Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Breast & Gynecologic Cancers

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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

- Research Grant: Alkermes
- 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

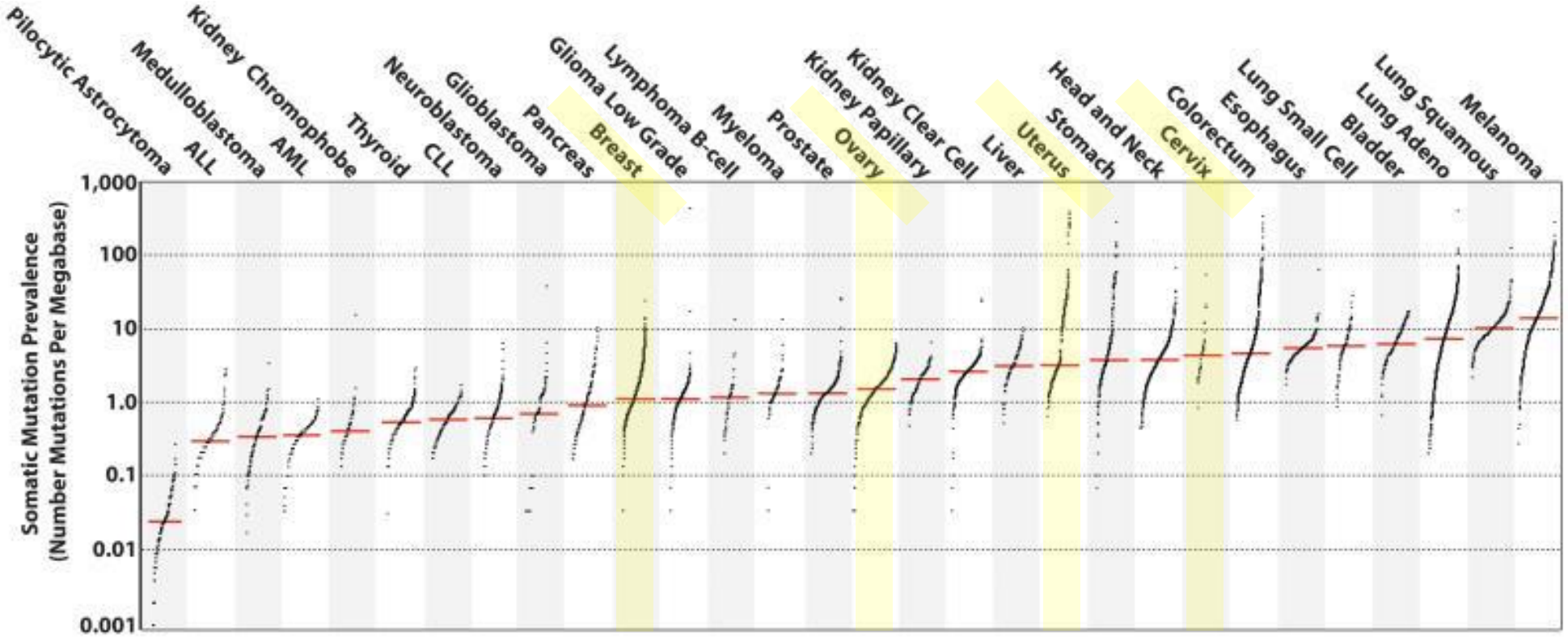
Female		
Breast	276,480	30%
Lung & bronchus	112,520	12%
Colon & rectum	69,650	8%
Uterine corpus	65,620	7%
Thyroid	40,170	4%
Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	34,860	4%
Kidney & renal pelvis	28,230	3%
Pancreas	27,200	3%
Leukemia	25,060	3%
All sites	**912,930**	

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

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

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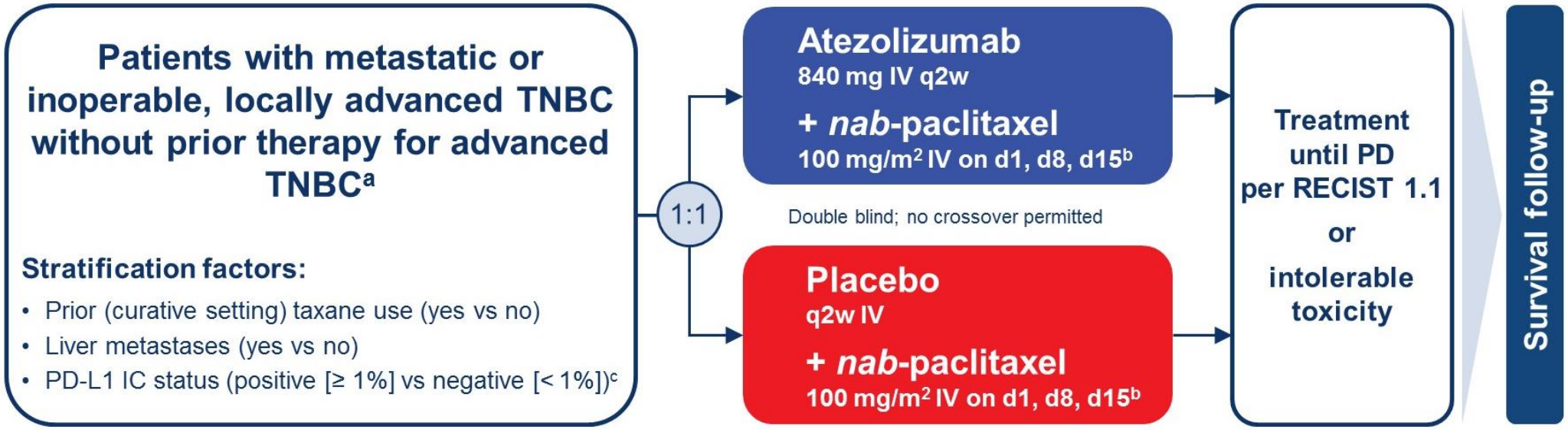
Clinical Data – IMpassion130 PD-L1+ TNBC

