Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Breast & Gynecologic Cancers

David B. Page, MD

Medical Oncology, Earle A. Chiles Research Institute,

Providence Cancer Institute

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

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Disclosures

- Consulting Fees: Genentech, Merck, Brooklyn Immunotherapeutics
- Fees for Non CE Services Received Directly from an Ineligible Entity or their Agents: Genetech, Novartis
- Contracted Research: Merck, Brooklyn Immunotherapeutics, BMS
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy in breast and gynecologic cancers

- Standard-of-care treatment usually involves surgery, chemotherapy, radiation
- Application of immunotherapy is still in early stages

Estimated new cases

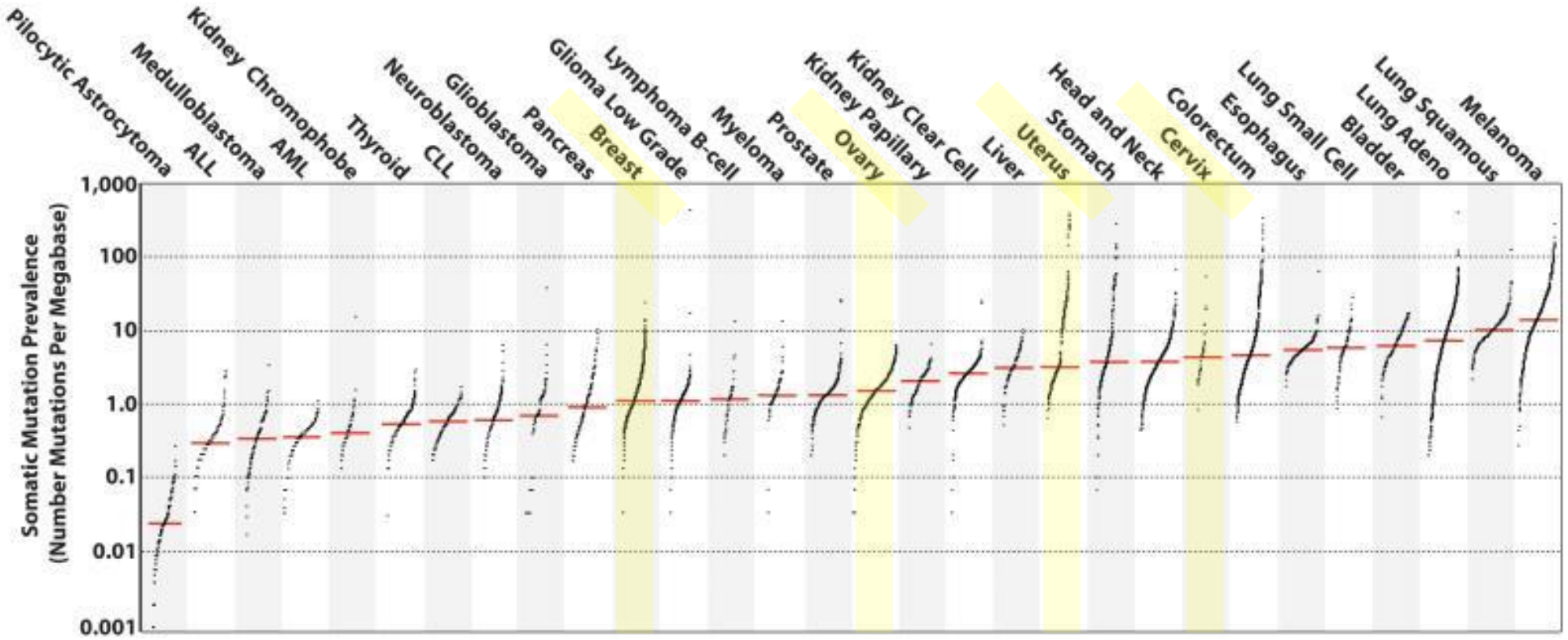
Female		
Breast	276,480	30%
Lung & bronchus	112,520	12%
Colon & rectum	69,650	8%
Uterine corpus	65,620	7%
Thyroid	40,170	4%
Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	34,860	4%
Kidney & renal pelvis	28,230	3%
Pancreas	27,200	3%
Leukemia	25,060	3%
All sites	**912,930**	

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.

Immunotherapy in breast and gynecologic cancers



Alexandrov, Nature 2013.

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Outline

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

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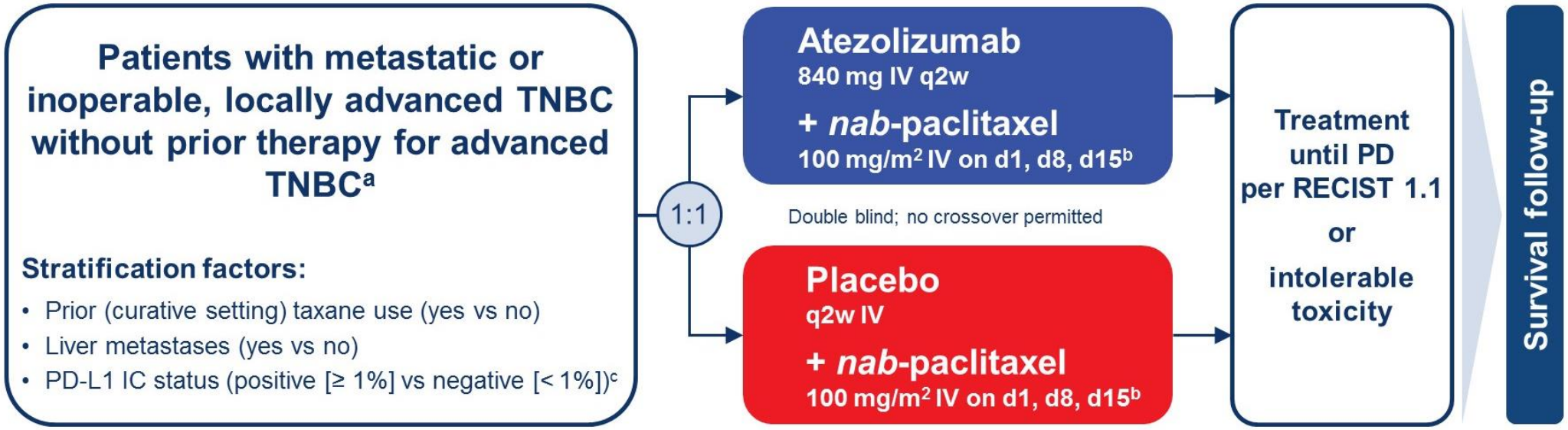
Current approvals in breast cancer

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	Advanced/Metastatic TNBC with PD-L1 ≥10% CPS	200mg Q3W or 400mg Q6W + chemotherapy: (gemcitabine/carboplatin, paclitaxel, or nab-paclitaxel)

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 Data – IMpassion130 PD-L1+ TNBC

