Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

# Immunotherapy for the Treatment of Breast & Gynecologic Cancers

Patrick Dillon, MD

Associate Professor, University of Virginia

AAEM American Academy of Emergency Medicine — Champion of the Emergency Physician

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

© 2020–2021 Society for Immunotherapy of Cancer

#LearnACI

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

# Disclosures

- Contracted Research: Radius Pharmaceuticals, Tolero Pharmaceuticals, Merck, Seattle Genetics
- I will be discussing non-FDA approved indications during my presentation.

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

sitc Society for Immunotherapy of Cancer

© 2020–2021 Society for Immunotherapy of Cancer

# 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** | |

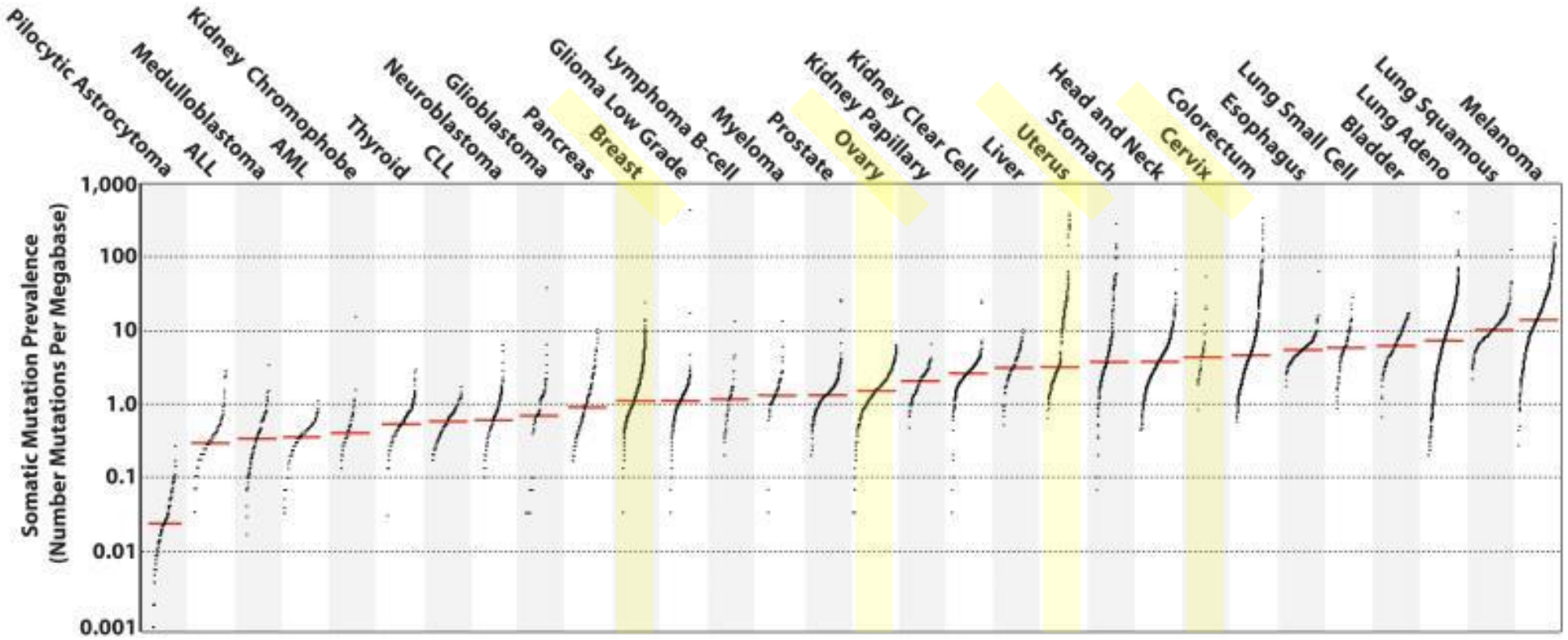
Estimated deaths

| 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.

© 2020–2021 Society for Immunotherapy of Cancer

# Immunotherapy in breast and gynecologic cancers




Alexandrov, Nature 2013.

#LearnACI

© 2020–2021 Society for Immunotherapy of Cancer

# Outline

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



© 2020–2021 Society for Immunotherapy of Cancer

# Outline

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



© 2020–2021 Society for Immunotherapy of Cancer

# Current approvals in breast cancer

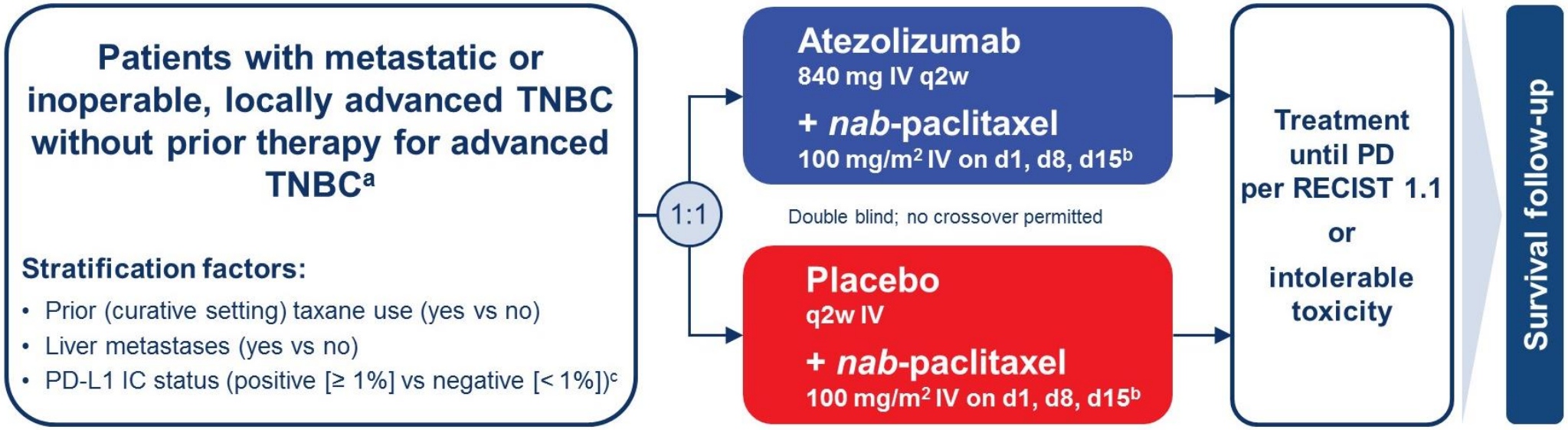
| Checkpoint inhibitor | Approved | Indication | Dose |
|---|---|---|---|
| **Pembrolizumab** | 2017 | MSI-H/dMMR **advanced cancer** with progression on previous treatment | 200 mg Q3W or 400 mg Q6W |
| **Atezolizumab + nab-paclitaxel or paclitaxel protein-bound** | 2019 | Advanced/Metastatic **TNBC** 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 + chemo** | 2020 | Metastatic TNBC with PD-L1 CPS of 10 or more | 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 |



