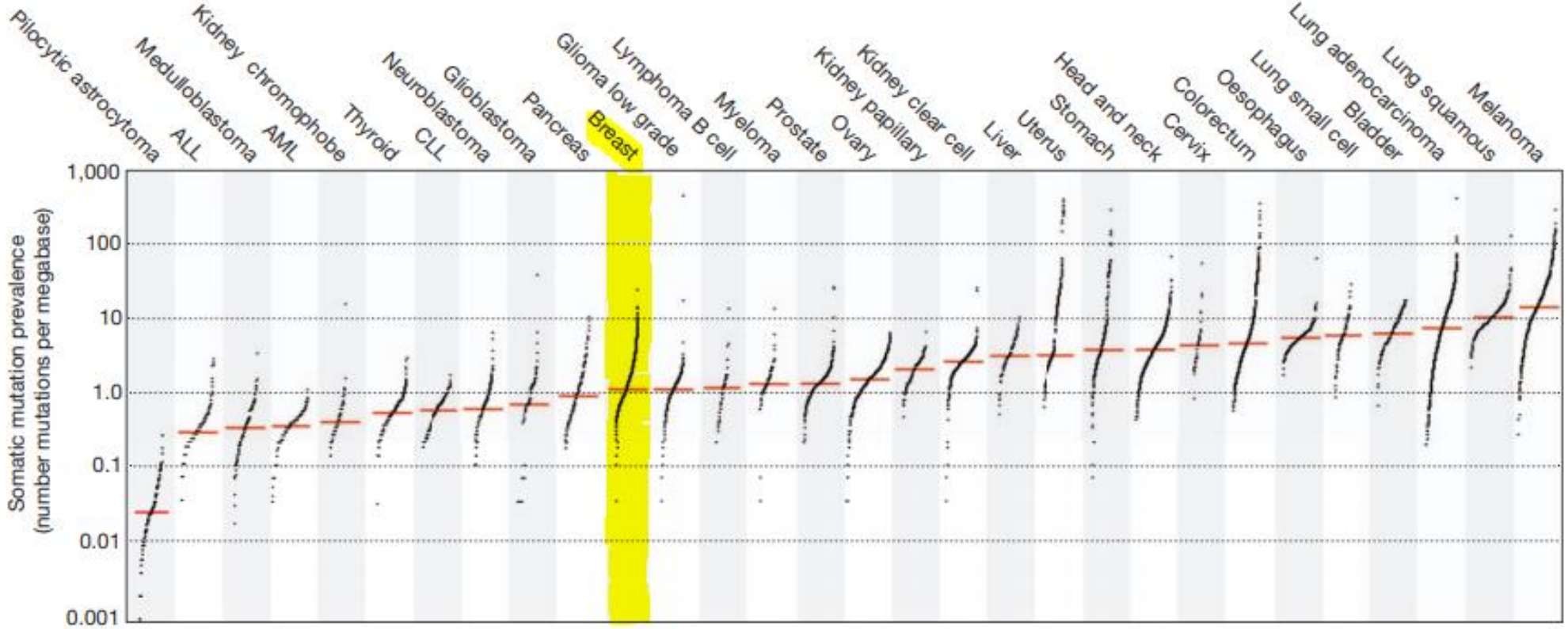
Immunotherapy in breast cancer



- TNBC is heterogeneous and chemotherapy alone is inadequate for many patients.

Alexandrov, Nature 2013.

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Outline

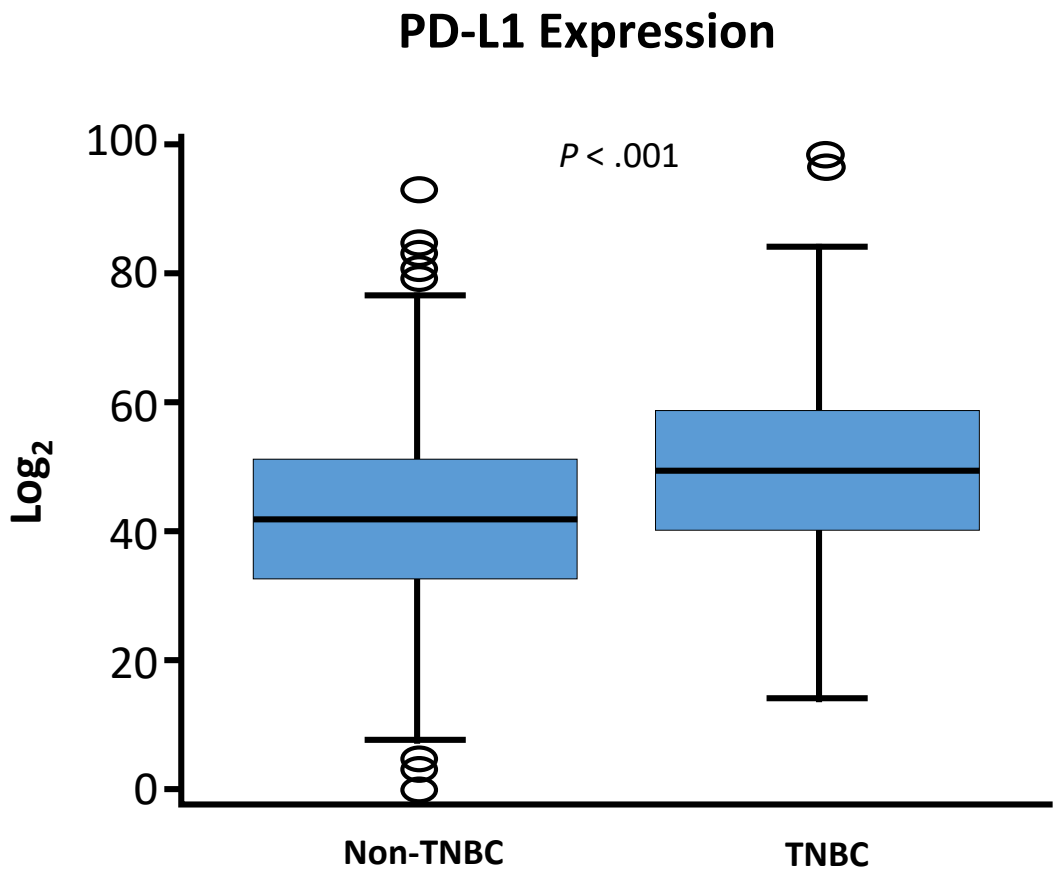
- Triple negative breast cancer
  - Biomarkers and immunotherapy responsiveness
  - Approvals
  - In the pipeline

Biomarkers

Molecular Biomarker	% TNBC	Main Function	Prognostic	Treatment
BRCA1 and BRCA2 mutation	11-31% (germline)	DNA double-strand break repair	Increased DFS	PARP inhibitors
PD-L1 expression	15-30%	Tumor immune evasion	Improved OS, higher sensitivity to chemo	Immune checkpoint inhibitors
Microsatellite instability (MSI-H/dMMR)	0-1.5% (all breast cancers)	High immunogenic activity	Response to pembro	Pembrolizumab (FDA approved)
Tumor mutational burden (TMB)	3.1-5% (all breast cancers)	Tumor antigenicity	Sensitivity to PD-1 inhibitors	Immune checkpoint inhibitors
Tumor infiltrating lymphocytes (TILs)	~20%	Immune response against tumor	Favorable survival, higher sensitivity to chemo	N/A

Cocco et al, Int J Mol Sci. 2020; 21(13):4379

Biomarkers and immunotherapy responsiveness in TNBC – PD-L1



	Atezolizumab	Pembrolizumab
PD-L1 Clone	SP142	22C3
PD-L1 IHC Manufacturer	Roche/Ventana	Agilent/Dako
Scoring System	Immune cell (IC) score	Combined positive score (CPS)
Cutoff	≥ 1% of tumor area	≥ 10 mut/Mb

CPS = (# of PD-L1 positive cells / total # of tumor cells) x 100

These assays are not interchangeable.

Mittendorf et al. Cancer Immunol Res. 2014;2:361.