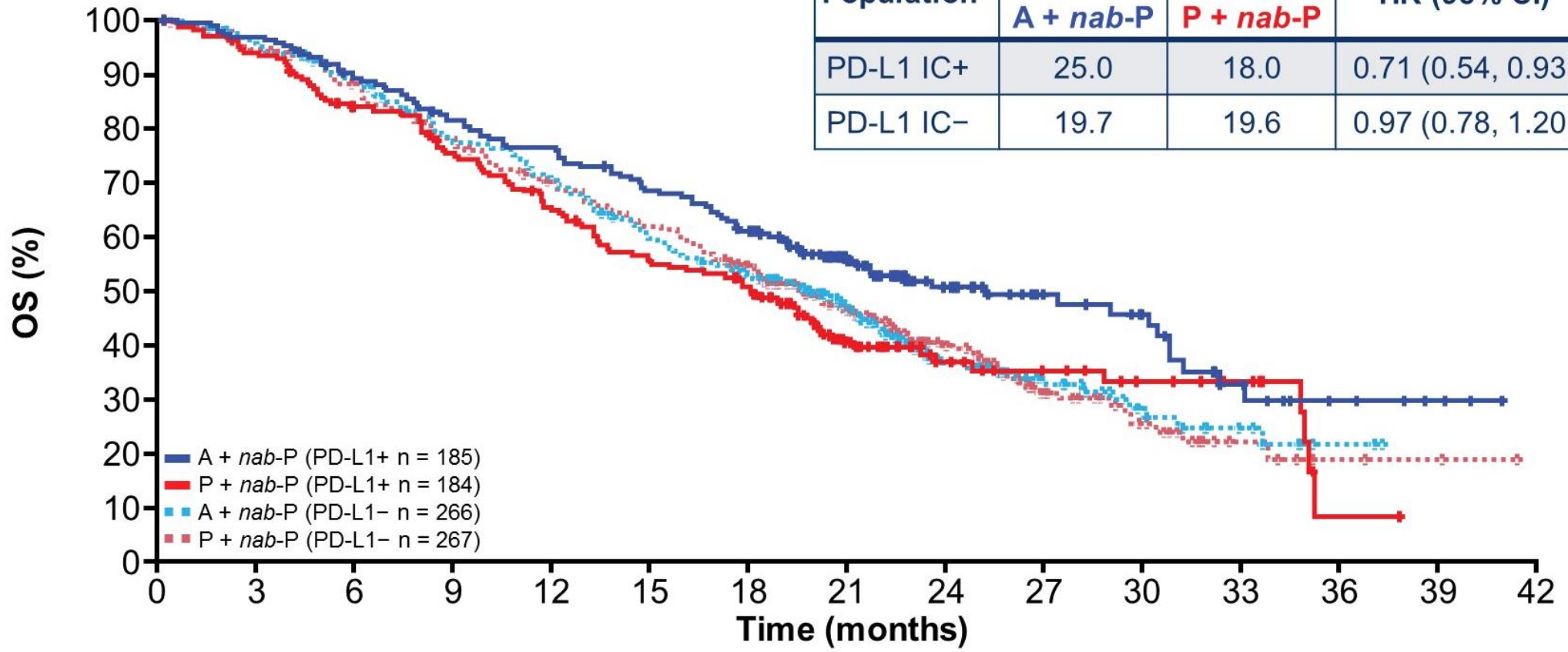


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

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.

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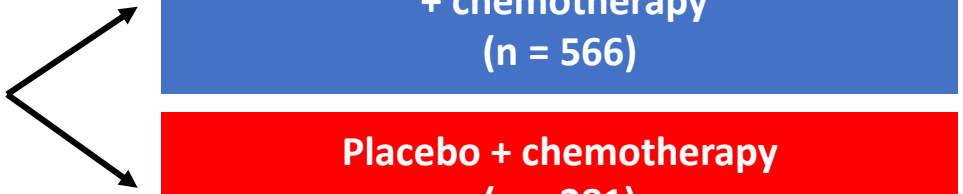
Clinical Data – Keynote 355
PD-L1+ TNBC

1st line advanced/metastatic TNBC
(curative intent chemo ≥ 6 mos)
Stratification:
1) Chemo (taxane v. gem/carbo)
2) PD-L1 CPS <1 v. >1%
3) Prior exposure to same chemo



Tx until progression, toxicity, or 35 cycles

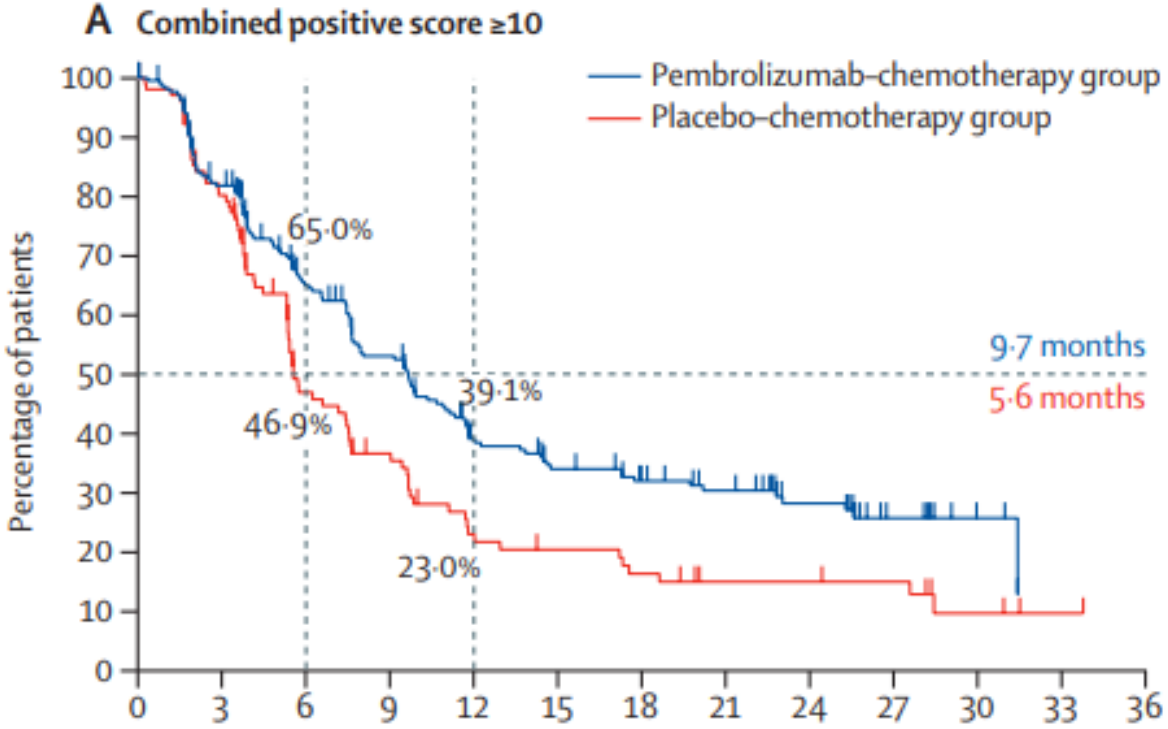
*Investigator's choice of chemotherapy:
- Nab-paclitaxel 100 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- Paclitaxel 90 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- Gemcitabine 1000 mg/m^2 + carboplatin AUC 2 on Days 1, 8 of 21-day cycle

