ACI Gynecologic Cancer Case Studies

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ADVANCES IN Cancer IMMUNOTHERAPY™

ACI Uterus and Cervix Cases

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Case 1

Metastatic uterine serous cancer, mismatch repair proficient

Shannon Westin, MD

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Case 1

- 44-year-old woman presents with increasing abdominal pain and bloating.
  - CA125 230 U/mL. CT CAP demonstrates enlarged uterus and omental thickening.
- Underwent tumor reductive surgery including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy.
  - Pathology demonstrates uterine serous carcinoma involving uterus and omentum.
  - Retained expression of mismatch repair proteins, HER2 expression negative.
- Completed 6 cycles of adjuvant paclitaxel and carboplatin.
  - NED for 7 months. Presents with early satiety and nausea.
  - CT CAP obtained.

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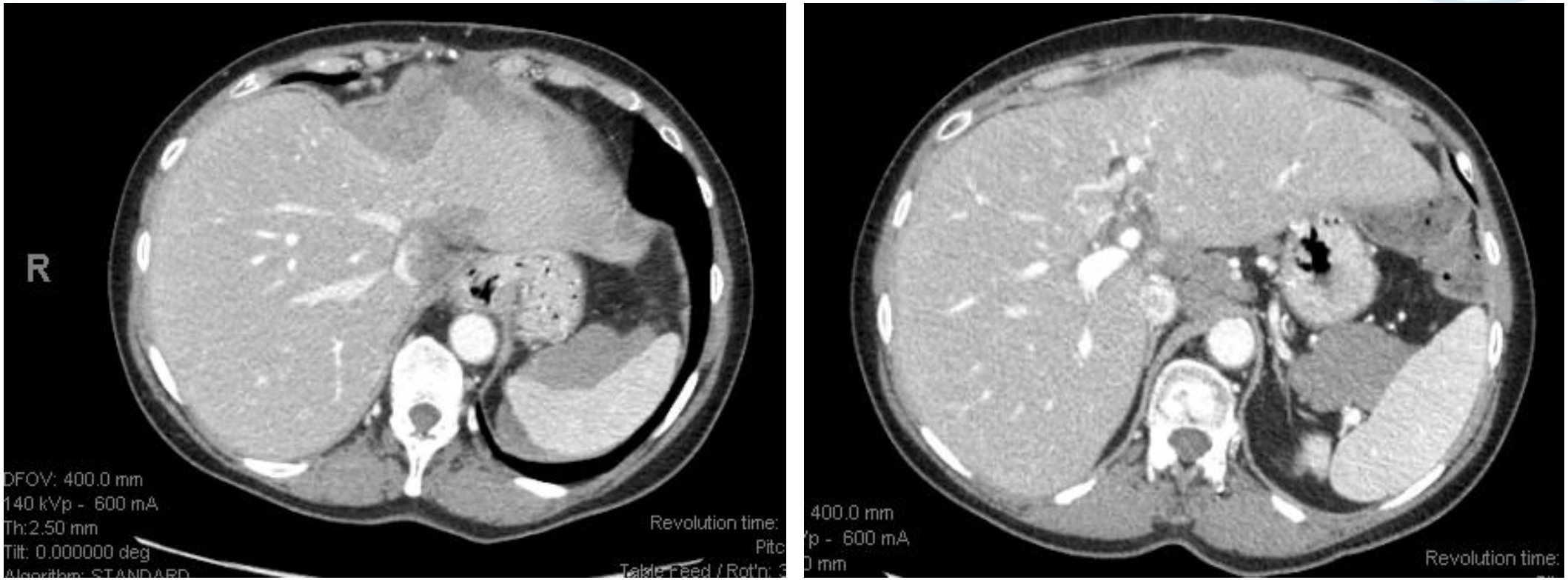

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What would you do next?

1. Re-treatment with paclitaxel and carboplatin
2. Pembrolizumab or dostarlimab
3. Pembrolizumab and lenvatinib
4. Bevacizumab

