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

- No relevant financial relationships to disclose
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy in breast cancer

- Standard-of-care treatment usually involves surgery, endocrine therapy and/or HER2 directed therapy by subtype, chemotherapy, and radiation
- Application of immunotherapy is still in early stages

Estimated new cases

Female		
Breast	276,480	30%
Lung & bronchus	112,520	12%
Colon & rectum	69,650	8%
Uterine corpus	65,620	7%
Thyroid	40,170	4%
Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	34,860	4%
Kidney & renal pelvis	28,230	3%
Pancreas	27,200	3%
Leukemia	25,060	3%
All sites	**912,930**	

Estimated deaths

Female		
Lung & bronchus	63,220	22%
Breast	42,170	15%
Colon & rectum	24,570	9%
Pancreas	22,410	8%
Ovary	13,940	5%
Uterine corpus	12,590	4%
Liver & intrahepatic bile duct	10,140	4%
Leukemia	9,680	3%
Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	7,830	3%
All sites	**285,360**	

American Cancer Society 2020.

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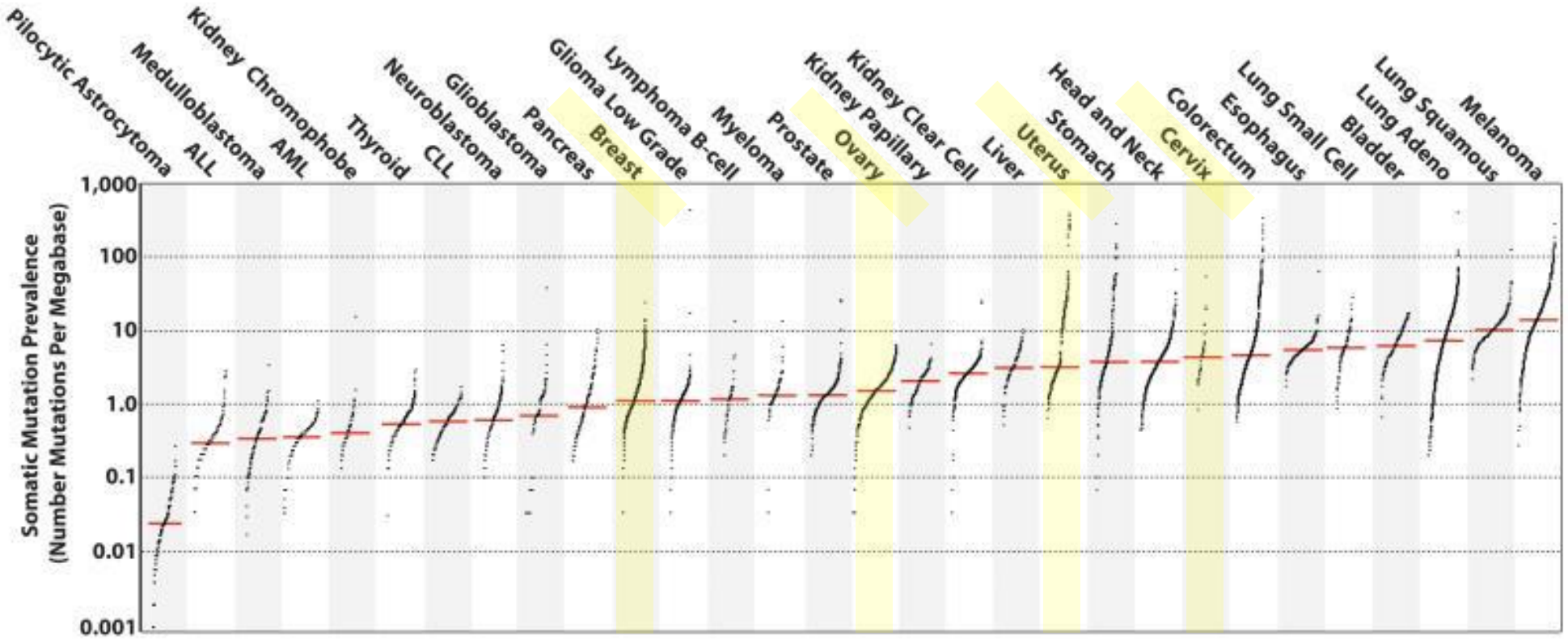
Immunotherapy in breast and gynecologic cancers



Alexandrov, Nature 2013.

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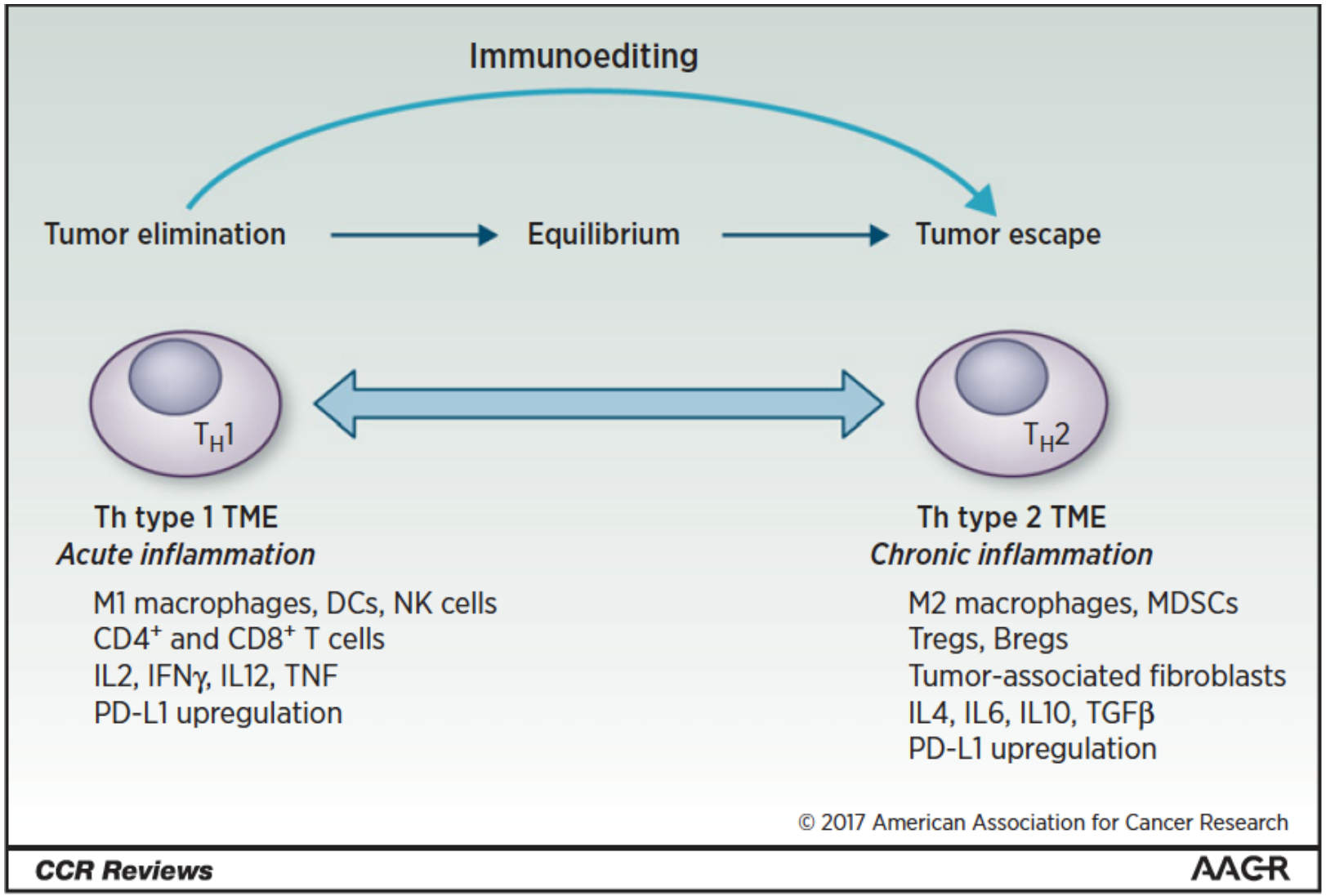

Emens L. DOI: 10.1158/1078-0432.CCR-16-3001

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Outline

- Breast cancer
  - Approvals
  - In the pipeline
  - Biomarkers and immunotherapy responsiveness