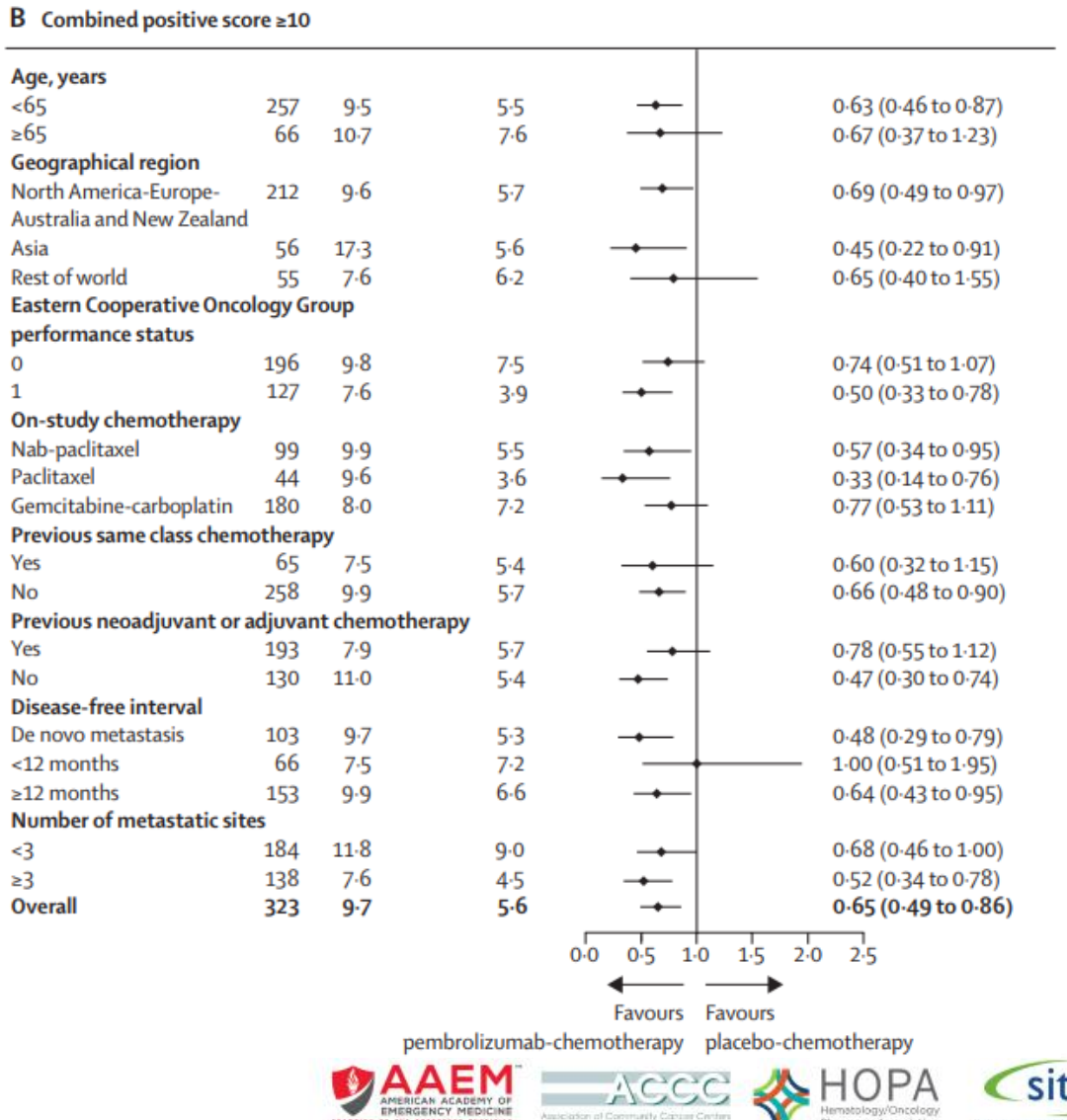
Co-primary endpoints: PFS and OS (PD-L1 CPS ≥ 10, PD-L1 CPS ≥ 1, and ITT)

Secondary endpoints: ORR, response duration, disease control rate, safety

Cortes. ASCO 2020. Abstr 1000; Cortes et al., Lancet 2020

Clinical Data – Keynote 355 PD-L1+ TNBC





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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.

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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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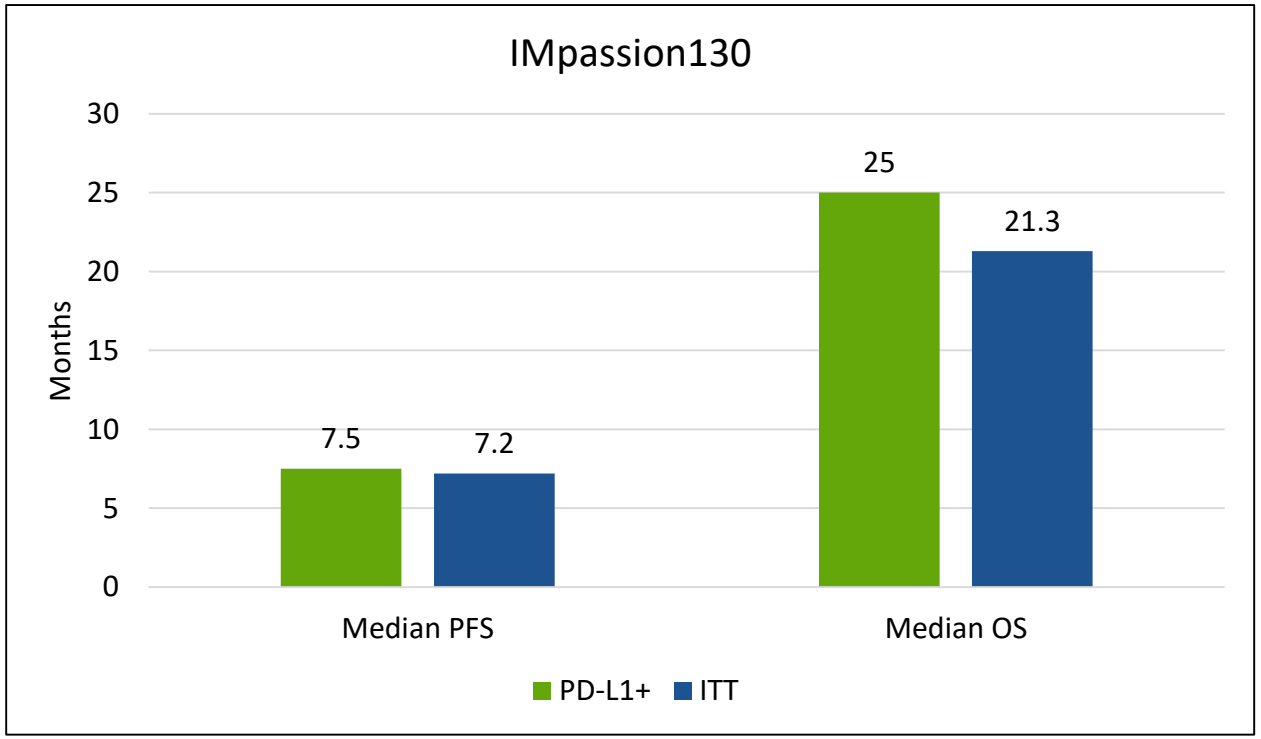
Biomarkers and immunotherapy responsiveness in breast cancers