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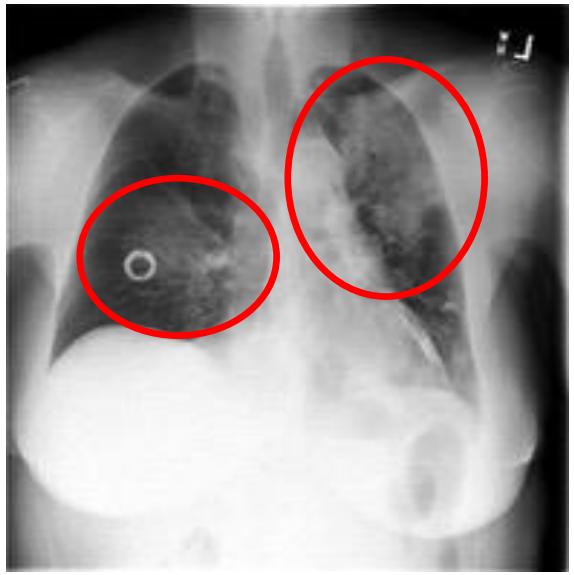
Case 1 – Cont'd

- She is started on pembrolizumab and lenvatinib.
  - Receives 4 cycles with partial response.
- She presents for routine assessment and notes increasing cough and shortness of breath.



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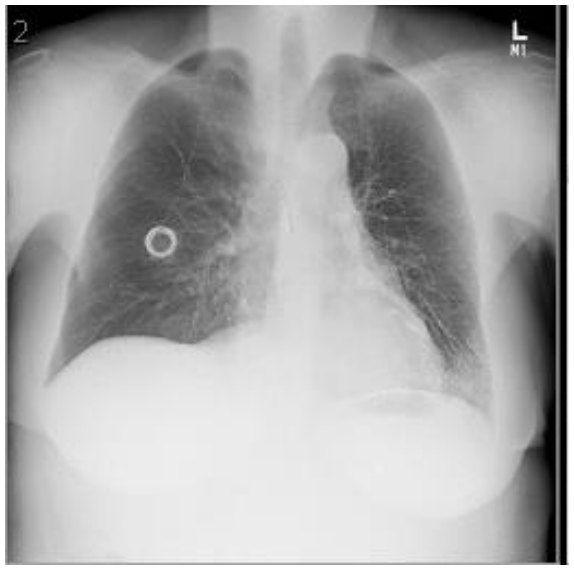
- Her pulmonary work up is negative for pulmonary embolus and infection
- She is diagnosed with G2 immune-related pneumonitis and treated with prednisone and dapsone for 2 weeks



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Would you re-start IO combination therapy?

Any precautions?

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Case 2

Metastatic cervical cancer, first line therapy decision

Chrisann Kyi, MD

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Case 2

- A 45-year-old female presents with pelvic pain and abnormal vaginal bleeding
- PET/CT shows cervical mass, retroperitoneal lymphadenopathy, and sacral lytic lesions, consistent with metastases
- Colposcopy, biopsy of endocervix: Invasive, poorly differentiated adenocarcinoma with features of invasive stratified mucinous carcinoma

- Molecular testing:
  - In situ hybridization for high risk HPV-16 is positive in tumor cells
  - Immunohistochemistry for p16: positive (diffuse, strong)
  - PD-L1 expression (clone E1L3N): Combined Positive Score (CPS): 4 (of 100);
    - Relative contribution of tumor cells to the CPS: 80%
    - Relative contribution of inflammatory cells to the CPS: 20%
  - HER2: Negative (1+)

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Case 2

A 45-year-old female with recurrent, metastatic stage 4B cervical cancer squamous cell cervical cancer to liver and bone, PD-L1 Positive (CPS>1)

What treatment would you offer this patient?

A. Chemoradiation with weekly cisplatin, followed by 4 cycles of Carboplatin/paclitaxel (Outback regimen)
B. Carboplatin/Paclitaxel/bevacizumab
C. Pembrolizumab/Cisplatin/Paclitaxel/bevacizumab
D. Pembrolizumab

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Pembrolizumab with chemotherapy or bevacizumab as front line therapy in advanced cervical cancer (CPS≥1)

Key Eligibility Criteria

- Persistent, recurrent, or metastatic cervical cancer not amenable to curative treatment
- No prior systemic chemotherapy (prior radiotherapy and chemoradiotherapy permitted)
- ECOG PS 0 or 1