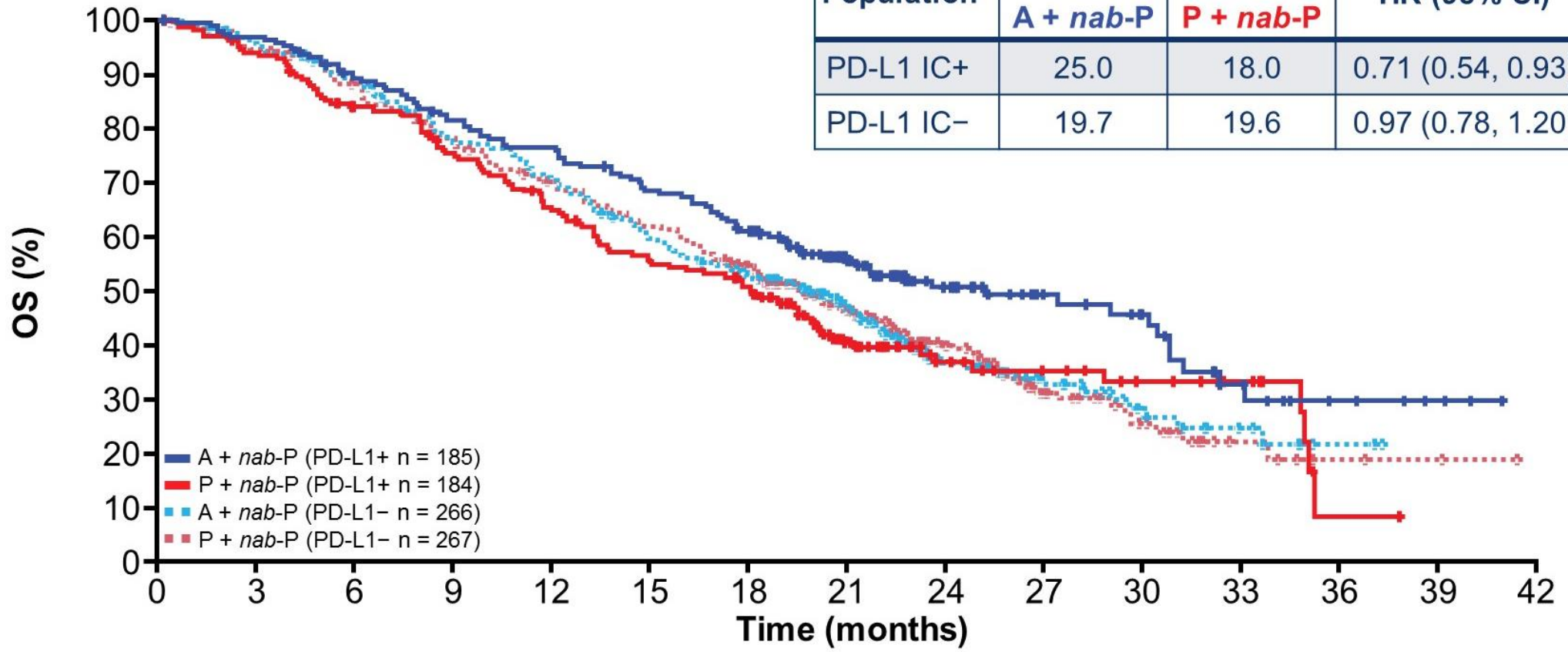


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

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 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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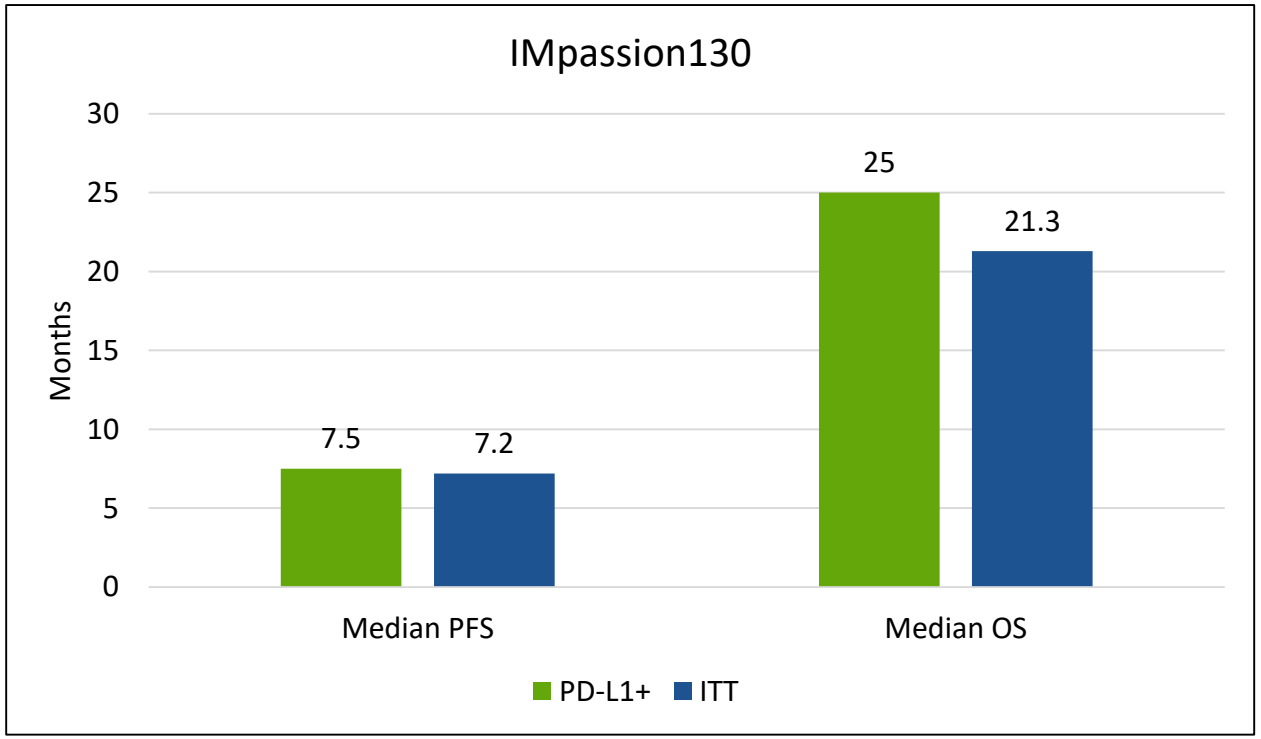