© 2020–2021 Society for Immunotherapy of Cancer

# Clinical Data – IMpassion130 PD-L1+ TNBC



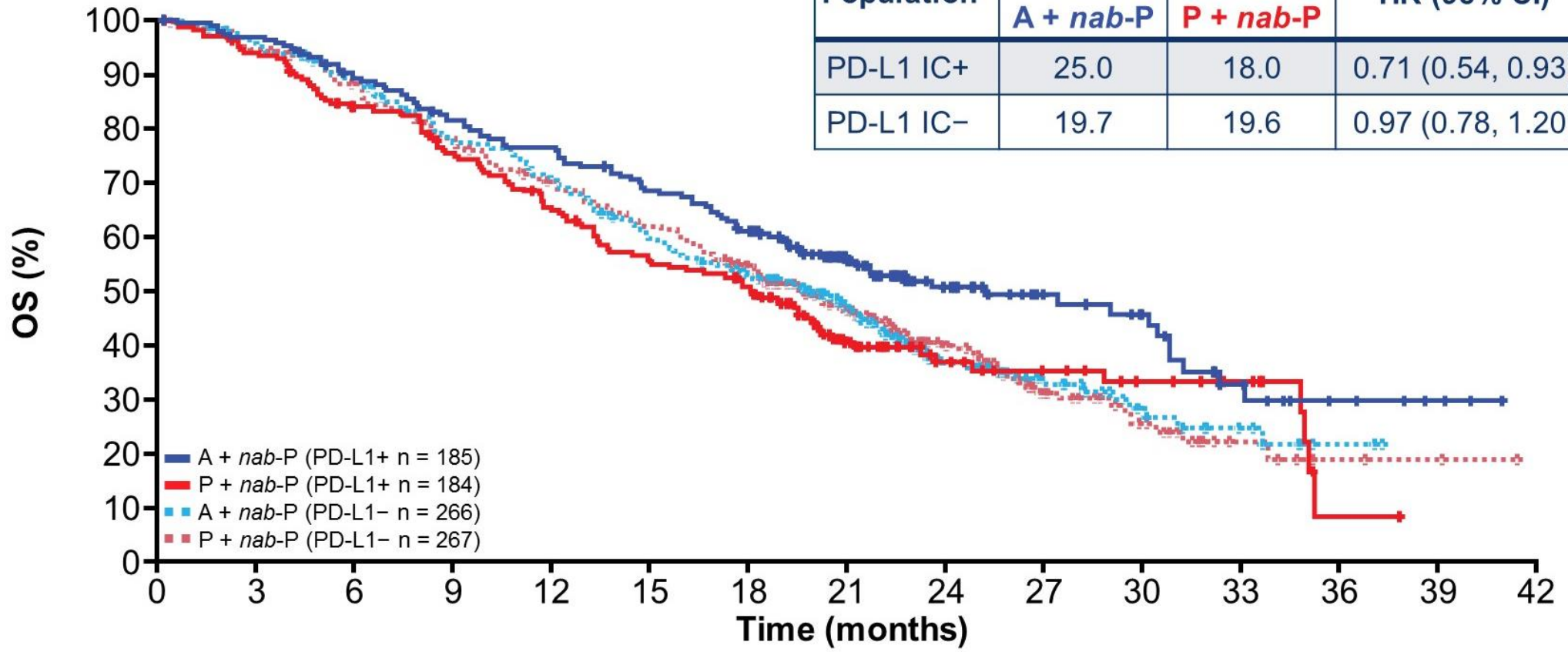

- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

Schmid, ASCO 2019.