- 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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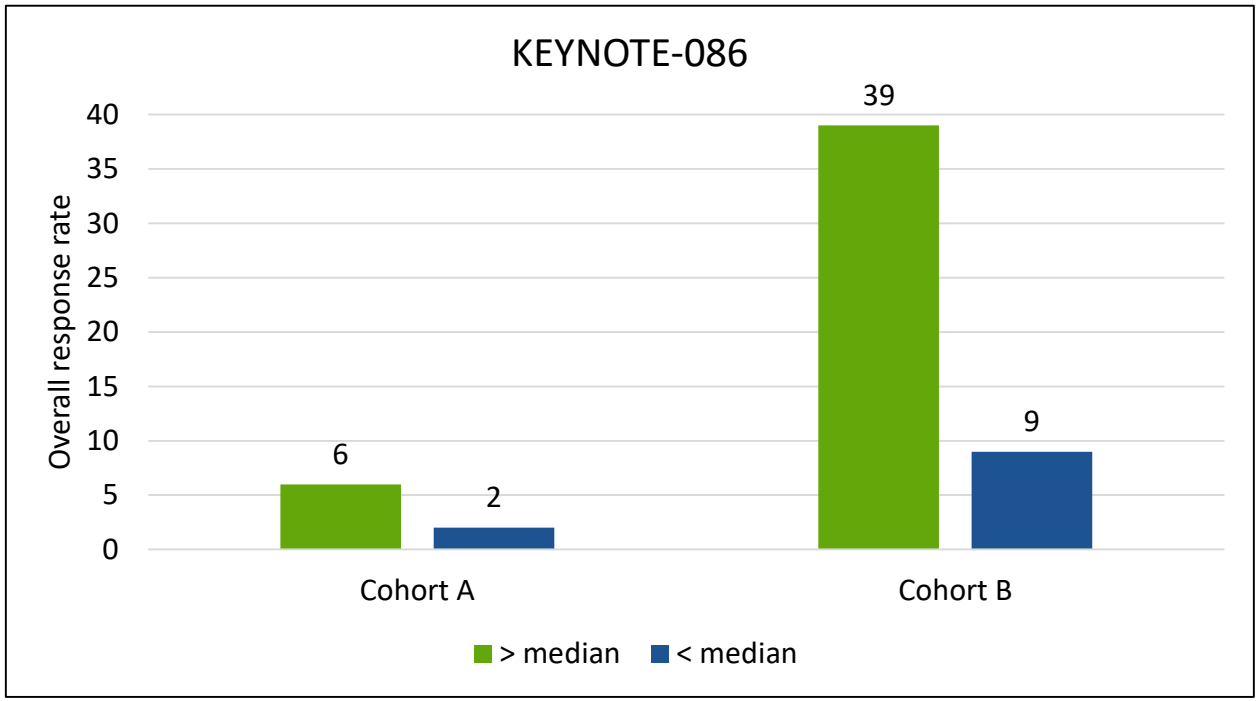
Biomarkers and immunotherapy responsiveness in breast cancers

- 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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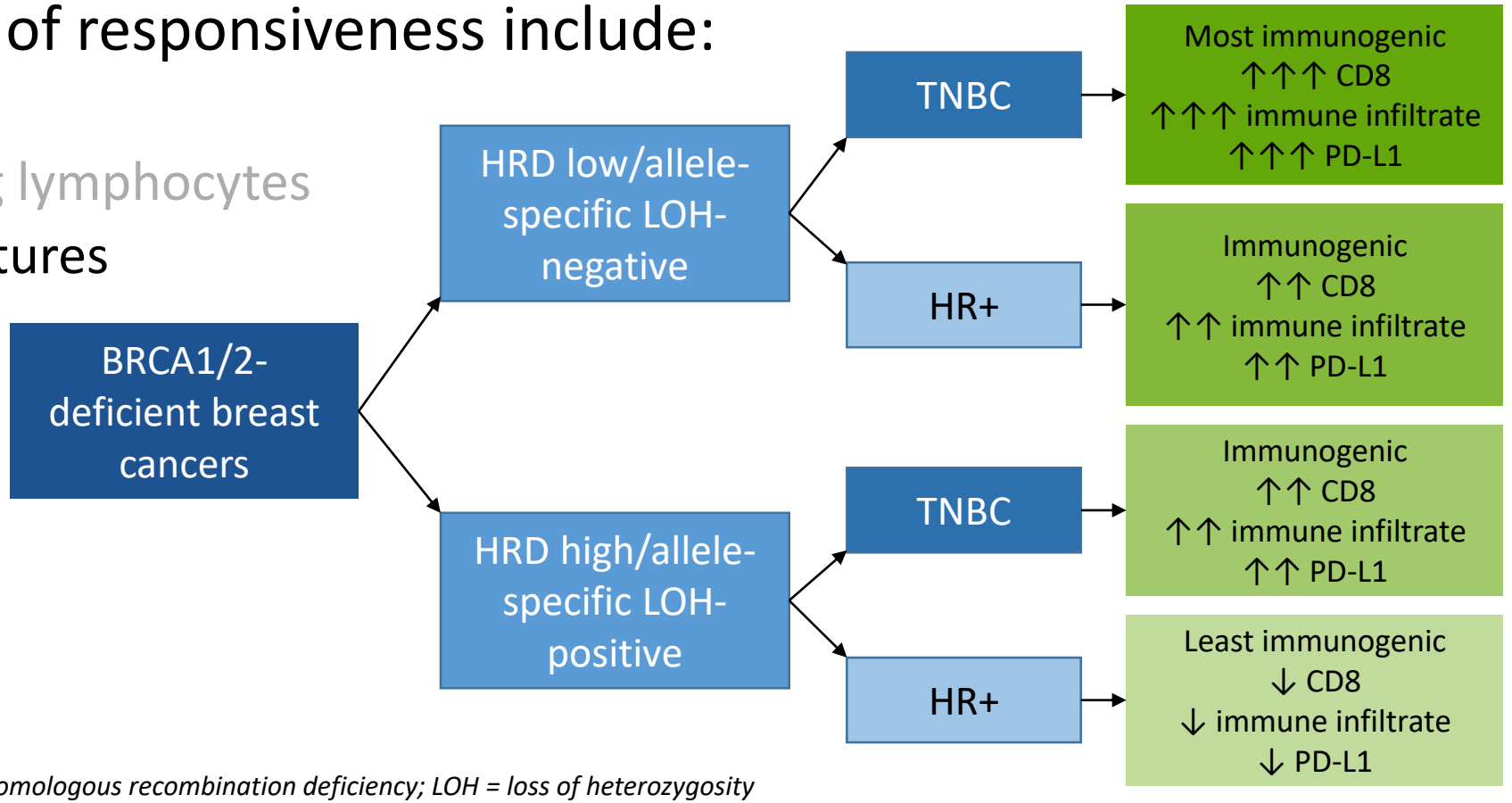
Biomarkers and immunotherapy responsiveness in breast cancers