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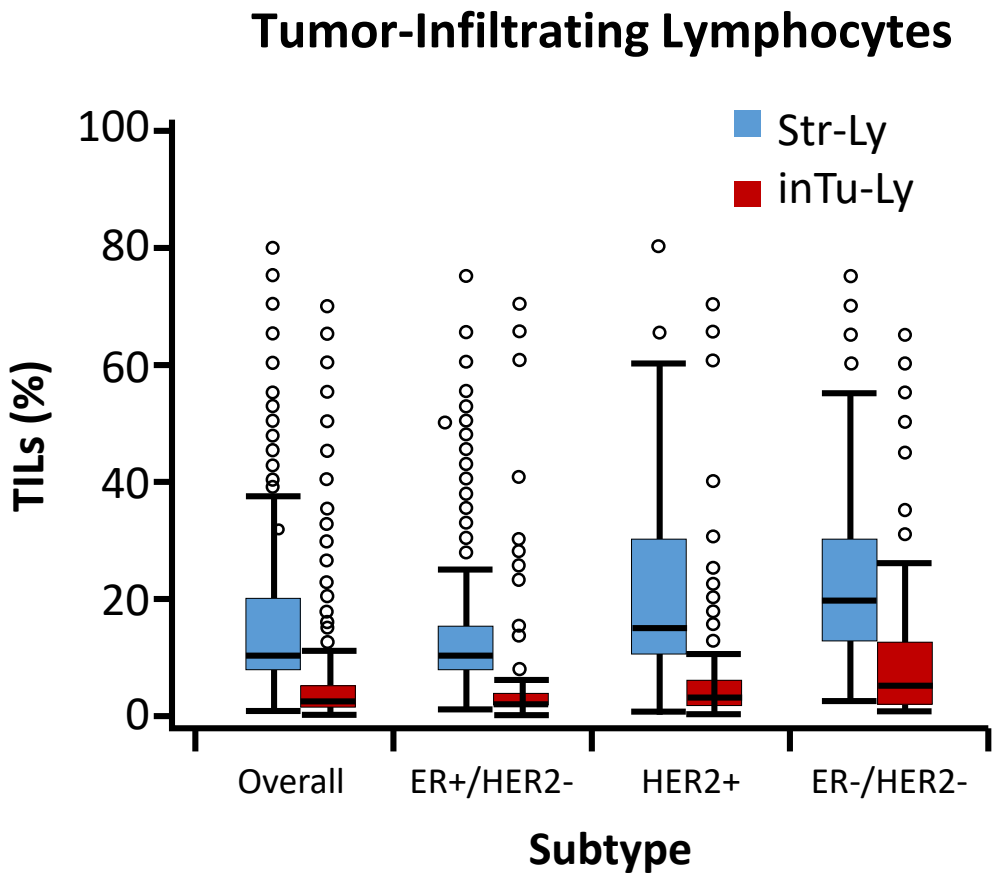
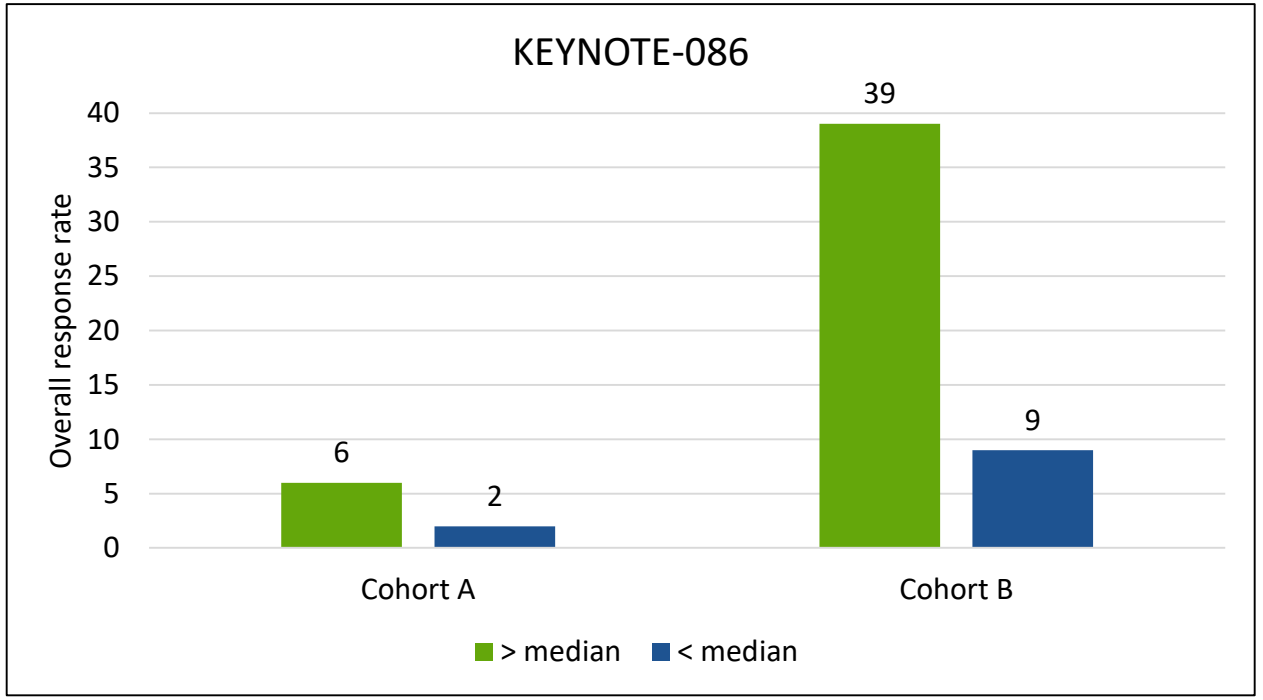
Biomarkers and immunotherapy responsiveness in TNBC – TILs





Loi et al. J Clin Oncol 2013.31(7): 860-7. Adams, Ann Oncol 2019. 30(3):405-11.

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Biomarkers and immunotherapy responsiveness in TNBC – TMB

Outcome	TMB ≥ 10 mut/Mb (n=26)		TMB < 10 mut/Mb (n=227)	
	Pembro (n=14)	Chemo (n=12)	Pembro (n=118)	Chemo (n=109)
ORR % (95% CI)	14.3 (4.0-39.9)	8.3 (0.4-35.4)	12.7 (7.9-19.9)	12.8 (7.8-20.4)
PFS, HR (95% CI)	1.14 (0.42-3.07)	--	1.24 (0.92-1.67)	--
OS, HR (95% CI)	0.58 (0.21-1.57)	--	0.81 (0.61-1.07)	--

Prevalence of TMB ~10%

- Although this is a small sample size, TMB ≥ 10 mut/Mb was associated with clinical benefit from pembrolizumab.

Winer et al. ASCO 2020. Abst 1013.

Outline

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Current approvals in breast cancer

Checkpoint inhibitor	Approved	Indication	Dose
Pembrolizumab	2017	MSI-H/dMMR **advanced cancer** with progression on previous treatment	200 mg Q3W or 400 mg Q6W
Atezolizumab + nab-paclitaxel	2019	Advanced/Metastatic **TNBC** with PD-L1 ≥1% immune cells	840 mg atezolizumab Q2W + 100 mg/m^2 nab-paclitaxel on days 1, 8, 15
Pembrolizumab	2020	TMB-high **solid tumors** with progression on prior treatment	200 mg Q3W or 400 mg Q6W
Pembrolizumab + chemo	2020	Advanced/Metastatic **TNBC** with PD-L1 ≥ 10	200 mg Q3W or 400 mg Q6W
Antibody-drug conjugate	**Approved**	**Indication**	**Dose**
Ado-trastuzumab emtansine	2019	Adjuvant treatment of **HER2-positive** early breast cancer	3.6 mg/kg Q3W
Fam-trastuzumab deruxtecan-nxki	2019	Unresectable/metastatic **HER2-positive** breast cancer after 2+ HER2 regimens	5.4 mg/kg Q3W
Sacituzumab govitecan	2020	Metastatic **TNBC** after two previous therapies	10mg/kg on D1&D8 of 21-day cycle

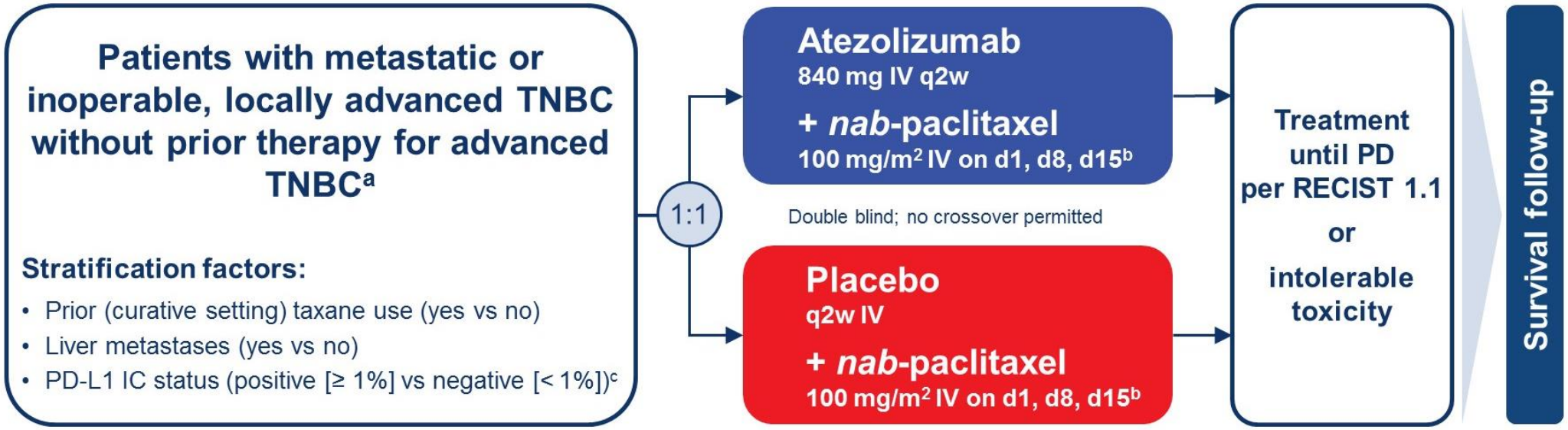
Clinical trials in metastatic TNBC (mTNBC)