© 2020–2021 Society for Immunotherapy of Cancer

# 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) |

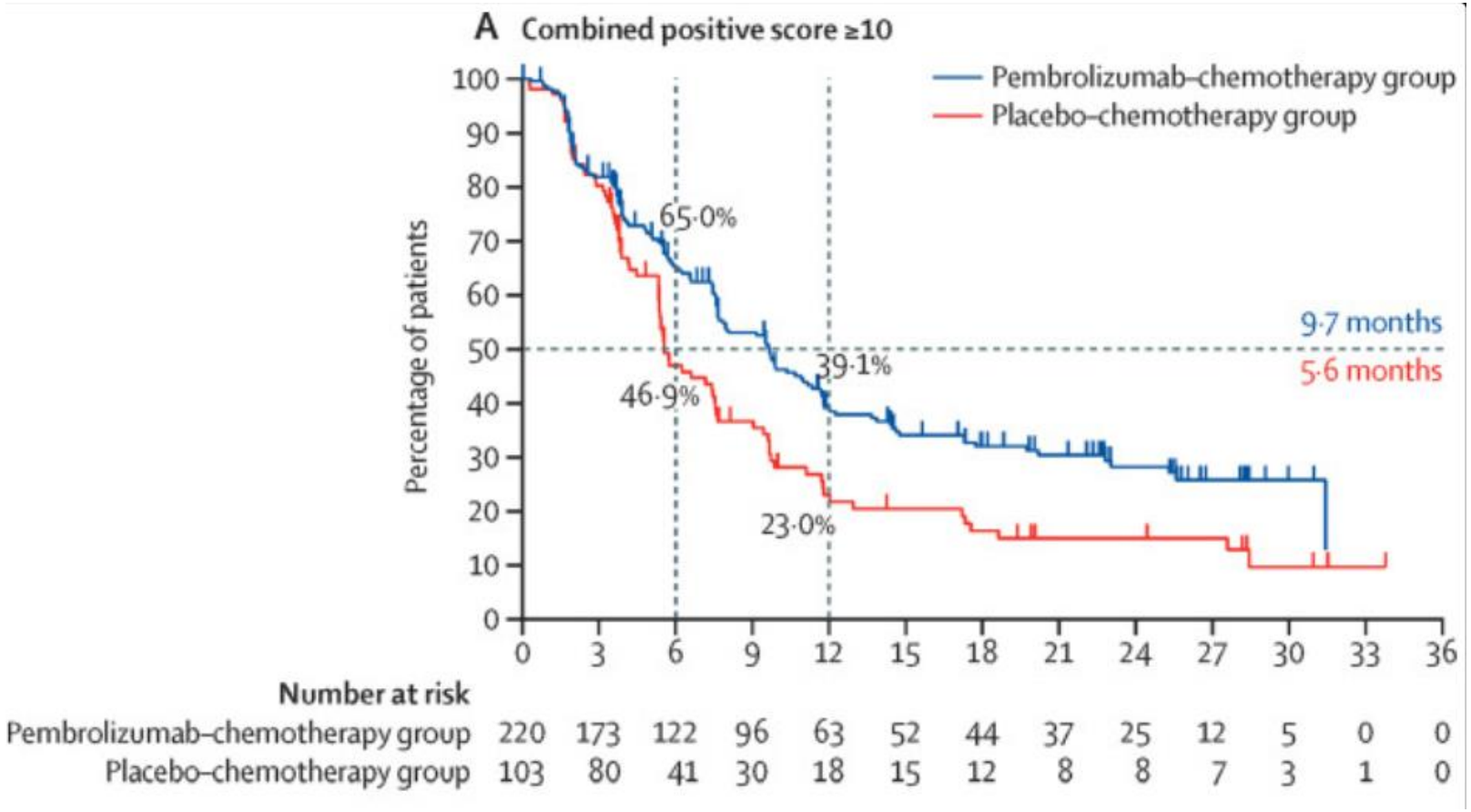



Schmid, ASCO 2019.

#LearnACI

© 2020–2021 Society for Immunotherapy of Cancer

# Clinical Data – Keynote-355 PD-L1+ TNBC




Cortes J, The Lancet 2020.

#LearnACI

© 2020–2021 Society for Immunotherapy of Cancer

# Outline

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



© 2020–2021 Society for Immunotherapy of Cancer

# Clinical trials in TNBC

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

© 2020–2021 Society for Immunotherapy of Cancer

# 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%<br>CR: 0% | 1.8 | 8.6 |
| KEYNOTE-014/PANACEA | Pembrolizumab + trastuzumab | HER2+ breast cancer with progression on trastuzumab | 58 | PD-L1+: 15%<br>CR: 4%<br><br>PD-L1-: 0% | | |
| KATE2 | Atezolizumab + trastuzumab emtansine | HER2+ advanced breast cancer with previous trastuzumab and a taxane | 133 | ITT: 45%<br>PD-L1+: 54% | ITT: 8.2<br>PD-L1+: 8.5 | ITT 1-year: 89.1%<br>PD-L1+: 94.3% |
| | Trastuzumab emtansine | | 69 | ITT: 43%<br>PD-L1+: 33% | ITT: 6.8<br>PD-L1+: 4.1 | ITT 1-year: 89.0%<br>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.

© 2020–2021 Society for Immunotherapy of Cancer

# Breast Cancer Pipeline

- Topacio Trial:  Pembrolizumab + niraparib
- Ladiratuzumab + Pembrolizumab
- Mediola:  Durvalumab + olaparib + VEGFRi
- COLET: Atezolizumab + taxanes + MEKi
- MC1632: Pembrolizumab + MEKi
- Dora:  Durvalumab + olaparib
- Kornelia: Nivolumab + eribulin
- Bracelet-1: Avelumab + Oncolytic Reovirus
- Destiny 1-11 trials:  Trastuzumab deruxtecan for multiple indications
- Bintrafusp Alpha: PD-L1 bispecific (several studies)
- T cell studies/TIL:  several studies +/- PD-L1



© 2020–2021 Society for Immunotherapy of Cancer

# Outline

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



© 2020–2021 Society for Immunotherapy of Cancer

# 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
- PD-L1+ by 22C3 (CPS score)

**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<br>*BRCA2* mutation | Germline sequencing | Olaparib<br>Talazoparib | Category 1<br>Category 1 | Preferred<br>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<br>• 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]<br>Entrectinib[e] | Category 2A<br>Category 2A | Useful in certain circumstances[e]<br>Useful in certain circumstances[e] |
| Any | MSI-H/dMMR | IHC, PCR (tissue block) | Pembrolizumab[f] | Category 2A | Useful in certain circumstances[f] |

NCCN Guidelines.

#LearnACI

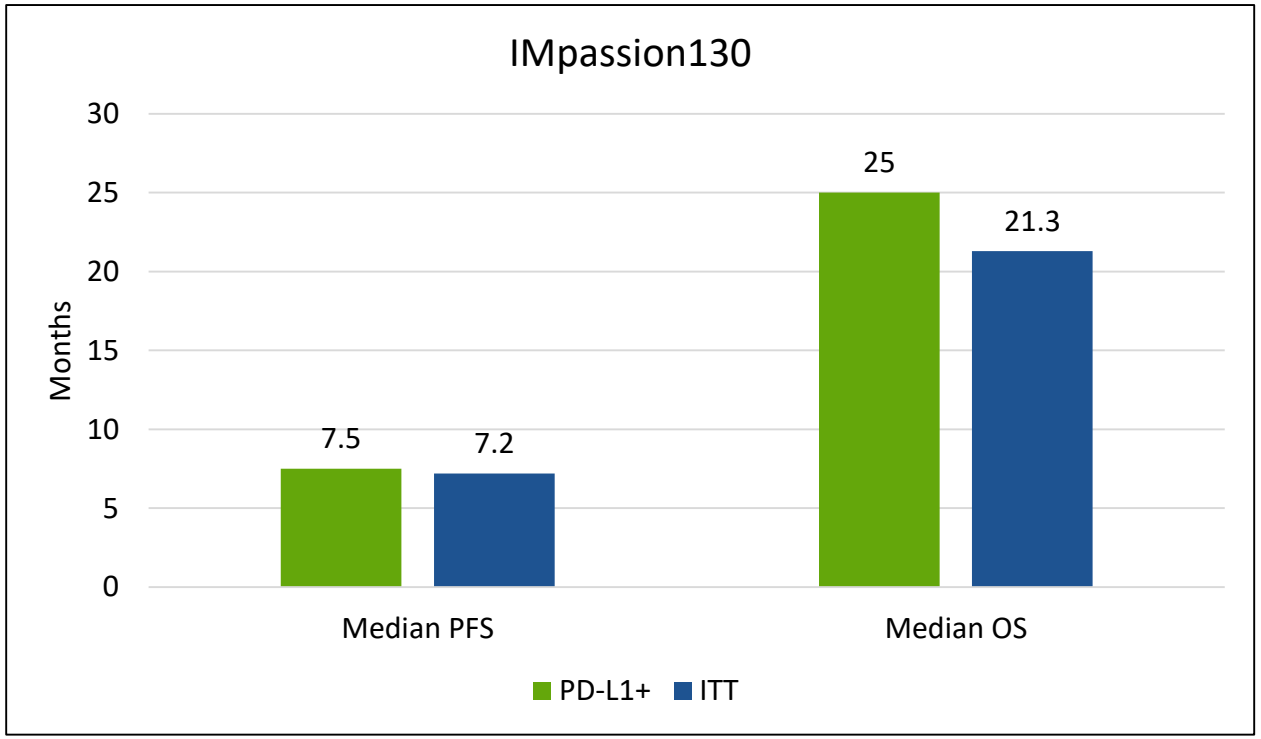
© 2020–2021 Society for Immunotherapy of Cancer

