Case Studies for Immunotherapy for the Treatment of Gynecologic Cancer

Claire Friedman, MD
Assistant Attending, Gynecologic Medical Oncology Service
Section Head, Complex Therapeutics, Early Drug Development Service
Memorial Sloan Kettering Cancer Center

Case 1: Stage IV Cervical Cancer

- 50 yo F who presented with malodorous vaginal discharge
- A pap smear was performed which was negative by cytology but positive for HR HPV
- PMHx: Breast Cancer, s/p bilateral mastectomy, chemotherapy and RT, on Aromasin at the time of original consult
- PSHx: Bilateral mastectomies with reconstruction
- Denies history of tobacco use
- No history of HPV vaccination

Case 1: Continued

- A D&C/hysteroscopy with ECC was performed:
- Pathology demonstrated invasive SCC, moderately differentiated, depth of invasion cannot be determined. Endometrial curettage sample positive for SCC
- CT Chest: No suspicious lung nodules.
- MRI Abdomen/pelvis: soft tissue mass centered on the cervix, suspicious for primary tumor

Case 1: Continued

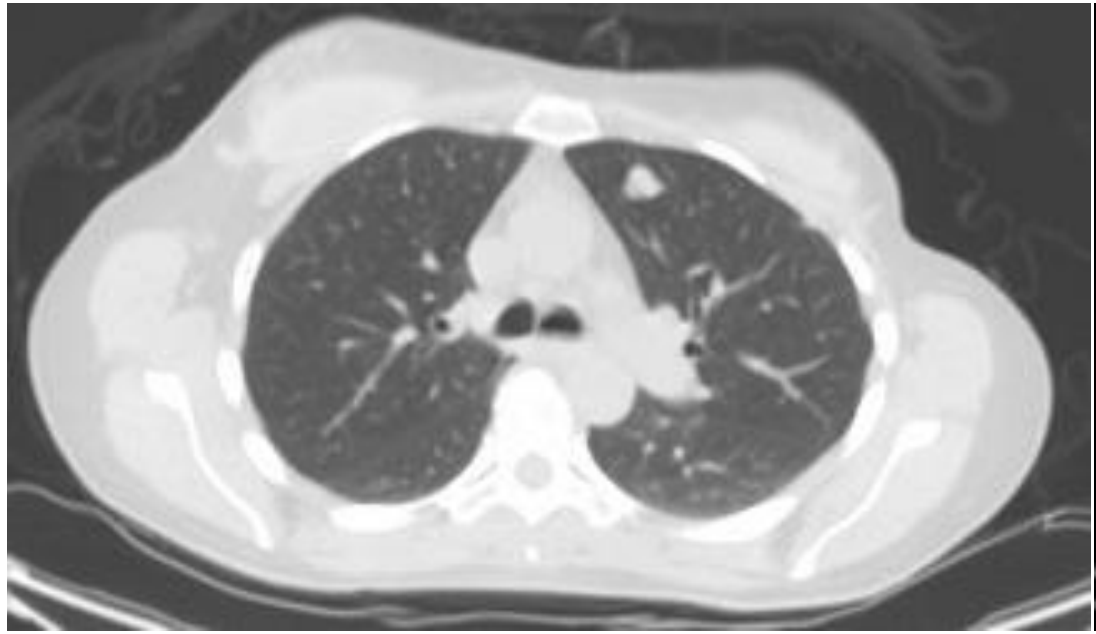
- Given clinically early-stage disease, she was taken to the OR; during surgical resection, was noted to have gross tumor extension to the rectosigmoid colon serosa. Biopsies taken, frozen sections positive for SCC, and surgery was aborted.
- Final pathology demonstrated invasive SCC, moderately differentiated, HR HPV positive, PDL CPS >1