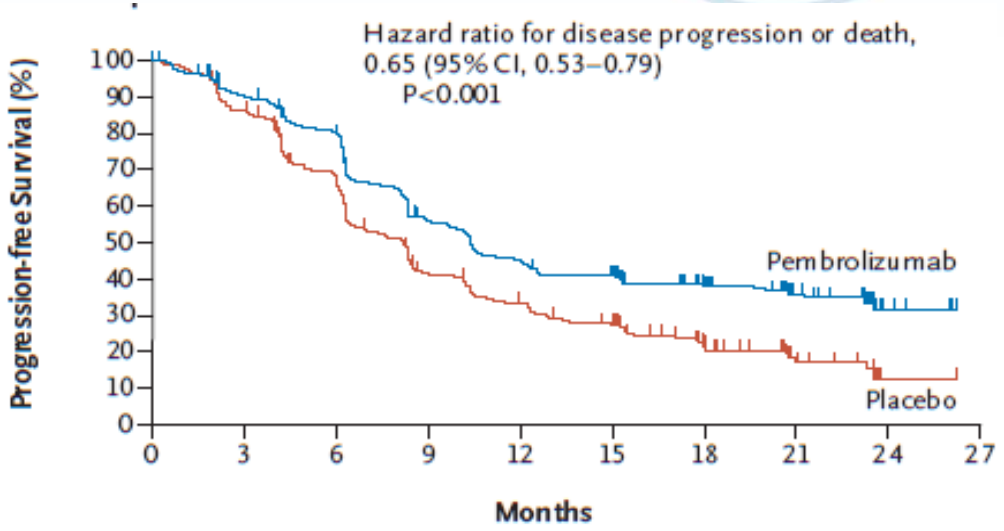
R 1:1

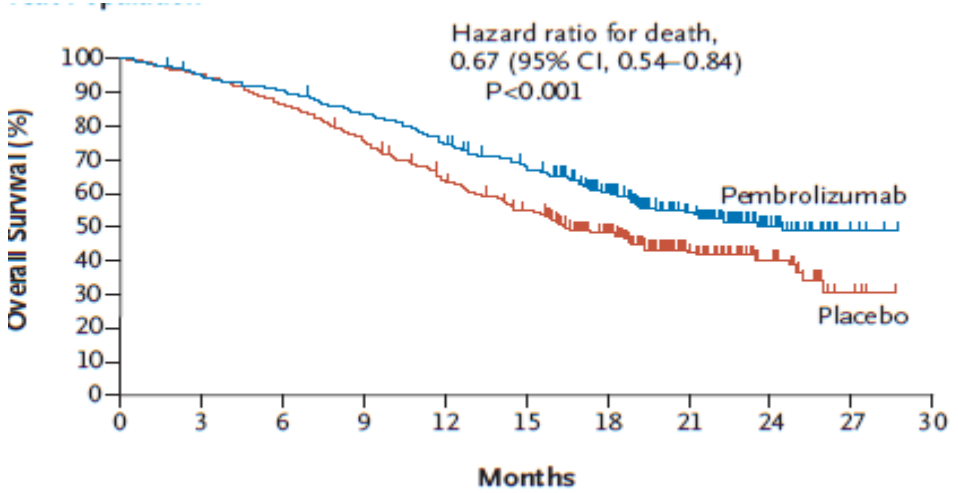
Pembrolizumab 200 mg IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

Placebo IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

Keynote 826

Columbo et al, NEJM, 2021
Schema from Dr. Leslie Randall





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ACI Ovarian Cases

Emese Zsiros, MD

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Case 3

Ovarian Cancer, recurrent and platinum-resistant

Emese Zsiros, MD, PhD

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Case 3

- 69-year-old woman comes in for 2nd opinion for further management of recurrent platinum-resistant high grade serous ovarian cancer.
- Underwent Ex-lap, TAH/BSO, omentectomy, cholecystectomy, loop ileostomy, sigmoid resection
- Treated with 2 cycles of **carboplatin** – as "too weak" to get doublet therapy per oncologist followed by 4 cycles of **carboplatin +paclitaxel (→ docetaxel,** due to severe allergic reaction)
- Reversal of loop ileostomy 3 months later – during surgery additional disease was found
- Treated with 2 cycles of **Carboplatin and gemcitabine** – but rising CA-125 and disease progression on CT scan
- CT scan: several 2-3 cm liver lesions, extensive retroperitoneal lymphadenopathy, pleural and peritoneal thickening
- Germline: BRCA neg
- ECOG 2 - she is a retired RN and desperate to find some other treatment

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Tumor tissue sequencing:

Marker	Test	Result
PD-L1	IHC	0% Tumor Proportion Score
TILS	RNA-Seq	Low (Non-inflamed)
CD3/CD8	IHC	Non-Infiltrating
Mutational Burden	DNA-Seq	2.628/Mb (Low)
Microsatellite Instability	PCR	On hold, will update report if normal received within 30 days.
PD-L1/L2 Copy Number	FISH	Not Amplified

TUMOR INFILTRATING LYMPHOCYTES (TILS)			
Marker	Rank	Interpretation	Function
CD2	3	Low	Cytotoxic T-cells/T-regs
CD3	1	Low	Cytotoxic T-cells/T-regs
CD4	8	Low	Cytotoxic T-cells/T-regs
CD8	6	Low	Cytotoxic T-cells/T-regs

Expression Interpretation Key:

What to do next?