# 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.

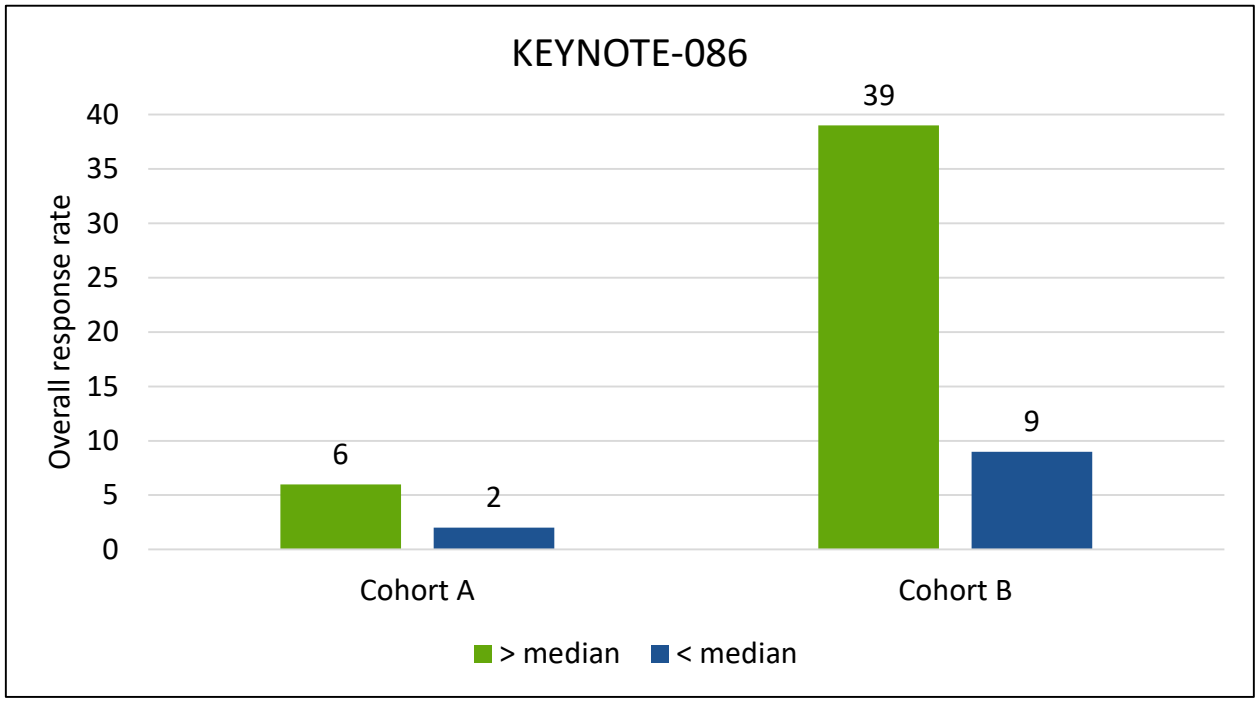
© 2020–2021 Society for Immunotherapy of Cancer

#LearnACI

# 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.

#LearnACI

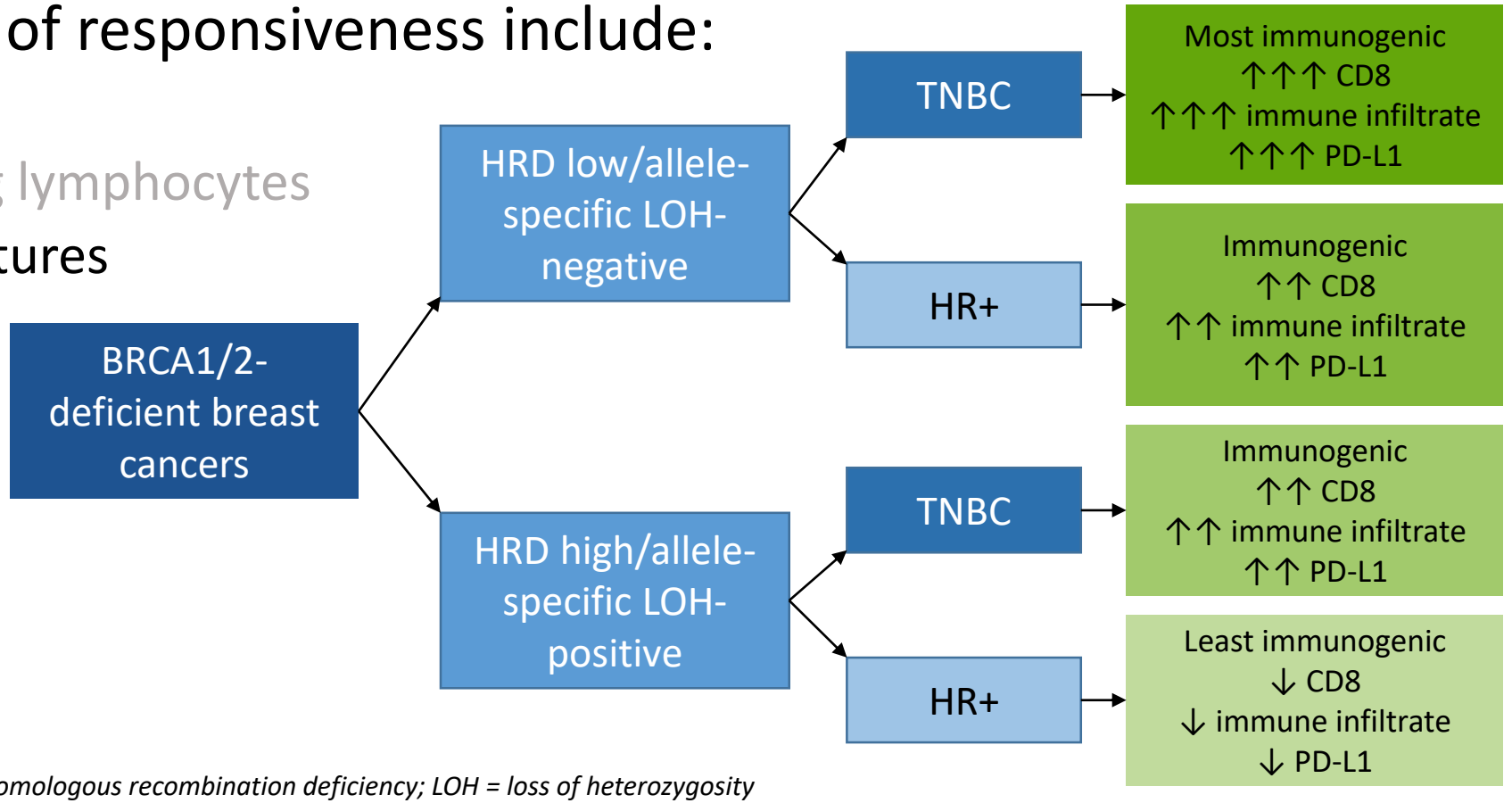
© 2020–2021 Society for Immunotherapy of Cancer

