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ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of 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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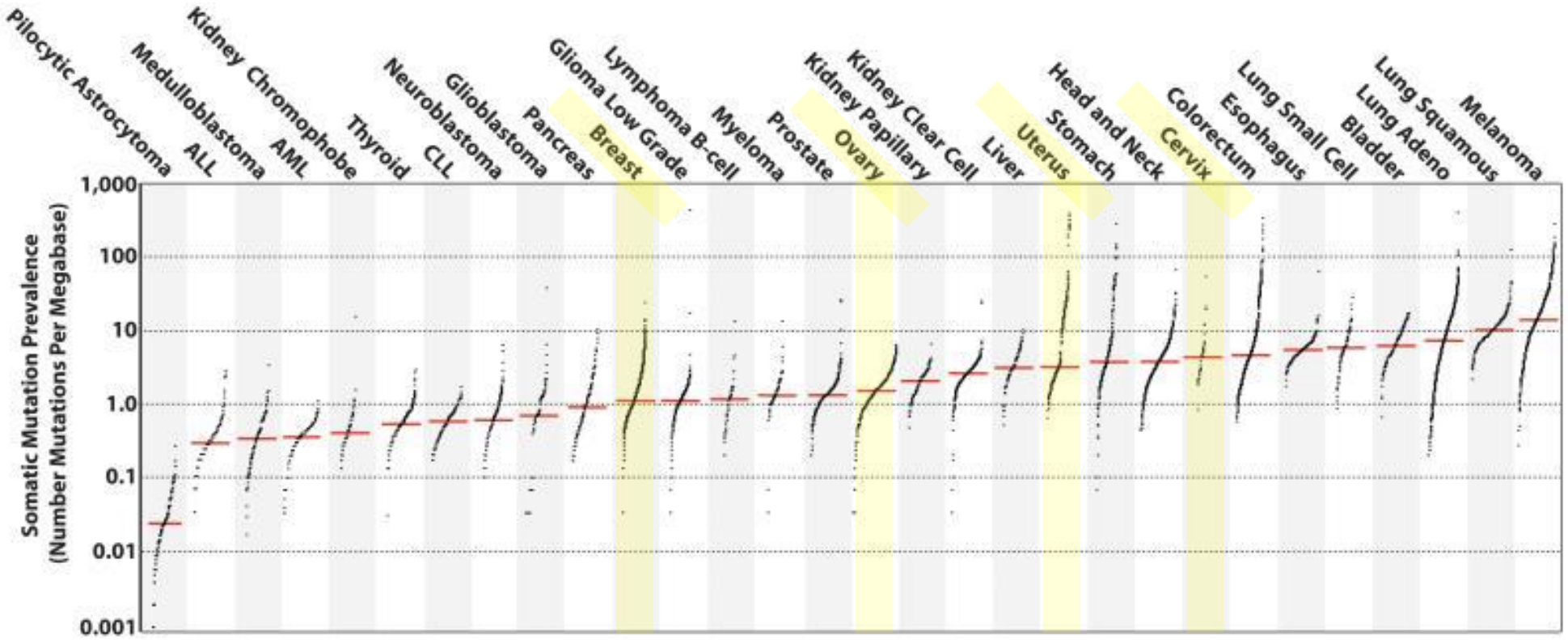
Disclosures

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

Outline

- Gynecologic cancers
  - Approvals
  - In the pipeline

Immunotherapy in gynecologic cancers



Alexandrov, Nature 2013.