Trial	Phase	Treatment arm(s)	Patient selection criteria	N	ORR, %	Median PFS, mo (95% CI)	Median OS, mo (95% CI)
KEYNOTE 012	Ib	Pembrolizumab	Heavily pretreated (≥ 2 lines), advanced TNBC PD-L1 + stroma/≥ 1% tumor cells	32	18.5	1.9 (1.7-5.5)	11.2 (5.3 –NR)
KEYNOTE-086	II	Pembrolizumab	Metastatic TNBC at 2nd line or greater	170	5.3	2.0 (1.9-2.0)	9.0 (7.6-11.2)
			PD-L1+ metastatic TNBC without prior therapy	84	21.4	2.1 (2.0-2.2)	18 (12.9-23.0)
KEYNOTE 119	III	Pembrolizumab vs chemo	Pretreated (1-2 lines), mTNBC, CPS ≥ 1 or < 1	622	9.6 vs 10.6	2.1 vs 3.3 HR=1.6	9.9 vs 10.8, HR=0.97
			CPS ≥ 10	194	17.7 vs 9.2	2.1 vs 3.4 HR=1.14	12.7 vs. 11.6 HR=0.78
			CPS ≥ 20	109	26.3 vs 11.5	3.4 vs 2.4 HR=0.76	14.9 s 12.5 HR=0.58
JAVELIN	Ib	Avelumab	Pretreated (≤ 3 lines) advanced or metastatic TNBC	58	5.2	5.9 (5.7-6.9)	9.2 (4.3-NR)
			≥ 10% immune cells	9	22.2		
			< 10% immune cells	39	2.6		

- Single-agent immunotherapy efficacy remains low (~5-25%).
  - Improved response in treatment naïve patients.

J Clin Oncol. 2016; 34(21):2460-7. Ann Oncol 2019;30(S5):v851-934. Ann Oncol 2019;30(3):405-11. Ann Oncol 2019;30(3):397-404. Breast Cancer Res Treat. 2018; 167(3):671-86.

IMpassion130 – Study design



- 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 et al, NEJM 2018. 379:2108-21.

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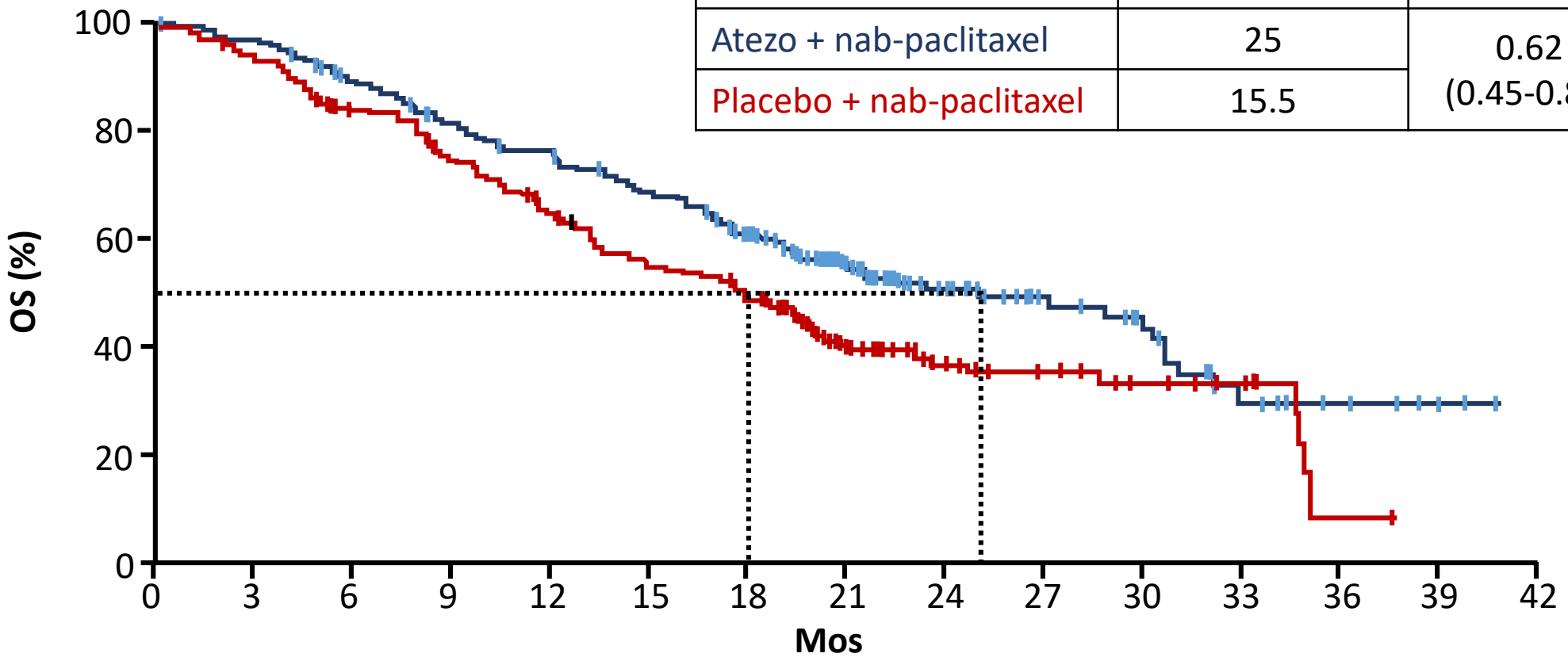
IMpassion130 – OS in PD-L1 (+) subgroup

Population	Median OS, mo	HR (95% CI)	2 year OS, %
Atezo + nab-paclitaxel	25	0.62 (0.45-0.86)	53.5
Placebo + nab-paclitaxel	15.5		36.6



Schmid et al, NEJM 2018. 379:2108-21.

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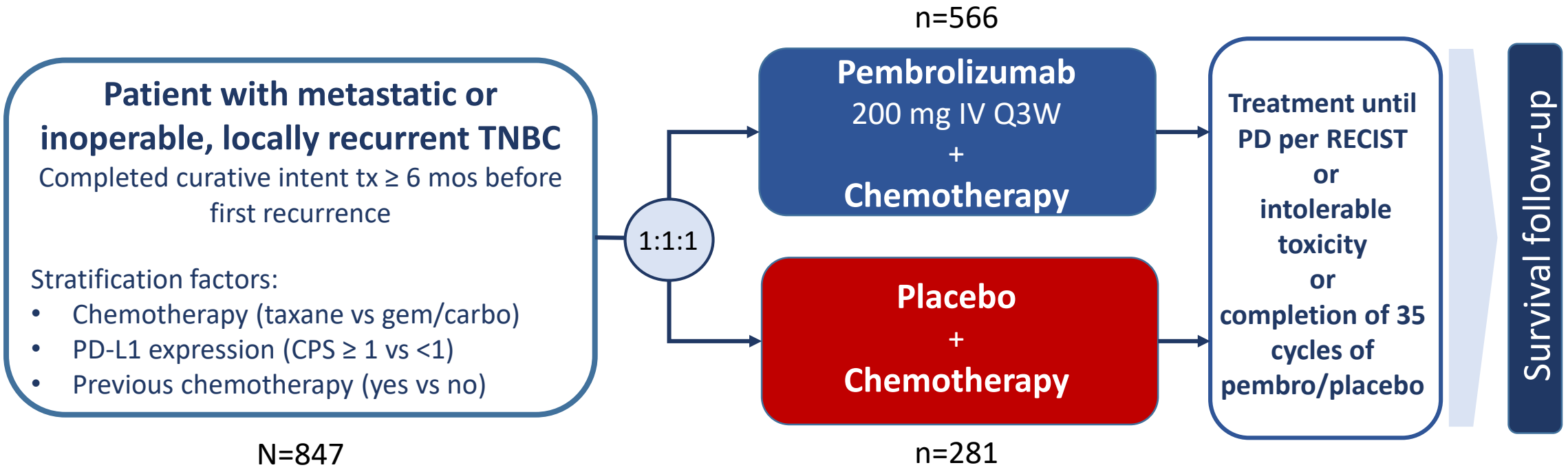
KEYNOTE-355 – Study design



- Chemotherapy investigator's choice:
  - Nab-paclitaxel 100 mg/m^2 IV days 1, 8, 15 of 28 day cycle
  - Paclitaxel 90 mg/m^2 IV days 1, 8, 15 of 28 day cycle
  - Gem 1000 mg/m^2 + carbo AUC 2 days 1, 8 of 21 day cycle

- Primary endpoint: PFS and OS
- PD-L1 CPS ≥ 10, CPS ≥ 1, ITT

Cortez et al, Lancet 2020; 396: 1817-28.