# 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.

© 2020–2021 Society for Immunotherapy of Cancer

# Outline

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



© 2020–2021 Society for Immunotherapy of Cancer

# 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 |



© 2020–2021 Society for Immunotherapy of Cancer

# 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

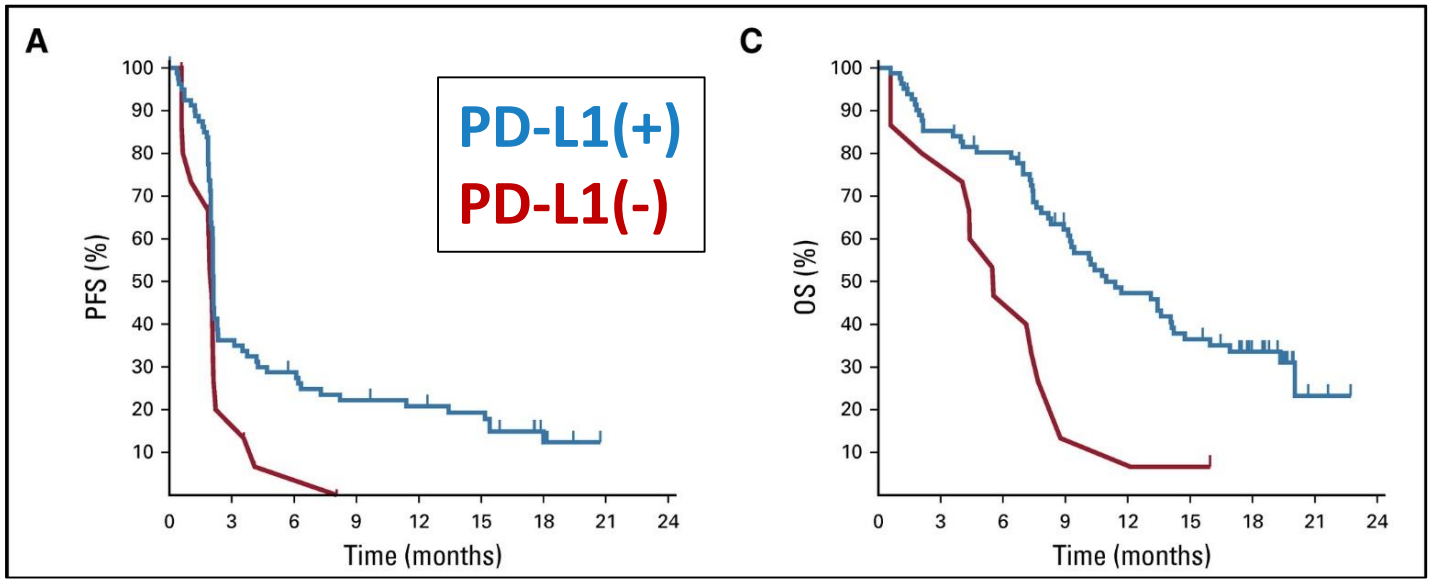
**Secondary:** Duration of response; Progression-free survival; Overall survival