- 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.

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Current approvals in gynecologic cancers

Drug	Approved	Indication	Dose
HPV vaccination	2006 and many subsequent	Prevention of HPV infection	Depends on product
Pembrolizumab	2017	MSI-H/dMMR **advanced cancer** with progression on previous treatment (includes especially **endometrial**)	200 mg Q3W or 400 mg Q6W
Pembrolizumab	2018	Recurrent/metastatic **cervical cancer** with PD-L1 (CPS ≥1) and progression on previous therapy	200 mg Q3W or 400 mg Q6W
Pembrolizumab + lenvatinib	2019	**Endometrial cancer** – not MSI-H/dMMR, after progression on systemic therapy	Pembrolizumab 200 mg Q3W + lenvatinib 20 mg daily
Pembrolizumab	2020	TMB-high **solid tumors** with progression on prior treatment	200 mg Q3W or 400 mg Q6W

Clinical Data – KEYNOTE-158
Cervical Cancer

Patients with advanced cervical cancer with progression on one or more standard therapies

ECOG 0-1
Measurable disease
No CNS metastases
No autoimmune disease
No prior checkpoint inhibitors

→

Pembrolizumab 200 mg Q3W

Up to two years

→

Primary: Objective response rate

Secondary: Duration of response; Progression-free survival; Overall survival

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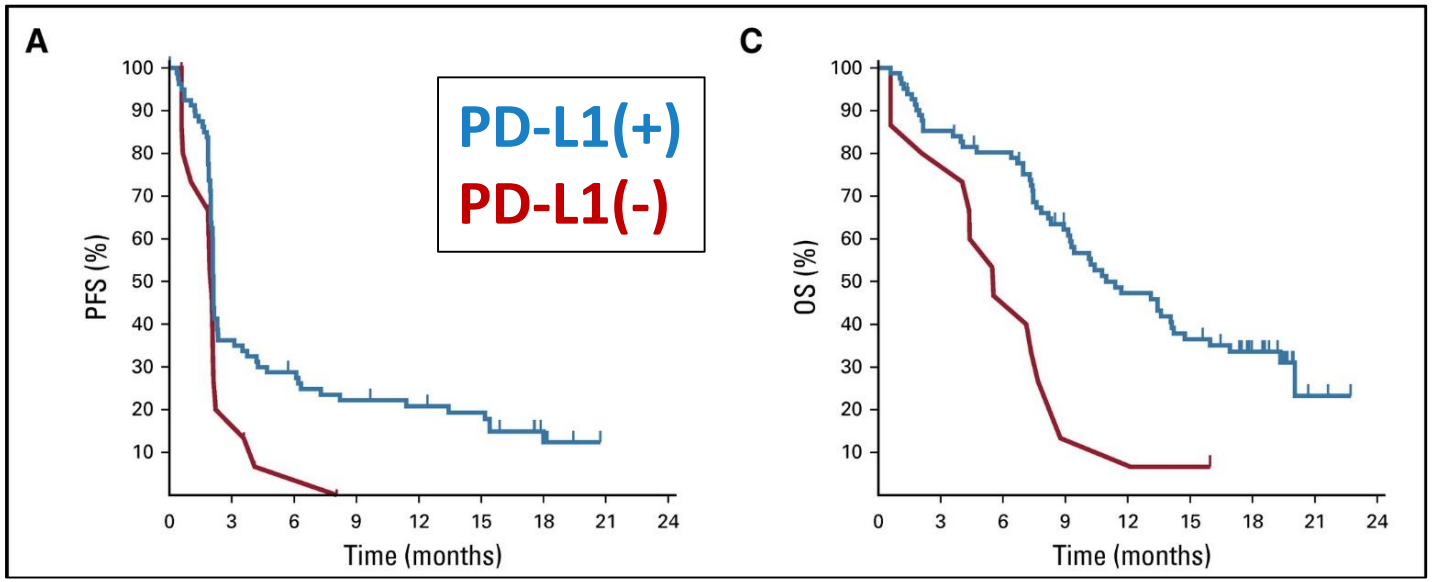
Clinical data – KEYNOTE-158
Cervical cancer

- Pembrolizumab monotherapy
- All responses were in PD-L1+ tumors
- Most patients had prior treatment
- Median duration of response was not reached at 10 months follow-up



Cheol Chung, J Clin Oncol 2019.

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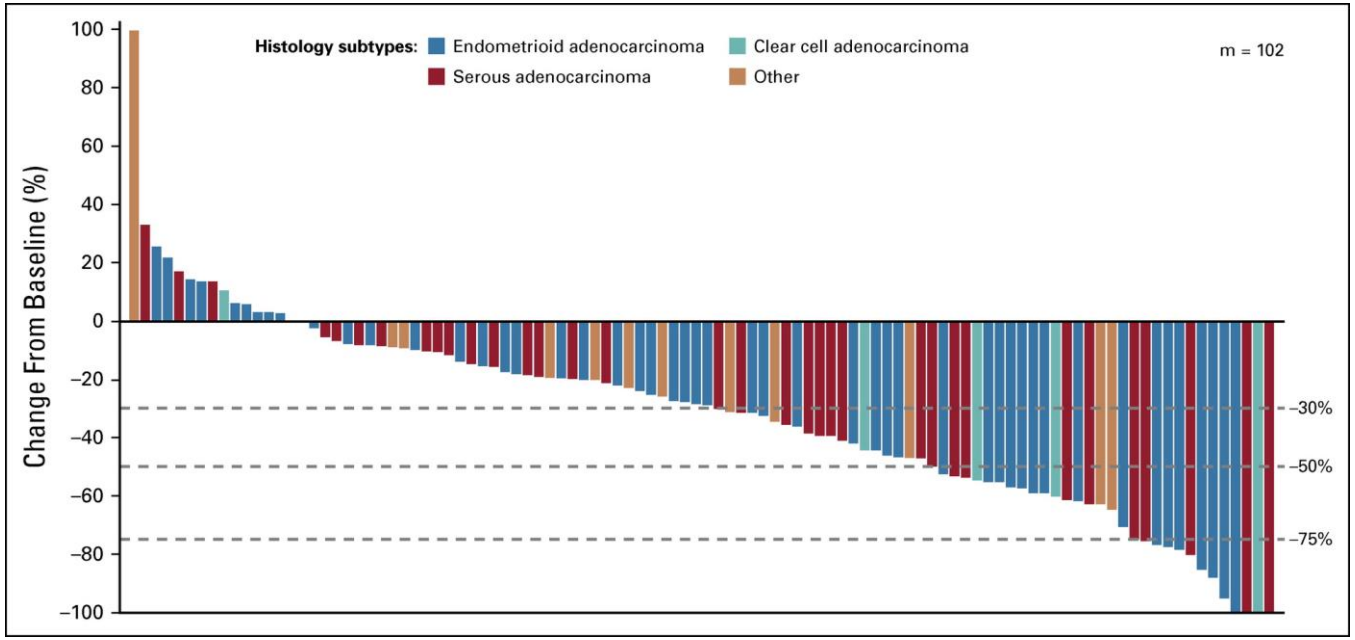
Clinical data – KEYNOTE-146
Endometrial cancer