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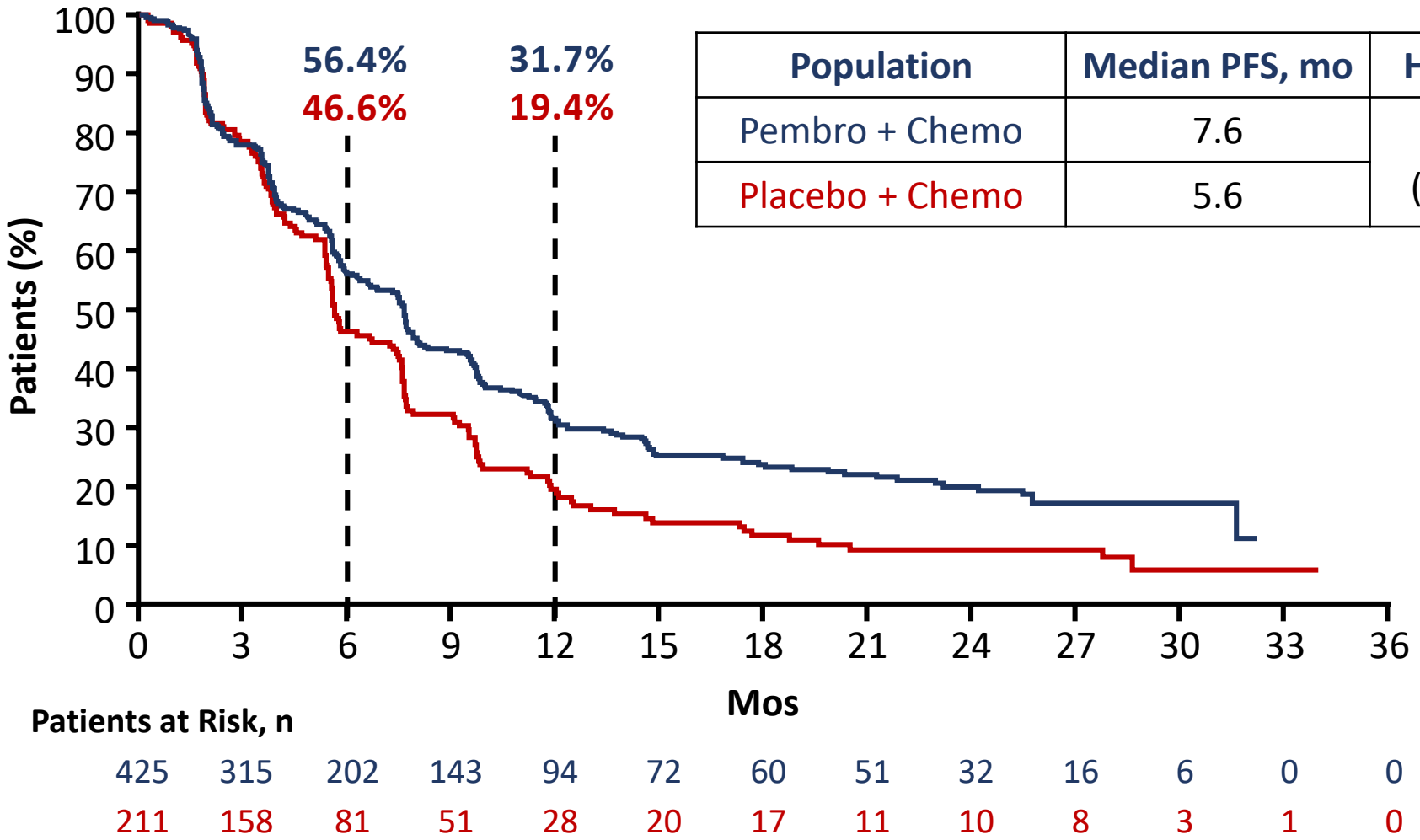
KEYNOTE-355 – PFS in PD-L1 ≥ 1



Population	Median PFS, mo	HR (95% CI)	P value
Pembro + Chemo	7.6	0.74 (0.61-0.90)	0.0014 (NS)
Placebo + Chemo	5.6		

Cortez et al, Lancet 2020; 396: 1817-28.

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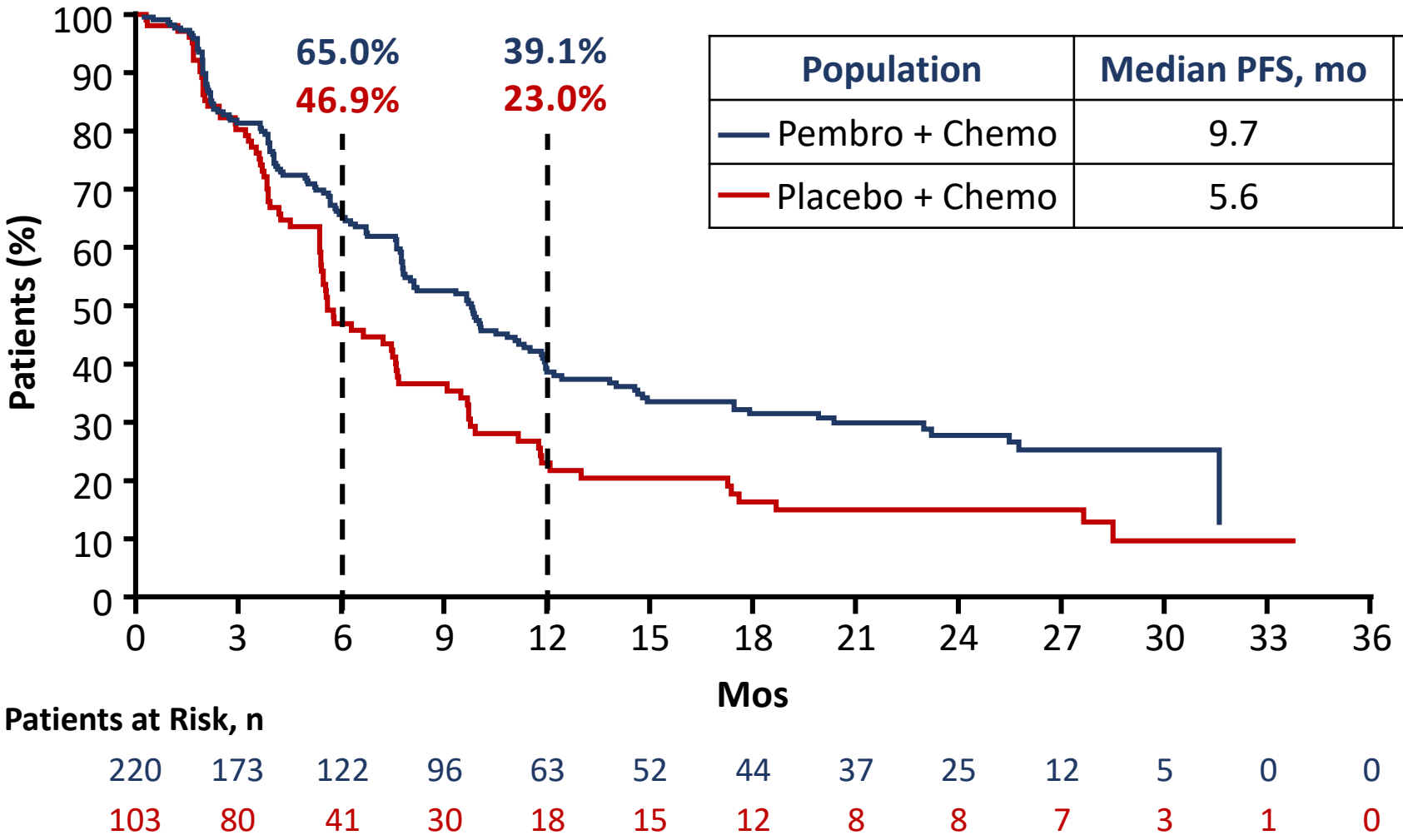
KEYNOTE-355 – PFS in PD-L1 ≥ 10



Population	Median PFS, mo	HR (95% CI)	P Value
Pembro + Chemo	9.7	0.65 (0.49-0.86)	0.0012
Placebo + Chemo	5.6		

Cortez et al, Lancet 2020; 396: 1817-28.

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Combination clinical trials in mTNBC

Trial	Phase	Treatment arm(s)	Patient selection criteria	N	ORR, %	Median PFS, mo	Median OS, mo
IMpassion131	III	Atezolizumab + paclitaxel	Untreated advanced or metastatic TNBC	651	ITT: 54 PD-L1+: 63	ITT: 5.7 PD-L1+: 6	ITT: 19.2 PD-L1+: 22.1
		Placebo + paclitaxel			ITT: 47 PD-L1+: 55	ITT: 5.6 PD-L1+: 5.7	ITT: 22.8 PD-L1+: 28.3
IMpassion132	III	Atezolizumab + chemo	Platinum pretreated advanced or metastatic TNBC	350	Ongoing		Primary endpoint
ENHANCE-1	Ib/II	Pembrolizumab + eribulin	Metastatic TNBC (≤ 2 lines)				
			0 lines	60	PD-L1-: 16.1	PD-L1-: 3.5	PD-L1-: 15.2
					PD-L1+: 34.5	PD-L1+: 6.1	**PD-L1+: 21.0**
			1-2 lines	89	PD-L1-: 18.2	PD-L1-: 3.9	PD-L1-: 15.5
					PD-L1+: 24.4	PD-L1+: 4.1	PD-L1+: 14.0

- Combination regimens have demonstrated improved outcomes in metastatic TNBC compared to single agent immunotherapy.
- In contrast to IMpassion130, atezolizumab did not improve PFS or OS in combination with paclitaxel.
- FDA safety alert 2020 regarding efficacy and safety concerns with atezolizumab in combination with paclitaxel.

ESMO 2020. Abstr LBA15., Cancer Res 2018;78(supp): Abstract PD6-13., Future Oncol. 2019;15(17):1951-61.