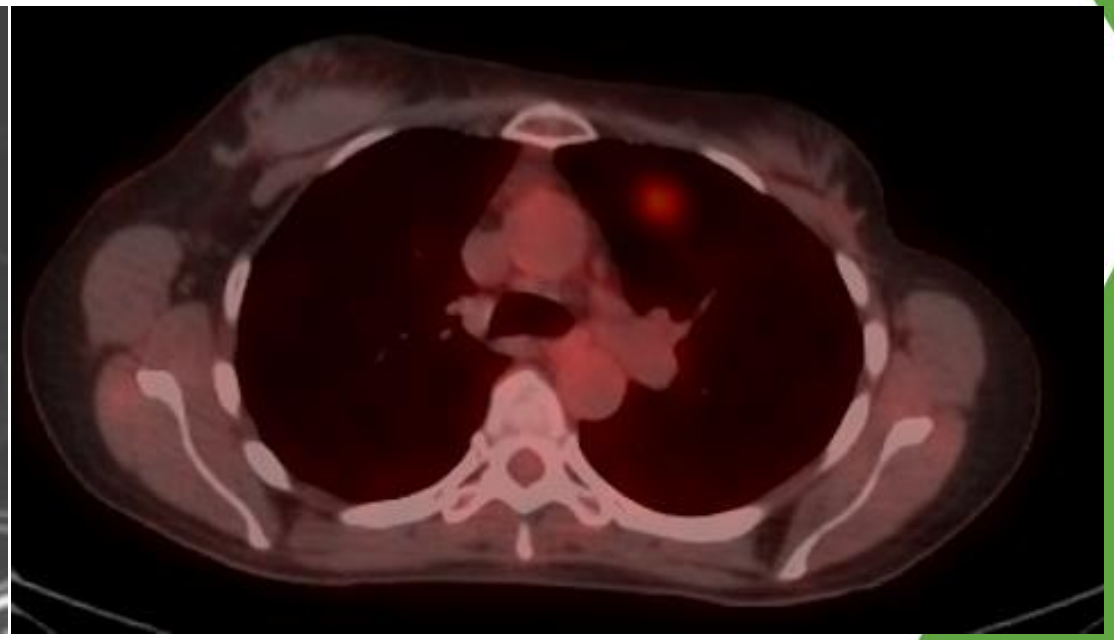
Case 1: Continued

- Patient underwent definitive chemoradiation with cisplatin 40mg/m2 x5 and 4500cGy to the pelvis followed by a cone down for additional 540 cGY and intracavitary brachytherapy with ring and tandem
- She then underwent 4 cycles of OUTBACK-style chemotherapy with carboplatin and paclitaxel
- End of treatment PET/MRI negative for disease

Case 1: Continued

- PET scan 6 months after EOT scan significant for FDG-avid lung nodules measuring up to 1.3x1.3cm