Biomarkers and immunotherapy responsiveness in breast cancers

- 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.

Biomarkers and immunotherapy responsiveness in breast cancers

- Potential markers of responsiveness include:
  - PD-L1
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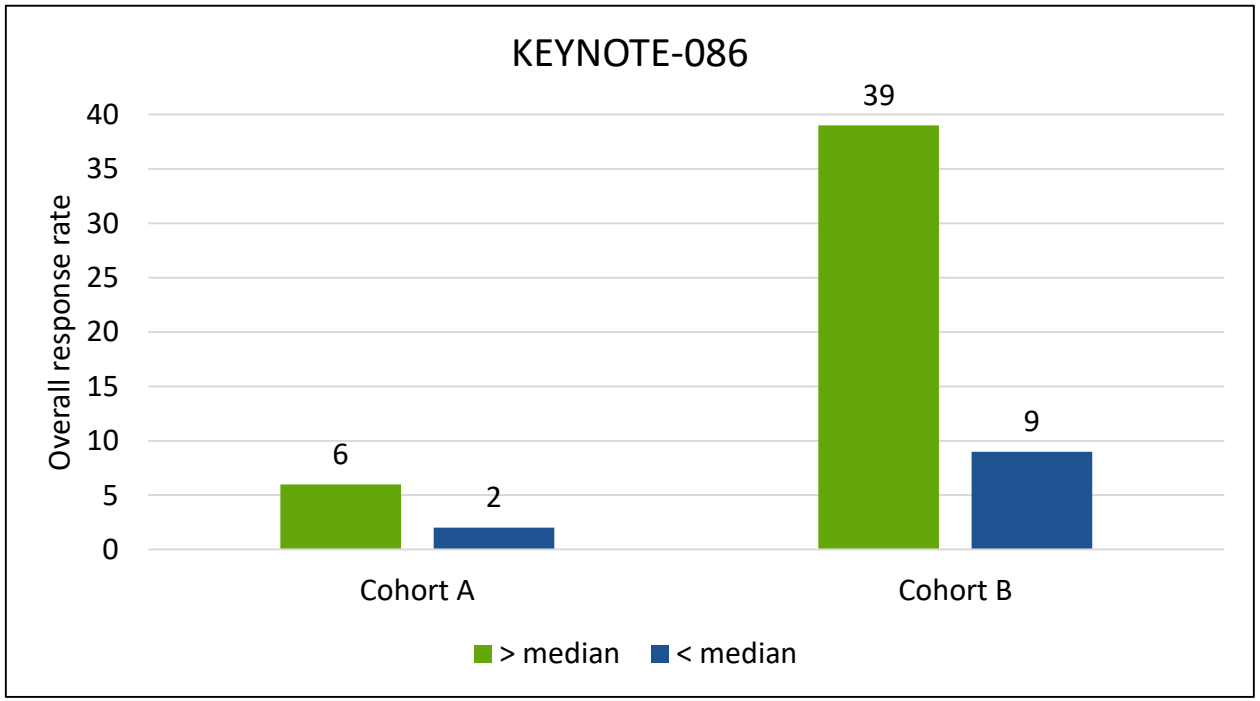
  - Mutational signatures