Outline

- Breast cancer
  - Approvals
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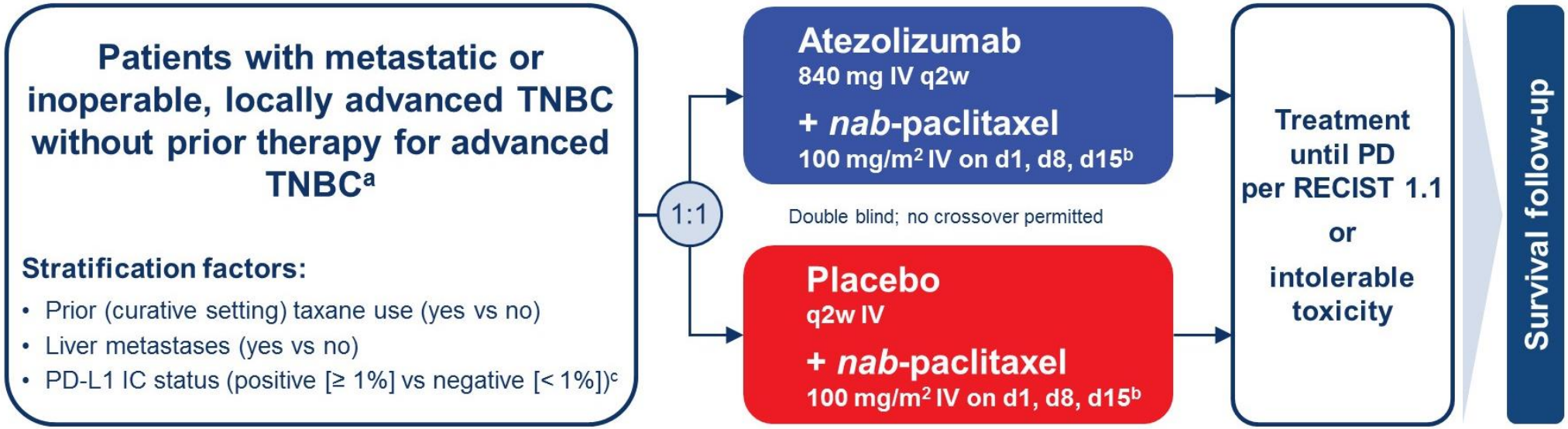
Current approvals in breast cancer

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 or paclitaxel protein-bound	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 + chemotherapy	2020	Locally recurrent/metastatic TNBC with PD-L1 CPS ≥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

IMpassion130



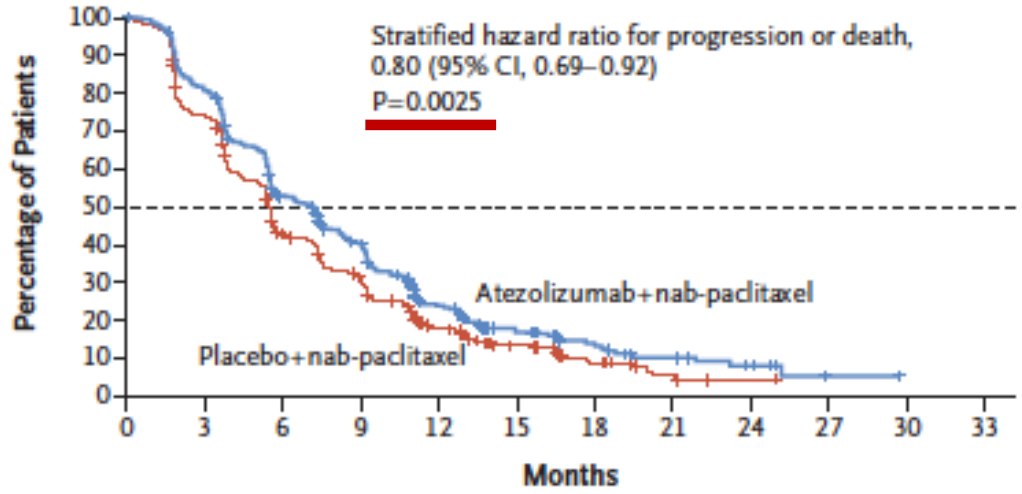
- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

Schmid, ASCO 2019.

Significant improvement in PFS

A Progression-free Survival in the Intention-to-Treat Population

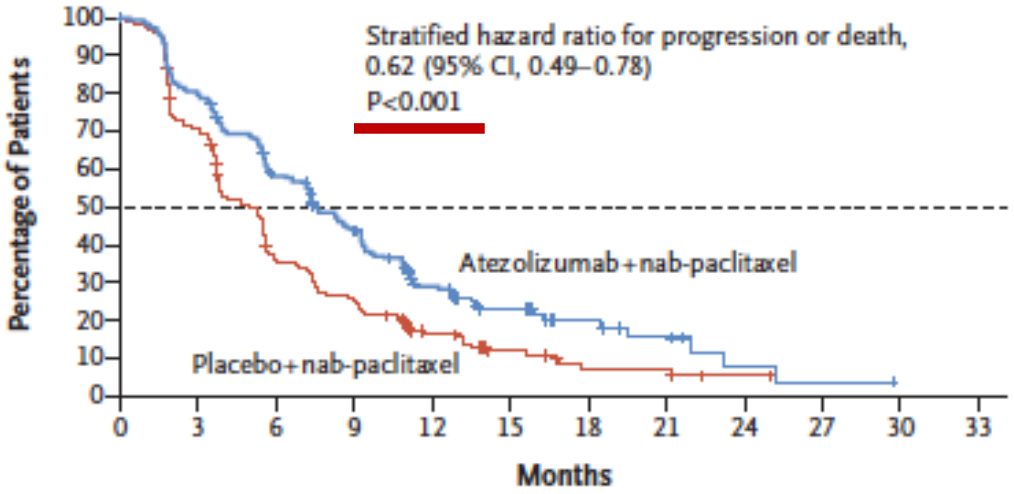
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	358/451	7.2 (5.6–7.5)	23.7 (19.6–27.9)
Placebo+Nab-Paclitaxel	378/451	5.5 (5.3–5.6)	17.7 (14.0–21.4)



No. at Risk												
Atezolizumab+ nab-paclitaxel	451	360	226	164	77	34	20	11	6	1	NE	NE
Placebo+ nab-paclitaxel	451	327	183	130	57	29	13	5	1	NE	NE	NE

B Progression-free Survival in the PD-L1–Positive Subgroup

	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo+Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)



No. at Risk												
Atezolizumab+ nab-paclitaxel	185	146	104	75	38	19	10	6	2	1	NE	NE
Placebo+ nab-paclitaxel	184	127	62	44	22	11	5	5	1	NE	NE	NE

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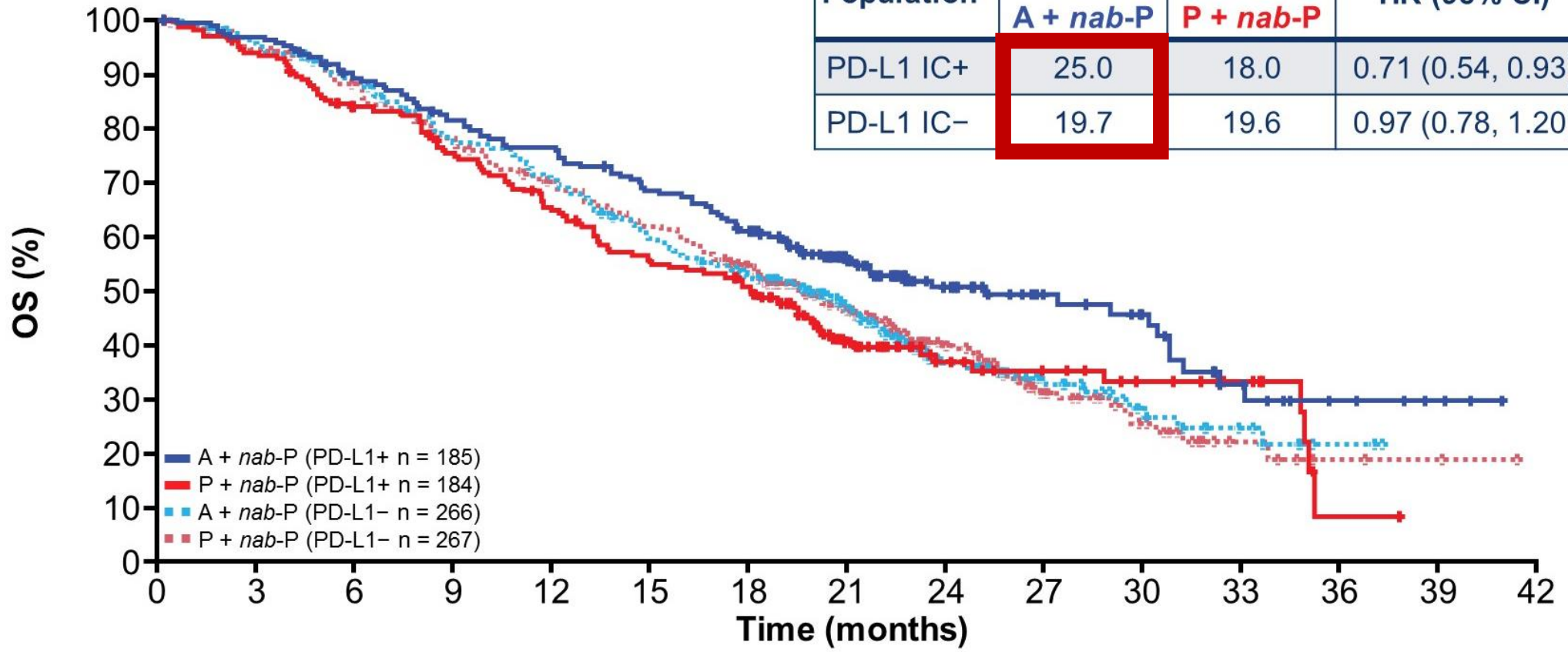
IMpassion130: PD-L1+ TNBC

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.