More chemo? Doxil?
PARPi?
Clinical trial?

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- Clinical trial with **Pembrolizumab 200 mg and Bevacizumab 15 mg/kg every 3 weeks and Cyclophosphamide 50 mg po QD**; regimen extended to every 6 weeks due to length of treatment – PARTIAL RESPONSE

- COMPLETED a total of 48 Cycles !!

When progressed, competed 3 cycles of Doxil - PD
Then 2 rounds of weekly Taxol before she died.

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ACI Immunotherapy-related Toxicities Cases

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Case 4

Toxicity with Combination Regimen

Pembrolizumab + Lenvatinib

Amy Bregar, MD

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Case 4

- 40-year-old obese female w/ recurrent Stage III UPSC, MSI-stable
- Comorbidities:
  - Hypertension
  - Renal Insufficiency
  - BMI >35
- Treatment Regimen
  - Pembrolizumab 200mg IV q 21 days with Lenvatinib 20mg PO daily

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"Expected" Complications that arose:

- Uncontrolled Hypertension within the first week
  - Held Lenvatinib and initiated losartan 25mg daily – NO improvement
  - Increased losartan 50mg daily – BP well controlled – reinitiated Lenvatinib 20mg daily….uncontrolled hypertension again
    - Held dose, BP normalized then resumed at 16mg daily
    - Repeat of events – patients BP stabilized with Lenvatinib 8mg daily over 16 months

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- Hypothyroidism
  - Within 1st month – drop in T3 and elevation in TSH (patient symptomatic – fatigue, hair loss, weight gain, etc)
  - Initiated on levothyroxine PO and symptoms resolved, T3/TSH normalized

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"Unexpected" Complications that arose:

- Photo hypersensitivity
  - Missed "a spot" when applying sunscreen – sun exposure less than 30 minutes – significant sunburn

- Delayed wound healing
  - Incidental "scrape" while out for a walk
  - Patient self treated at home
  - Clinical assessment - >3 x 3 cm ulcerating, infected lesion
    - Required hospitalization for management
    - Required antibiotics for 21 days, high dose steroids (with taper)
    - Treatment delay over two months

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Pembrolizumab Adverse Effects

- Fatigue
- Diarrhea/abdominal pain
- Decreased appetite
- Immune-mediated reactions
  - Colitis
  - Pneumonitis
  - Endocrinopathies
  - Hepatitis
  - Dermatologic

Lenvatinib Adverse Effects

- Diarrhea
- Hypertension
- Fatigue
- Nausea/vomiting
- Stomatitis
- Peripheral edema
- Arthralgia/myalgia
- Hypothyroidism
- Rash

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Dermatologic	Pneumonitis	Gastrointestinal
RASH: **Grade 1/2- Continue therapy** • Oral Antihistamine • TOPICAL corticosteroids **Grade 3- HOLD therapy** • ORAL steroids (prednisone 0.5-1 mg/kg daily) until resolution *then taper* **PRURITIS:** **Grade 1-Continue therapy** • topical treatment **Grade 2- Dermatology referral** topical treatment/oral antihistamine/steroids **Grade 3- Dermatology referral** • GABA agonists; oral steroids (prednisone 0.5-1 mg/kg daily- then taper over 2 weeks)	**Grade 1- HOLD THERAPY** –resume when symptoms resolve with close monitoring Consideration oxygenation **Grade 2- HOLD THERAPY** – consider hospitalization; consider re-challenge if symptoms resolve • Methylprednisolone 1mg/kg/d – after symptoms resolve taper over 1 month **Grade 3/4- DISCONTINUE THERAPY** Hospitalization (possible ICU) & pulmonary consult. • Initiate methylprednisolone 2 mg/kg/d • If symptoms improve decrease to 1 mg/kg/d then taper over 2 months • If NO improvement- add alternative agent (i.e. infliximab)	**Diarrhea/colitis:** **Grade 1- Continue therapy** • Initiate anti-motility agent **Grade 2/3 - HOLD THERAPY**, abdominal x-ray; consider sigmoidoscopy to rule out colitis • Antimotility agent; • If no improvement initiate prednisone 1 mg/kg/d PO ** if improves within 72 hours then gradual taper;*** If no improvement within 72 hours manage as grade 3. **Grade 4: DISCONTINUE THERAPY**; rule out colitis, consider imaging + surgical consult (r/o megacolon) • Initiate methylprednisolone 1-2 mg/kg/d • If NO improvement after 24 hr- add alternative agent (i.e. infliximab 5mg/kg IV at week 1,2,& 6); add mycophenolate if needed; once symptoms resolve over 4-6 weeks **Hepatitis:** **Grade 1- Continue therapy**; monitor LFTs **Grade 2/3 HOLD therapy;** can resume when taper less than 10 mg/day & ≤ grade 1 **Grade 4: DISCONTINUE THERAPY** **Grades 2-4 Tx with** Prednisone 1-2 mg/kg/d PO daily; taper after symptoms improve; consider mycophenolate, liver biopsy if no response