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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
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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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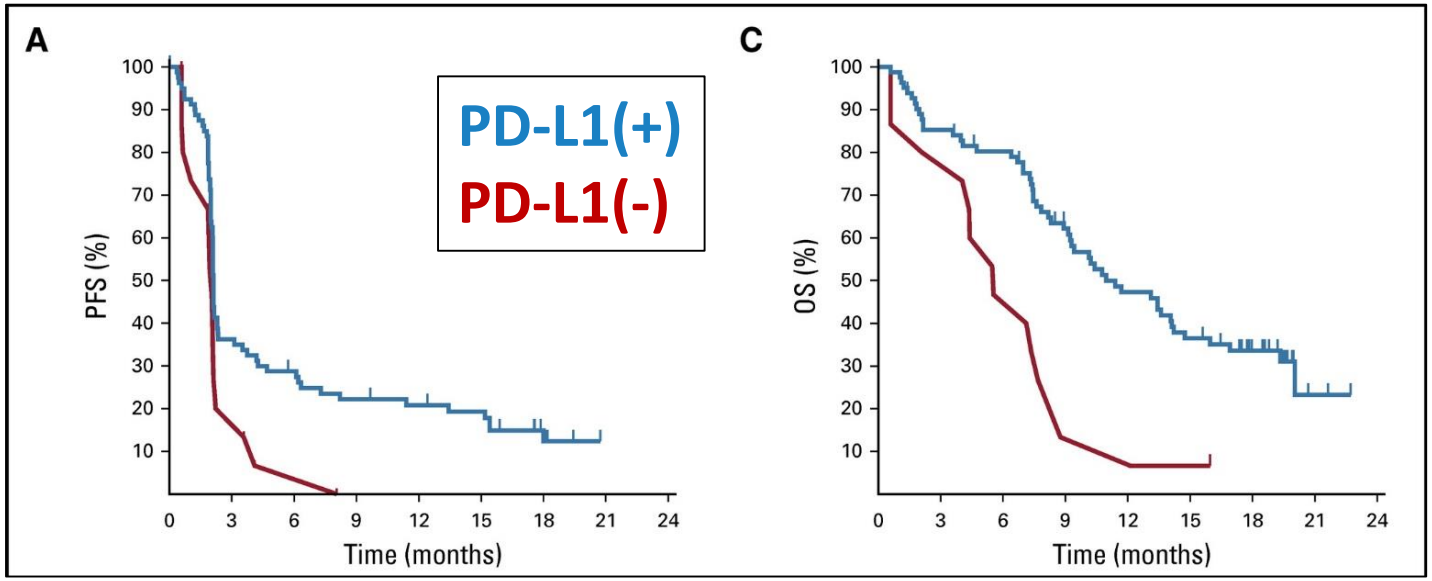
Clinical data – KEYNOTE-158
Cervical cancer

- Pembrolizumab monotherapy
- All responses were in PD-L1+ tumors
- ORR: 17%
- Median duration of response was not reached at 13 months follow-up