- Previously treated
- Pembrolizumab + lenvatinib
- No difference by PD-L1 status
- Higher response rate in MSI-high than MSS: 63.6% vs 37.2% ORR



Makker, J Clin Oncol 2020.

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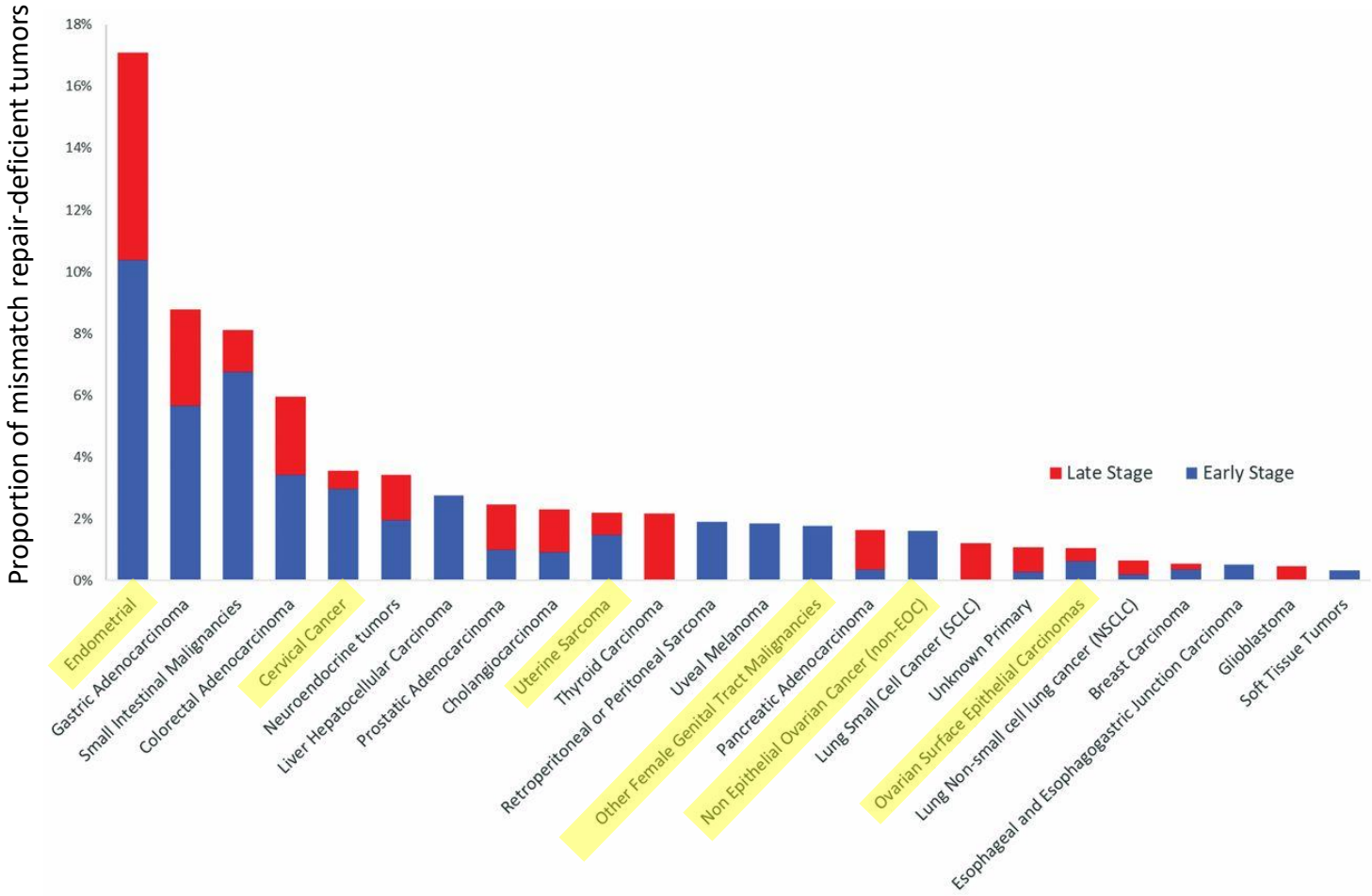
Clinical data – pembrolizumab in MSI-high cancers



Le, Science 2017.