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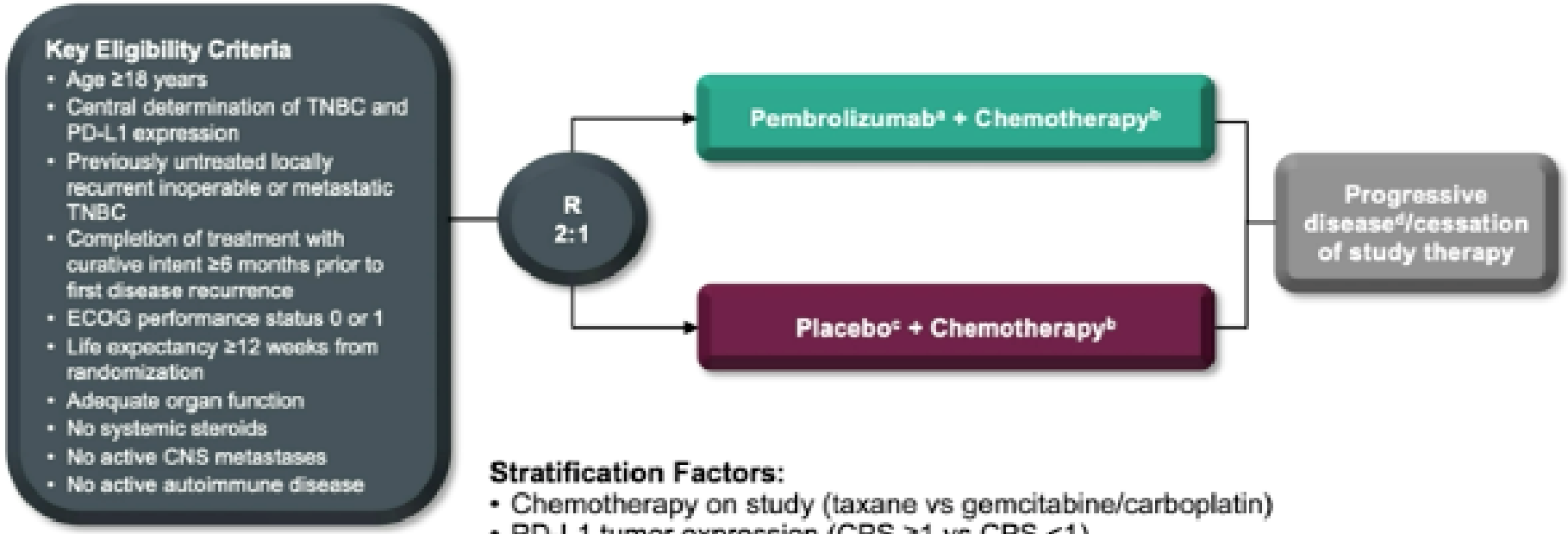
KEYNOTE-355 Study Design (NCT02819518)



[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m² IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m² IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m²/carboplatin AUC 2 on days 1 and 8 every 21 days

[c]Normal saline
[d]Treatment may be continued until confirmation of progressive disease
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer

Presented by Javier Cortes at ASCO 2020

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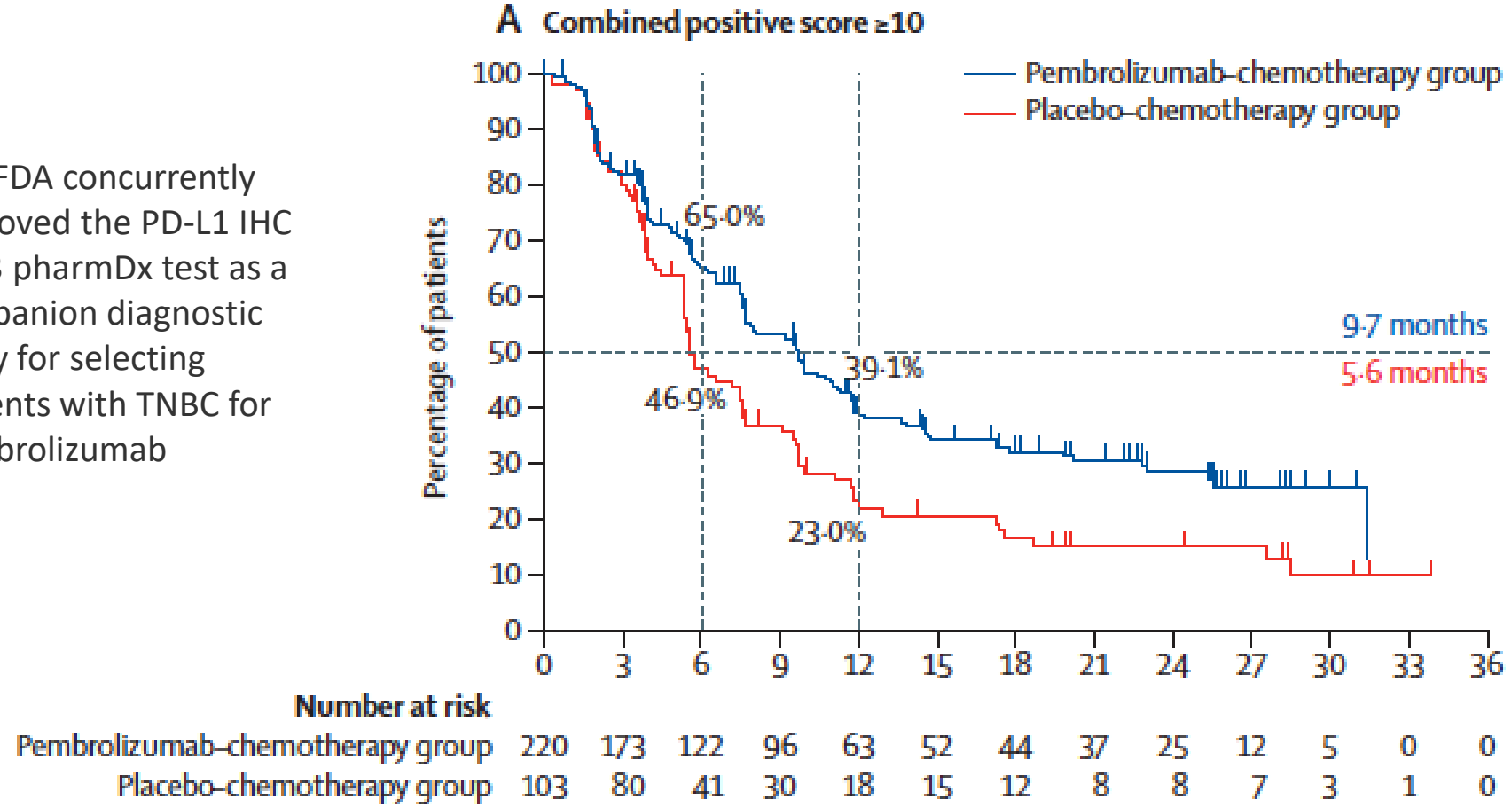
PFS Benefit in CPS≥10

The FDA concurrently approved the PD-L1 IHC 22C3 pharmDx test as a companion diagnostic assay for selecting patients with TNBC for pembrolizumab



Hazard ratio [HR] for progression or death, 0·65, 95% CI 0·49–0·86; one-sided p=0·0012 [primary objective met]).