Cheol Chung, J Clin Oncol 2019.
Cheol Chung, SGO Oral Presentation, 2021

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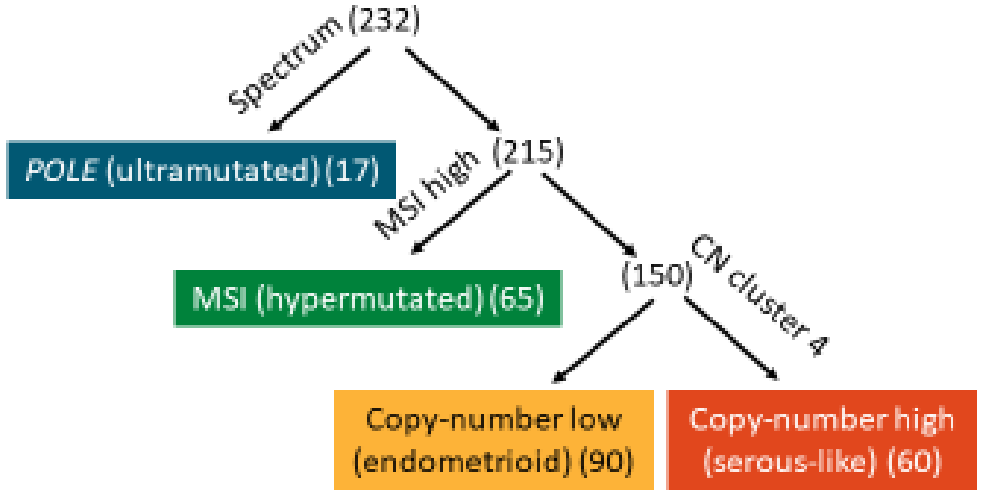
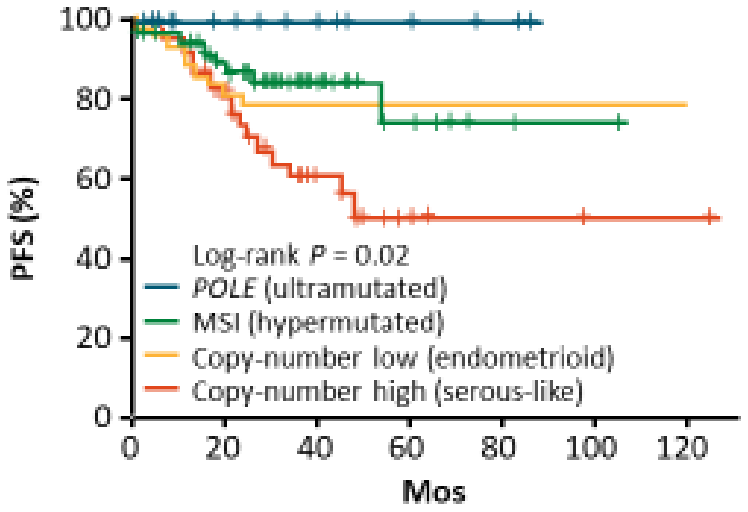
Endometrial cancer classification

The "Modern" Molecular Classification: TCGA Classification





- **POLE (ultramutated malignancies):**
  - Their hallmark are mutations in the exonuclease domain of POLE
  - POLE encodes the catalytic subunit of DNA polymerase epsilon which plays a relevant role in DNA repair.
- **MSI-High: Tumors that harbor a high rate of mutations resulting from impaired DNA MMR pathway:**
  - A DNA repair system that corrects errors such as single-base mismatches or short insertions and deletions that spontaneously occur during DNA replications
  - The most implicated genes are: MLH1, MSH2, MSH6, PMS2

Cancer Genome Atlas Research Network. Nature. 2013;497:67.