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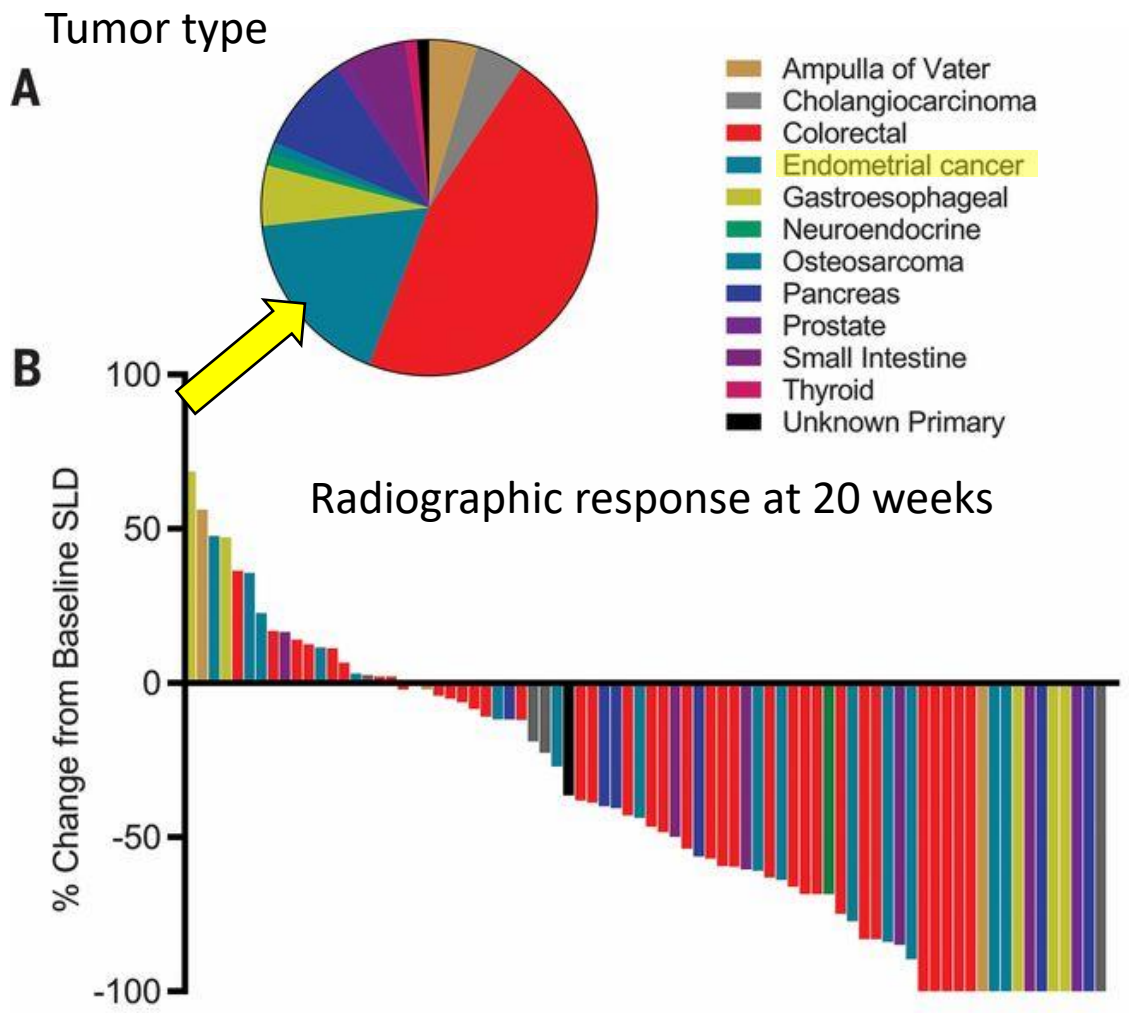
Clinical data – pembrolizumab in MSI-high cancers



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

Le, Science 2017.

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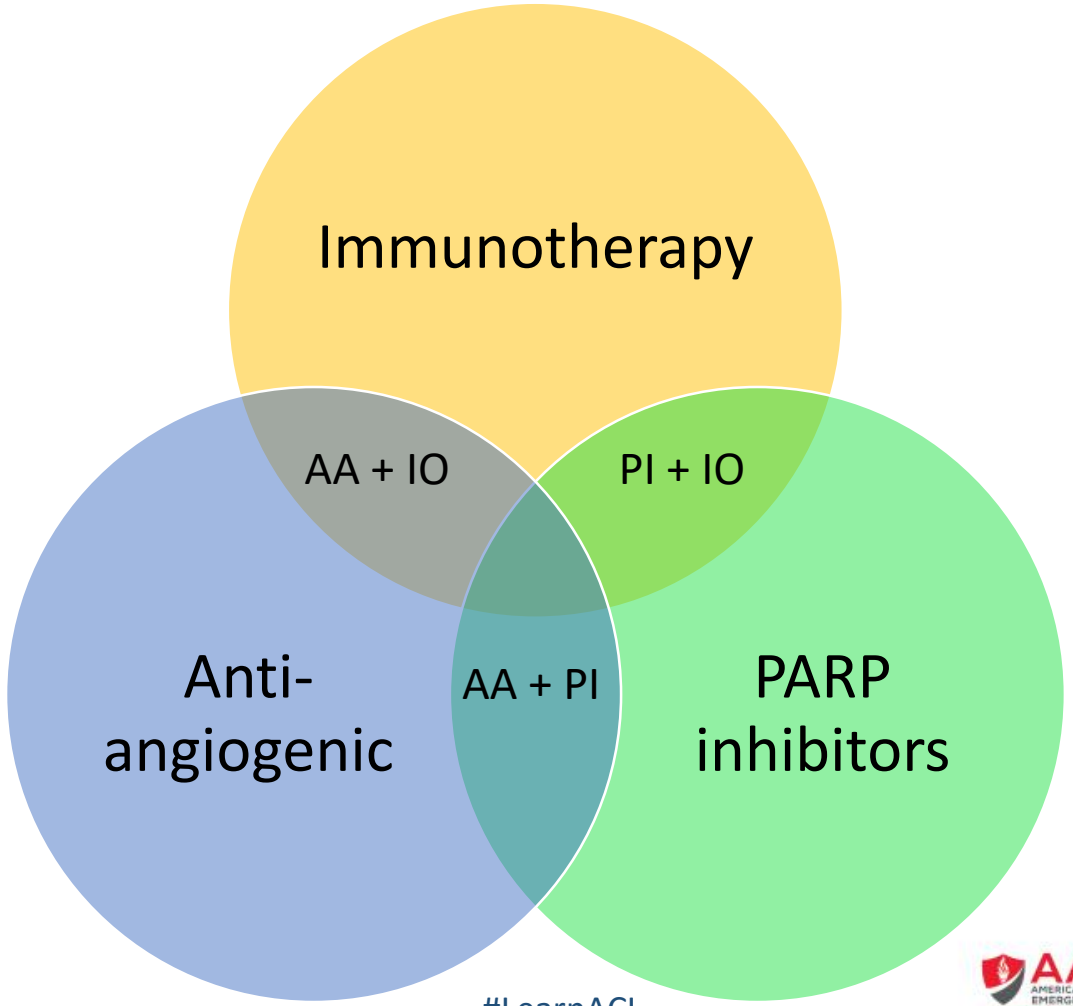
In development: Therapeutic strategies in ovarian cancer