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:
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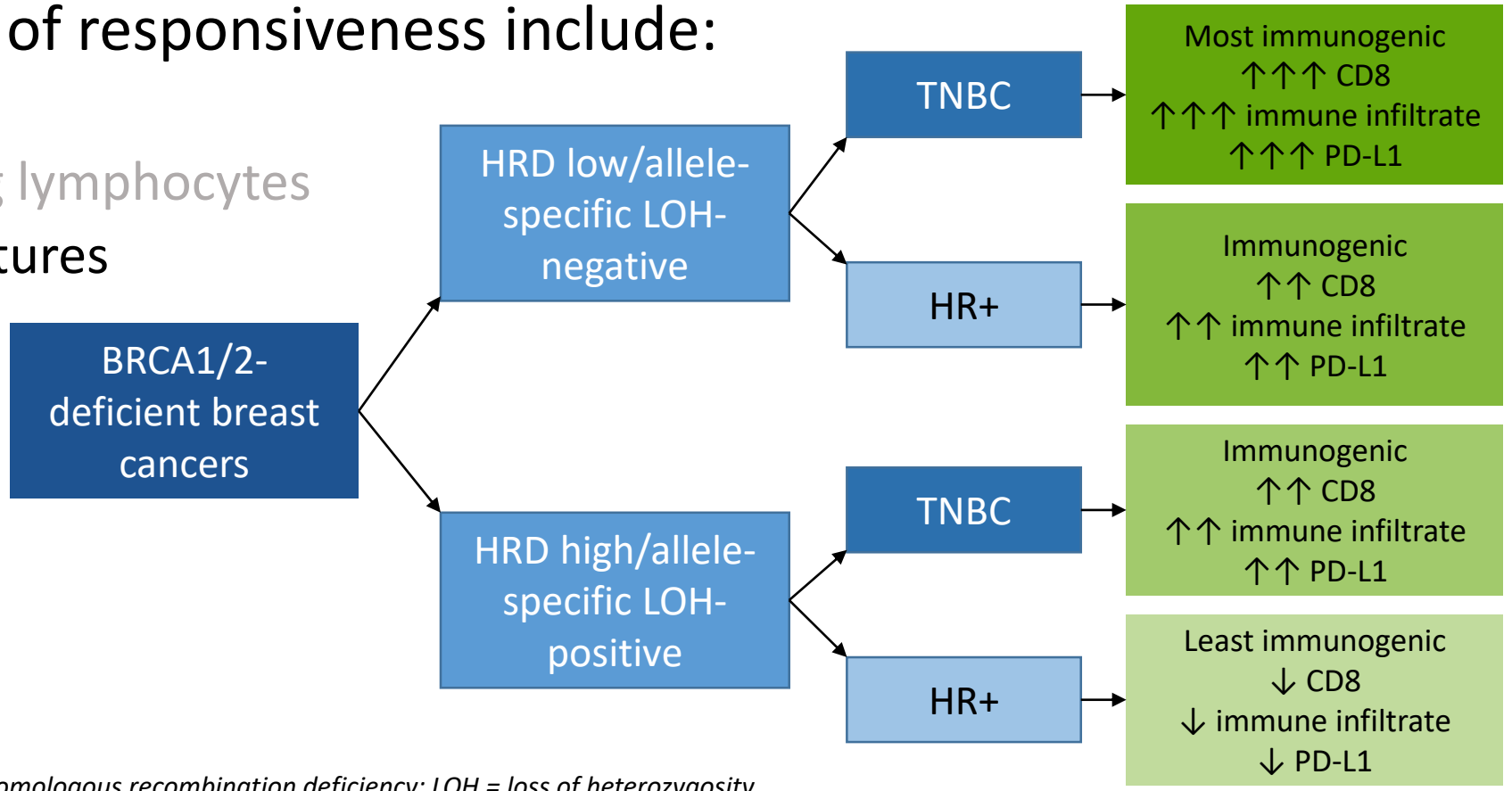
  - Mutational signatures