Slide credit: clinicaloptions.com

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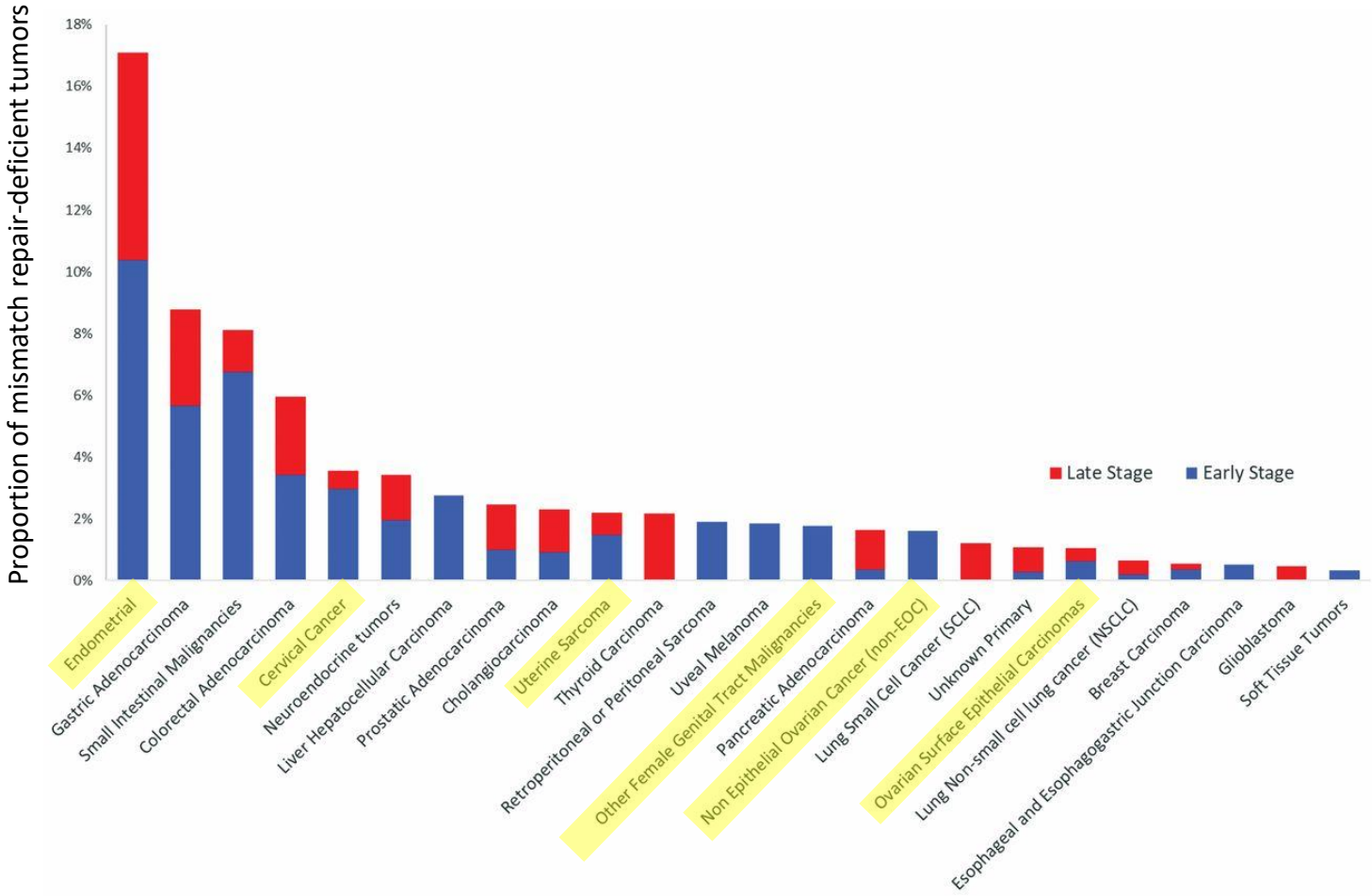
Clinical data – pembrolizumab in MSI-high cancers



Le, Science 2017.