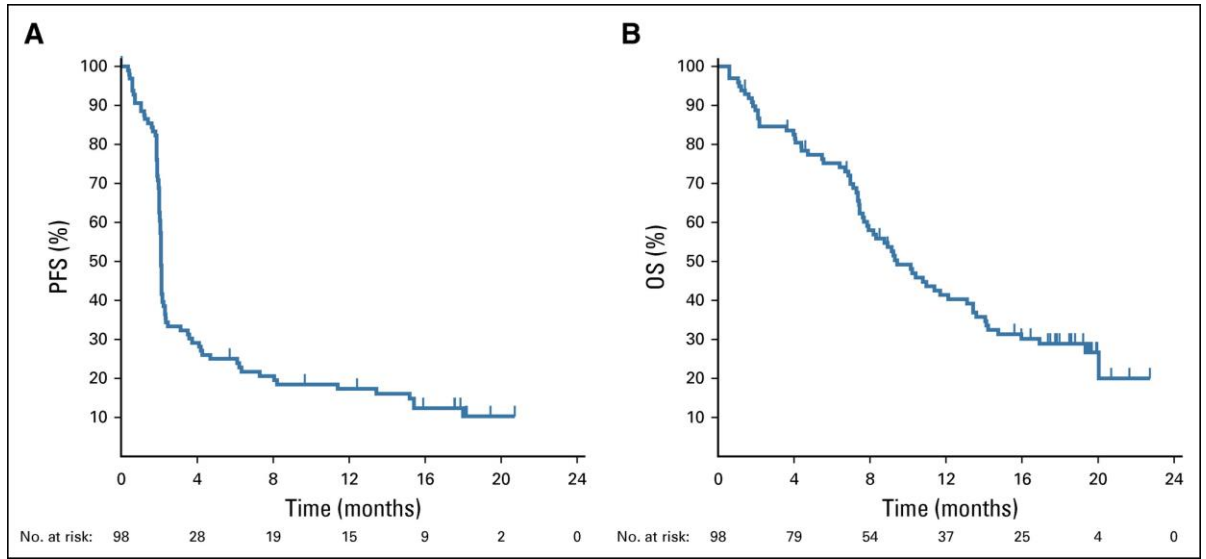


Immunotherapy in Cervical Cancer

Drug	No. of Patients	Response Rate	Disease Control Rate	Toxicity (G3-4 AEs)	Median Overall Survival	Citation
Nivolumab CheckMate 358	19 cervical	26.3%	68.4%	15.8%	21.9 months	Naumann et al, JCO 2019
Pembrolizumab KEYNOTE-028	24	12.5%	25%	20.8%	66.7% at 6 months	Frenel et al, JCO 2016
Ipilimumab	42	2.9%	32.4%	28.6%	8.5 months	Leheruex et al, JAMA Onc 2018
Ipilimumab plus Nivolumab CheckMate 358	176	38% in the N1 plus ipi3 arm; 31% in the N3 l1 arm	NA	29-46% in combo	15.2 in N3l1 and 20.9 in N1l3	Oaknin et al, ESMO 2022

KEYNOTE-158: Pembrolizumab Monotherapy

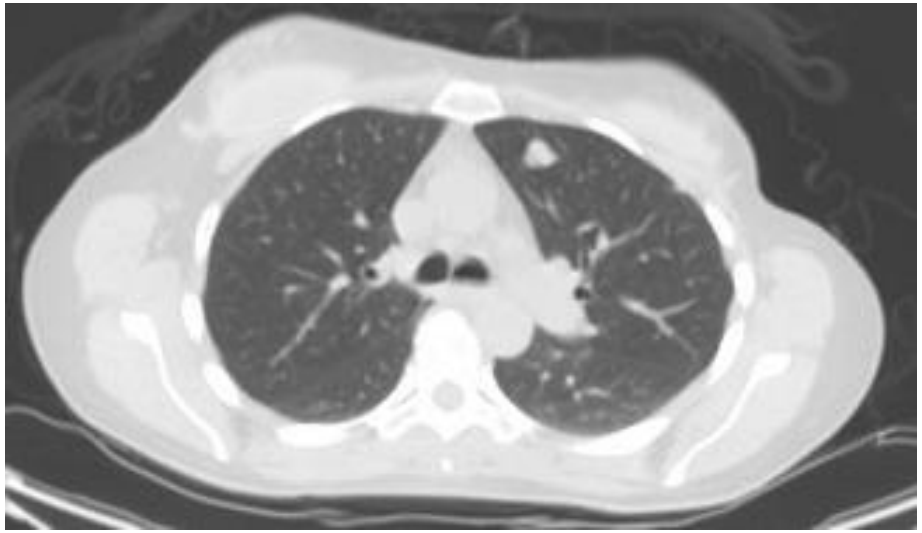
- 98 Patients - 82 with PD-L1–positive tumors (CPS>1)
- Progression on 1+ prior line of therapy
- ORR 14.6% in PD-L1–positive patients; median DOR had not been reached (range, 3.7+ to 18.6+)
- PFS rate at 6 months: 25%
- Median OS: 9.4 months, with range, 7.7-13.1 months
- Led to FDA approval in June 2018 with PD-L1–staining companion diagnostic

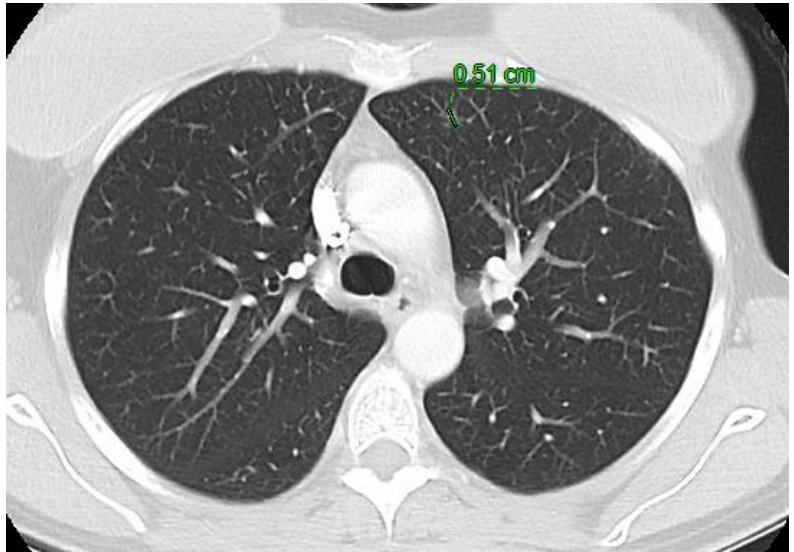


Chung et al, JCO 2019

Case 1: Continued

- Patient initiated single agent pembrolizumab 8 months after finishing chemotherapy
- She tolerated therapy without complications
- Repeat CT scan 3 months later demonstrated major response
- Repeat CT scan 6 months later essentially demonstrated resolved disease