Cortes J. et al ***Lancet* 2020; 396: 1817–28**

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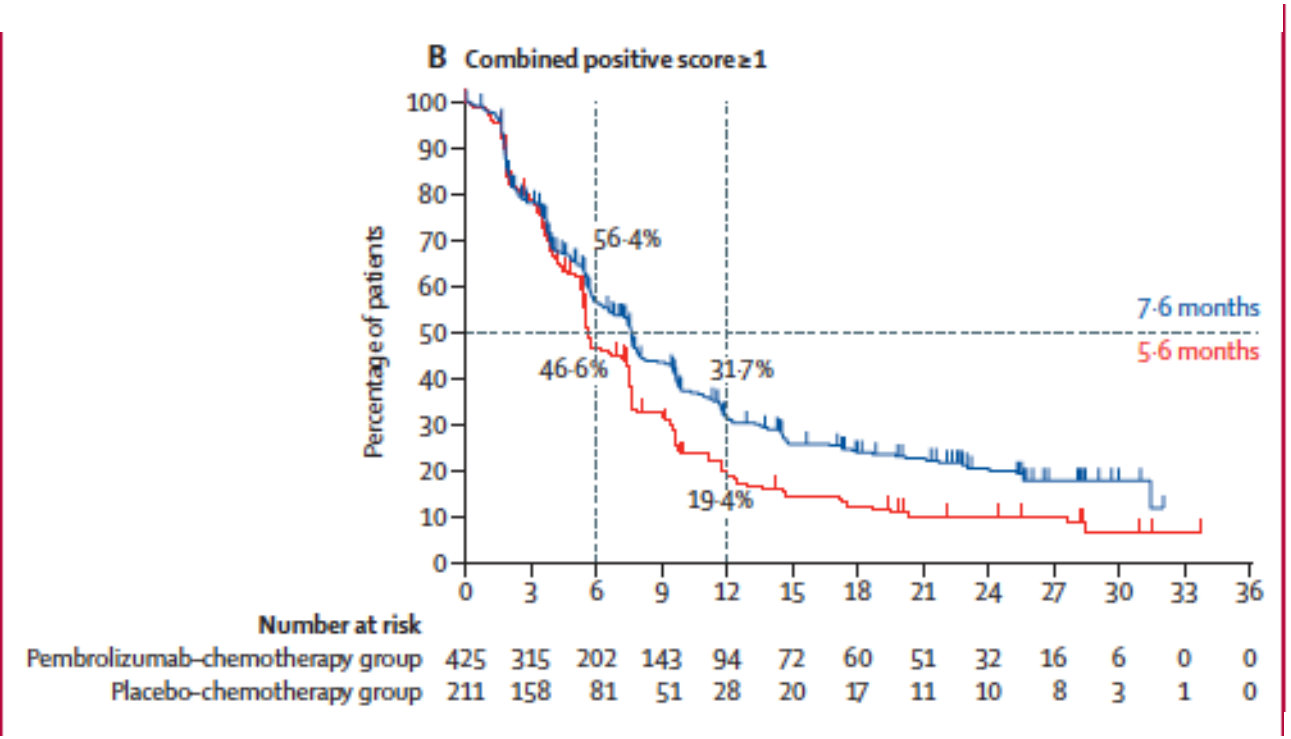
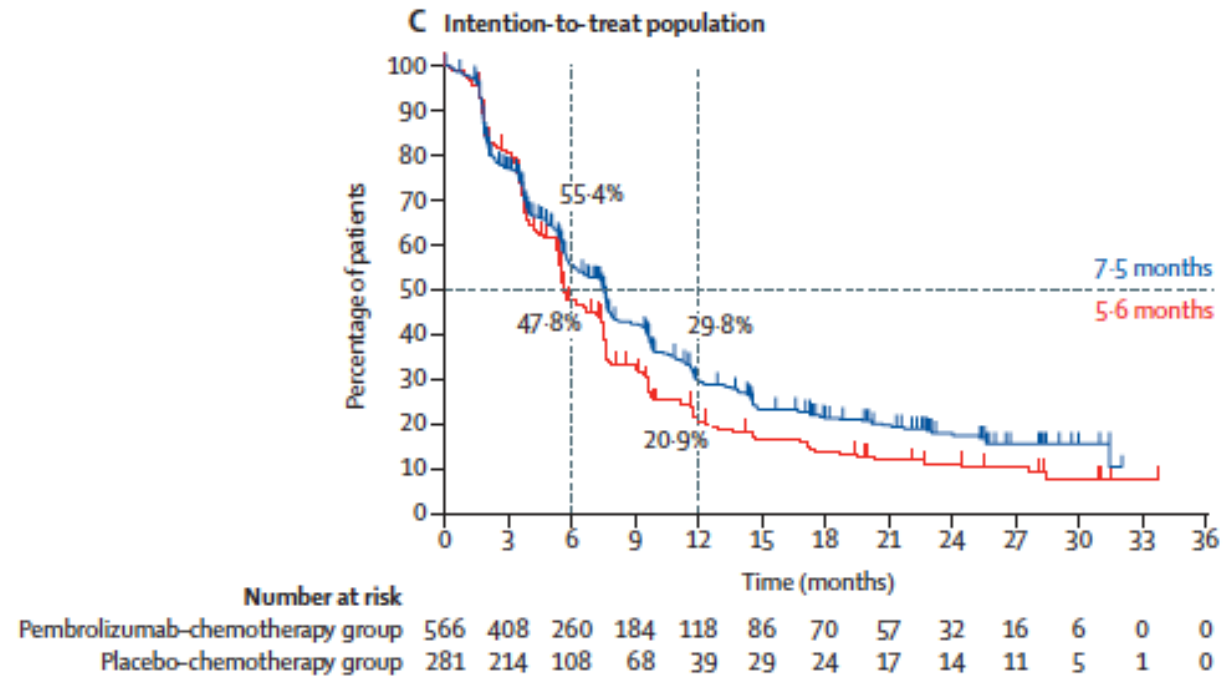
CPS ≥1 and ITT:





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Immune Effects of HER2 directed therapy

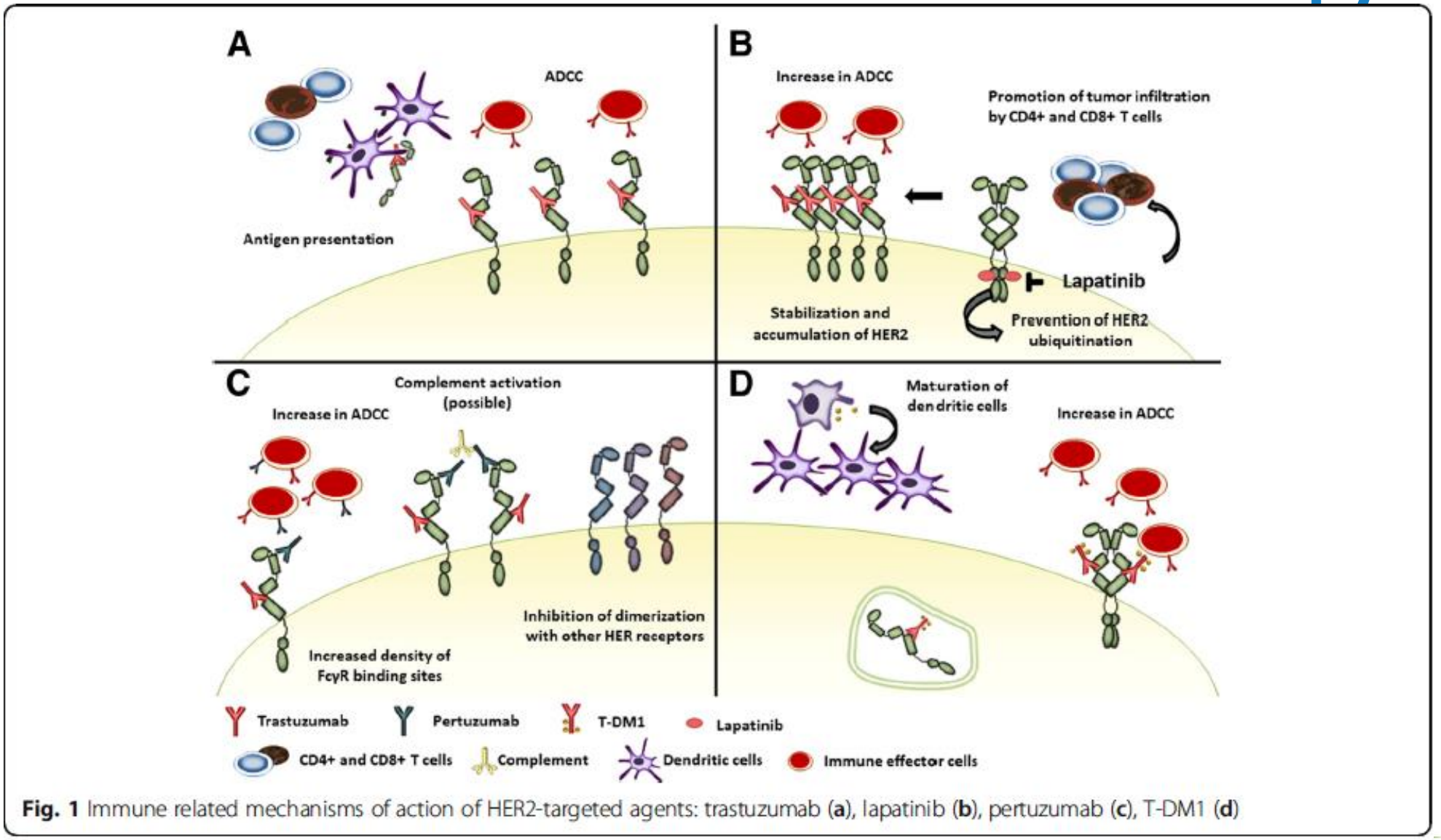

Fig. 1 Immune related mechanisms of action of HER2-targeted agents: trastuzumab (**a**), lapatinib (**b**), pertuzumab (**c**), T-DM1 (**d**)