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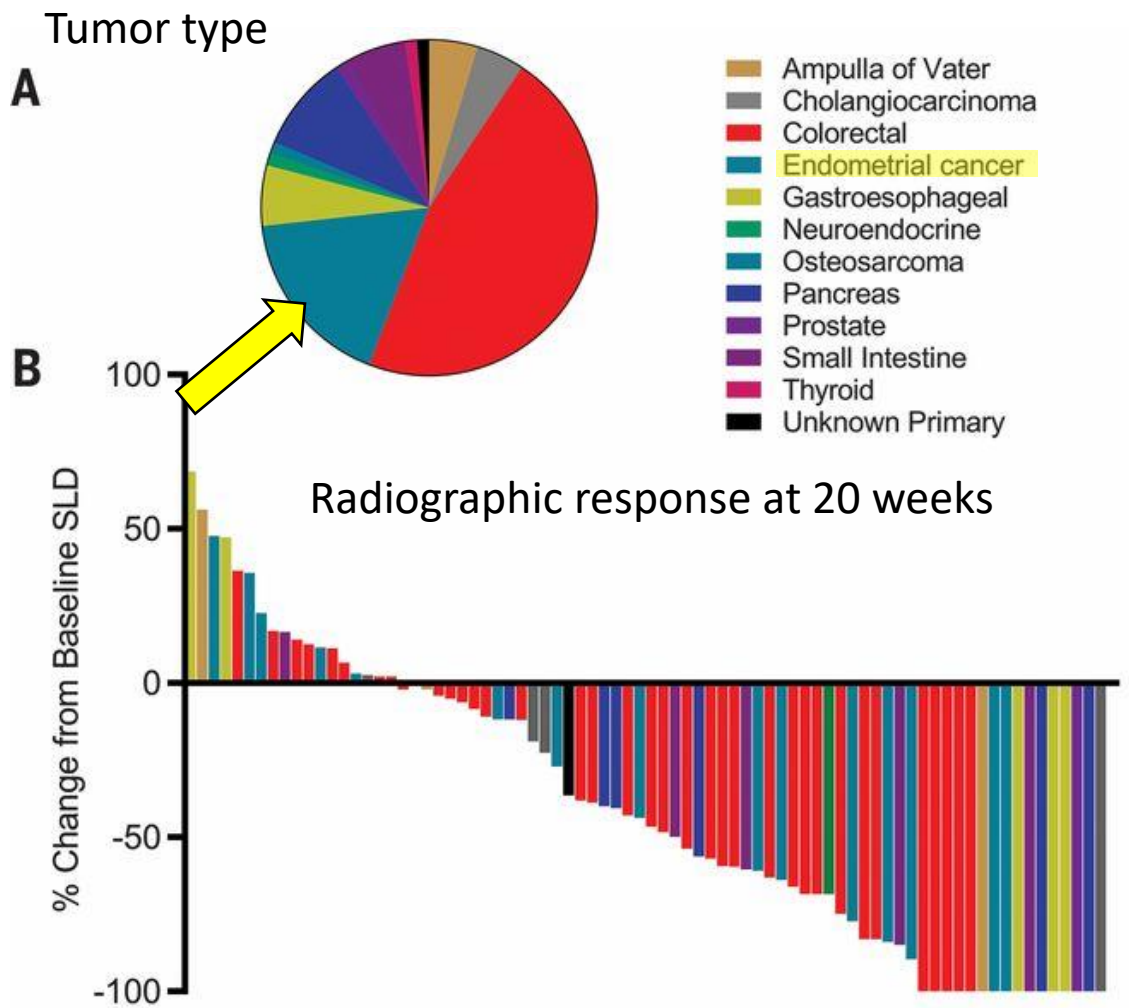
Clinical data – pembrolizumab in MSI-high cancers



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

Le, Science 2017.

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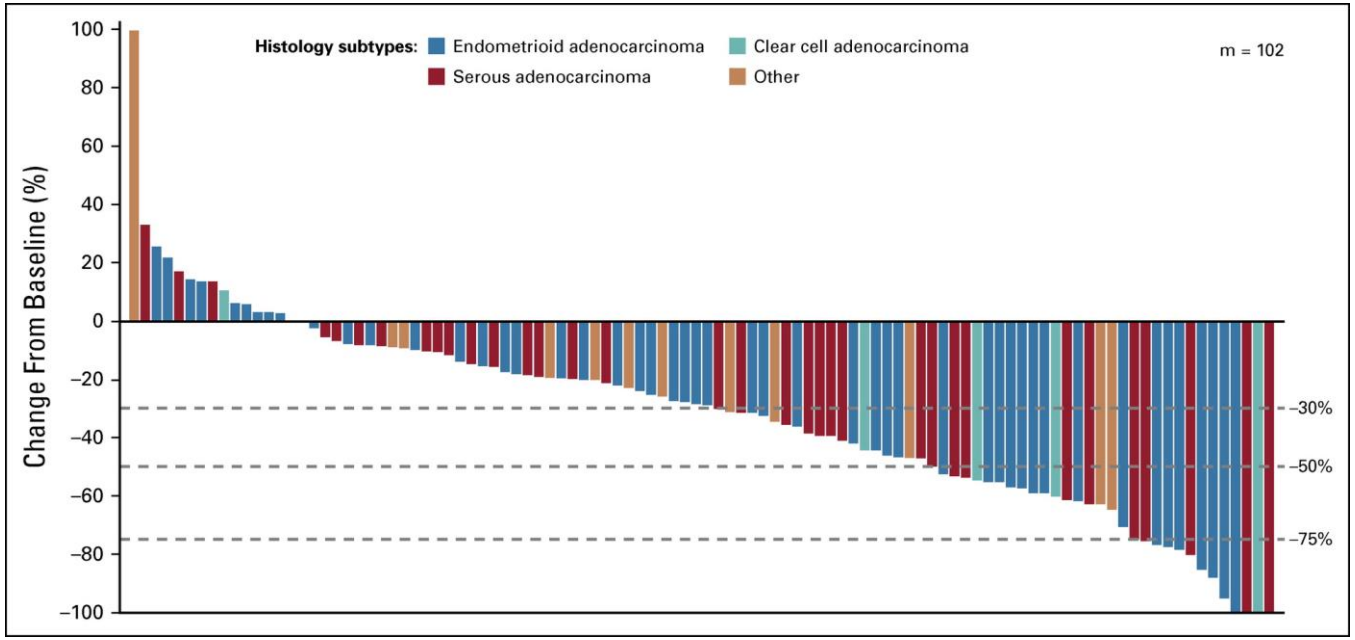
Clinical data – KEYNOTE-146
Endometrial cancer