Immune related adverse events (irAEs)

Event	IMpassion130 (n=452)		KEYNOTE-355 (n=562)	
	Any Grade, %	Grade 3 or 4, %	Any Grade, %	Grade 3 or 4, %
Hypothyroidism	17.3	0	15	5
Hyperthyroidism	4.4	0.2	5	< 1
Pneumonitis	3.1	0.2	2	1
Colitis	1.1	0.2	2	< 1
Skin reactions	34.4	0.9	2	2
Hepatitis	15.3	5.1	NR	NR

- KEYNOTE-355 does not report hepatitis as an irAE; however, elevated ALT is reported as any grade=20% and grade >3= 6%.

Schmid et al, NEJM 2018. 379:2108-21, Cortez et al, Lancet 2020; 396: 1817-28.

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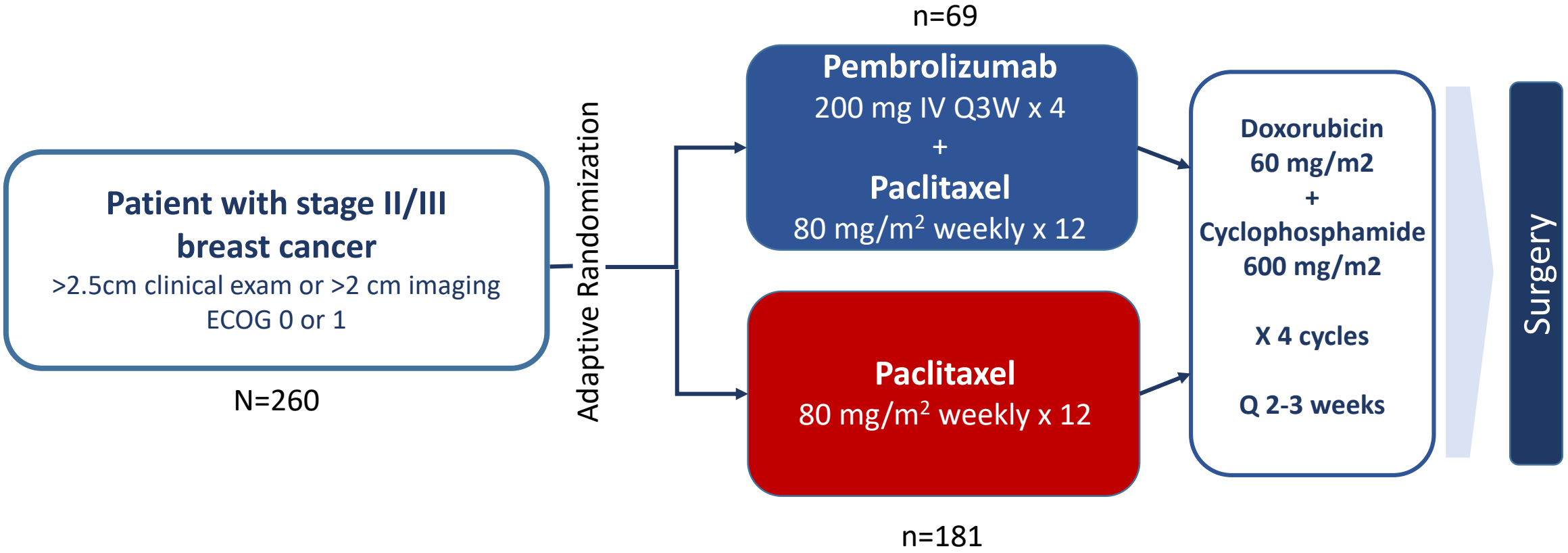
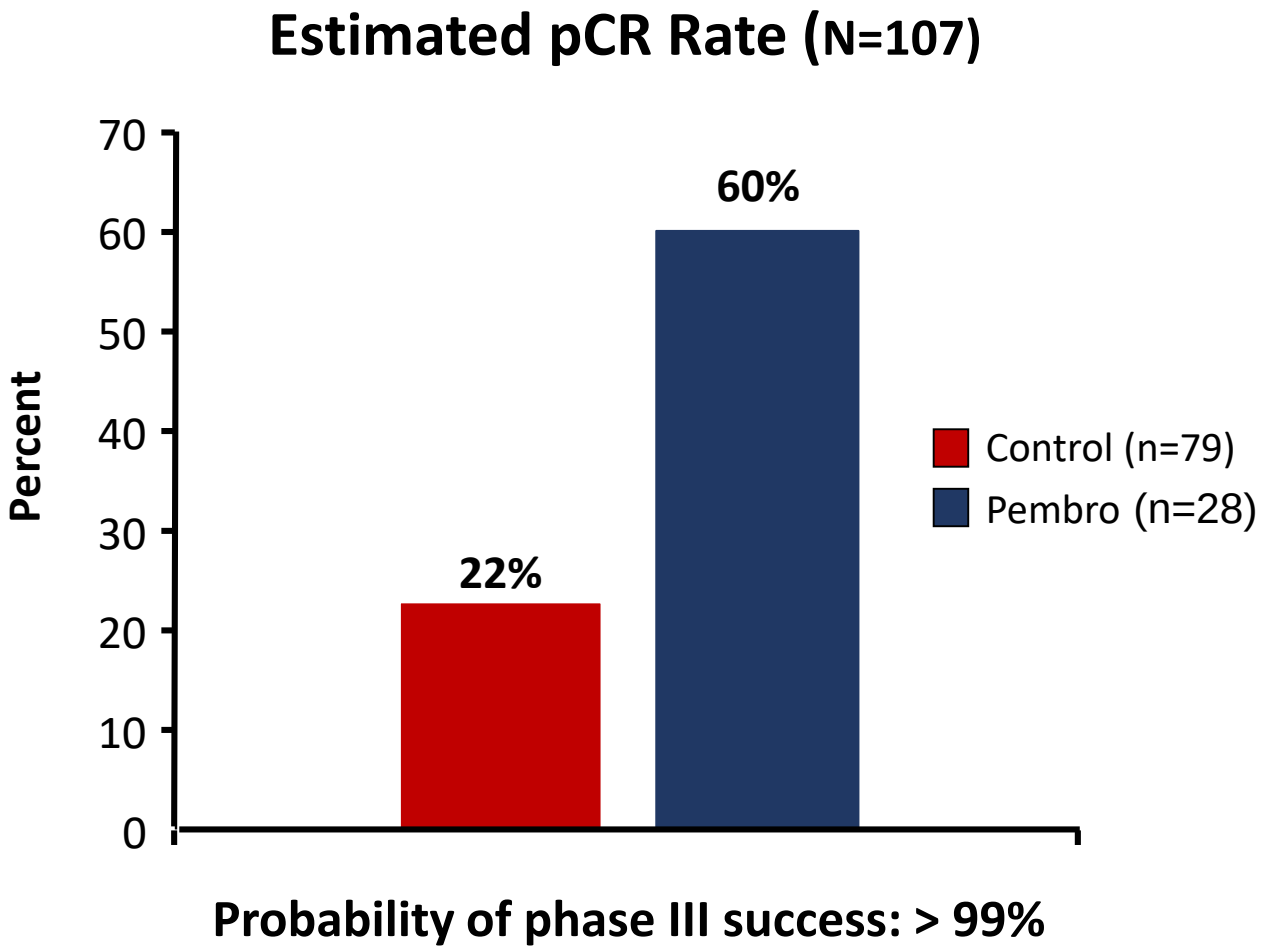
I-SPY2 – Study design