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

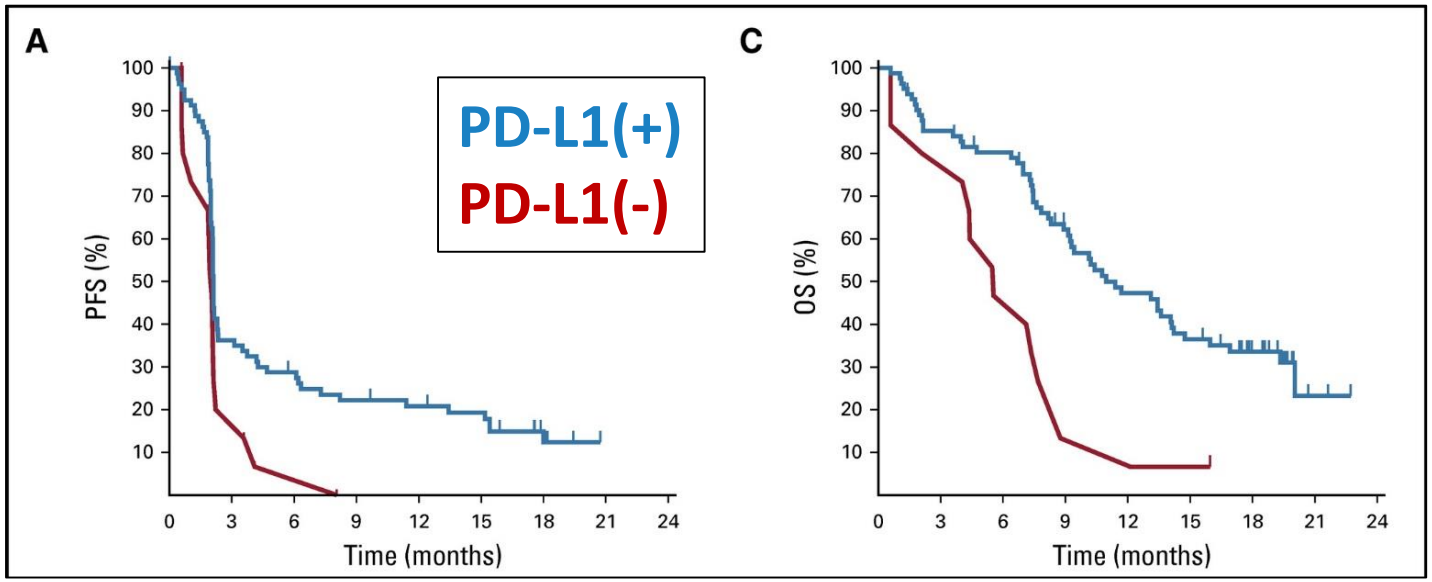
→

Primary: Objective response rate

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

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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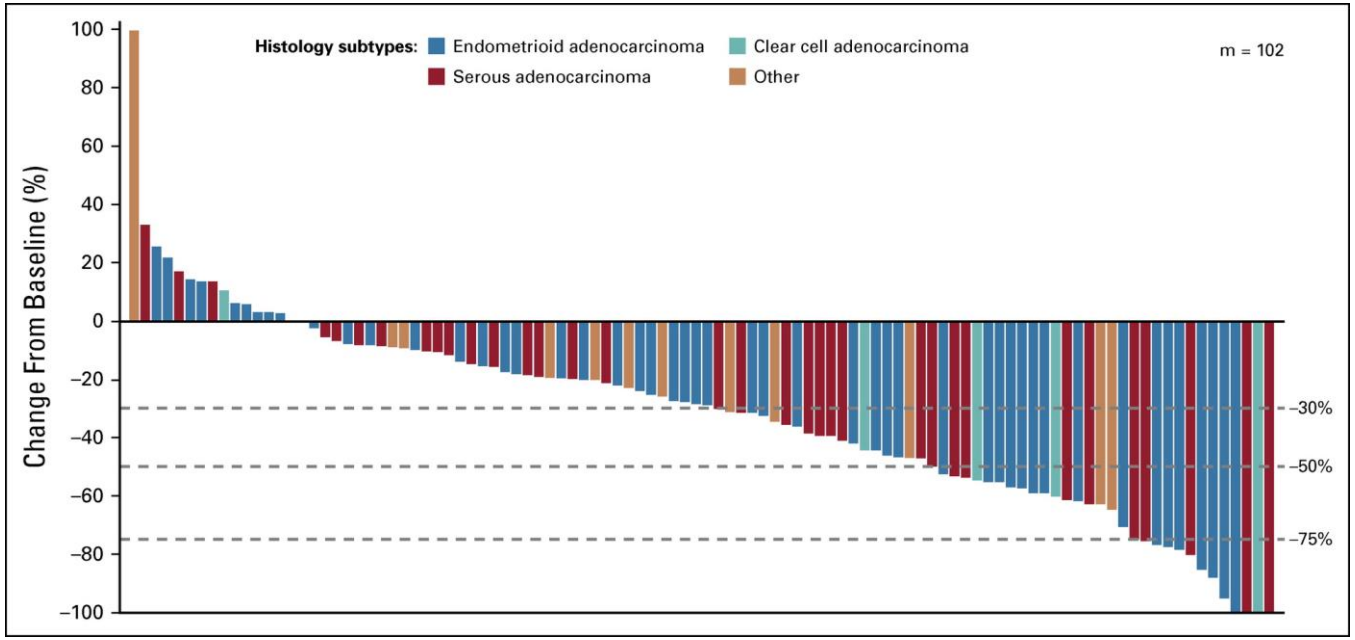
Clinical data – KEYNOTE-146
Endometrial cancer