- 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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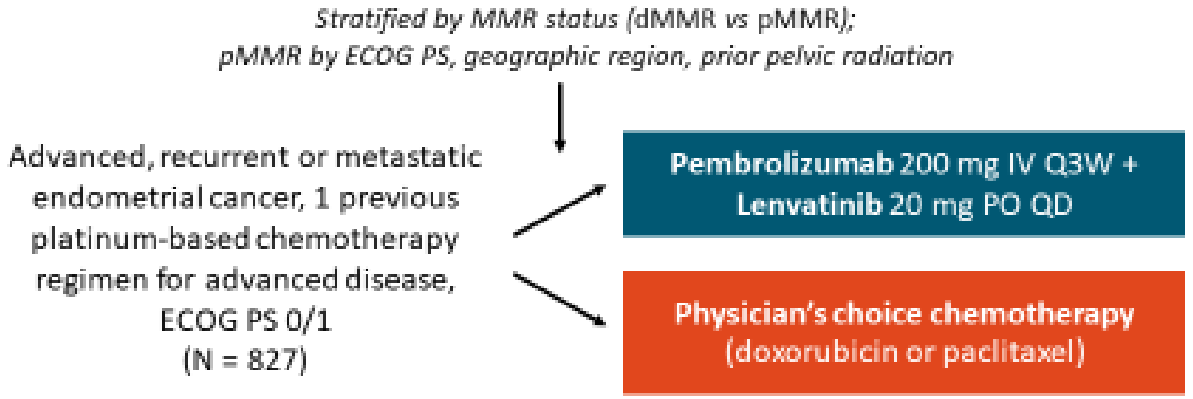
Clinical data – KEYNOTE-775
Endometrial cancer

- Improved PFS
- Improved OS

Phase III KEYNOTE-775: Second-line Pembrolizumab + Lenvatinib vs Chemotherapy in Advanced EC



Primary endpoints: PFS, OS

Secondary endpoints: ORR, HRQoL, safety and tolerability, PK

NCT03517449.