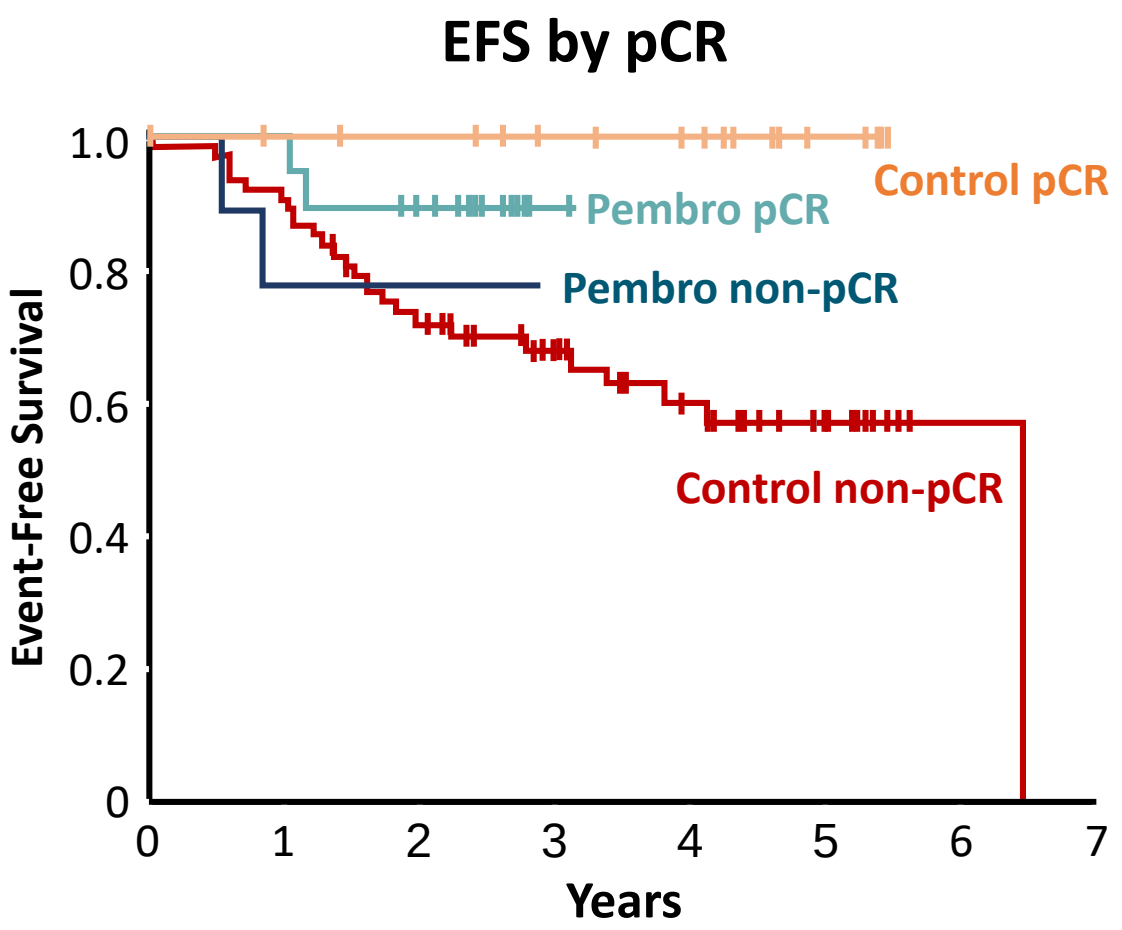


- Primary endpoint: pathologic complete response (pCR)

Nanda et al, JAMA Oncol 2020; 6(5):676-84.

I-SPY2 – pCR and EFS in TNBC





Nanda et al, JAMA Oncol 2020; 6(5):676-84.

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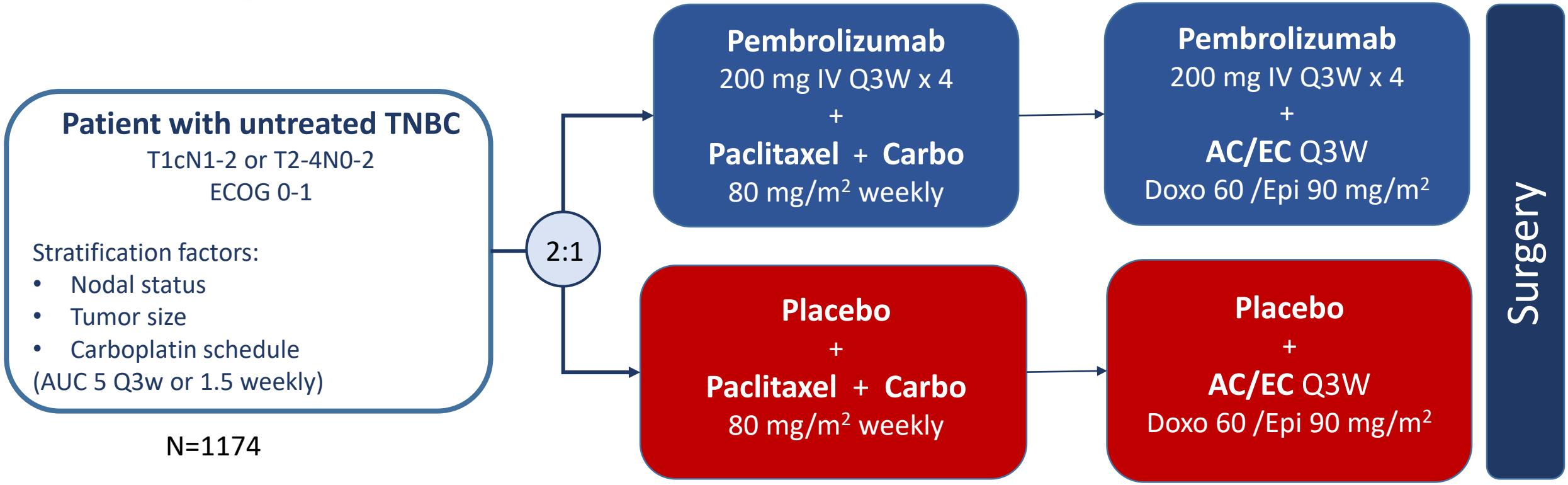
KEYNOTE-522 – Study design



- Surgery after first or second neoadjuvant treatment
- Adjuvant treatment: pembrolizumab 200 mg or placebo Q3W x 9 cycles
- Primary endpoints: pCR and event-free survival

Schmid et al, NEJM 2020; 382:810-21.

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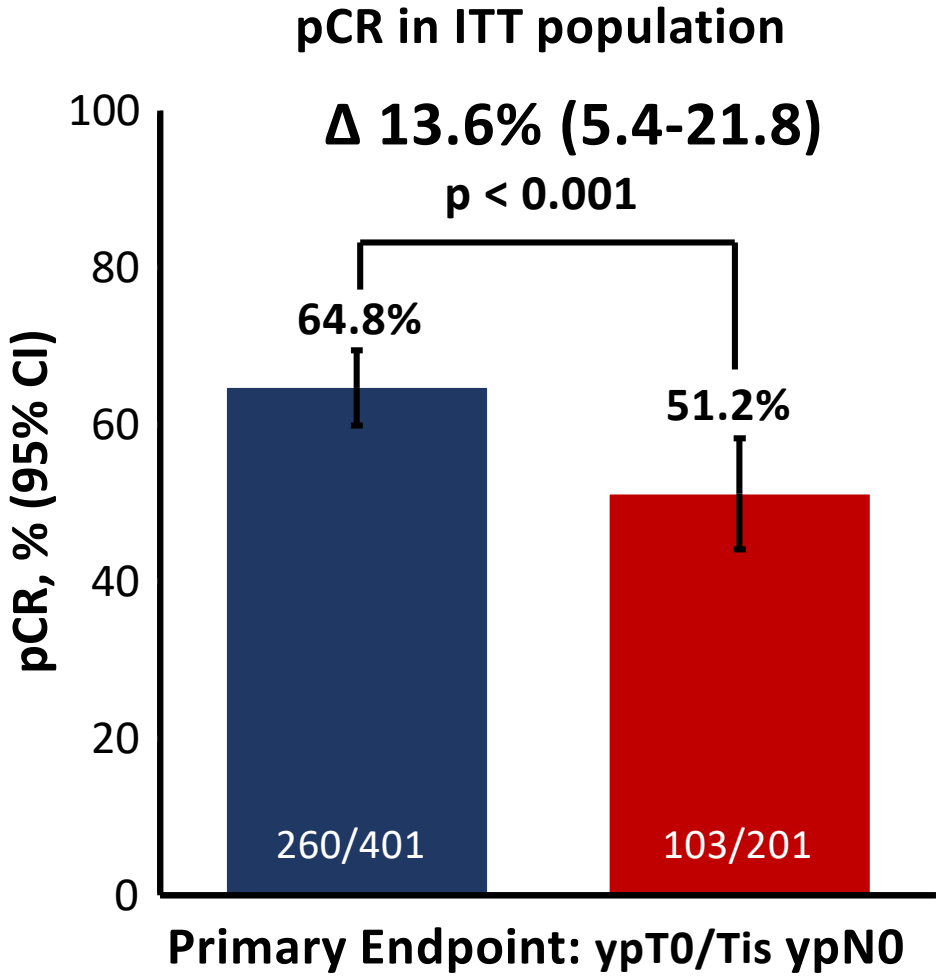
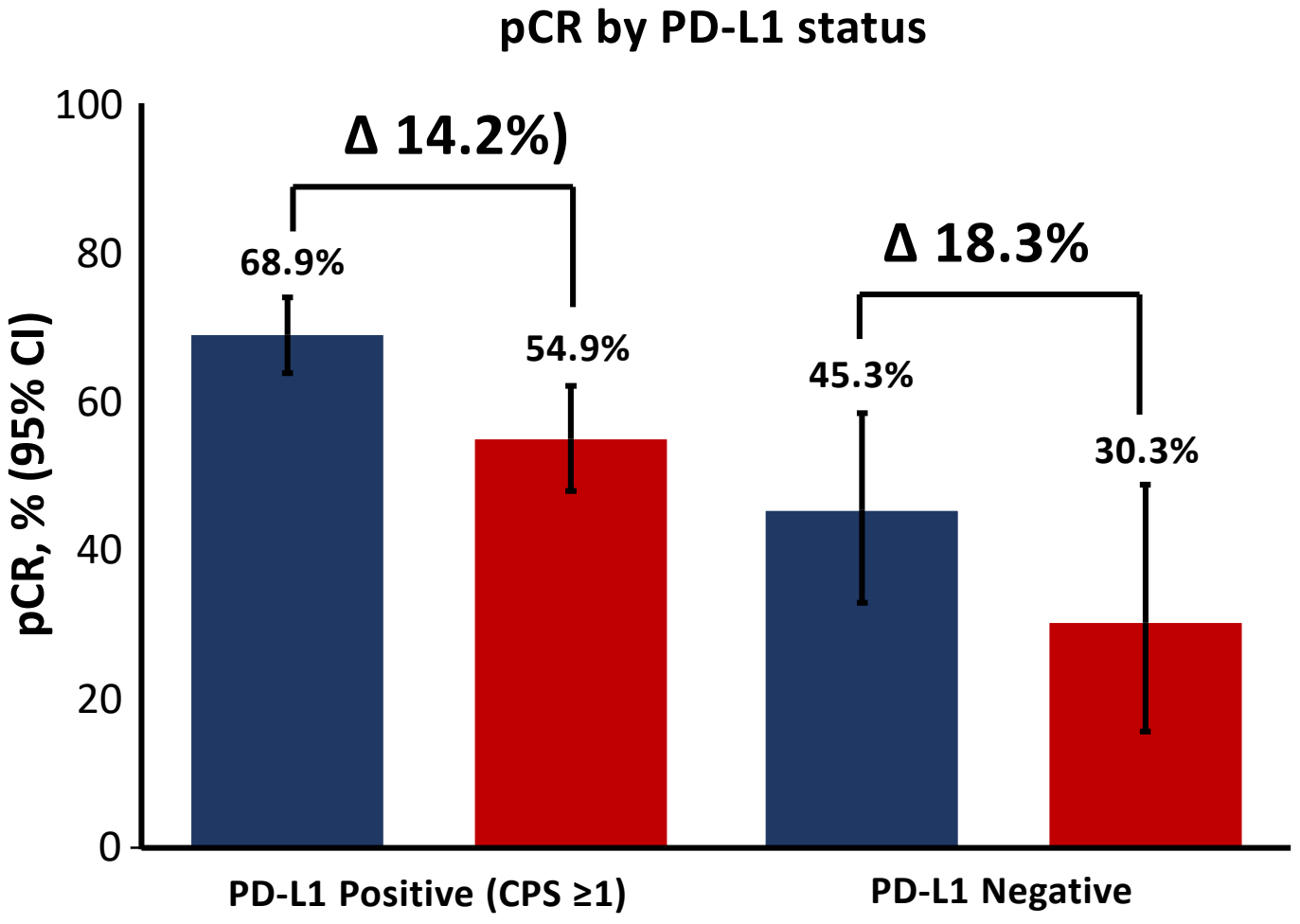
KEYNOTE-522 – pCR