Case 1: Continued

- Patient completed 3 years of pembrolizumab and remains NED one year later

SITC Consensus Guidelines

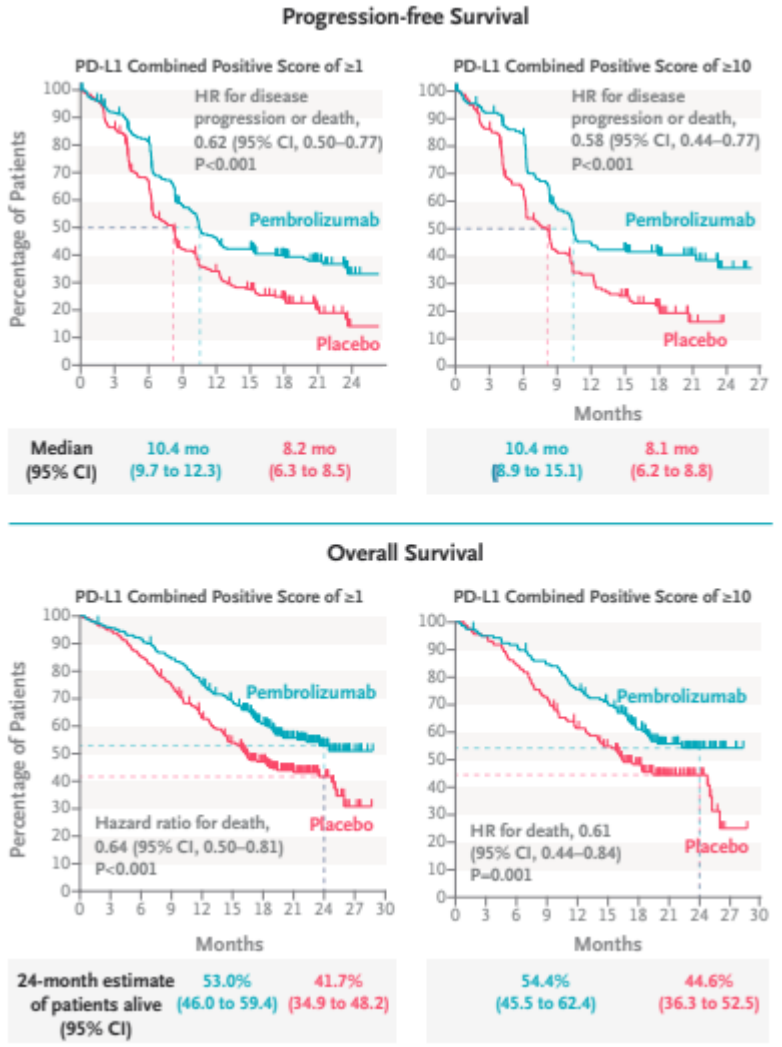
Expert Panel recommendations

- For patients with recurrent or metastatic cervical cancer that is PD-L1-positive (CPS≥1) and has progressed on or after chemotherapy, pembrolizumab should be considered (LE:3).
- For patients with metastatic cervical cancer that is PD-L1-positive (CPS≥1), pembrolizumab with chemotherapy with or without bevacizumab should be considered (LE:2).
- For patients with anti-PD-(L)1-resistant cervical cancer, currently there are no data to inform the sequencing of therapies and/or rechallenge with an ICI.

Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer

Nicoletta Colombo, M.D., Ph.D., Coraline Dubot, M.D., Domenica Lorusso, M.D., Ph.D., M. Valeria Caceres, M.D., Ph.D., Kosei Hasegawa, M.D., Ph.D., Ronnie Shapira-Frommer, M.D., Krishnansu S. Tewari, M.D., Pamela Salman, M.D., Edwin Hoyos Usta, M.D., Eduardo Yañez, M.D., Mahmut Gümüş, M.D., Mivael Olivera Hurtado de Mendoza, M.D., et al., for the KEYNOTE-826 Investigators*

- 617 patients with advanced cervical cancer
- NO prior systemic treatment
- 81.8% rate of grade 3-5 events in pembro group, 75.1% in placebo
- In PD-L1 CPS >1, mPFS was 10.4 months compared to 8.2 months in placebo
- Landmarked OS at 24 months was 53% vs 41.7%