Puzanov I, et al. *J Immunother Cancer*. 2017;5(1):95., DeSouza K, et al. *J Cancer Prev Curr Res*. 2016;6(1):00187

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Clinical Pearls for Lenvatinib Toxicity Prevention and Management

- Baseline thyroid panel (monthly thereafter)
- Blood pressure monitoring at baseline; periodically thereafter
- Urine protein monitoring at baseline and periodically
  - Hold if ≥ 2+ grams/proteinuria in 24 hours
- Antidiarrheals/antiemetics recommended as needed

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Case 5

Patient presents with elevated troponin after one dose of Pembrolizumab for metastatic MSI-H endometrial cancer

Kerry Reynolds, MD

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Case 5

- Patient is a 69-year-old female with fatigue found to have elevated troponin to 120
- PMH: metastatic endometrial cancer (s/p 1st cycle pembrolizumab), T2DM, HLD, and known RBBB
- EKG – RBBB
- ECHO – Normal ejection fraction

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Case 5

What would you do next?

1. Follow troponin in 1 week
2. Cardiac biopsy
3. Start prednisone at 1 mg/kg daily
4. Admit and start IV solumedrol at 1 gram/day

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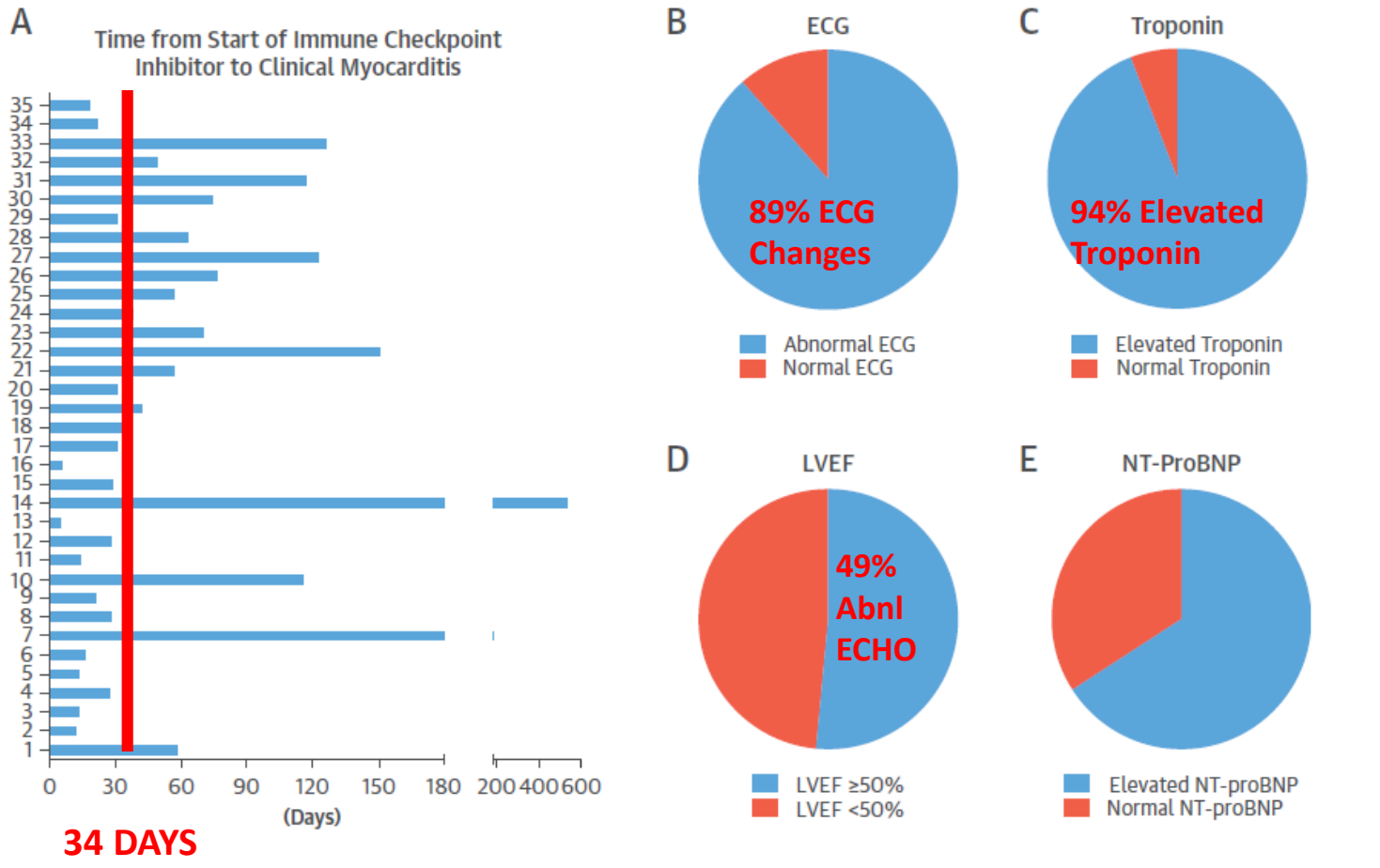
Key Discussion Points