Griguolo et al. Journal for ImmunoTherapy of Cancer (2019) 7:90
https://doi.org/10.1186/s40425-019-0548-6

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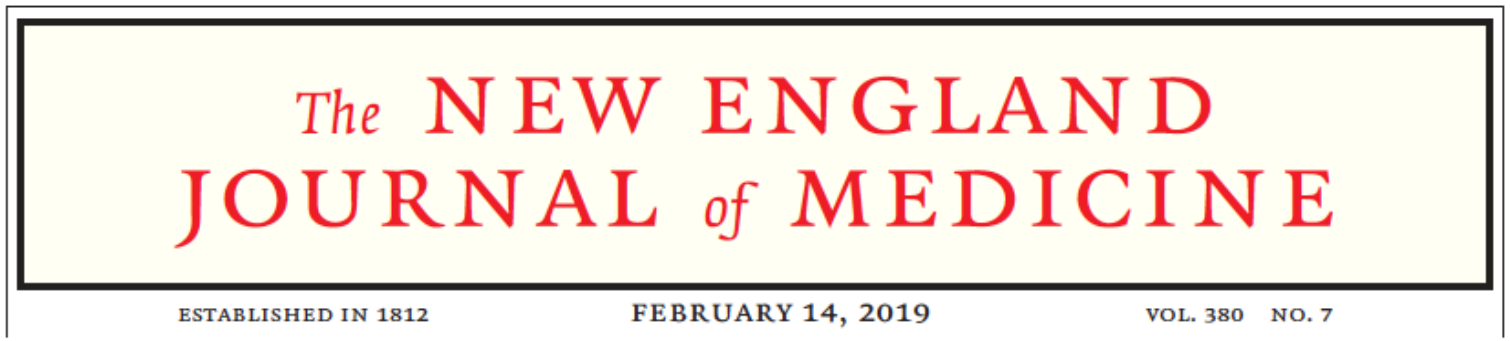
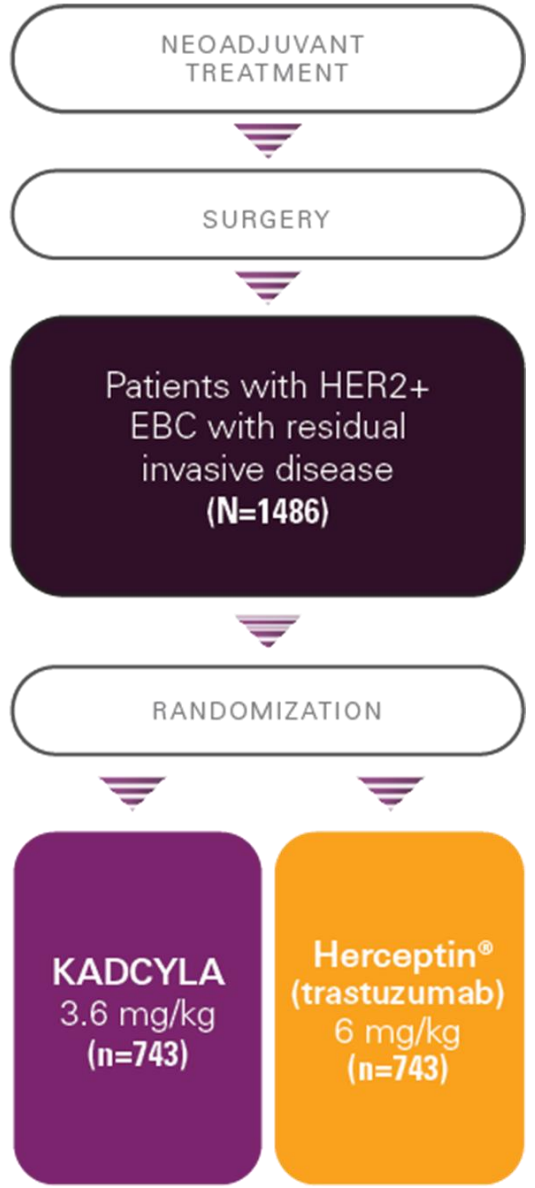
T-DM1 in adjuvant setting



Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. Lam, D. Tesarowski, M. Smitt, H. Douthwaite, S.M. Singel, and C.E. Geyer, Jr., for the KATHERINE Investigators*

N Engl J Med 2019;380:617-28.
DOI: 10.1056/NEJMoa1814017



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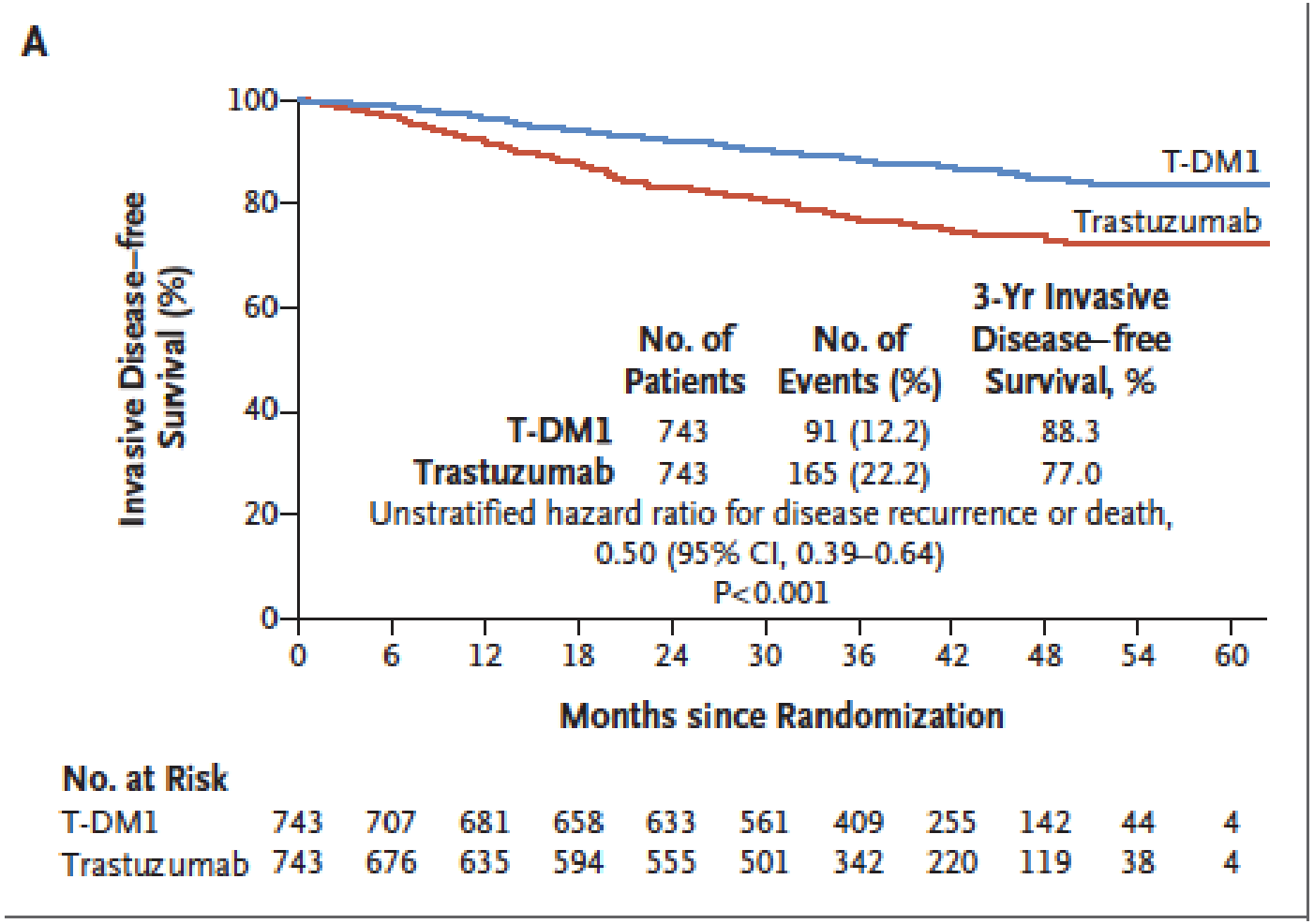
3 year iDFS improvement of 11%