Case 2: pMMR Endometrial cancer

- 58 yo F who presented with post menopausal bleeding
- She underwent a pap smear and endometrial biopsy which demonstrated high grade endometrial adenocarcinoma
- PMHx: Breast cancer s/p lumpectomy, RT, and anastrozole. Also diagnosed with HTN, osteopenia, GERD
- PSHx: Left breast lumpectomy
- Genetics: germline negative

Case 2: Continued

- Screening CT CAP demonstrated enlarged heterogenous uterus, no definite metastatic disease
- She went to the OR for TAH/BSO/SLNB. Pathology demonstrated serous carcinoma, 7/19mm invasion, SLNs negative. IHC demonstrated pMMR, TP53 aberrant, HER2 2+
- HER 2 FISH negative

Case 2: Molecular Data

Interpretation

Summary: 5 mutations, 3 copy number alterations, 2 structural variants detected.

MSI Status: MICROSATELLITE STABLE (MSS). The MSIsensor score is 0.9.

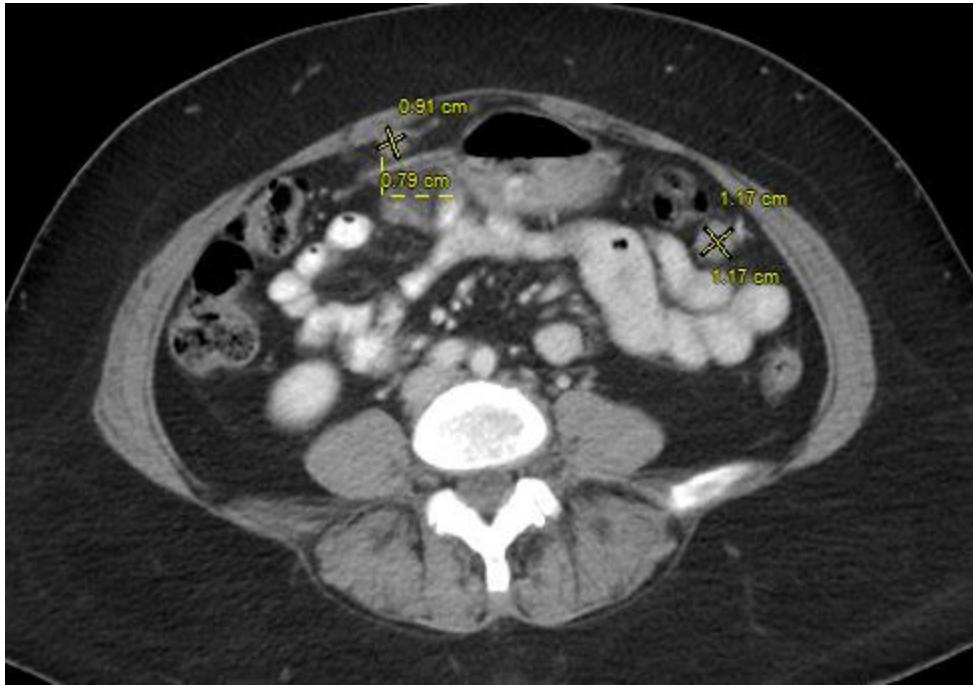
TUMOR MUTATION BURDEN: The estimated tumor mutation burden (TMB) for this sample is 4.1 mutations per megabase (mt/Mb).