FIGURE 1 Clinical Presentation of Patients With ICI-Associated Myocarditis



S Mahmood, T Neilan, JACC, 2018

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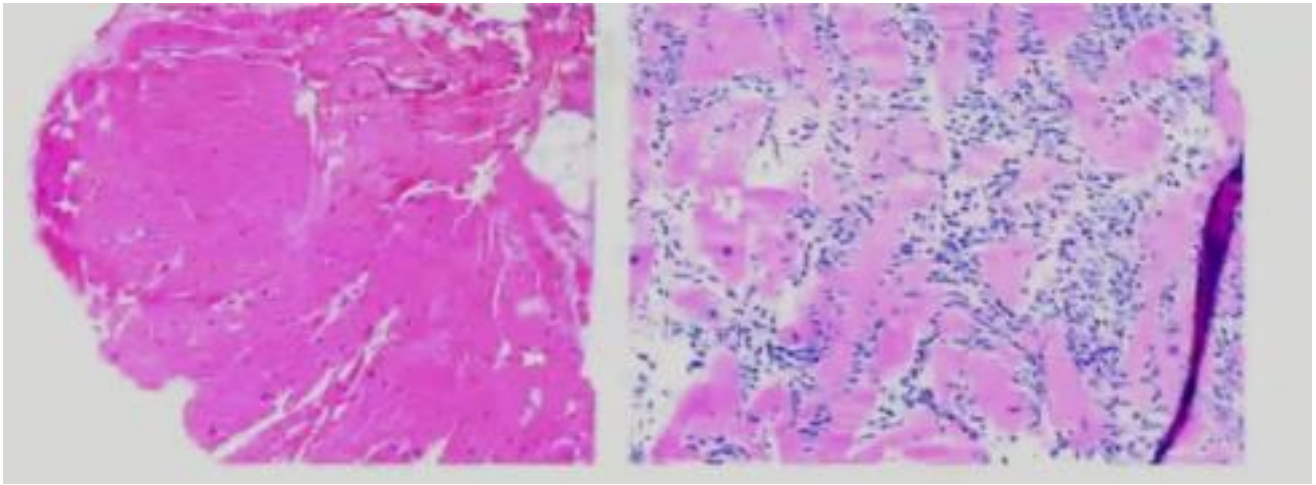
Key Discussion Points

- Pathological findings - Reminiscent of those in acute allograft rejection after cardiac transplantation.



- Management - **HIGH dose** 1 gram of solumedrol daily
- Have High Suspicion For Another irAE – overlap with myositis/pericarditis/myasthenia gravis

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Additional cases if time permits

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Case 6

Metastatic cervical cancer scheduled to start treatment with Pembrolizumab, T spot +

Kerry Reynolds, MD

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Case 6

- 41-year-old woman from southern Africa with advanced cervical cancer
- Plan to start pembrolizumab
- Hepatitis B core antibody negative
- Hepatitis B surface antigen negative
- Hepatitis B surface antibody positive
- HIV 1/2 antibody/antigen negative
- T spot positive

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What would you do next for a patient with a positive T spot?