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Outline

- Breast cancer
  - Approvals
  - In the pipeline
  - Biomarkers and immunotherapy responsiveness
- Gynecologic cancers
  - Approvals
  - In the pipeline

Clinical trials in TNBC

Trial	Treatment arm(s)	Patient selection criteria	n	ORR	Median PFS (months)	Median OS (months)
IMpassion130	Atezolizumab + nab-paclitaxel* **FDA-approved*	Metastatic TNBC without prior therapy	902	ITT: 56.0% PD-L1+: 58.9%	ITT: 7.2 PD-L1+: 7.5	ITT: 21.3 PD-L1+: 25.0
	Placebo + nab-paclitaxel			ITT: 45.9% PD-L1+: 42.6%	ITT: 5.5 PD-L1+: 5.0	ITT: 17.6 PD-L1+: 15.5
KEYNOTE-086	Pembrolizumab	A: Metastatic TNBC at 2nd line or greater	170	5.3% CR: 1.2%	2.0	9.0
		B: PD-L1+ metastatic TNBC without prior therapy	84	21.4% CR: 4.7%	2.1	18.0
IMMU-132-01	Sacituzumab govitecan-hziy* (Anti-Trop-2)	Advanced TNBC with at least 2 prior therapies	108	33.3%	5.5	13.0
KEYNOTE-355	Pembrolizumab + chemotherapy	Locally recurrent inoperable or metastatic TNBC without prior therapy	566		ITT: 7.5 CPS >10: 9.7	
	Placebo + chemotherapy		281		ITT: 5.6 CPS >10: 5.6	
KEYNOTE-522	Neoadjuvant pembrolizumab + paclitaxel/carboplatin, adjuvant pembrolizumab	Stage II or III TNBC without prior therapy	1174	Pathological complete response rates: ITT: 64.8% vs 51.2% PD-L1+: 68.9% vs 54.9% PD-L1-: 45.3% vs 30.3%		
	Neoadjuvant placebo + paclitaxel/carboplatin, adjuvant placebo					

Cortes, ASCO 2020; Schmid, N Engl J Med 2018; Schmid, N Engl J Med 2020; Adams, Ann Oncol 2019; Loi, Lancet Oncol 2019; Bardia, N Engl J Med 2019.

Clinical trials in HR+ or HER2+ breast cancer

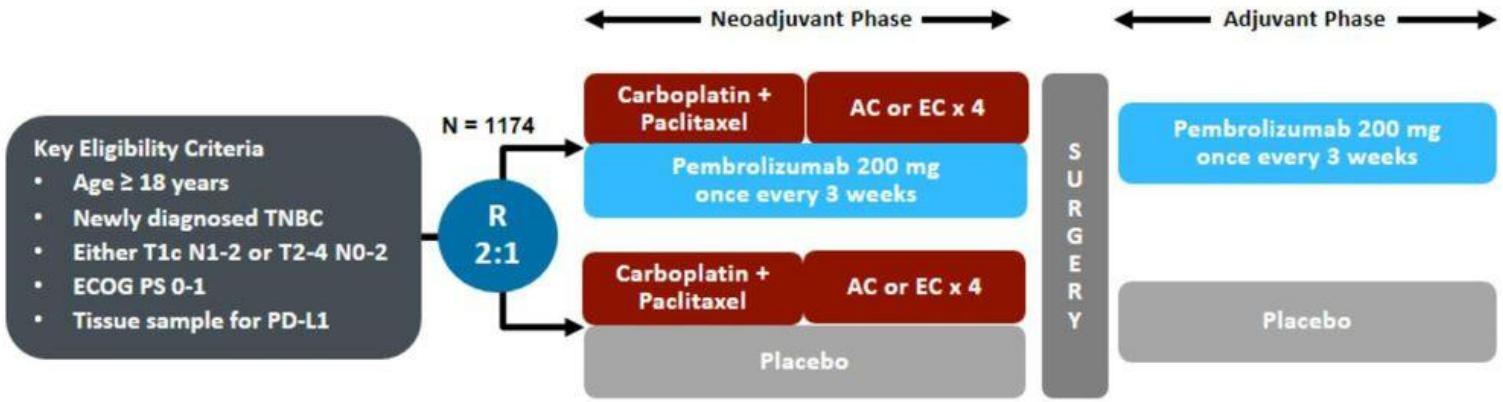
Trial	Treatment arm(s)	Patient selection criteria	n	ORR	Median PFS (months)	Median OS (months)
KEYNOTE-028	Pembrolizumab	ER+/HER2-, PD-L1+ breast cancer	25	12.0% CR: 0%	1.8	8.6
KEYNOTE-014/PANACEA	Pembrolizumab + trastuzumab	HER2+ breast cancer with progression on trastuzumab	58	PD-L1+: 15% CR: 4% PD-L1-: 0%		
KATE2	Atezolizumab + trastuzumab emtansine	HER2+ advanced breast cancer with previous trastuzumab and a taxane	133	ITT: 45% PD-L1+: 54%	ITT: 8.2 PD-L1+: 8.5	ITT 1-year: 89.1% PD-L1+: 94.3%
	Trastuzumab emtansine		69	ITT: 43% PD-L1+: 33%	ITT: 6.8 PD-L1+: 4.1	ITT 1-year: 89.0% PD-L1+: 87.9%
KATHERINE	Trastuzumab emanstine* (Anti-HER2)	HER2-positive early breast cancer after neoadjuvant therapy	1486	3-year invasive disease-free survival: 88.3% vs. 77.0%		
DESTINY-Breast01	Trastuzumab deruxtecan*	HER2-positive metastatic breast cancer after trastuzumab emanstine	184	60.9%	16.4	NR

Rugo, Clin Cancer Res 2018; Loi, Lancet Oncol 2019; Emens ESMO 2019 and SABCS 2018; von Minckwitz, N Engl J Med 2019; Modi, N Engl J Med 2020.

KEYNOTE 522:Neoadjuvant Study

KEYNOTE-522

Confirming Benefit of Pembrolizumab-Containing Neoadjuvant Therapy



Stratification Factors:

- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (once weekly vs once every 3 weeks)

Schmid P, et al. ESMO 2019. Abstract LBA8.

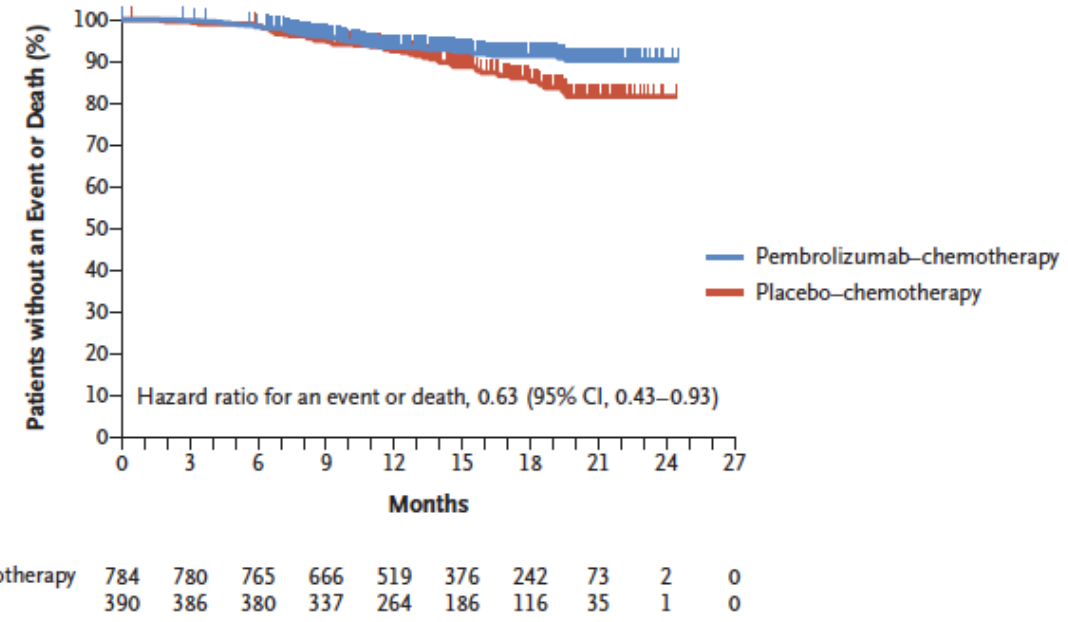


Figure 2. Kaplan–Meier Estimates of Event-free Survival, According to Trial Group in the Intention-to-Treat Population. Tick marks indicate data censored at the last time the patient was known to be alive and without an event (disease progression that precludes definitive surgery; local or distant recurrence or a second primary tumor; or death from any cause). The hazard ratio and confidence interval were analyzed with the use of a Cox regression model with treatment as a covariate stratified according to the randomization stratification factors of nodal status (positive or negative), tumor size (T1 to T2 or T3 to T4), and frequency of carboplatin administration (once weekly or once every 3 weeks).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, T. Foukakis, P.A. Fasching, F. Cardoso, M. Untch, L. Jia, V. Karantza, J. Zhao, G. Aktan, R. Dent, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

- pCR: **64.8%** (pembro-chemo) vs. **51.2%** (placebo-chemo)

After a median follow-up of 15.5 months EFS events occurred in:

- 58 of 784 patients (7.4%) in the pembro–chemo group
- 46 of 390 patients (11.8%) in the placebo–chemo group
- (hazard ratio, 0.63; 95% CI, 0.43 to 0.93).