Pembro + chemo
Placebo + chemo





Schmid et al, NEJM 2020; 382:810-21.

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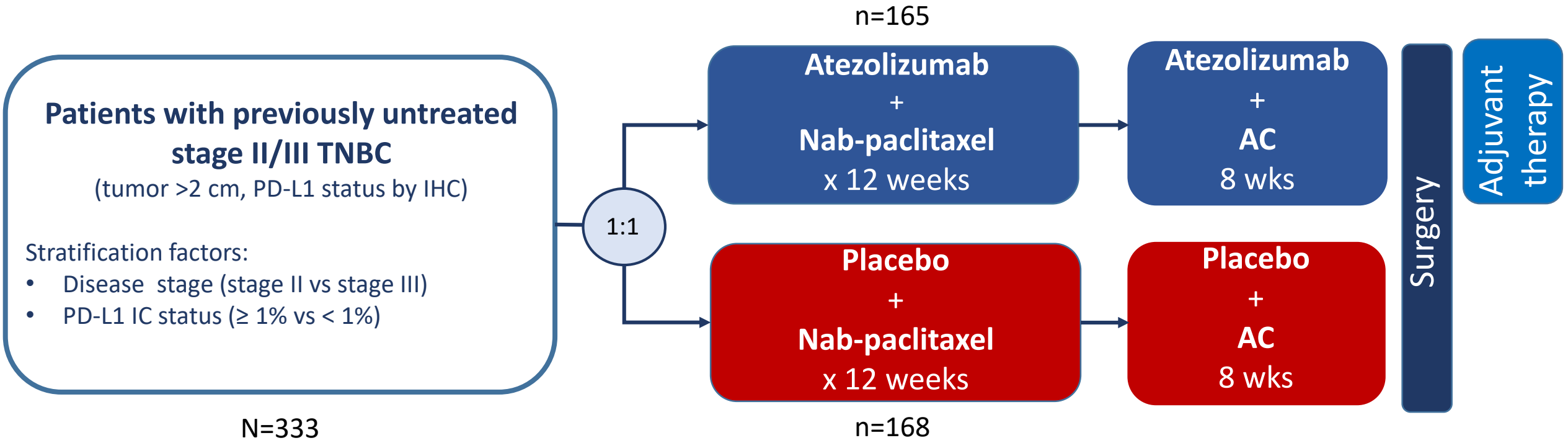
KEYNOTE-522 – EFS

	Pembro + Chemo (N=784)	Placebo + Chemo (N=390)	HR (95% CI)
Event-free survival (95% CI)	91.3% (88.8-93.3)	85.3% (80.3 – 89.1)	0.63 (0.43-0.93)
Any grade adverse events	99%	99.7%	
Grade ≥ 3 adverse events	76.8%	72.2%	

- Median event-free survival was not reached for either group.
- Median follow-up only 15.5 months. Not long enough to demonstrate a sustained response.
- The addition of pembrolizumab to chemotherapy did not increase adverse events associated with chemotherapy.

Schmid et al, NEJM 2020; 382:810-21.

IMpassion031 – Study design



- Neoadjuvant treatment: atezolizumab 840 mg Q2W, nab-paclitaxel 125 mg/m^2 weekly, doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 Q2W
- Adjuvant treatment: atezolizumab 1200 mg Q3W x 11 cycles (~12 months)
- Co-primary endpoints in ITT and PD-L1+: pCR

Mittendorf et al, Lancet 2020; 396: 1090-100.

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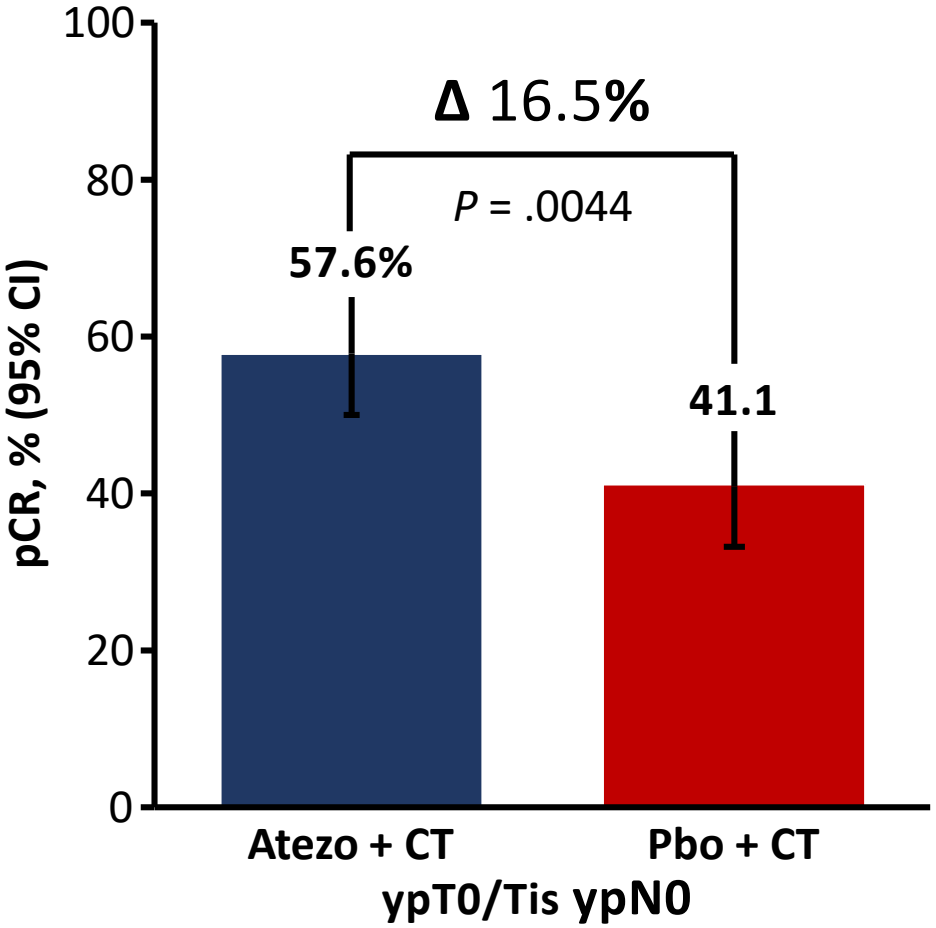
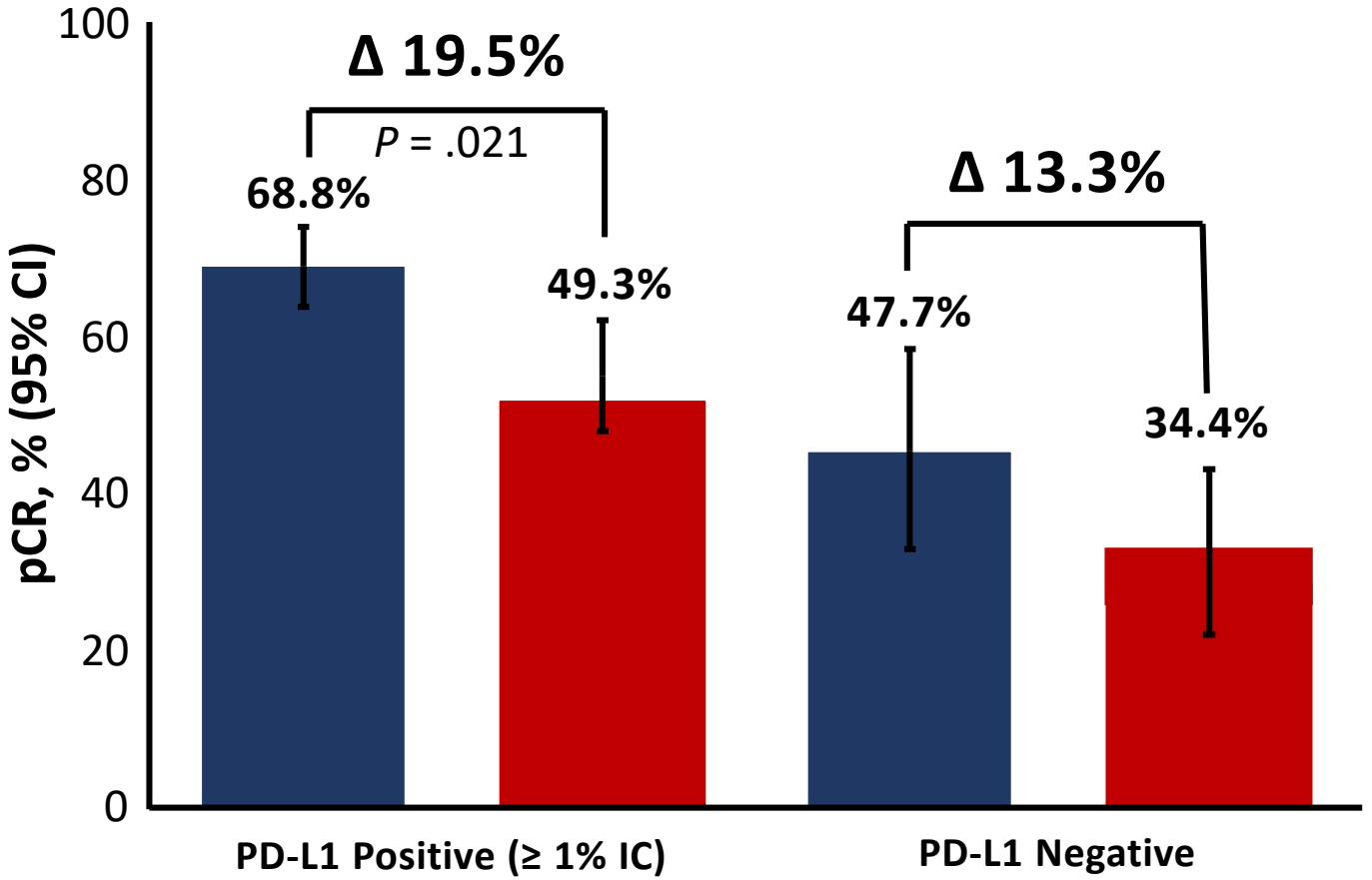
IMpassion031 – pCR ITT and PD-L1 status