- 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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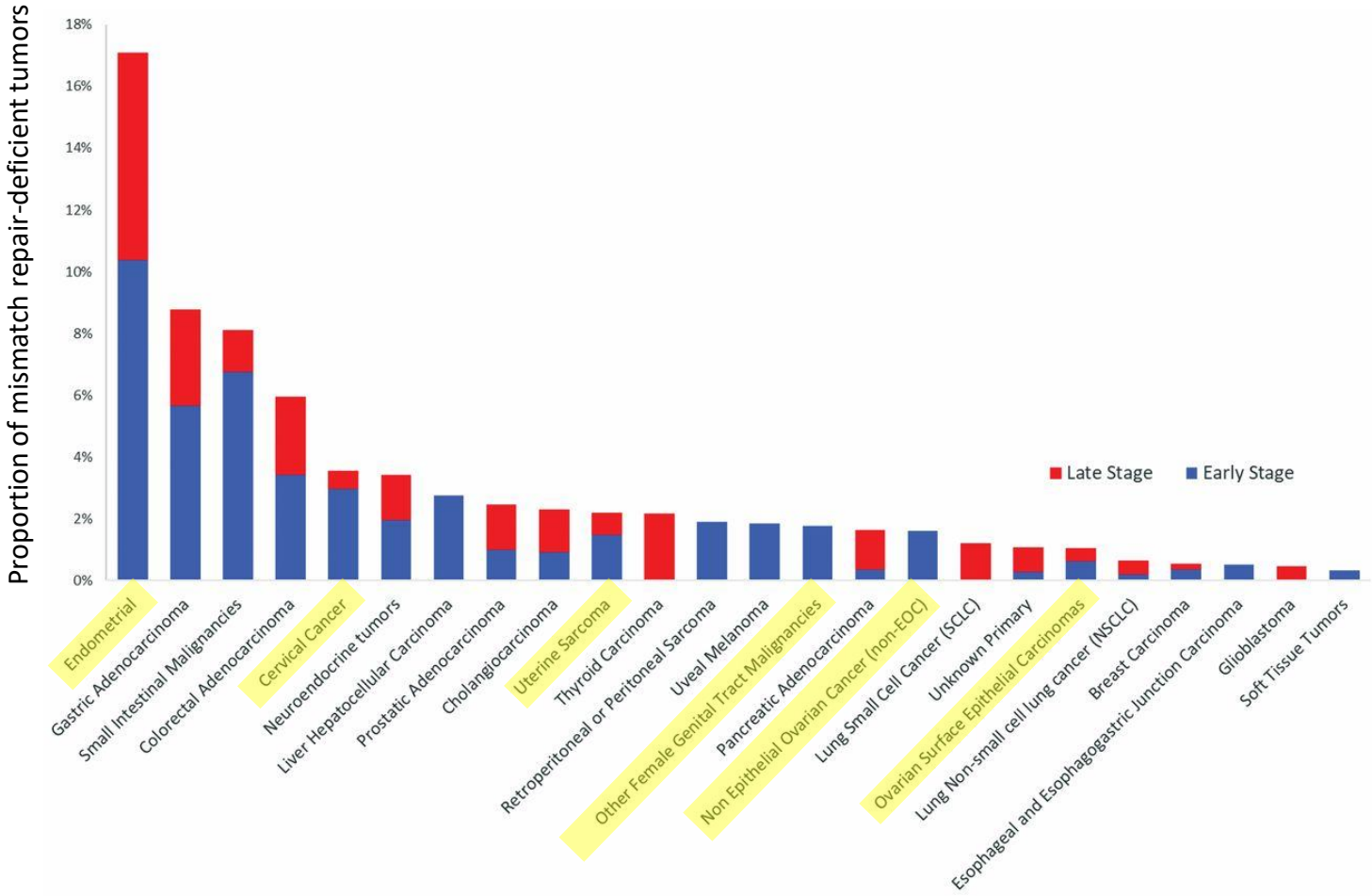
Clinical data – pembrolizumab in MSI-high cancers



Le, Science 2017.

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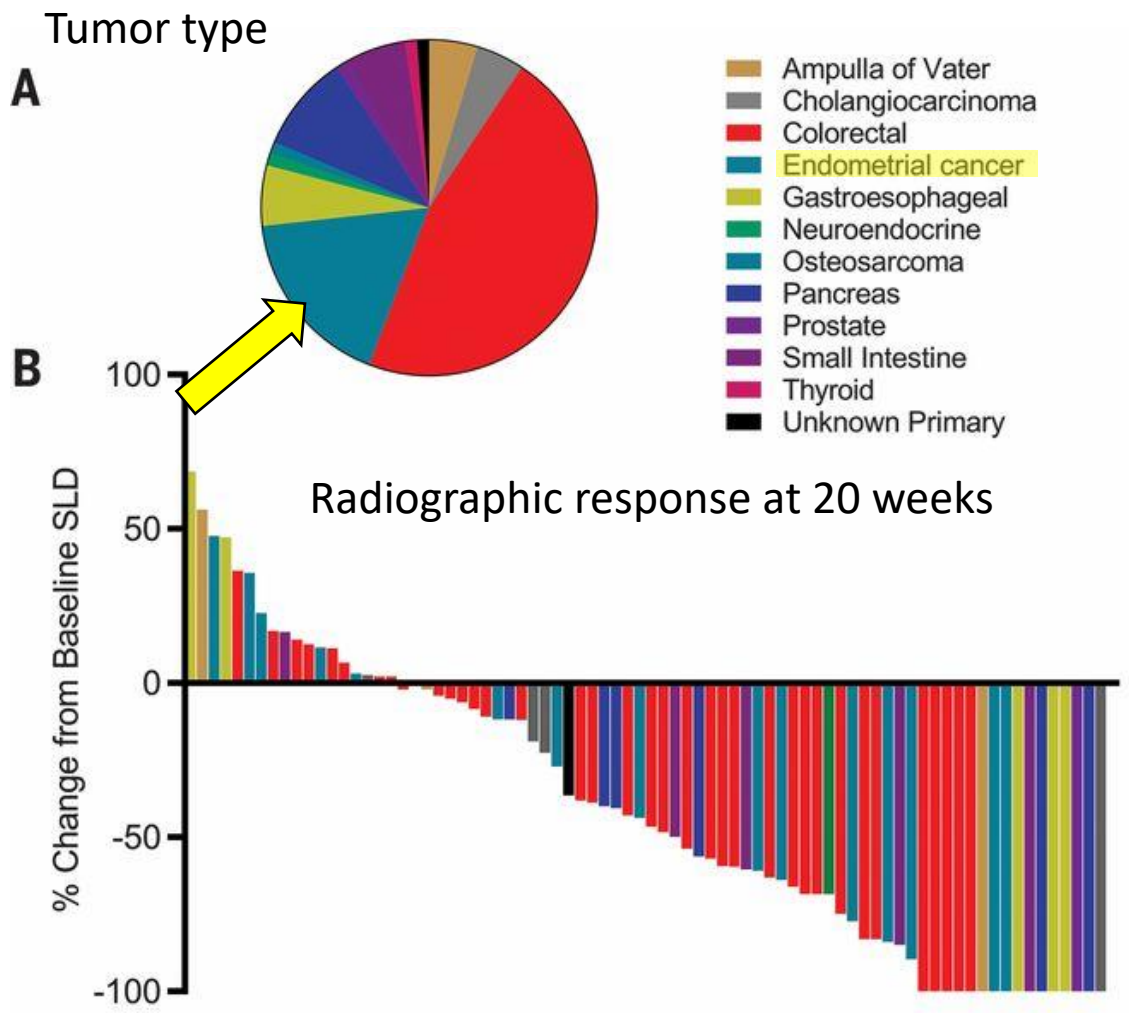
Clinical data – pembrolizumab in MSI-high cancers