#LearnACI

© 2020–2021 Society for Immunotherapy of Cancer

# 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



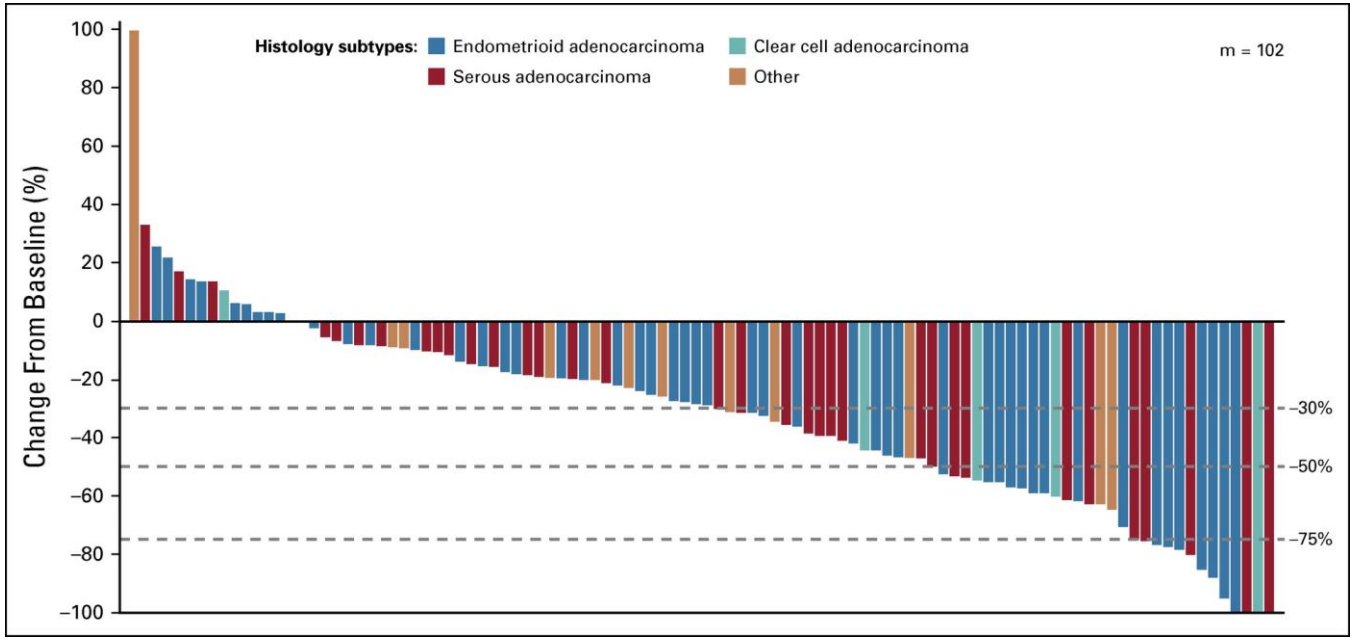

Cheol Chung, J Clin Oncol 2019.

#LearnACI

© 2020–2021 Society for Immunotherapy of Cancer

# 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

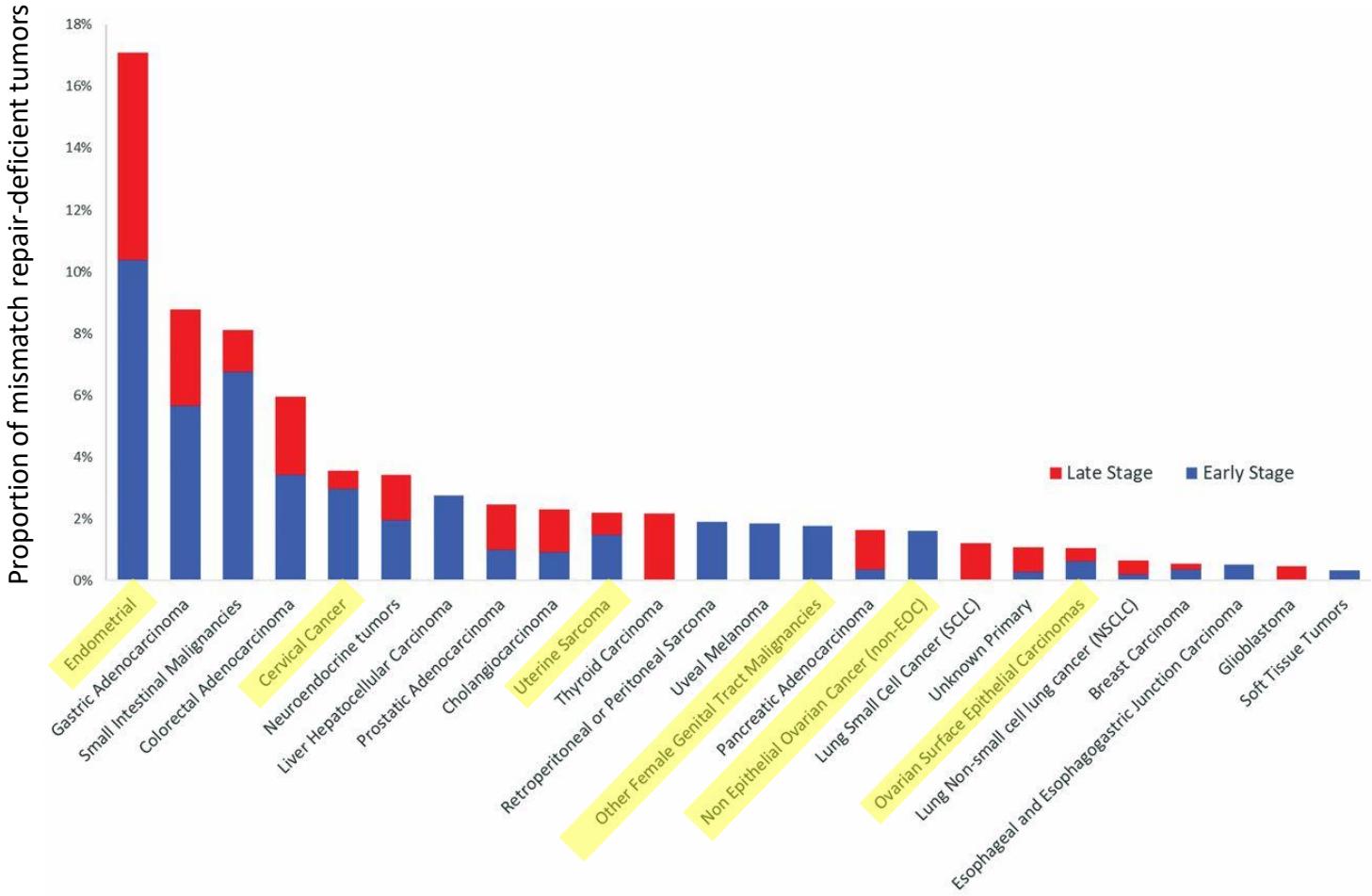



Makker, J Clin Oncol 2020.