Slide credit: clinicaloptions.com

Makker, J Clin Oncol 2020
Makker, SGO Annual Conf, 2021

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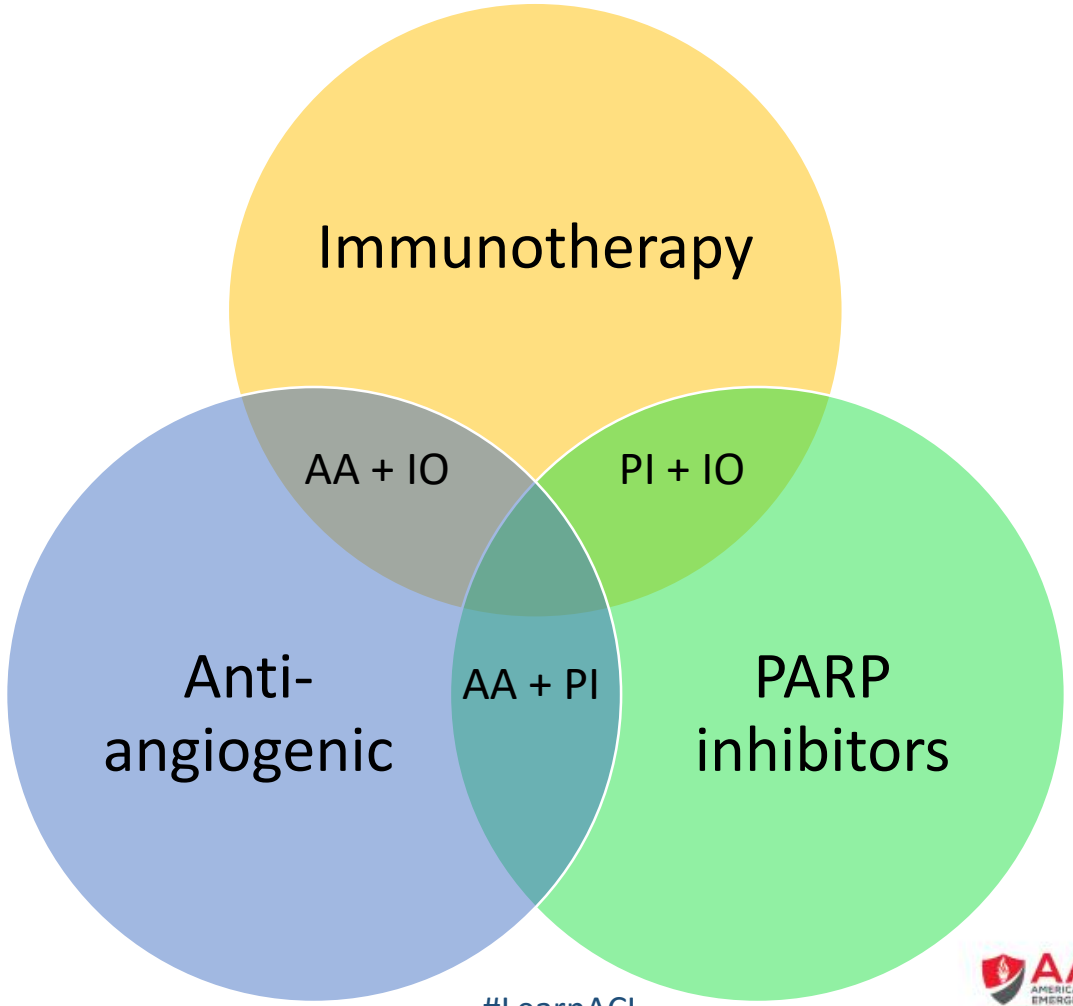
In development: Therapeutic strategies in ovarian cancer