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

Le, Science 2017.

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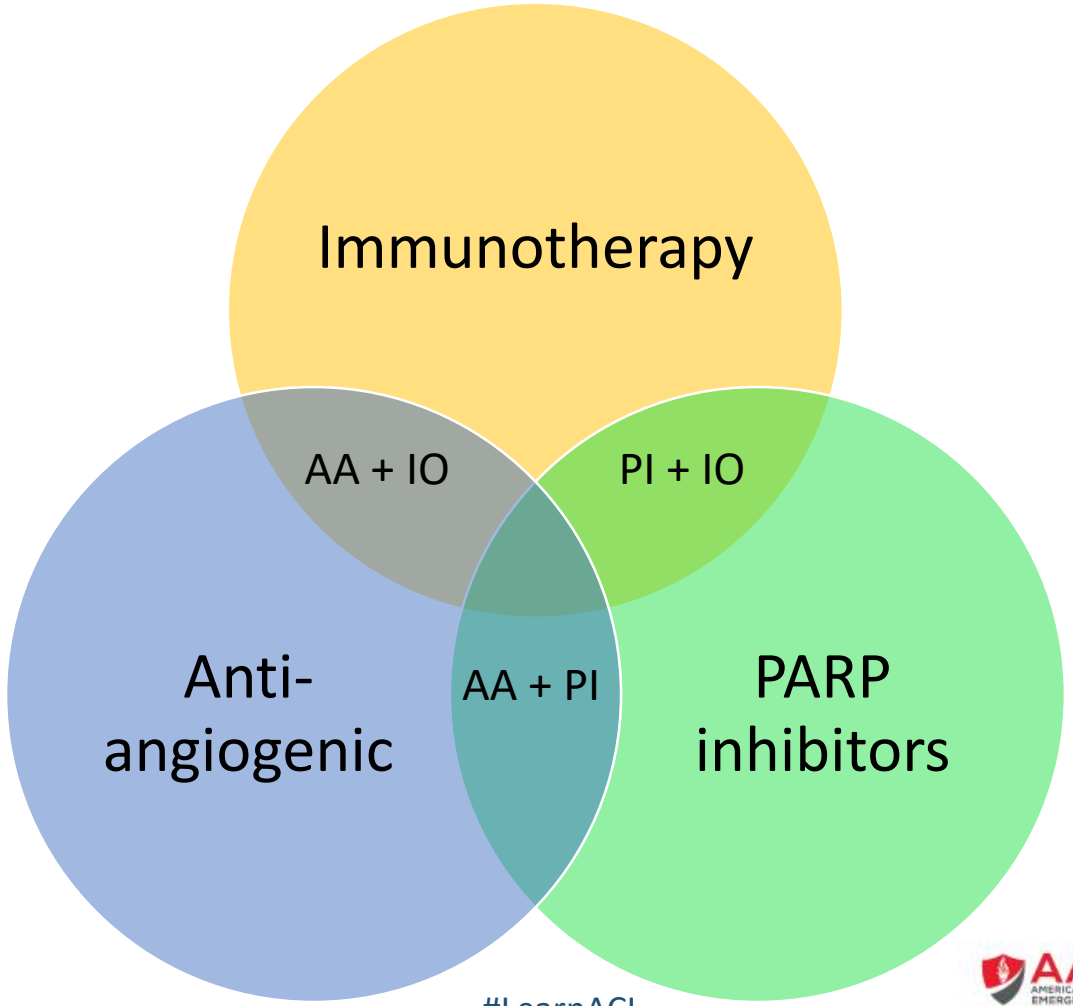
In development: Therapeutic strategies in ovarian cancer