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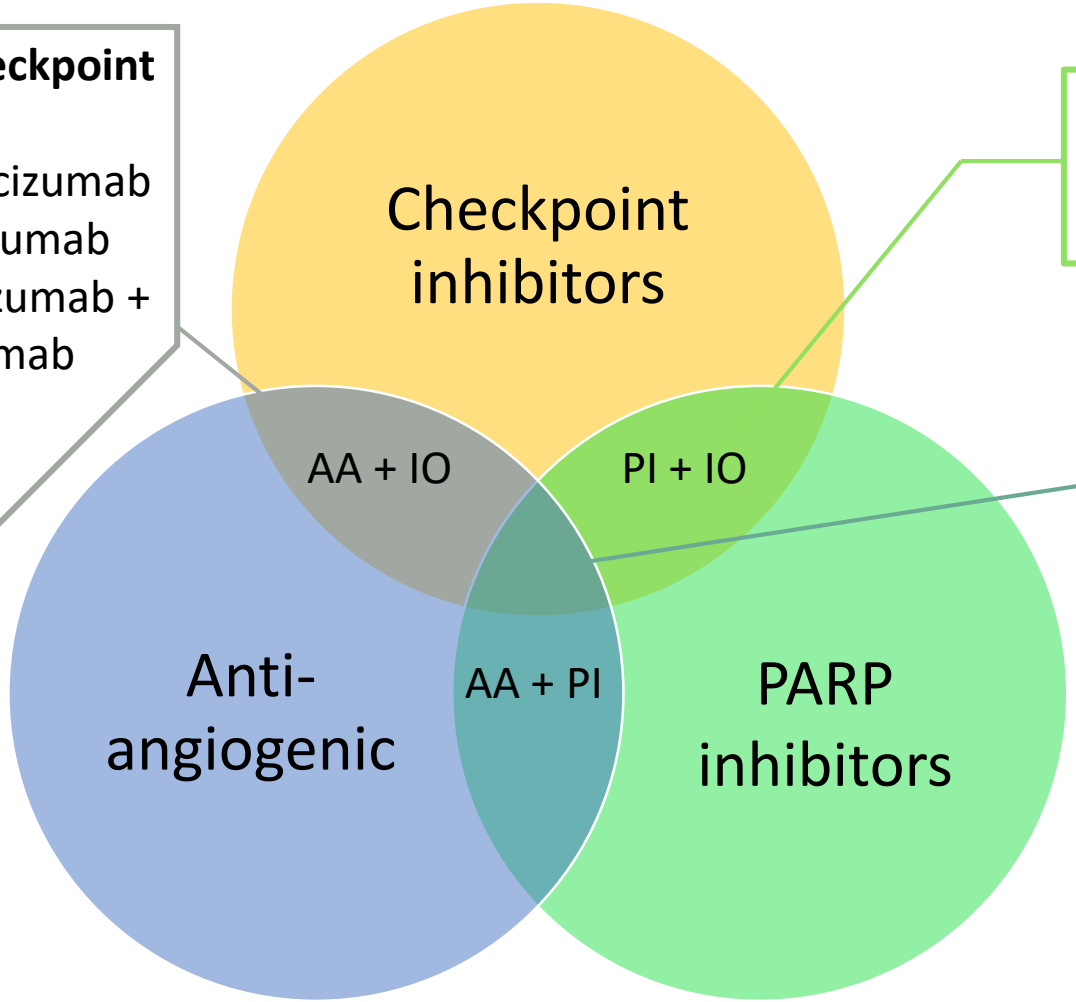
In development: Therapeutic strategies in ovarian cancer

Anti-angiogenic + checkpoint inhibitor

- IMaGYN050: Bevacizumab + chemo + atezolizumab
- ATALANTE: Bevacizumab + chemo + atezolizumab
- NRG-GY009: PLD + atezolizumab + bevacizumab



PARP inhibitors + checkpoint inhibitors

- ATHENA: Rucaparib + nivolumab
- ANITA: Niraparib + atezolizumab

Anti-angiogenic + PARP inhibitor + checkpoint inhibitor

- FIRST: niraparib + anti-PD-1 ± bevacizumab
- ENGOT-ov46/DUO-O: bevacizumab + durvalumab + olaparib
- ENGOT-ov43: Pembrolizumab + olaparib ± bevacizumab

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In development: Therapeutic strategies in cervical cancer

HPV-targeted strategies

Checkpoint inhibitors
+
Radiotherapy

Checkpoint inhibitors
+
Targeted therapy

Two checkpoint inhibitors

In development: Therapeutic strategies in cervical cancer

- HPV-specific TIL therapy
- HPV peptide vaccination ± checkpoint inhibitors

HPV-targeted strategies

Checkpoint inhibitors + Radiotherapy

- NiCOL: nivolumab + chemoradiation
- NCT02635360: pembrolizumab + chemoradiation
- ATEZOLACC: atezolizumab + chemoradiation

- NCT03816553: anti-PD-1 + apatinib
- NCT02921269: atezolizumab + bevacizumab

Checkpoint inhibitors + Targeted therapy

Two checkpoint inhibitors

- NCT03894215 and NCT03495882: anti-PD-1 + anti-CTLA-4

Kagabu, Healthcare 2019.

Conclusions

- Immunotherapy in breast and gynecologic cancers is expanding rapidly
- Immunotherapy in breast cancer shows promise in certain subtypes
- Single-agent immunotherapy in ovarian cancer has low response rates, so combinations currently under investigation
- Cervical cancer and HPV-associated cancers present unique treatment options

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Case Studies

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

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Case Study 1

35y F presented in 2018 with clinical stage II (3cm, node positive) triple negative breast cancer in left breast.

Treatment:

- neoadjuvant chemotherapy (adriamycin, cyclophosphamide, paclitaxel)
- Lumpectomy, selective LN dissection (excellent near- complete response “RCB-1”)
- Adjuvant radiotherapy

2 years later, shortness of breath, COVID-19+ but pulmonary nodules on CT chest, biopsy proven stage IV TNBC:

- PD-L1 CPS score: 50%
- Tumor exome sequencing: high tumor mutational burden (TMB)

Case Study 1

Question 1: What are FDA-approved first line therapies for this patient?

A. Pembrolizumab 400mg IV q6wk
B. Pembrolizumab 200mg IV q3wk + paclitaxel (3 weeks on, 1 week off)
C. Atezolizumab 840mg IV q2wk + nab-paclitaxel (3 weeks on, 1 week off)
D. All of the above
E. B & C
F. A & B

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C. Atezolizumab 840mg IV q2wk + nab-paclitaxel (3 weeks on, 1 week off)
D. All of the above
E. B & C
F. A & B

Explanation: Tumor is both high TMB and PD-L1-positive by CPS (companion diagnostic for pembrolizumab)

Case Study 1

Question 2: Patient opts for pembrolizumab 200mg IV q3wk + paclitaxel. How should the patient be counseled on the expected outcome of anti-PD-1/L1 in TNBC?

A. Shown to improve overall survival when added to chemo
B. Shown to improve progression free survival when added to chemo
C. Frequently results in durable disease-free survival (which could indicate cure)
D. A & B
E. B & C

Case Study 1

Question 2: Patient opts for pembrolizumab 200mg IV q3wk + paclitaxel. How should the patient be counseled on the expected outcome of anti-PD-1/L1 in TNBC?

A. Shown to improve overall survival when added to chemo
B. Shown to improve progression free survival when added to chemo
C. Frequently results in durable disease-free survival (which could indicate cure)
D. A & B
E. B & C

Explanation: OS has not yet been formally evaluated. Durable responses are less common in TNBC