Atezolizumab + chemo
Placebo + chemo

pCR in ITT population



pCR by PD-L1 status



Mittendorf et al, Lancet 2020; 396: 1090-100.

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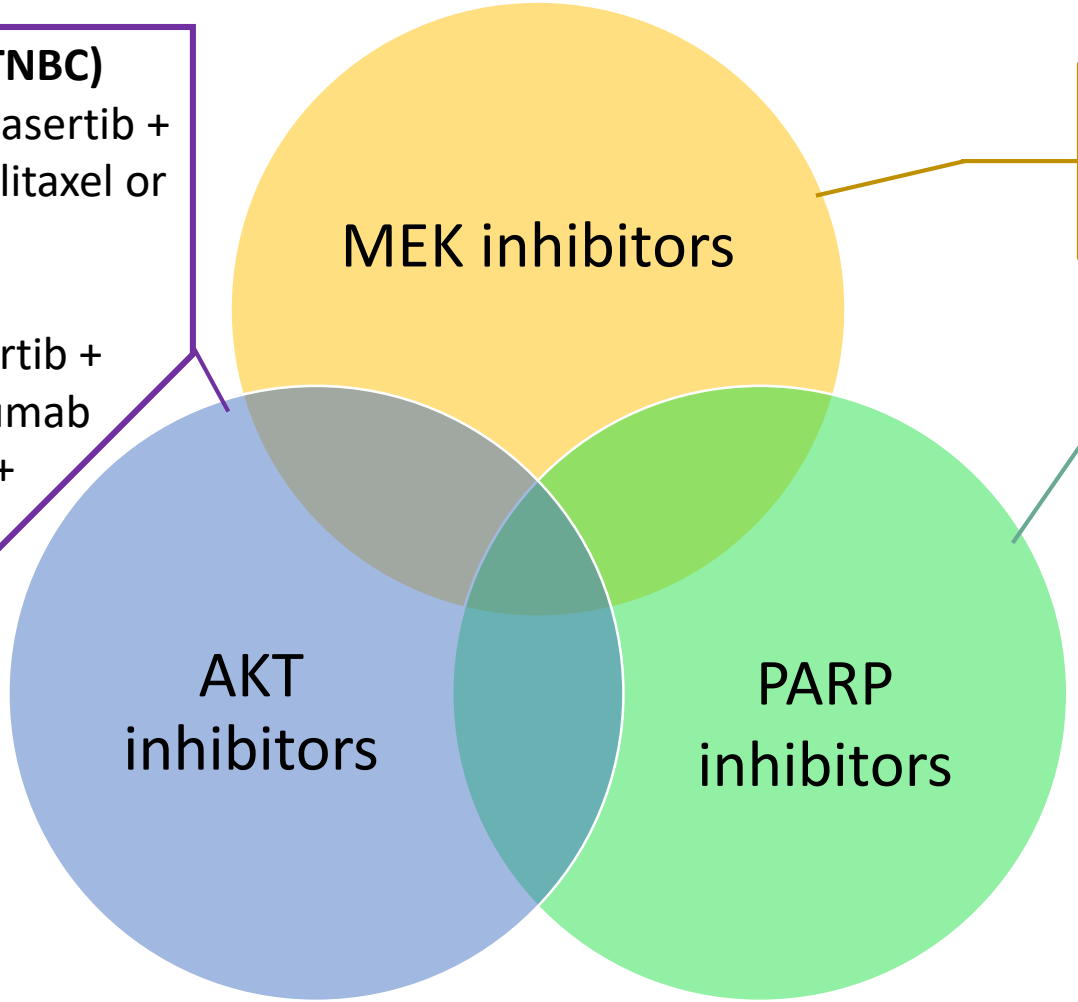
Future directions – Targeted therapy

AKT inhibitors (mTNBC)

- NCT03800836: ipatasertib + atezolizumab + paclitaxel or nab-paclitaxel (ORR 73%)
- BEGONIA: capivasertib + paclitaxel + durvalumab
- PAKT: capivasertib + paclitaxel



MEK inhibitors (mTNBC)

- COLET: Cobimetinib + atezolizumab + taxane
- NCT03106415: Binimetinib + pembrolizumab

PARP inhibitors (mTNBC, gBRCAm)

- TOPACIO: niraparib + pemrolizumab (ORR 47%, PFS 8.3 mos)
- MEDIOLA: olaparib + durvalumab (ORR 58.%, PFS 4.9 mos)
- ETCTN: olaparib + atezolizumab
- DORA: olaparib + durvalumab
- I-SPY 2: adjuvant olaparib + durvalumab (early stage)

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Conclusions

- TNBC is more likely to express PD-L1, have higher levels of TILs, and a higher mutation burden.
- PD-L1 assays are not interchangeable and can only be used to select treatment with the companion drug.
- There are two FDA approved checkpoint inhibitors in mTNBC: atezolizumab and pembrolizumab.
- Immunotherapy in early stage TNBC breast cancer shows promise.

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Case Studies

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Patient Case – 64yo Female

- 2015: Diagnosis of early-stage ER/PR + breast cancer.
  - Received neoadjuvant ddAC x 4→ddTaxol x 4
  - Right modified radical mastectomy
  - Final stage IIIC (ypT3N3aM0) – grade 2, 6.3 cm residual disease 14/16+ lymph nodes
  - Chest wall and lymph node XRT
  - Started adjuvant aromatase inhibitor (2016-2019)
- 2019: Diagnosed with mTNBC

What is the next step to determine treatment?

Patient Case – 64yo Female

- Which of the following biomarker assays would you complete on the tumor biopsy to determine if she may benefit from immunotherapy?

  A. Next-generation sequencing for microsatellite stability

  B. Next-generation sequencing for tumor mutation burden

  C. PD-L1 testing with SP142 antibody assay

  D. PD-L1 testing with 28-8 antibody assay

Patient Case – 64yo Female

- The patient's tumor was tested for PD-L1 expression using SP142 antibody assay and the testing reveals PD-L1 ≥ 1%. What is the most appropriate first-line treatment?

  A. Atezolizumab + paclitaxel

  B. Pembrolizumab + paclitaxel

  C. Atezolizumab + nab-paclitaxel

  D. Pembrolizumab + nab-paclitaxel