1. Review symptoms, continue with Pembrolizumab infusion
2. Get chest x-ray to look for active TB
3. Hold infusion, refer to infectious disease
4. Start Isoniazid

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Key Discussion Points

- Chest X-ray to look for active TB (i.e. cavitary lung lesions)
- Risk Factors for TB: (From endemic region, prior TB test +, family member with TB, healthcare, prison, homeless, illicit drug use)
- Review symptoms:
  - Fevers
  - Night sweats
  - Weight loss
  - Cough of > 2 weeks duration
  - Hemoptysis
- Refer to Infectious Diseases
- Regimens Prevention of Progression to active TB (decrease risk 60-90%)
  - Isoniazid / B6 x 9 months
  - Rifampin x 4 months
  - Isoniazid + Rifapentine x 3 months
- Ideally get 2-4 weeks of treatment in prior to starting pembro

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Key Discussion Points

- Chest X-ray to look for active TB (i.e. cavitary lung lesions)
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  - Rifampin x 4 months
  - Isoniazid + Rifapentine x 3 months
- Ideally get 2-4 weeks of treatment in prior to starting pembrolizumab

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Case 7

Metastatic endometrial cancer, dMMR, second line therapy decision

Chrisann Kyi, MD

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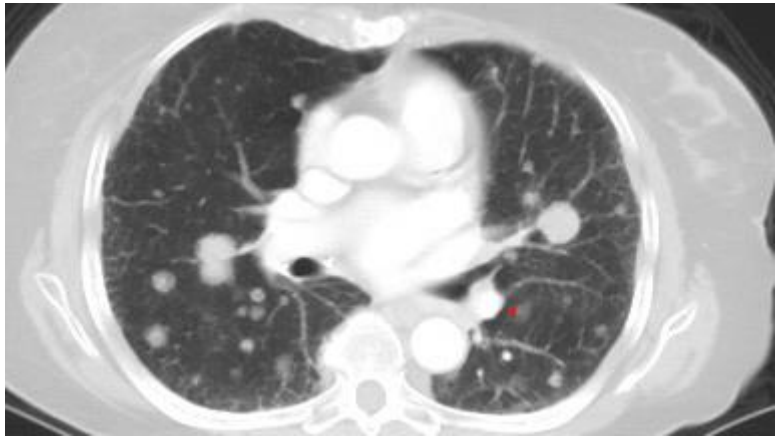
Case 7

- 72-year-old woman stage IIIC grade 3 endometrioid endometrial cancer

- Underwent staging hysterectomy/bilateral salpingo-oophorectomy and sentinel lymphadenectomy
  - Pathology showed grade 3 endometrioid carcinoma, 3/18 pelvic LN involved, FIGO Stage 3C1. MLH1 and PMS2 staining absent.
- Completed 6 cycles of adjuvant chemotherapy (carboplatin + Paclitaxel) and intravaginal brachytherapy.

- Five months later, she presents with cough. CT chest demonstrates multiple lung lesions. Biopsy confirmed recurrence.



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Case 7

72-year-old woman 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 confirms recurrence. MLH1 and PMS2 staining absent.

What treatment would you offer this patient?

A. Perform Next Generation Sequence analysis
B. Carboplatin/Paclitaxel
C. Tamoxifen/megestrol acetate
D. Pembrolizumab
E. Pembrolizumab/Lenvatinib