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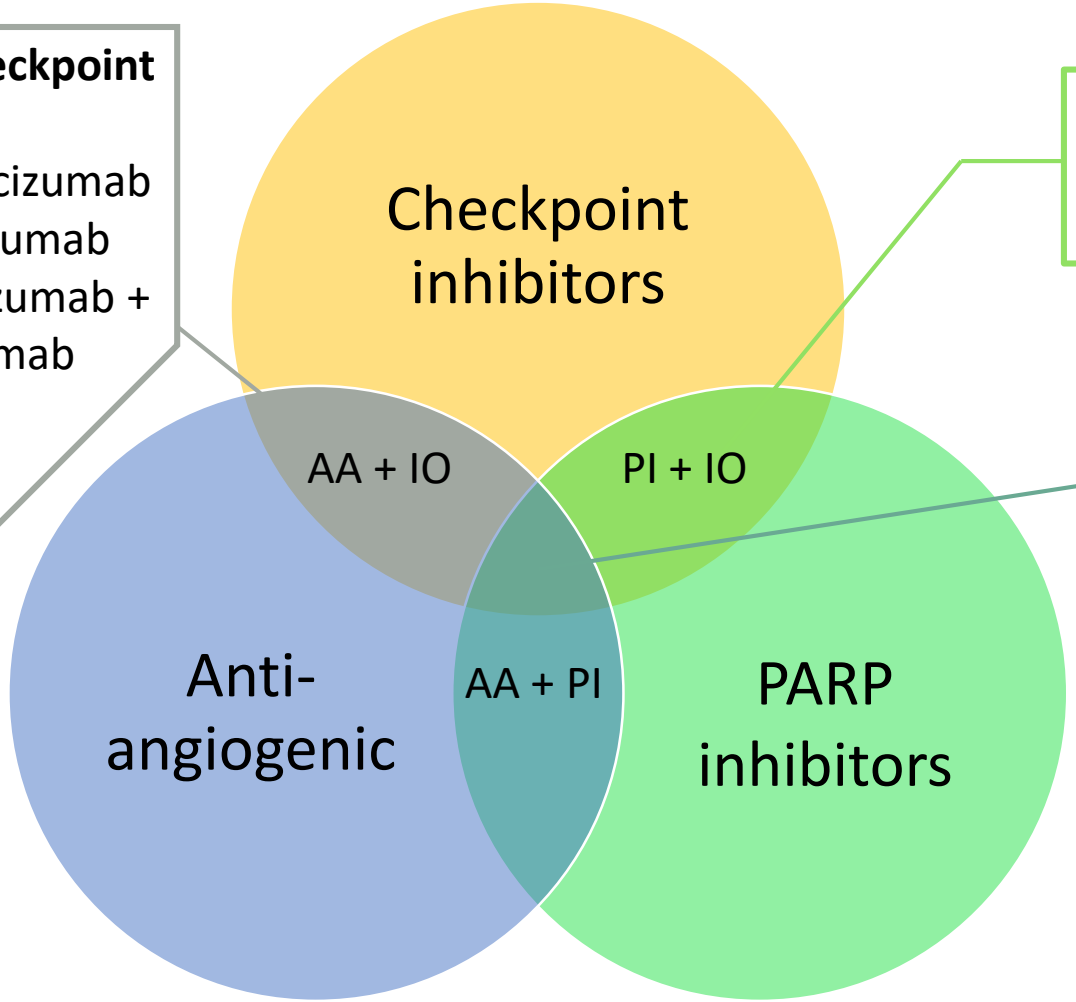
In development: Therapeutic strategies in ovarian cancer

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 gynecologic cancers is expanding rapidly
- 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

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Instructions - Case Study 1

60 year old female with stage IIIC grade 3 endometrioid endometrial cancer had staging hysterectomy/bilateral salpingo-oophorectomy and sentinel lymphadenectomy followed by adjuvant chemotherapy and pelvic radiation therapy. Five months later, she presents with cough. CT chest demonstrates multiple lung lesions. Biopsy confirmed recurrence. Molecular testing demonstrated MSI-H.

What treatment would you offer this patient?

A. Carboplatin/Paclitaxel
B. Tamoxifen/megestrol acetate
C. Pembrolizumab
D. Pembrolizumab/Lenvatinib

Instructions - Case Study 2

A 45 year old female with newly diagnosed stage IV squamous cell cervical cancer, PD-L1 Positive (CPS>1)

1. What treatment would you offer this patient?
    A. Cisplatin/Paclitaxel/bevacizumab
    B. Carboplatin/paclitaxel
    C. Topotecan
    D. Pembrolizumab

2. After 3 cycles of above chosen therapy, she develops progression of disease. What is your next treatment choice?

    A. Pembrolizumab
    B. Pemetrexed
    C. Abraxane
    D. Nivolumab/Ipilimumab