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ALLIANCE CALGB 40603:
Addition of caroboplatin led to pCR 54% v 41%; P .0029

The use of neoadjuvant platinum with taxane for treatment of early stage TNBC improve pCR rate, but toxicity limits dosing of carboplatin

In Arm 3 (taxol/carbo/ddAC arm)

- 56% in the carbo arm had Grade 3-4 neutropenia
- 20% had Grade 3-4 thrombocytopenia
- 10 pts had febrile neutropenia

Table 3. Grade 3 to 4 Treatment-Related Toxicities

	Arm One: Control (%)	Arm Two: Control + Bev (%)	Arm Three: Control + Carbo (%)	Arm Four: Control + Bev and Carbo (%)
Leukopenia	12	13	13	**25**
Neutropenia	22	27	**56**	**67**
Thrombocytopenia	4	3	**20**	**26**
Hemoglobin	0	2	4	5
Febrile neutropenia	7	9	12	**24**
Nausea	4	4	3	8
Vomiting	2	2	2	4
Mucositis	2	0	1	4
Diarrhea	0	3	2	3
Hypertension	2	**12**	0	**10***
ALT elevation	0	3	0	3
Hypokalemia	3	1	6	2
Peripheral neuropathy	2	6	7	4
Fatigue	10	12	10	**20**
Pain	3	6	3	**11**

NOTE. Bold font indicates significant difference in incidence compared with other treatment arms. Early surgical complications requiring intervention ± bevacizumab: 9% versus 5%; delayed surgical complications requiring intervention ± bevacizumab: 4% versus 1%.

Abbreviations: Bev, bevacizumab; Carbo, carboplatin.

*One treatment-related fatality.

J Clin Oncol 33:13-21.
DOI: 10.1200/JCO.2014.57.0572

Neoadjuvant chemotherapy regimens in TNBC

- **ISPY2** demonstrated addition of pembrolizumab improves pCR rate:
  - **pCR 60%** in pembro-chemo (P+C) arm vs **20%** in standard chemo (C) alone arm
  - Standard chemo: 12 weekly pacliaxel →AC (q2-3 wks)

- **KEYNOTE-522**
  - **pCR: 64.8%** in the pembro–chemo group vs. **51.2%** in chemo alone group
  - Toxicity: treatment-related AE ≥ grade 3: 78.0% in (P+C) and 73.0% in chemotherapy group
  - febrile neutropenia: 14.6% (P+C) and 12.1% (C)
  - discontinuation of any trial drug: 23.3% (P+C), 12.3% (C)

N Engl J Med 2020; 382:810-821 DOI: 10.1056/NEJMoa1910549
JAMA Oncol. 2020;6(5):676-684. doi:10.1001/jamaoncol.2019.6650

Outline

- Breast cancer
  - Approvals
  - In the pipeline
  - Biomarkers and immunotherapy responsiveness
- Gynecologic cancers
  - Approvals
  - In the pipeline

Biomarkers and immunotherapy responsiveness in breast cancers

- Potential markers of responsiveness include:
  - PD-L1
  - Tumor infiltrating lymphocytes
  - Mutational signatures

FDA-approved biomarkers only include:
- PD-L1+ by SP142
- TMB 10 or more
- MSI high

ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies					
Breast Cancer Subtype	**Biomarker**	**Detection**	**FDA-Approved Agents**	**NCCN Category of Evidence**	**NCCN Category of Preference**
Any[a]	*BRCA1* mutation *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1 Category 1	Preferred Preferred
HR-positive/ HER2-negative[b]	*PIK3CA* mutation	PCR (blood or tissue block if blood negative), molecular panel testing	Alpelisib + fulvestrant[d]	Category 1	Preferred second-line therapy
HR-negative/ HER2-negative[c]	PD-L1 expression • Threshold for positivity: ≥1% on tumor-infiltrating immune cells	IHC	Atezolizumab + albumin-bound paclitaxel	Category 2A	Preferred
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[e] Entrectinib[e]	Category 2A Category 2A	Useful in certain circumstances[e] Useful in certain circumstances[e]
Any	MSI-H/dMMR	IHC, PCR (tissue block)	Pembrolizumab[f]	Category 2A	Useful in certain circumstances[f]

NCCN Guidelines.

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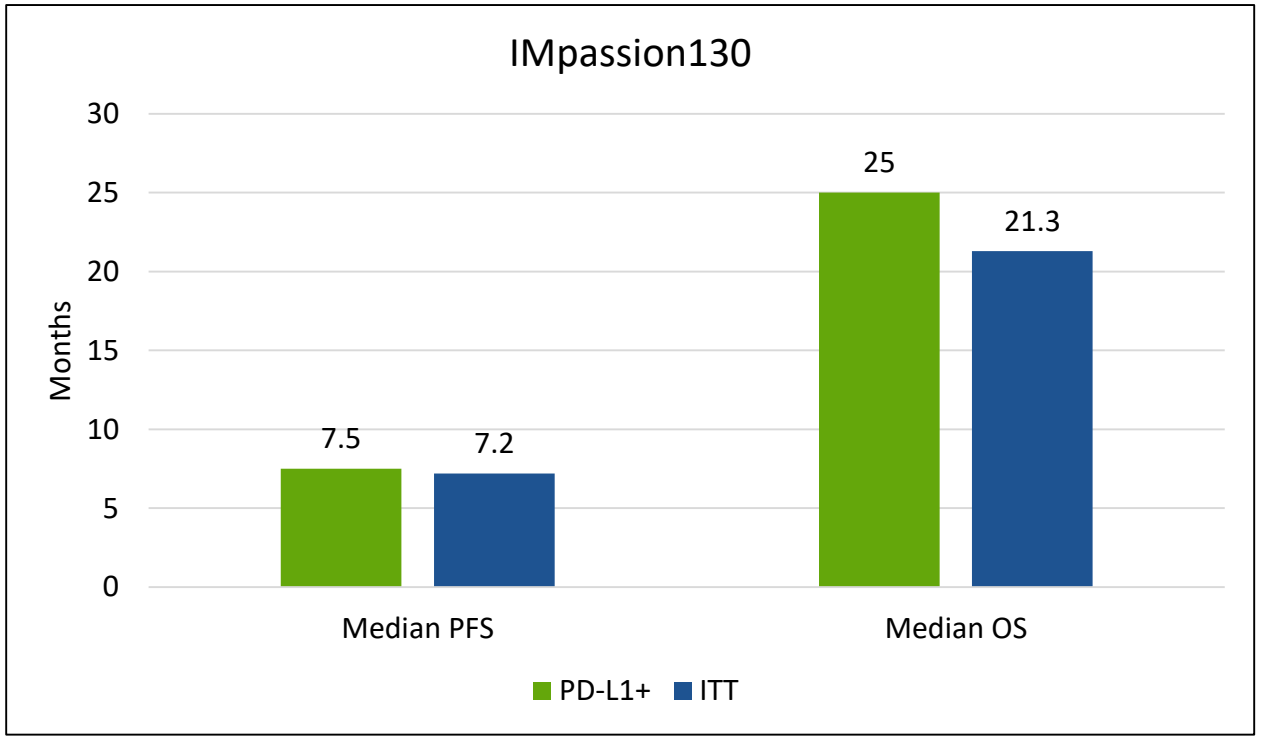
Biomarkers and immunotherapy responsiveness in breast cancers

- Potential markers of responsiveness include:
  - PD-L1
  - Tumor infiltrating lymphocytes
  - Mutational signatures

Here, patients with PD-L1 on ≥ 1% of tumor-infiltrating immune cells had improved outcomes on atezolizumab + chemotherapy compared to the general population (OS HR 0.62 vs 0.84)

However, PD-L1 expression does not always correlate with response to all ICIs.



Schmid, N Engl J Med 2018.