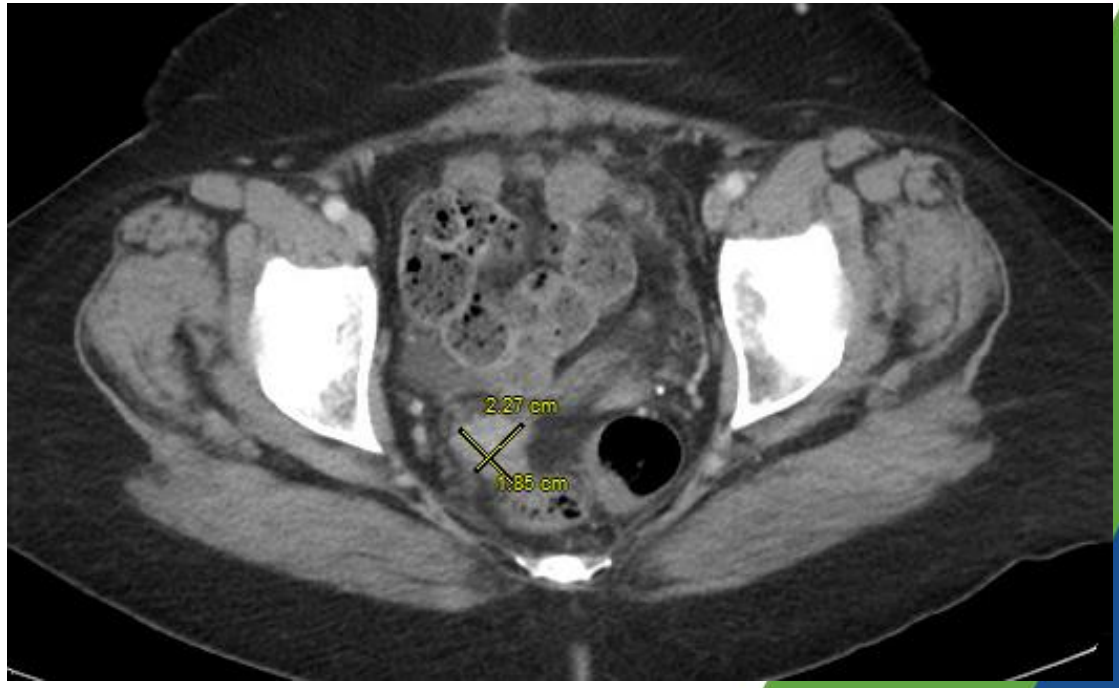
POSITIVE FOR THE FOLLOWING SOMATIC ALTERATIONS:
1. PIK3CA (NM_006218) exon10 p.E545G (c.1634A>G)
2. TP53 (NM_000546) exon7 p.Y236H (c.706T>C)
3. ERBB2 (NM_004448 - 17q12) Gain (Fold Change: 1.8) (Note: 3)
4. FGFR3 (NM_000142 - 4p16.3) Amplification (Fold Change: 3.1)
5. WHSC1 (NM_001042424 - 4p16.3) Amplification (Fold Change: 3.1)
6. BRCA2 (NM_000059) exon10 p.D301E (c.903T>G)
7. CDH1 (NM_004360) exon10 p.S496C (c.1487C>G)
8. KLF5 (NM_001730) exon2 p.P302R (c.905C>G)
9. SMARCA4 (NM_003072) - LDLR (NM_000527) rearrangement: c.4171-1791:SMARCA4_c.941-666:LDLRdel (Note: 1)
10. CPNE5 (NM_020939) - CDKN1A (NM_078467) rearrangement: c.737+124:CPNE5_c.313:CDKN1Ainv (Note: 2)

Notes:
1. The SMARCA4 - LDLR rearrangement is a deletion that results in a fusion of SMARCA4 exons 1 - 30 to LDLR exons 7 - 18. One of the breakpoints is within SMARCA4 exon 30.
2. The CPNE5 - CDKN1A rearrangement is an inversion that results in a fusion of CPNE5 exons 1 - 10 to CDKN1A exons 3 - 4. One of the breakpoints is within CDKN1A exon 3. Functional significance is undetermined.
3. The ERBB2 copy number gain falls slightly below the cut off criteria for amplification. Confirmatory testing by an alternate method is suggested, if clinically indicated.

Case 2: Continued

- She completed 6 cycles of carboplatin and paclitaxel along with IVRT
- 6 months after completing chemotherapy, CT CAP consistent with recurrence with peritoneal implants





SITC Guidelines

Expert Panel recommendations

- For first-line treatment of recurrent or metastatic endometrial cancer, carboplatin plus paclitaxel with or without trastuzumab (if HER2+ serous endometrial cancer) was the standard of care at the time of guideline publication (LE:2). Anti-PD-1 ICIs in combination with carboplatin plus paclitaxel demonstrated statistically significant and clinically meaningful improvements in PFS over chemotherapy alone for the treatment of previously untreated stage III or IV or first recurrent (after prior neoadjuvant or adjuvant chemotherapy) endometrial cancer. The observed benefit was regardless of MMR status (LE:2), however, this combination was not FDA-approved at the time of guideline publication.
- For second-line treatment of patients with pMMR/MSS advanced or recurrent endometrial cancer, pembrolizumab plus lenvatinib is recommended, as indicated. For second-line treatment of patients with TMB-H/pMMR/MSS endometrial cancer (LE:2), pembrolizumab plus lenvatinib is the standard of care option (LE:2) however, anti-PD-1 monotherapy may also be an option (LE:3).
- For patients with dMMR/MSI-H advanced or recurrent endometrial cancer who have disease progression following prior systemic therapy in any setting and who are not candidates for curative surgery or radiation, pembrolizumab monotherapy is recommended (LE:3). For patients with dMMR/MSI-H advanced or recurrent endometrial cancer who have disease progression following prior platinum-containing regimen in any setting and who are not candidates for curative surgery or radiation, dostarlimab monotherapy is recommended (LE:3).

Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer

Vicky Makker, M.D., Nicoletta Colombo, M.D., Antonio Casado Herráez, M.D., Alessandro D. Santin, M.D., Emeline Colomba, M.D., David S. Miller, M.D., Keiichi Fujiwara, M.D., Sandro Pignata, M.D., Sally Baron-Hay, M.B., B.S., Isabelle Ray-Coquard, M.D., Ronnie Shapira-Frommer, M.D., Kimio Ushijima, M.D., et al., for the Study 309–KEYNOTE-775 Investigators*

In patients with pMMR disease, len/pem had a median PFS of 6.6 months compared to 3.8 months with physician choice chemotherapy

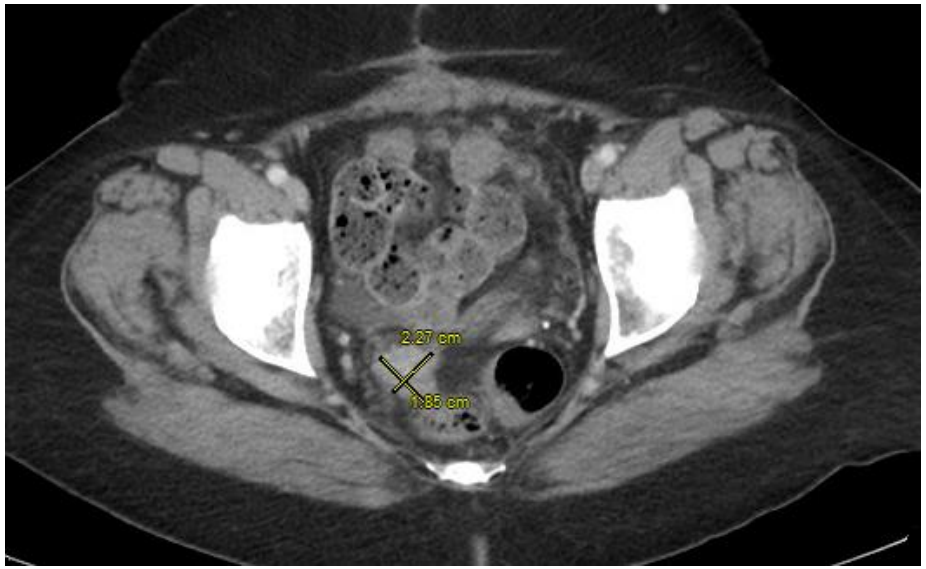
The median overall survival was longer with lenvatinib plus pembrolizumab than with chemotherapy (pMMR population: 17.4 vs. 12.0 months; hazard ratio for death, 0.68; 95% CI, 0.56 to 0.84; P<0.001