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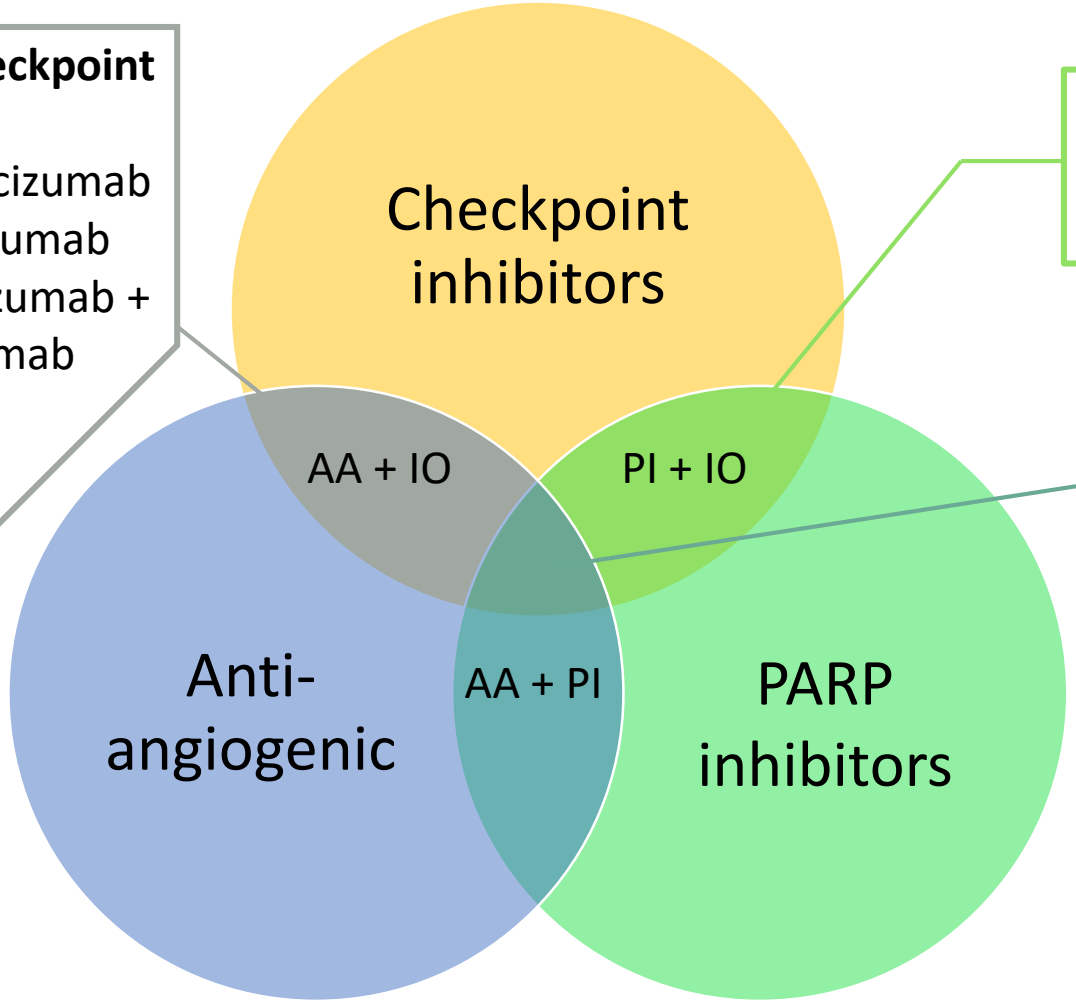
In development: Therapeutic strategies in ovarian cancer

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-targeted strategies

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

Checkpoint inhibitors + Radiotherapy

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

Checkpoint inhibitors + Targeted therapy

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

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

- Patient MK is a 35 yo woman with stage IVB squamous cell carcinoma of the cervix
- She has recent disease progression on cisplatin/paclitaxel/bevacizumab. She desires further anti-cancer treatment.
- ECOG 0
- Histology: HPV+, PDL-1 >1%
- What is the best next treatment?

Case Study 1

A) Pembrolizumab

* 2nd option given chance of durable response, 12% response rate, 11 month overall survival

B) Topotecan

* 3rd option, 12% response rate, no realistic chance of durable response, 6.6 month overall survival

C) Clinical trial with dual checkpoint inhibitor

* 1st option if feasible given excellent performance status, encouraging early phase trial results and relatively low response rates for single agent checkpoin1 inhibition (~12%)

Case Study 2

- Patient RD is a 65 yo woman with recurrent, metastatic grade 3 endometrioid endometrial cancer with recent progression on carboplatin/paclitaxel. She desires further anti-cancer treatment.
- ECOG 0
- What additional information do you want to determine potential use of immunotherapy?
  - MSI status

What are FDA approved immunotherapy options?

MSI high

- Pembrolizumab
  - 57% RR

MSS

- Pembrolizumab + Lenvatinib
  - 63% RR