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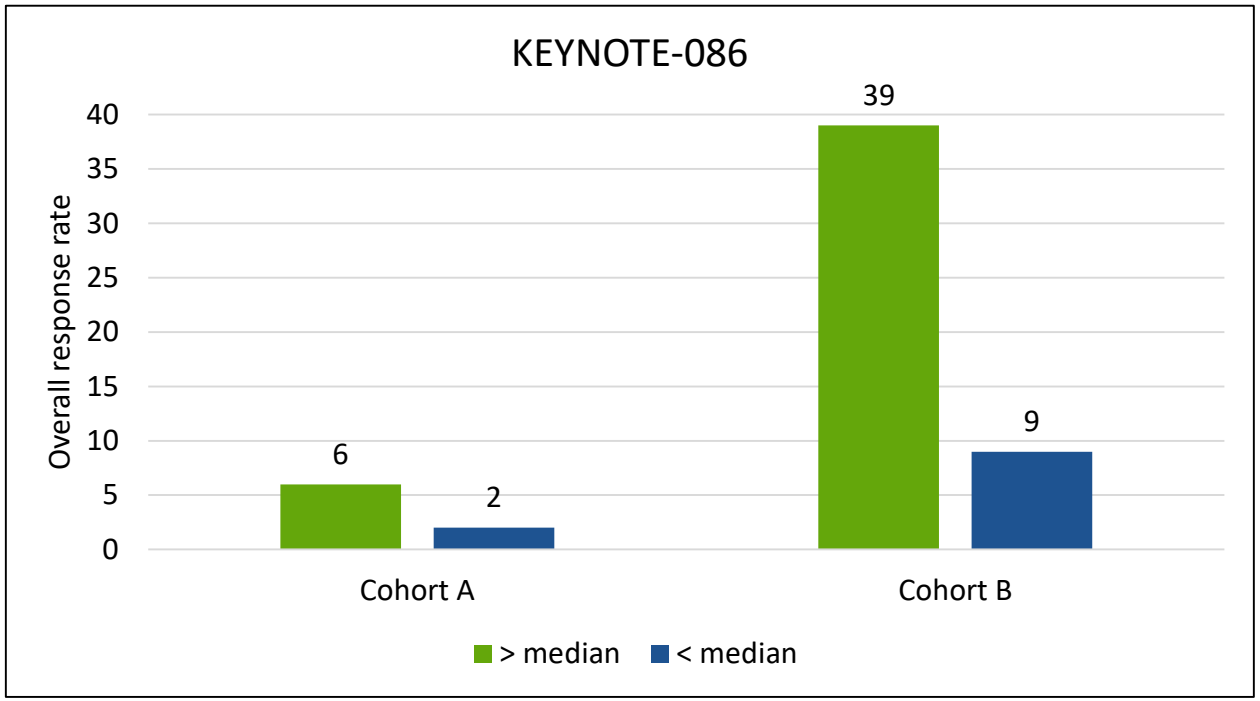
Biomarkers and immunotherapy responsiveness in breast cancers

- Potential markers of responsiveness include:
  - PD-L1
  - Tumor infiltrating lymphocytes
  - Mutational signatures

Here, patients with a tumor infiltrating lymphocyte level greater than the median level had improved outcomes when treated with pembrolizumab, particularly in the front-line setting (cohort B).



**Not an FDA-approved biomarker for treatment selection*

Adams, Ann Oncol 2019.

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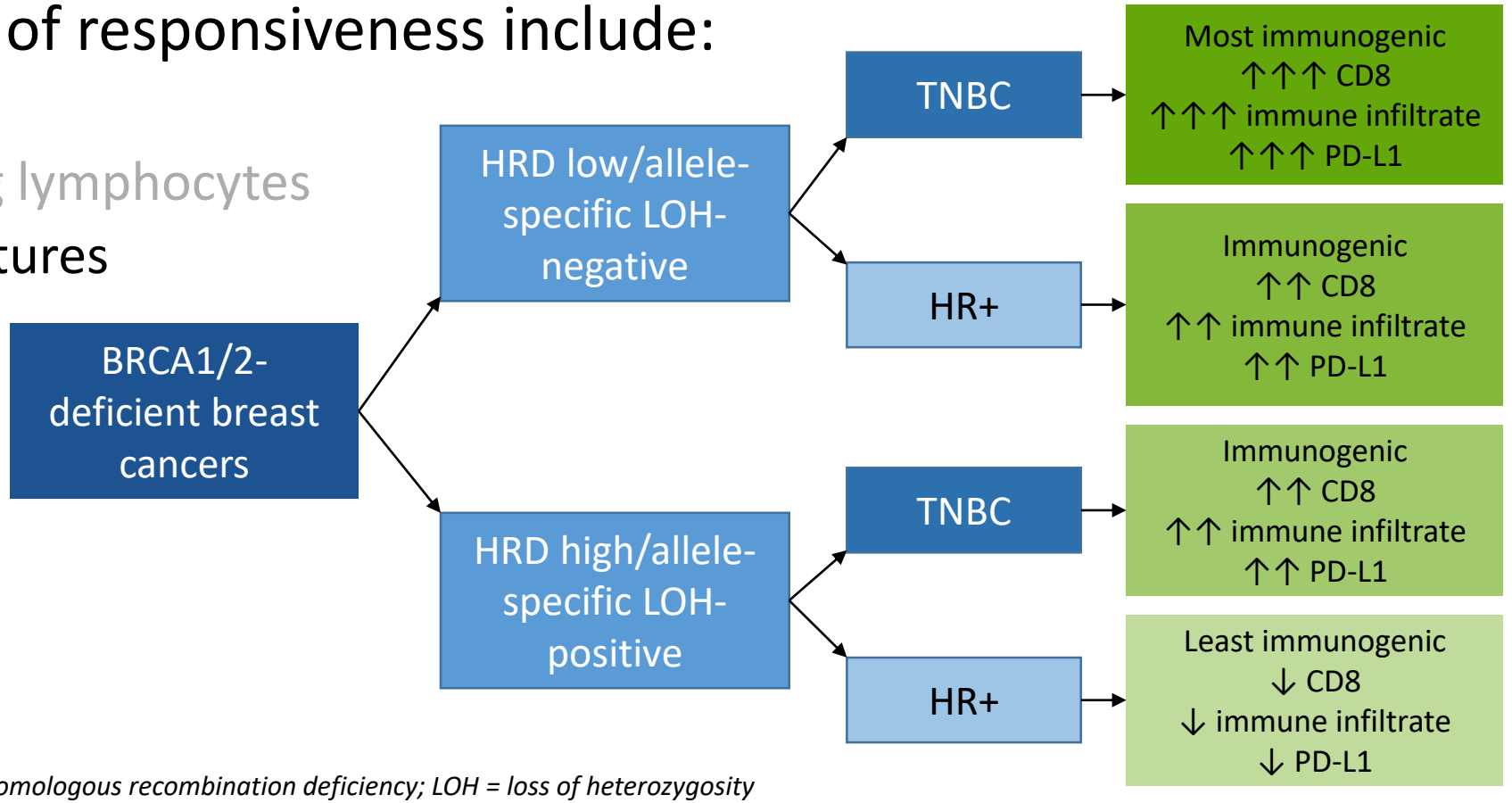
Biomarkers and immunotherapy responsiveness in breast cancers

- Potential markers of responsiveness include:
  - PD-L1
  - Tumor infiltrating lymphocytes
  - Mutational signatures

Pembrolizumab is also approved for MSI-H/TMB-H tumors

**BRCA/HRD not FDA-approved biomarkers for immunotherapies*



HRD = homologous recombination deficiency; LOH = loss of heterozygosity

Kraya, Clin Cancer Res 2019.

Conclusions

- Immunotherapy in breast cancers is expanding rapidly
- Immunotherapy in breast cancer shows promise in certain subtypes

Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Case Studies

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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Case Study 1

65 y.o. woman with de novo stage 4 TNBC with metastatic disease to the bone, liver, and lung presents for initial consultation. She has not received any treatment in the metastatic setting.

1. What is the first step in evaluating her disease to determine the 1st line therapy?
    A. Initiate chemotherapy with Gemcitabine plus carboplatin
    B. Biopsy metastatic site and send off for PD-L1 IHC
    C. Initiate radiation to the liver lesions
    D. Initiate endocrine therapy with tamoxifen

2. The patient initiates 1st line therapy, on her first restaging scan at 3 months, she has achieved PR. She feels well and continues on current therapy. What are the routine labs for patients like her?
    A. CBC with diff
    B. CMP
    C. TFTs
    D. All of the above

3. Her TSH on routine labs was found to be elevated at 10, she is asymptomatic, what is the next step?
    A. Admit patient to the hospital
    B. Do nothing
    C. Begin levothyroxine
    D. All of the above