© 2020–2021 Society for Immunotherapy of Cancer

#LearnACI

# Clinical data – pembrolizumab in MSI-high cancers

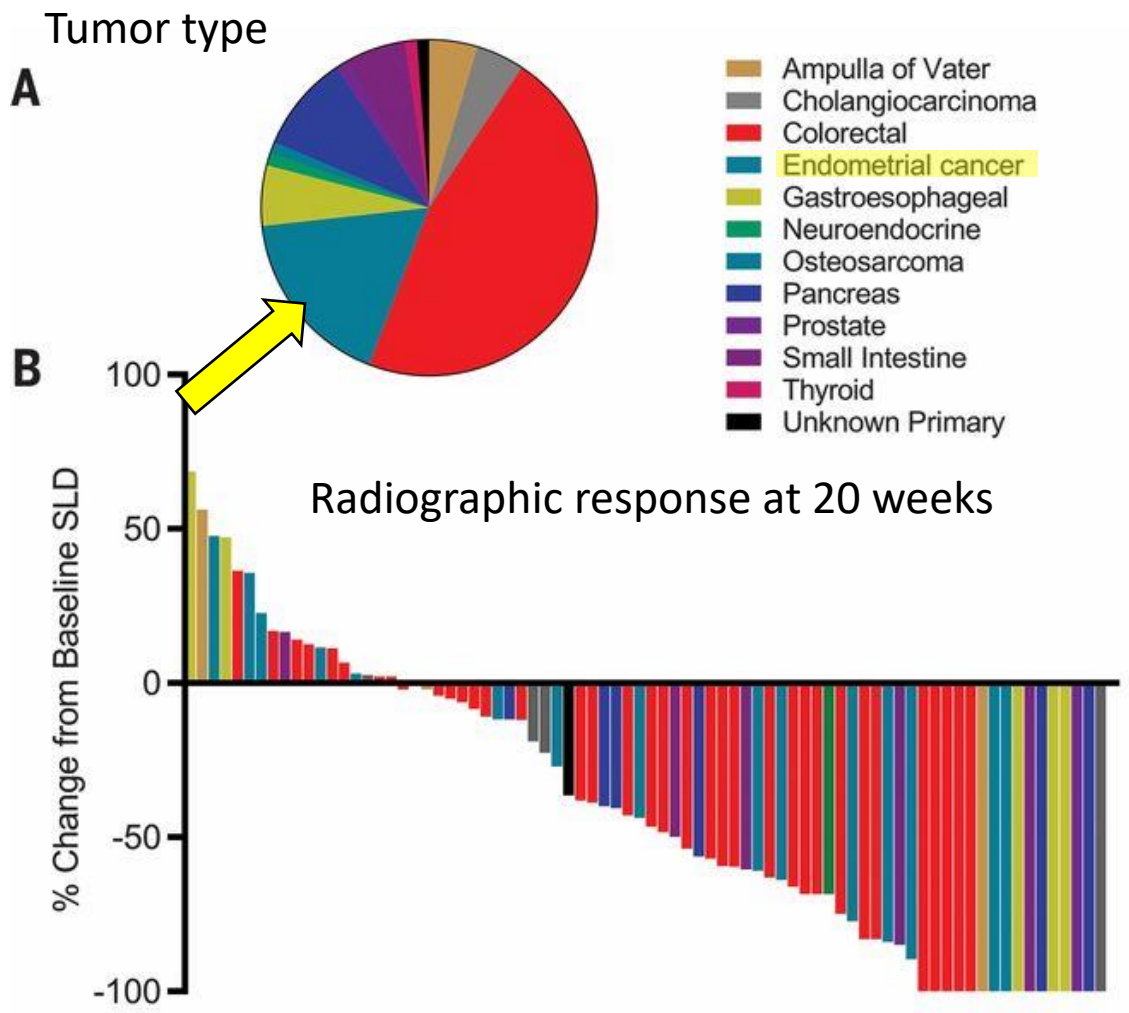



Le, Science 2017.

#LearnACI

© 2020–2021 Society for Immunotherapy of Cancer

# Clinical data – pembrolizumab in MSI-high cancers




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

Le, Science 2017.