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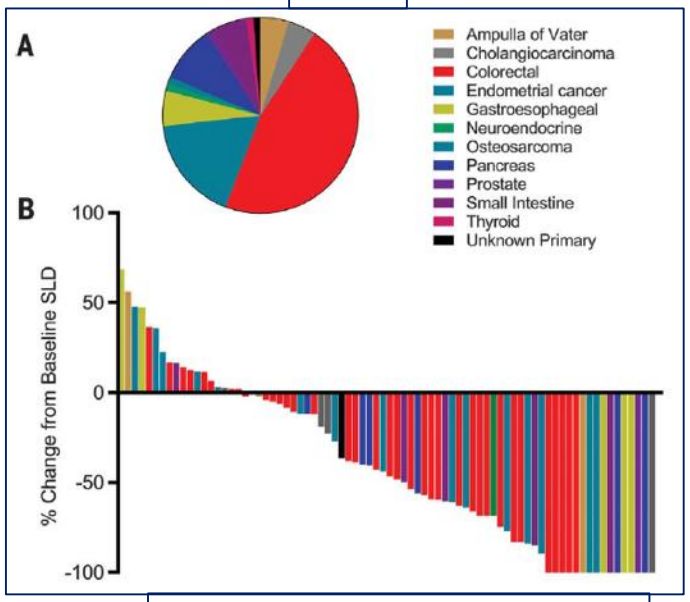
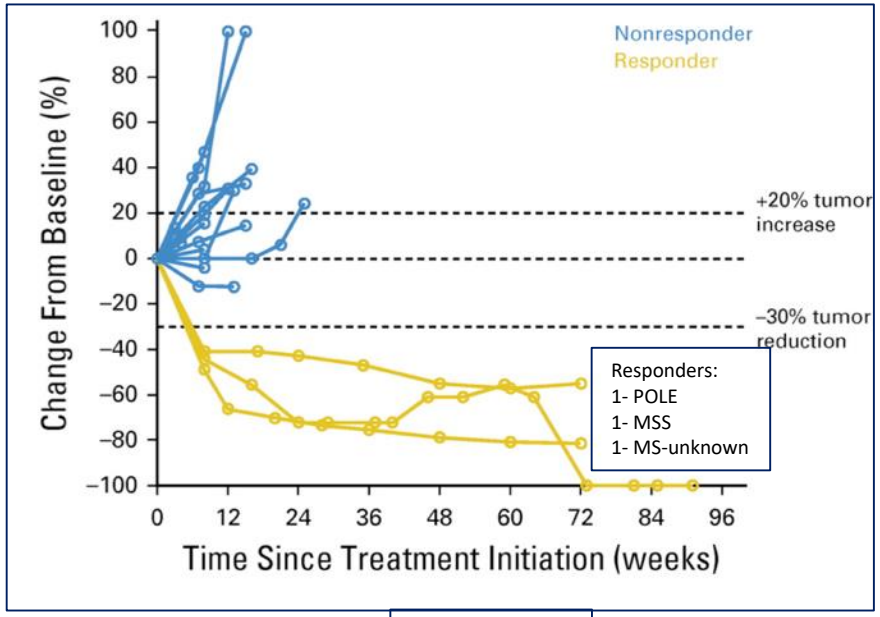
Response to single-agent PD-1 blockade in Endometrial Cancer

MSI



Endometrial cohort (n=15)
CR: 3 (20%)
PR: 5 (33%)
SD: 3 (20%)

Non-MSI Endometrial (PD-L1)+)



ORR 13%

Science. 2017 Jul 28;357(6349):409-413; J Clin Oncol. 2017 Aug 1;35(22):2535-2541.

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KN158: Pembrolizumab Monotherapy in MSI-H/dMMR Solid Tumors

TABLE 3. Antitumor Activity for Tumor Types With Greatest Enrollment

Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)	NR (6.3 to 28.4+)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 to NR)	24.3 (6.5 to NR)	NR (4.1+ to 24.9+)
Pancreatic	22	1	3	18.2 (5.2 to 40.3)	2.1 (1.9 to 3.4)	4.0 (2.1 to 9.8)	13.4 (8.1 to 16.0+)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)	NR (4.3+ to 31.3+)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)	NR (4.2 to 20.7+)
Brain	13	0	0	0.0 (0.0 to 24.7)	1.1 (0.7 to 2.1)	5.6 (1.5 to 16.2)	–

NOTE. Efficacy analyses included all patients who received at least one dose of pembrolizumab. Only confirmed responses are included. Response was assessed per RECIST version 1.1 by independent central radiologic review.

Abbreviations: +, no progressive disease by the time of last disease assessment; CR, complete response; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

Published in: Aurelien Marabelle; Dung T. Le; Paolo A. Ascierto; Anna Maria Di Giacomo; Ana De Jesus-Acosta; Jean-Pierre Delord; Ravit Geva; Maya Gottfried; Nicolas Penel; Aaron R. Hansen; Sarina A. Piha-Paul; Toshihiko Doi; Bo Gao; Hyun Cheol Chung; Jose Lopez-Martin; Yung-Jue Bang; Ronnie Shapira Frommer; Manisha Shah; Razi Ghori; Andrew K. Joe; Scott K. Pruitt; Luis A. Diaz Jr; *Journal of Clinical Oncology* 2020 381-10.
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