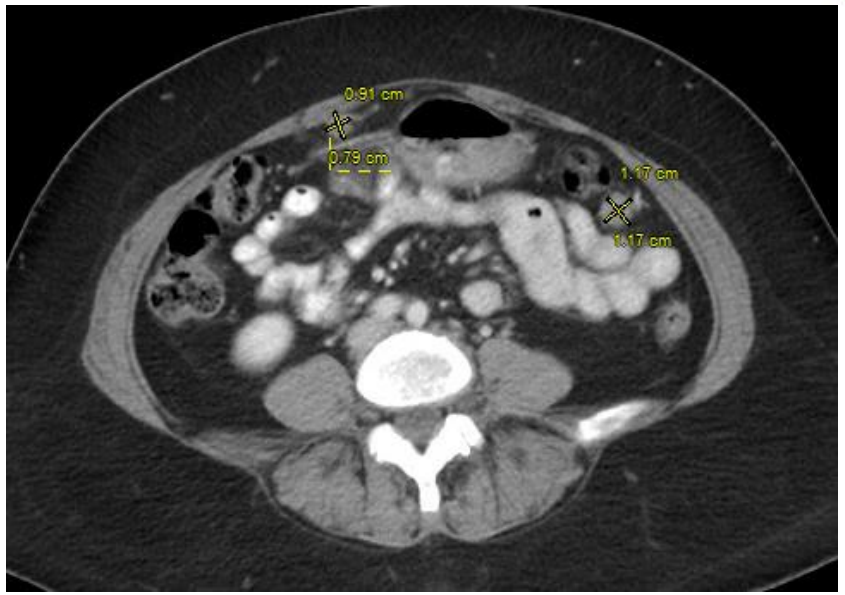
Makker, et al, NEJM 2022

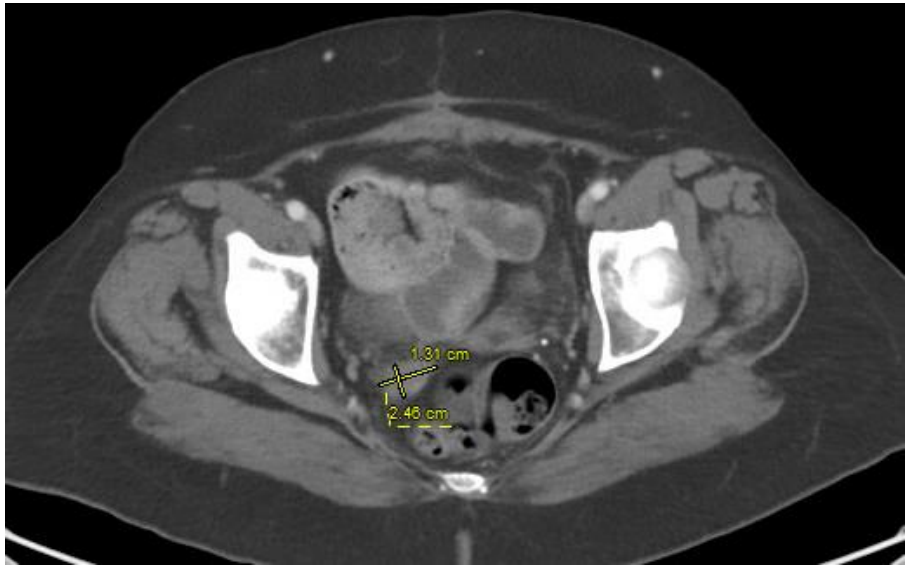
Case 2: Continued

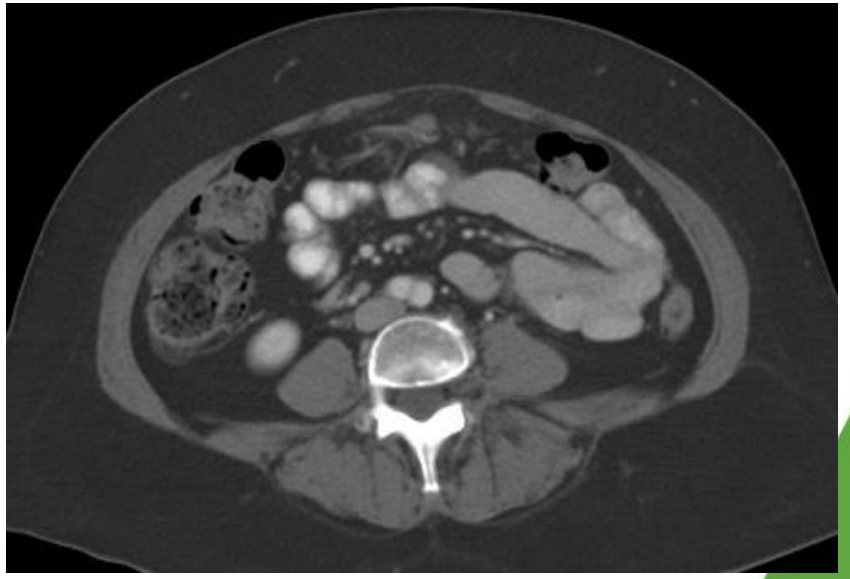
- Patient started on lenvatinib and pembrolizumab
- Patient with poor tolerance of lenvatinib – diarrhea, increased blood pressure, and intolerable fatigue. She was dose reduced from 20mg→14mg→10mg→8mg with improvement
- She also developed hypothyroidism related to pembrolizumab and was started on levothyroxine

Case 2: Continued









Case 2: Continued

- Patient remains on pembrolizumab and Lenvatinib in a partial response
- She is tolerating 8mg lenvatinib by mouth daily