#LearnACI

© 2020–2021 Society for Immunotherapy of Cancer

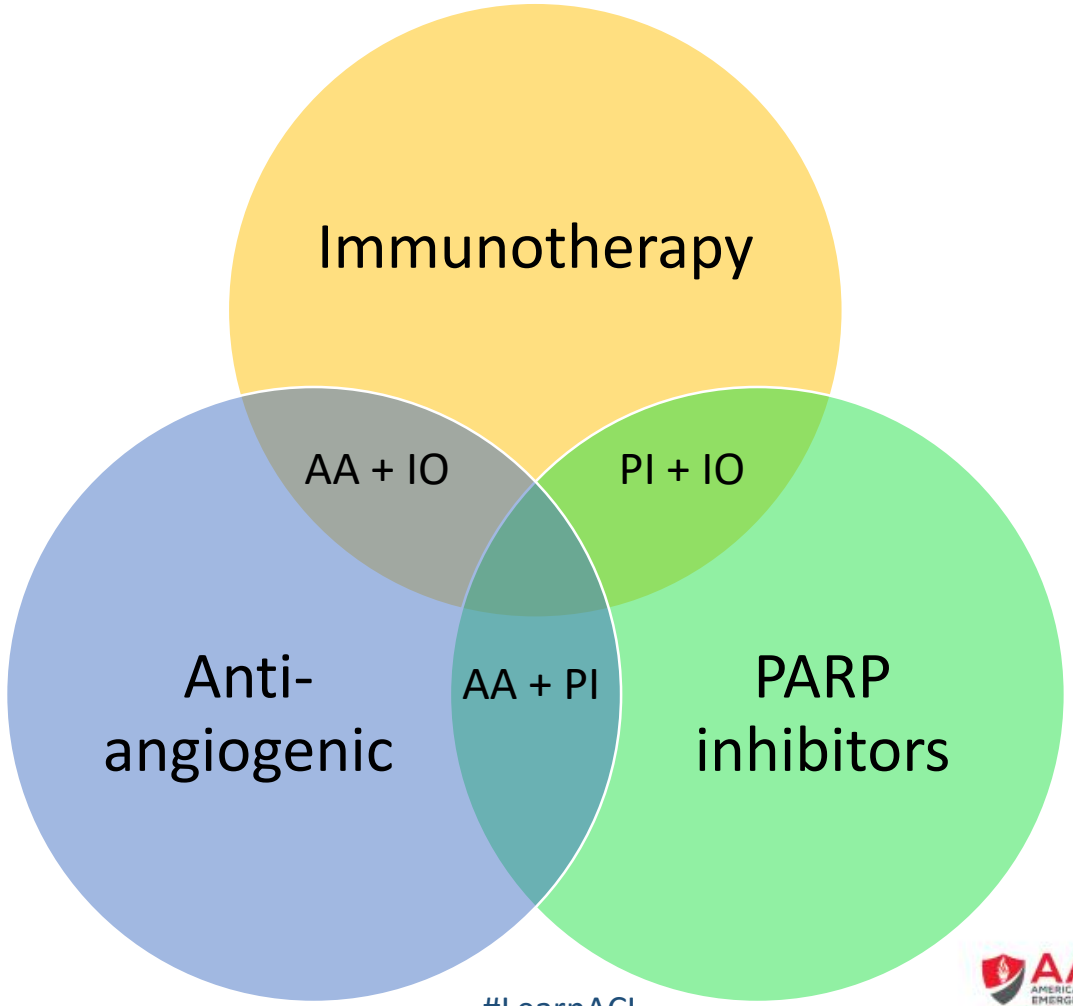
# Outline

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



© 2020–2021 Society for Immunotherapy of Cancer

# **In development:** Therapeutic strategies in ovarian cancer



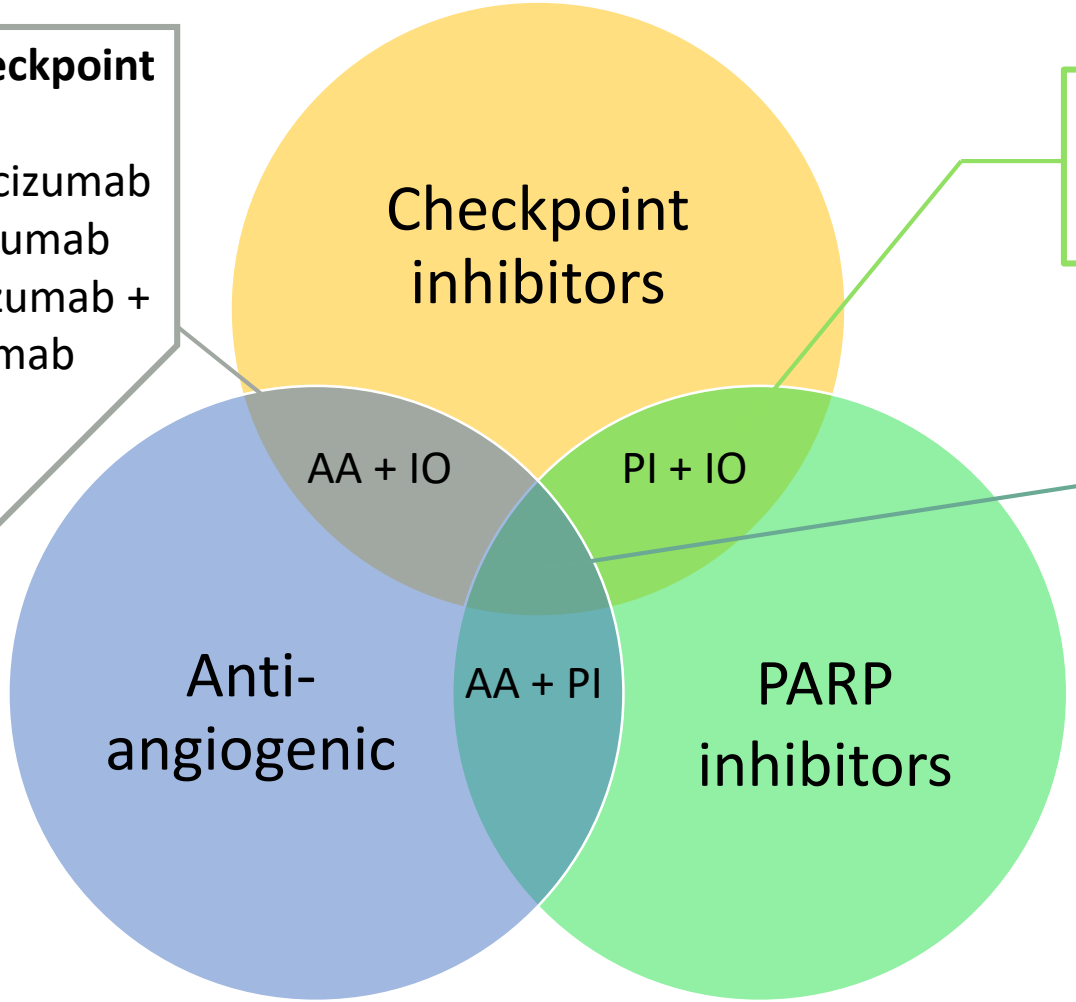

#LearnACI

© 2020–2021 Society for Immunotherapy of Cancer

# **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

#LearnACI

© 2020–2021 Society for Immunotherapy of Cancer

# 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



© 2020–2021 Society for Immunotherapy of Cancer

# Case Study 1

A 45yo woman with a history of BRCA1 mutation and triple negative breast cancer treated with neo-adjuvant AC-carbo/taxol in 2018, now presents to your office with biopsy confirmed lung and liver metastases. The liver biopsy shows carcinoma cells negative for ER, PR and HER2 and are morphologically similar to the prior cancer from 2018. It is PD-L1+. She is in good health, with mild symptoms from her known metastases.

1. Question 1, What would you offer for first line treatment in the metastatic TNBC setting?
   A. Atezolizumab and nab-paclitaxel
   B. Carboplatin and taxol
   C. Abemaciclib
   D. Olaparib



© 2020–2021 Society for Immunotherapy of Cancer

# Case 1

Your patient enjoys an excellent partial response to Atezolizumab and abraxane for 12 months. At the 12 month mark, she experiences seizures and is found to have a new 1.4cm right cerebral hemisphere lesion without bleeding. There is mild edema on MRI around the tumor, but no herniation.

Question 2: What is the next step?

A. Sacituzumab govitecan
B. Pembrolizumab
C. Gamma knife
D. Olaparib



© 2020–2021 Society for Immunotherapy of Cancer

# Case 1 Answers/Outcome

A 45yo woman with a history of BRCA1 mutation and triple negative breast cancer treated with neo-adjuvant AC-carbo/taxol in 2018, now presents to your office with biopsy confirmed lung and liver metastases. The liver biopsy shows carcinoma cells negative for ER, PR and HER2 and are morphologically similar to the prior cancer from 2018. It is PD-L1+. Your patient enjoys an excellent partial response to Atezolizumab and abraxane for 12 months. At the 12 month mark, she experiences seizures and is found to have a new 1.4cm right cerebral hemisphere lesion without bleeding. There is mild edema on MRI around the tumor, but no herniation.

Question 1, What would you offer for first line treatment in the metastatic TNBC setting?

A. Atezolizumab and nab-paclitaxel – Correct. Impassion 130 showed benefit. FDA approved for first line Rx.
B. Carboplatin and taxol – Reasonable choice, but option A is superior. Also the patient had prior carbo and taxol.
C. Abemaciclib – Not indicated in TNBC.
D. Olaparib- This is indicated in first line TNBC with BRCA mutation if prior chemo. Cross-trial comparison suggests inferiority to A.

Question 2: What is the next step?

A. Sacituzumab govitecan – Poor CNS penetration. Not approved in second line.
B. Pembrolizumab- Unclear CNS activity. Not approved as a single agent in breast cancer.
C. Gamma knife – Correct. Optimal local control is the first priority.
D. Olaparib – Poor CNS penetration. No indication for CNS. Data suggests it might have a role in leptomeningeal disease.

**OUTCOME:** The patient responded well to gamma knife and went on to a course of Talazoparib with good early response.



© 2020–2021 Society for Immunotherapy of Cancer